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Bromine-Catalyzed Aerobic Oxidation of Alcohols

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Dedicated to the 150th anniversary of Japan–UK diplomatic relations

The oxidation of alcohols to the corresponding carbonyl compounds is one of the most fundamental and important transformations in synthetic organic chemistry.^[1] Molecular oxygen is the most ideal oxidant because it is both atomeconomically and environmentally benign. To date, numerous transition-metal-catalyzed aerobic oxidations of alcohols have been developed.^[1,2] Recently, the TEMPO (a nitroxy radical)-catalyzed aerobic oxidation of alcohols has also been reported.^[3] However, there is a strong need for cheaper, more efficient, more chemoselective, and greener methods for such transformations, particularly in the pharmaceutical industry.^[4]

Over the past two decades, hypervalent iodine compounds have been the focus of considerable attention, owing to their mild and chemoselective oxidizing properties and their environmentally benign character in contrast to toxic-metal reagents.^[5] Very recently, we reported a highly-efficient and chemoselective oxidation of various alcohols to carbonyl compounds, such as aldehydes, carboxylic acids, and ketones with powdered Oxone (2KHSO₅·KHSO₄·K₂SO₄) in the presence of catalytic amounts of 2-iodoxybenzenesulfonic acid (IBS), which is generated in situ from 2-iodobenzenesulfonic acid (Scheme 1).^[6]

On the other hand, Liu and co-workers reported a hypervalent iodine-catalyzed oxidation of alcohols using molecular oxygen as a terminal oxidant.^[7] Accordingly, the aerobic oxidation of a broad range of primary and secondary alcohols to aldehydes and ketones, respectively, in water was effectively catalyzed by iodoxybenzene (PhIO₂, 1 mol%) in

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Scheme 1. IBS-catalyzed selective oxidation of alcohols.

the presence of catalytic amounts of Br_2 and $NaNO_2$ (Scheme 2). The catalytic mechanism they proposed for this reaction involves three redox cycles (Scheme 3). PhIO₂ is the active oxidant that oxidizes the alcohol to the corresponding carbonyl compound, and is reduced to dihydroxyiodobenzene (PhI(OH)₂). PhI(OH)₂ is reoxidized to PhIO₂ with Br_2 , which is reduced to HBr. The oxidation of NO with O₂ produces NO₂, which re-oxidizes HBr to Br_2 . In addition, HNO₃ produced by dissolving NO₂ in water can also oxidize HBr to Br_2 .



Scheme 2. PhIO2-catalyzed aerobic oxidation of alcohols.[7]



Scheme 3. Mechanism proposed by Liu and co-workers for the PhIO₂catalyzed aerobic oxidation of alcohols.^[7]

We were interested in Liu's oxidation system.^[7] Unfortunately, however, the oxidation of benzyl alcohol (1a) gave only a trace amount of benzaldehyde (2a) under both Liu's



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conditions and more severe conditions (higher temperature (55–100 °C) and a reaction time up to 24 h) [Eq. (1)]. However, when a large amount of bromine (50 mol %) was used, brominated compounds were produced together with small amounts of carbonyl compounds [Eq. (2)]. Thus, we concluded that Liu's oxidation could not be reproduced.^[8]

$$PhCH_{2}OH (1a) \xrightarrow{PhIO_{2} (1 \text{ mol\%})}_{Air \text{ or } O_{2} (balloon)} \xrightarrow{PhCHO (2a)}_{(trace!)} PhCHO (2a)$$
(1)

$$1a \quad \frac{PhIO_{2} (10 \text{ mol}\%)}{O_{2} (balloon), H_{2}O, 55 \text{ °C}, 10 \text{ h}} \stackrel{2a + byproducts}{(ca. 30\%)} (2)$$

Barton and co-workers reported the PhIO₂-mediated oxidation of benzylic alcohols to the corresponding aldehydes in organic solvents, and the reaction rate is accelerated in protic solvent such as acetic acid.^[9] We confirmed that the PhIO₂-promoted oxidation of **1a** did not take place in water under neutral (PhIO₂ was not dissolved) or acidic (PhIO₂ was completely dissolved) conditions [Eq. (3)]. In contrast, if 1 equiv of HBr was added to the suspension of 1a and PhIO₂ in water, a brown homogeneous solution was obtained immediately, and 2a was obtained in 76% yield with a small amount of benzoic acid (3a) [Eq. (4)]. Additionally, we performed the oxidation of 1a with bromine $(2 \mod \%)$ and NaNO₂ (1 mol%) in acetonitrile instead of water, and 2a was obtained in 10% yield in the absence of PhIO₂ [Eq. (5)]. These results suggest that the actual oxidant for the oxidation of alcohol should be bromine rather than PhIO₂, and PhIO₂ might oxidize Br⁻ to Br₂.^[7]

$$1a + PhIO_2 (1 equiv) \xrightarrow{HCI (0 or 1 equiv)}_{H_2O, 50-70 °C, 24 h} \text{ no reaction}$$
(3)

$$1a \quad \frac{Br_2 (2 \text{ mol}\%), \text{ NaNO}_2 (1 \text{ mol}\%)}{CH_3 \text{CN}, \text{O}_2 (\text{balloon}), 70 \text{ °C}, 24 \text{ h}} \quad \begin{array}{c} 2a \\ (10\%) \end{array}$$
(5)

In fact, numerous bromine-catalyzed aerobic oxidations of alcohols in the presence of acid additives and/or light sources have been reported to date.^[10–12] Minisci and co-workers developed a bromine-catalyzed selective aerobic oxidation of primary benzyl alcohols to the corresponding aldehydes in aqueous 1,2-dichloroethane.^[10] However, large amounts of bromine (5–40 mol%) and HNO₃ (32–65 mol%) were required.^[10] In contrast, Ito and co-workers reported aerobic oxidation of primary and secondary alcohols to the corresponding carboxylic acids and ketones, respectively, in the presence of a catalytic amount (7–20 mol%) of a bro-

mine source (such as Br₂, LiBr, HBr, and so forth) under UV or visible irradiation.^[11] However, it is difficult to selectively oxidize primary alcohols to the corresponding aldehydes under these conditions.^[11] The same group also reported the aerobic oxidation of primary benzylic alcohols to the corresponding benzaldehyde in the presence of a catalytic amount (10 mol%) of molecular iodine under visible irradiation.^[11g] However, it is difficult to oxidize aliphatic alcohols under these conditions.^[11g]

To find a more efficient aerobic oxidation of alcohols, initially, we optimized the reaction conditions in the presence of catalytic amounts of a bromine source (Table 1). A mixture of 1a (5 mmol), Br₂ (2 mol%), and NaNO₂ (1 mol%) in acetonitrile (5 mL) was heated at 70 °C even in the presence of 1 mol% of p-toluenesulfonic acid (TsOH) to give 2a and 3a in 83% and 5% yield, respectively (entry 2). In sharp contrast, 2a was obtained in only 10% yield in the absence of TsOH under the same conditions (entry 1). A small amount of water was added as a co-solvent to dissolve insoluble TsONa, which is generated in acetonitrile (entry 3).^[13] Oxidation did not occur in the absence of bromine or NaNO₂ and in the presence of iodine in place of bromine (entries 4-6). Thus, bromine and NaNO₂ were essential for the present aerobic oxidation. Next, we screened acid catalysts. Strong acids, such as TFA, Tf₂NH, HCl, and H₂SO₄, showed catalytic activities similar to those of TsOH (entries 7-10). On the other hand, a relatively weak acid

Table 1. Optimization of aerobic oxidation reaction conditions.^[a] 1a $\frac{\text{acid/Br}_2/\text{NaNO}_2}{\text{solvent O} (\text{halloon}) 70 \,^{\circ}\text{C} 24 \text{ h}}$ 2a + 3a

Entry	Acid	Acid/Br ₂ /NaNO ₂ [mol %]	Solvent	2a (3a) Conv. [%] ^[b]
1	None	-/2/1	CH ₃ CN	10 (0)
2	TsOH	1/2/1	CH ₃ CN ^[c]	83 (5)
3	TsOH	1/2/1	CH ₃ CN/H ₂ O ^[d]	85 (5)
4	TsOH	1/2/-	CH ₃ CN/H ₂ O ^[d]	<5 (<1)
5	TsOH	1/-/1	CH ₃ CN/H ₂ O ^[d]	<1 (<1)
6	TsOH	1/2/1 ^[e]	CH ₃ CN/H ₂ O ^[d]	<1 (<1)
7	CF ₃ SO ₃ H	2/1/1	CH ₃ CN/H ₂ O ^[d]	77 (2)
8	Tf ₂ NH	1/2/1	CH ₃ CN/H ₂ O ^[d]	91 (8)
9	HCl ^[f]	1/2/1	CH ₃ CN/H ₂ O ^[d]	79 (4)
10	H_2SO_4	1/2/1	CH ₃ CN/H ₂ O ^[d]	80 (4)
11	$C_6F_5CO_2H$	2/1/1	CH ₃ CN/H ₂ O ^[d]	6 (<1)
12	$HBr^{[g]}$	5/-/1	CH ₃ CN/H ₂ O ^[d]	86 (14)
13	HBr ^[g]	4//1	CH ₃ CN/H ₂ O ^[d]	78 (4)
14	$HBr^{[g]}$	3/-/1	CH ₃ CN/H ₂ O ^[d]	34 (<1)
15	HBr ^[g]	5/-/1	CH ₃ CN	94 (3)
16	$HBr^{[g]}$	5/-/1	THF	39 (1)
17	HBr ^[g]	5/-/1	EtOAc	4 (0)
18	HBr ^[g]	5/-/1	ClCH ₂ CH ₂ Cl	12 (0)
19	HBr ^[g]	5/-/1	Benzene	39 (4)
20	HBr ^[g]	10/-/2 ^[h]	CH ₃ CN	82 (6)

[a] Unless otherwise noted, **1a** (5 mmol), acid, NaNO₂ and Br₂ were placed in a Schlenk apparatus equipped with a condenser, and the mixture was magnetically stirred at 70 °C under balloon pressure of oxygen. [b] ¹H NMR analysis. [c] TsONa was precipitated. [d] CH₃CN/H₂O (40:1 ν/ν). [e] I₂ was used instead of Br₂. [f] An aqueous 2N HCl solution (prepared freshly from 12N HCl) was used. [g] An aqueous 48% HBr solution was used. [h] An aqueous 69% HNO₃ solution was used instead of NaNO₂.

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such as pentafluorobenzoic acid was inefficient (entry 11). Furthermore, we found that an aqueous 48% HBr solution was effective as both an acid and a "Br" source. The aerobic oxidation was rapid in the presence of HBr (5 mol%) and NaNO₂ (1 mol%), however, a large amount of **3a** was also produced in an acetonitrile-water solvent system (entry 12). In addition, the oxidation rate was strongly dependent on the catalytic amounts of HBr and NaNO₂ (entries 12–15). Oxidation was very slow in the presence of 3 mol% of HBr and 1 mol% of NaNO₂, and gave 2a in only 34% yield (entry 14). The selectivity of 2a was increased under nearly nonaqueous conditions,^[14] and 2a and 3a were obtained in 94% and 3% yields, respectively (entry 15). Acetonitrile was superior to other solvents such as tetrahydrofuran, ethyl acetate, dichloroethane, and benzene (entries 15-19). Notably, HNO₃ could be also used instead of NaNO₂ (entry 20).

To explore the generality of the present aerobic oxidation of alcohols, various primary benzylic alcohols **1** were examined as substrates under optimized conditions [HBr (5 or 10 mol%), NaNO₂ (1 or 2 mol%) in acetonitrile at 70 or 80 °C under balloon pressure of pure O₂] (Table 2). Most of benzyl alcohols with the electron-donating or electron-with-

Table 2. Aerobic oxidation of primary benzylic alcohols 1 to aldehydes $\mathbf{2}^{[a]}$

	ArCH ₂ OH (1)	CH3	$\frac{\text{HBr/NaNO}_2}{\text{CN, O}_2 \text{ (balloon)}}$	 ArCHO 	(2)	
Entry	Product	2	HBr/NaNO ₂ [mol%]	Temp. [°C]	Time [h]	Yield [%] ^[b]
1	СНО	2a	5/1	70	24	90
2	Ме	2 b	5/1	80	22	88
3	CHO	2 c	10/2	80	20	82
4	<i>t</i> Bu CHO	2 d	10/2	80	46	80
5	CI	2 e	5/1	80	2	87
6	CHO	2 f	5/1	80	3	85
7	СНО	2g	10/2	80	48	72
8	Br	2h	10/2	80	16	87
9	F CHO	2i	10/2	80	6	96
10	СНО	2j	10/2	80	48	77
11	O ₂ N CHO	2k	10/2	80	72	58 ^[c]

[a] Unless otherwise noted, **1** (5 mmol), NaNO₂ and aqueous 48% HBr solution were placed a Schlenk apparatus equipped with a condenser, and the mixture was magnetically stirred at 70 or 80 °C under balloon pressure of oxygen. [b] Yield of isolated product of **2**. [c] 4-Nitrobenzoic acid **3** was obtained in 19% yield (¹H NMR).

drawing groups were selectively oxidized to the corresponding aldehydes 2 (entries 1–10). However, the oxidation of 4nitrobenzyl alcohol 1k was very slow and the product selectivity was low under these conditions (entry 11). Unfortunately, the aerobic oxidations of aliphatic primary alcohols were not successful under these conditions.

Next, the oxidation of secondary alcohols was examined (Table 3). The oxidation of 1-phenylethanol **4a** in acetonitrile^[14] gave acetophenone **5a** in 38% yield with byproducts including α -bromoacetophenone (entry 1). Br₂ was consumed for the α -bromination of enolizable ketones that are initially formed under these conditions with the inhibition of catalysis.^[10,15] Fortunately, we found that the use of a small amount of water was effective for the selective oxidation of **4a** to **5a** in high yield (entry 2). The oxidation of benzyl alcohol **4** was faster in the presence of two-fold amounts of catalysts (10 mol% HBr and 2 mol% NaNO₂) and gave **5** in high yields (entries 3–5). Furthermore, the oxidation of secondary aliphatic alcohols **4** gave the corresponding ketones **5** in high yields under these conditions (entries 6–9).

Finally, we found that air could also be used as an oxygen source instead of pure O_2 under our conditions (Table 4). Notably, the addition of a catalytic amount of HNO₃ significantly accelerated the reaction rate (entry 2 versus entry 1). Thus, air oxidation of **1a** in the presence of HBr (10 mol%)/NaNO₂ (2 mol%)/HNO₃ (2 mol%) gave **2a** in 90% yield (entry 2). The use of twice amounts of NaNO₂ or HNO₃ was not effective (entries 3 and 4). Additionally, **2a** was obtained in 46% yield in the presence of HCl as an acid additive instead of HNO₃. These results suggest that the addition of both NaNO₂ and HNO₃ was essential for the air oxidation of alcohols under these conditions, however the additional role of HNO₃ was not clear. Noteworthy, air oxidation of **4g** gave ketone **5g** in 99% yield under these modified conditions (entry 4).

Our proposed mechanism for the present aerobic oxidation is similar to that of Liu (Scheme 3),^[7] although Br_2 is the active oxidant that oxidizes the alcohol to the corresponding carbonyl compounds (Cycle I, Scheme 4). The reaction of NaNO₂ or HNO₃ with HBr initially gives NOBr or



Scheme 4. Proposed mechanism for the bromine-catalyzed aerobic oxidation of alcohols.

NO₂Br which decomposes into NO or NO₂ and Br₂ [Eqs. (6)–(9)].^[15,16] NO₂ is generated also by the oxidation of NO with O₂, and oxidizes HBr to Br₂ [Eqs. (10) and (11), Cycle II].^[16] In addition, HNO₃ can be also produced by dissolving NO₂ in water [Eq. (12)].^[16]

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In conclusion, we found that a simple and environmentally benign catalytic system consisting of HBr/NaNO2 was

very effective for the aerobic oxidation of alcohols. Primary benzylic alcohols could be selectively oxidized to the corre-

sponding aldehydes under balloon pressure of O₂ in acetoni-

trile. Secondary alcohols were oxidized to the corresponding ketones in the presence of a small amount of water. Further-

more, the aerobic oxidation of alcohols could also be ach-

ieved under balloon pressure of air instead of pure O2 with

this HBr/NaNO₂/HNO₃ catalytic system.

NaNO₂ + 2HBr → NOBr + NaBr + H₂O (6)

2NOBr == 2NO + Br₂ (7)

 $HNO_3 + HBr \longrightarrow NO_9Br + H_9O$ (8)

2NO₂Br = 2NO₂ + Br₂

 $2NO + O_2 \rightarrow 2NO_2$ (10)

 $NO_2 + 2HBr \longrightarrow NO + Br_2 + H_2O$ (11)

$$3NO_2 + H_2O \longrightarrow 2HNO_3 + NO$$
 (12)

Table 3.	Aerobic oxidation	of secondary	alcohols 4	to ketones 5. ^[a]
			1 (4)	HBr/NaNO ₂

solvent, O_2 (balloon)							
Entry	Product	5	HBr/NaNO ₂ [mol %]	Solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	0	5a	10/2	CH ₃ CN	80	44	38 ^[d]
2		5a	5/1	CH ₃ CN/H ₂ O ^[c]	80	28	85 ^[e]
3		5a	10/2	CH ₃ CN/H ₂ O ^[c]	80	5	76
4	Me	5 b	10/2	CH ₃ CN/H ₂ O ^[c]	80	4	72
5	ci Ci	5c	10/2	CH ₃ CN/H ₂ O ^[c]	80	24	74
6	Ph	5d	10/2 ^[f]	CH ₃ CN/H ₂ O ^[c]	80	24	72 ^[f]
7		5e	10/2	CH ₃ CN/H ₂ O ^[c]	80	24	75
8	A po	5 f ^[g]	10/2	CH ₃ CN	80	48	95 ^[e]
9	Á.	5 g ^[h]	10/1	CH ₃ CN	80	22	95

(9)

[a] See footnote for Table 2. [b] Yield of isolated product of 5. [c] CH₃CN/H₂O (40:1 v/v). [d] 2-Bromoacetophenone and unidentified products were obtained. [e] ¹H NMR analysis. [f] An aqueous 69% HNO₃ solution (2 mol%) was used as additive. 5d was obtained in 66% yield (¹H NMR analysis) in the absence of HNO₃. [g] Product via exo-norborneol 4 f. [h] Product via borneol 4g.

2a or 5

Time

[h]

24

24

24

24

24

24

48

Table 4. Bromine-catalyzed air-oxidation of alcohols 1a and 4. HBr/NaNO₂/HNO₃ 1a or 4 CH₃CN/H₂O (40:1 v/v), air (balloon), 80 °C

HNO

0

2

0

4

4

2

[a] See footnote for Table 2. Air was used instead of pure O22. [b] An

aqueous 69% HNO3 solution was used. [c] Yield of isolated product of carbonyl compound. [d] ¹H NMR analysis. [e] An aqueous 2N HCl solu-

tion (2 mol%, prepared freshly from 12 N HCl) was used instead of

2^[e]

 $[mol \%]^{[b]}$

HBr/NaNO₂

[mol%]

10/2

10/2

10/4

10/0

10/2

20/4

10/2

Experimental Section

Representative procedure for the aerobic oxidation of benzyl alcohols: To a Schlenk apparatus equipped with a condenser and Teflon-coated stirrer chip were added successively NaNO₂ (3.5 mg, 0.05 mmol), acetonitrile (5.0 mL), and 1a (520 μ L, 5.0 mmol). The flask was charged with oxygen, and commercial aqueous 48% HBr solution (28 µL, 0.25 mmol) was added rapidly. The resulting mixture was heated to 70 °C and stirred for 24 h under balloon pressure of oxygen. The resulting mixture was cooled to room temperature and poured into saturated NaHSO3 solution, and the organic layer was washed with saturated NaHCO3 solution. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over anhydrous MgSO4 and evaporated under vacuo. The residue was chromatographed on SiO_2 to give 2a (478 mg, 4.5 mmol) in 90% yield.

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Product

2a

2 a

2a

2 a

2 a

5a

5g

Entry

1

2

3

4

5

5

6

HNO₃

Yield

[%]^[c]

47^[d]

86

49^[d]

51^[d]

46^[d]

86

99

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