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Oxidative bromination reaction using vanadium catalyst and aluminum halide under molecular oxygen

Kotaro Kikushima, Toshiyuki Moriuchi *, Toshikazu Hirao *

Department of Applied Chemistry, Graduate School of Engineering, Osaka University Yamada-oka, Suita, Osaka 565-0871, Japan

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ABSTRACT

The vanadium-catalyzed oxidative bromination reaction of arenes, alkenes, and alkynes was performed in the presence of $AlBr_3$ to provide an alternative method for conventional bromination using hazardous bromine. The catalytic cycle is formed under molecular oxygen, which is more advantageous to vanadium bromoperoxidase (VBrPO) requiring hydrogen peroxide as a terminal oxidant.

Organic bromides are widely used as synthetic precursors for various coupling reactions in organic and pharmaceutical synthesis. The bromination reaction has been still attracting attention to develop the more practical method without the use of hazardous and highly toxic elemental bromine (Fig. 1, i). Considerable efforts have been devoted to achieve a bromination process utilizing a bromonium cation-like species, generated from totally two-electron oxidation of a bromide ion. From this point of view, the oxidative bromination reactions with a stoichiometric strong oxidant (e.g., hydrogen peroxide,[1] Oxone®,[2] cerium ammonium nitrate (CAN),[3] sodium periodate,[4] lead tetraacetate,[5] and Selectfluor®)[6] (Fig. 1, ii) or a combination of a metal catalyst and a stoichiometric amount of hydrogen peroxide (Fig. 1, iii)[7,8] have been developed. Particularly, the latter bromination is inspired by vanadium bromoperoxidase (VBrPO),[9–11] a naturally occurring enzyme. These alternative bromination reactions, however, require a stoichiometric amount of a strong oxidant. Few bromination reactions using atmospheric molecular oxygen as a terminal oxidant have been reported by cat. $H_5PMo_{10}V_2O_{40}$/HBr gas/air or cat. $NaNO_2$/48% aq HBr/air (Fig. 1, iv).[12] In a previous paper, the vanadium-catalyzed oxidative bromination was demonstrated to be achieved in a strong protic acid under molecular oxygen.[13] Use of a Lewis acid in place of a Brønsted acid is expected to provide a more practical protocol for the oxidative bromination. We herein report the versatile vanadium-catalyzed bromination reaction of arenes, alkenes, and alkynes in the presence of aluminum halide under molecular oxygen (Fig. 1, v).

Initially, $AlCl_3$ was selected as a Lewis acid under the similar conditions employed for the reaction in the presence of trifluoroacetic acid (TFA) (Table 1, entries 1 and 2). It should be noted that the bromination reaction proceeded smoothly to give the dibromide **2a** quantitatively. This finding is in contrast to the result with TFA that the monobromide **1a** was obtained in 80% yield. $AlCl_3$ is indicated to be the more effective than TFA. The amounts of $AlCl_3$ and Bu_4NBr were successfully reduced to 120 mol % at 80 °C, in which the monobromide **1a** was selectively produced in 92% isolated yield (entry 3). Other metal chlorides such as $ZnCl_2$, $FeCl_3$, and $CoCl_2$ were not effective except $CuCl_2$ (entries 4–7). In every case, the chlorination did not occur under the conditions employed here. The bromination moderately proceeded with $BF_3{\cdot}Et_2O$ (entry 8), indicating that the Lewis acidity is one of the key factors to facilitate the reaction. The bromination reaction in the presence of 120 mol % of $AlBr_3$ and Bu_4NBr resulted in the efficient bromination to afford the dibromide **2a** in 97% yield (entry 9), which is comparable to the 300 mol % $AlCl_3$–Bu_4NBr system. $AlBr_3$ is expected to serve as both a Lewis acid and bromide source. Actually, the dibromination proceeded quantitatively even in the absence of Bu_4NBr (entry 10). Two Br atoms of $AlBr_3$ are at least employable in this transformation, so 50 mol % of $AlBr_3$ was enough to attain a high yield for the monobromination (entry 11). The results obtained from the reaction in the absence of NH_4VO_3 or molecular oxygen indicated that the vanadium catalyst and molecular oxygen are essential (entries 12 and 13). On the basis of these results, the effects of solvents, reaction temperature, and time were screened. Although dimethoxyethane and MeCN were found to be significantly less effective than 1,4-dioxane (entries 14 and 15), the high

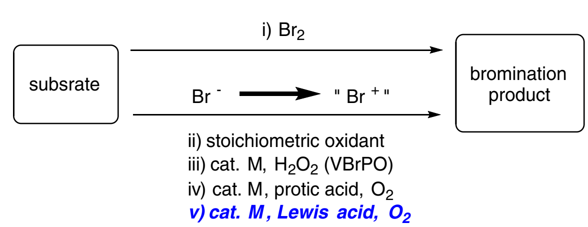

Figure 1. Development of bromination reaction methods.

* Corresponding authors. Tel.: +81 6 6879 7413; fax: +81 6 6879 7415.
E-mail addresses: moriuchi@chem.eng.osaka-u.ac.jp (T. Moriuchi), hirao@chem.eng.osaka-u.ac.jp (T. Hirao).

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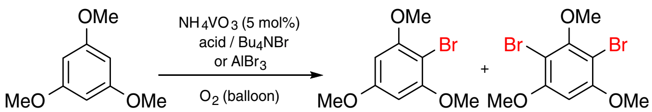
Table 1
Bromination reaction of 1,3,5-trimethoxybenzene under various conditions[a]



Entry	Acid (mol %)	TBAB (mol %)	Solvent	NMR yield (%)	
				1a	**2a**
1	TFA/300	300	1,4-Dioxane	80[b]	0
2	$AlCl_3$/300	300	Dioxane	0	Quant[b]
3	$AlCl_3$/120	120	Dioxane	92[b]	0
4	$CuCl_2$/120	120	Dioxane	87	0
5	$ZnCl_2$/120	120	1,4-Dioxane	12	0
6	$FeCl_3$/120	120	Dioxane	0	0
7	$CoCl_2$/120	120	Dioxane	0	0
8	$BF_3{\cdot}OEt_2$/120	120	Dioxane	48	0
9[c]	$AlBr_3$/120	120	Dioxane	3	97
10[c]	$AlBr_3$/120	—	Dioxane	0	Quant[b]
11[c]	$AlBr_3$/50	—	Dioxane	92[b]	0
12[c,d]	$AlBr_3$/50	—	Dioxane	0	0
13[c,e]	$AlBr_3$/50	—	Dioxane	5	0
14[c]	$AlBr_3$/50	—	Dimethoxyethane	22	0
15[c]	$AlBr_3$/50	—	MeCN	18	0
16[f]	$AlBr_3$/50	—	Ether	99[b]	0
17[f]	$AlBr_3$/120	—	Ether	0	98[b]

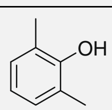
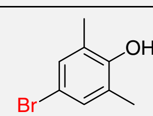
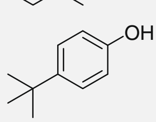
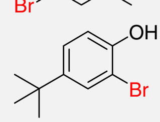
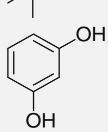
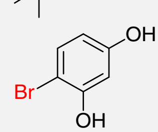
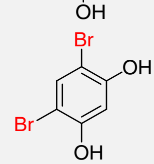
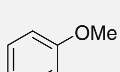
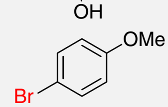
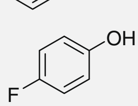
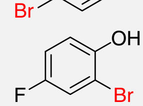
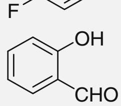
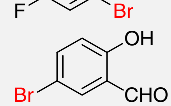
[a] Reaction conditions: 1,3,5-trimethoxybenzene (0.50 mmol), NH_4VO_3 (0.025 mmol), and additives in solvent (1.5 mL) at 80 °C for 18 h under atmospheric oxygen unless otherwise stated.
[b] Isolated yield.
[c] Reaction time, 4 h.
[d] Absence of NH_4VO_3.
[e] Reaction under Ar.
[f] Reaction temperature, room temperature.

reactivity was observed in ether even at room temperature. Under these conditions in the presence of 120 mol % of $AlBr_3$, the dibromide **2a** was produced quantitatively (entry 17). Again, only the monobromide **1a** was obtained by reducing the amount of $AlBr_3$ to 50 mol % (entry 16).

To investigate the scope of the present bromination reaction, other substrates were surveyed using two conditions, in 1,4-dioxane at 80 °C (Method A) and in ether at room temperature (Method B). 2,6-Dimethylphenol underwent the bromination to the monobromide **1b** in a high yield under both reaction conditions (Table 2, entries 1 and 2). 2-Bromination product **1c** was formed in 98% yield from 4-*tert*-butylphenol (entry 3). The bromination reaction of 3-hydroxyphenol proceeded with 40 mol % of $AlBr_3$ to give the monobromide **1d** in 80% yield (entry 4). However, the use of 80 mol % of $AlBr_3$ led to the dibromide **2d** (entries 5 and 6). In the present bromination system, simple aromatic compound such as anisole was subjected to the monobromination (entry 7). Additionally, the phenol derivative bearing the electron-withdrawing group was brominated smoothly to the monobromide: 4-fluorophenol was also converted to the *o*-bromination product **1f** in 95% yield (entry 8), whereas the bromination of 2-formylphenol resulted in the formation of 4-bromo-2-formylphenol (**1g**) and 2-bromo-6-formylphenol in 86% and 13% yields, respectively, (entry 9). In the latter case, further oxidation of the aldehyde moiety was not observed. In the bromination of TBS-protected *o*-cresol, the TBS group was survived under the conditions employed here (entry 10).

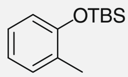
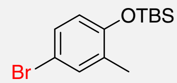
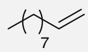
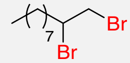
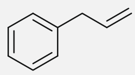
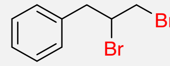
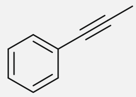
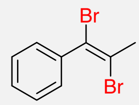
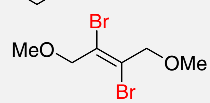
This bromination method could be successfully applied to the bromination of alkenes and alkynes, although the presence of the additional bromide salts was required. The bromination reaction of 1-decene proceeded well to afford the dibromide **3i** in 99% yield by using 5 mol % of NH_4VO_3, 120 mol % of $AlBr_3$, and 120 mol % of Bu_4NBr in MeCN at 50 °C (entry 11). As a bromide salt, the less expensive KBr could be also effective as a bromide anion source (entry 12). Allylbenzene underwent the selective dibromination to 1,2-dibromo-3-phenylpropane (**3j**) in 93% yield (entry 13). Moreover, the selective *anti*-dibromination of aromatic and aliphatic alkynes like 1-phenylpropyne and 1,4-dimethoxy-2-bu-

Table 2
Bromination reaction of arenes, alkenes, and alkynes

Entry	Substrate	$AlBr_3$ (mol %)	Method[a]	Product		Isolated yield (%)
1 2		60 60	A B		**1b**	94 95
3		60	A		**1c**	98
4		40	A		**1d**	80
5 6		80 80	A B		**2d**	66 51
7		120	A		**1e**	96
8		120	A		**1f**	95
9		60	A		**1g**	86[b]

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	$AlBr_3$ (mol %)	Method[a]	Product		Isolated yield (%)
10		120	B		**1h**	Quant
11		120	C		**3i**	99
12		120	D			76
13		120	C		**3j**	93
14		120	E		**4k**	98
15		120	E		**4l**	97

[a] Method A: a substrate (0.50 mmol), NH_4VO_3 (0.025 mmol), and $AlBr_3$ in 1,4-dioxane under atmospheric oxygen at 80 °C for 8 h. Method B: a substrate (0.50 mmol), NH_4VO_3 (0.025 mmol), and $AlBr_3$ in ether under atmospheric oxygen at rt for 18 h. Method C: a substrate (0.50 mmol), NH_4VO_3 (0.025 mmol), $AlBr_3$ (0.60 mmol), and Bu_4NBr (0.60 mmol) in MeCN under atmospheric oxygen at 50 °C for 18 h. Method D: a substrate (0.50 mmol), NH_4VO_3 (0.025 mmol), $AlBr_3$ (0.60 mmol), and KBr (5.0 mmol) in MeCN under atmospheric oxygen at 50 °C for 18 h. Method E: a substrate (0.50 mmol), NH_4VO_3 (0.025 mmol), $AlBr_3$ (0.60 mmol), and Bu_4NBr (0.60 mmol) in MeCN under atmospheric oxygen at 80 °C for 18 h.

[b] Together with 2-bromo-6-formylphenol (13%).

tyne was observed to give the *trans*-dibromides **4k** and **4l**, respectively (entries 14 and 15). These findings suggest the involvement of a bromonium cation-like species as an intermediate for *anti*-bromination.

Benzyl bromide or dimerization products through radical reaction were not observed in the reaction of 2,6-dimethylphenol (Table 2, entries 1 and 2). A similar reaction mechanism might be operative for this bromination as reported in the reaction with protic acid. The related oxidation of the bromide ion with the stoichiometric oxo-metal has been reported: oxygen-atom transfer with the Mn- or Ru-induced formation of a hypobromite species[14] and Cr-induced one-electron transfer.[15] A key intermediate is proposed to be a bromonium cation-like species, which is generated from the oxidation of a bromide ion via oxygen-atom transfer of an oxo-vanadium species activated by a Lewis acid, although the mechanism via one-electron oxidation of the bromide or substrate could not be ruled out.

In summary, the aerobic selective vanadium-catalyzed bromination reaction was demonstrated to be achieved in the presence of $AlBr_3$, which serves as a bromide source and Lewis acid. This potential method was applied to the bromination of various arenes, alkenes, and alkynes to give the bromination products selectively in high yields. Further synthetic versatility and reaction mechanism are under investigation.

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Supplementary data

Supplementary data (general information, experimental procedures and NMR spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.016.

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