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Oxidative Bromination Reactions in Aqueous Media by Using $Bu_4NBr/TFA/H_2O_2$ System

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Oxidative Bromination Reactions in Aqueous Media by Using $Bu_4NBr/TFA/H_2O_2$ System

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Dedicated to the late Professor Yoshihiko Ito on the occasion of the 10th anniversary of his sudden death.

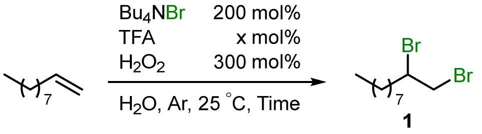
Metal-free oxidative bromination reactions in aqueous media were performed by using tetrabutylammonium bromide, trifluoroacetic acid, and hydrogen peroxide under mild conditions. Oxidative bromination reaction of alkenes was found to afford the corresponding *vic*-bromides. Furthermore, this oxidative bromination system is applicable to the oxidative bromination of alkynes, arenes, and 3,4-dihydronaphthalen-1(2*H*)-one. A gram-scale brominaton reaction was also performed successfully.

Keywords: Oxidative bromination | Metal-free | Aqueous media

The bromination of organic compounds is regarded as one of the important reactions in organic synthesis, providing key precursors for various transformation reactions. Toxic and hazardous elemental bromine is utilized in conventional bromination reaction. In this context, oxidative bromination reaction by using a bromide ion as a bromide source instead of bromine has attracted much attention, in which a bromonium cation-like species is generated as a key intermediate by two-electron oxidation of a bromide ion.[1] In these systems, a stoichiometric amount of a potentially hazardous oxidant is required. From a viewpoint of environmentally benign, molecular oxygen and hydrogen peroxide (H_2O_2) are preferred as non-toxic oxidants. Recently, we have already demonstrated the vanadium-catalyzed oxidative bromination reactions with molecular oxygen to provide the more advanced catalytic systems[2] rather than the enzyme, vanadium bromoperoxidase[3] (VBrPO), which catalyzes two-electron oxidation of the bromide ion in the presence of hydrogen peroxide. By using this vanadium-catalyzed oxidative system, catalytic chlorination and iodination of ketones have been also performed.[4] A transition metal-free bromination system is considered to be a convenient approach for development of environmentally friendly protocols. The bromination reaction with DMSO/HBr[5] and H_2O_2/HBr[6] systems as transition metal-free bromination systems have been reported. More environmentally friendly methodologies under mild conditions are to be developed. Trifluoroacetic acid (TFA) is less acidic than HBr. The utilization of trifluoroacetic acid as an acid is envisioned to be one strategy for the development of environmentally acceptable oxidative bromination systems under mild conditions. Hydrogen peroxide is regarded as a green oxidant because water is the only by-product in oxidation reactions. Tetrabutylammonium bromide (Bu_4NBr), which is a quaternary ammonium salt with a bromide ion, is known to serve as a phase transfer catalyst. From the viewpoint of green chemistry, we herein report the metal-free oxidative bromination reactions in aqueous media by using Bu_4NBr as a bromide source, TFA as an acid, and H_2O_2 as an oxidant under mild conditions.

The oxidative bromination reaction of 1-decene with 200 mol% Bu_4NBr, 300 mol% TFA, and 300 mol% H_2O_2 in an ultrapure water was investigated (Table 1). The bromination reaction proceeded at 25 °C to afford the corresponding *vic*-dibromide **1** in 78% yield (Entry 1). A decrease in the amount of TFA resulted in a gradual decrease of the yields (Entries 2-4). This oxidative bromination reaction proceeded smoothly in 5 h (Entry 5) although a shorter reaction time caused a decrease in yield (Entries 6 and 7).

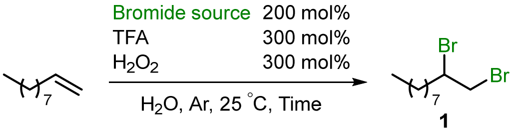
Table 1 Bromination reaction of 1-decene in water by using $Bu_4NBr/TFA/H_2O_2$ system.[a]



Entry	TFA (x mol%)	Time (h)	NMR yield (%)
1	300	24	78
2	200	24	64
3	100	24	39
4	50	24	21
5	300	5	81
6	300	4	76
7	300	2	66

[a] Reactions conditions: 0.25 mmol of 1-decene, 0.50 mmol of Bu_4NBr, TFA, 0.75 mmol of H_2O_2, 0.5 mL water, under Ar at 25 °C.

Table 2 Effect of bromide source in bromination reaction of 1-decene in water by using $Bu_4NBr/TFA/H_2O_2$ system.[a]

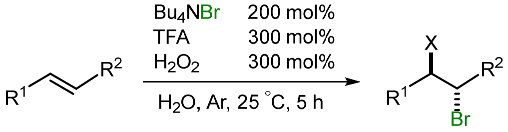


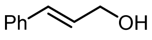
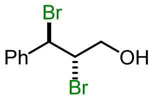
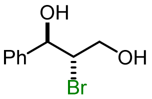
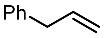
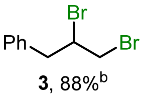
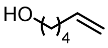
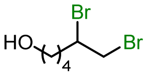
Entry	Bromide source (x mol%)	Time (h)	NMR yield (%)
1	Bu_4NBr (200)	5	81
2	LiBr (200)	6	50
3	KBr (200)	6	49
4	Bu_4NBr (50) + LiBr (150)	5	59
5	Bu_4NBr (100) + LiBr (100)	5	71

[a] Reactions conditions: 0.25 mmol of 1-decene, 0.50 mmol of bromide source, 0.75 mmol of TFA, 0.75 mmol of H_2O_2, 0.5 mL water, under Ar at 25 °C.

The effect of bromide sources was investigated (Table 2). The use of LiBr or KBr instead of Bu4NBr exhibited nearly 30% drop in yield (Entries 2 and 3). The combination of Bu4NBr and LiBr showed good results although a slight decrease in yield was observed (Entries 4 and 5). Among the various conditions examined, the reaction with Bu4NBr (300 mol%), TFA (300 mol%), and H_2O_2 (300 mol%) in an ultrapure water at 25 °C for 5 h was superior.

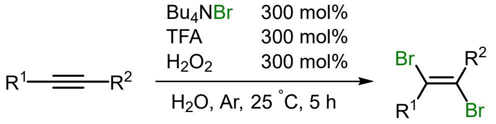
Table 3 Bromination reactions of alkenes by using $Bu_4NBr/TFA/H_2O_2$ system.[a]

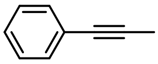
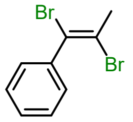
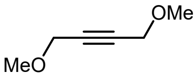
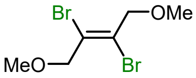


Entry	Substrate	Product NMR yield
1		 **2a**, 38%  **2b**, 48%
2		 **3**, 88%[b]
3		 **4**, 70%[c]

[a] Reactions conditions: 0.25 mmol of substrate, 0.50 mmol of bromide source, 0.75 mmol of TFA, 0.75 mmol of H_2O_2, 0.5 mL water, under Ar at 25 °C. [b] Solvent: 0.25 mL water and 0.25 mL CH_2Cl_2, Reaction time: 12 h. [c] Bu4NBr (300 mol%) was used. Solvent: 0.25 mL water and 0.25 mL CH_2Cl_2, Reaction time: 12 h.

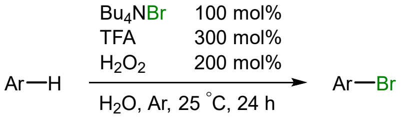
Table 4 Bromination reactions of alkynes in water by using $Bu_4NBr/TFA/H_2O_2$ system.[a]

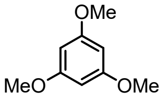
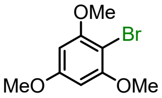
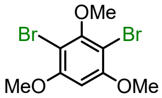
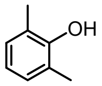
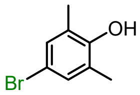


Entry	Substrate	Product NMR yield
1		 **5**, 86%
2		 **6**, 75%[b]

[a] Reactions conditions: 0.25 mmol of substrate, 0.75 mmol of bromide source, 0.75 mmol of TFA, 0.75 mmol of H_2O_2, 0.5 mL water, under Ar at 25 °C. [b] Reaction time: 24 h.

Table 5 Bromination reactions of phenols in water by using $Bu_4NBr/TFA/H_2O_2$ system.[a]



Entry	Substrate	Product NMR yield
1		 **7a**, 89%  **7b**, 2%
2		 **8**, 72%

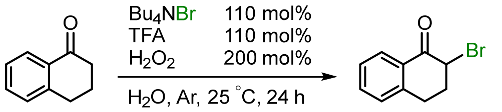
[a] Reactions conditions: 0.25 mmol of substrate, 0.25 mmol of bromide source, 0.75 mmol of TFA, 0.5 mmol of H_2O_2, 0.5 mL water, under Ar at 25 °C.

To explore the validity of this $Bu_4NBr/TFA/H_2O_2$ bromination system, the reaction of other substrates was surveyed. The bromination reaction of (2*E*)-3-phenyl-2-propen-1-ol resulted in the formation of 38% of the dibromide **2a** and 48% of the bromohydrin **2b** regioselectively (Table 3, Entry 1). Allylbenzene underwent the bromination reaction in an ultrapure water and dichloromethane to give the corresponding *vic*-dibromide **3** in 88% yield (Entry 2). 5-Hexene-1-ol was converted into the dibromide **4** in 70% yield, with the hydroxy group intact (Entry 3).

The present bromination system could be applied to the bromination of alkynes (Table 4). The bromination reaction of 1-phenylpropyne proceeded well to afford the corresponding *trans*-1,2-dibromoalkene **5** in 86% yield (Entry 1). The *trans*-1,2-dibromoalkene **6** was also obtained in 75% yield from 1,4-dimethoxy-2-butyne although a longer reaction time was required (Entry 2).

The bromination reaction of 1,3,5-trimethoxybenzene was found to yield the monobromaide **7a** and the dibromide **7b** in 89% and 2% yields, respectively (Table 5, Entry 1). The monobromination product **8** could be obtained in 72% yield by the bromination reaction of 2,6-dimethylphenol (Entry 2).

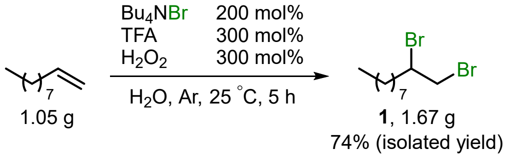
The α-bromination of ketone was also performed. 3,4-Dihydronaphthalen-1(2*H*)-one was brominated in the presence of 110 mol% Bu4NBr, 110 mol% TFA, and 200 mol% H_2O_2 to allow the formation of the α-bromination product **9** in 76% yield (Scheme 1).



9
76% (NMR yield)

Scheme 1 Bromination reaction of 3,4-dihydronaphthalen-1(2*H*)-one in water by using $Bu_4NBr/TFA/H_2O_2$ system.

It is noteworthy to mention that a gram-scale practical reaction was successfully carried out to give the bromination product, as exemplified by the bromination of 1-decene to the dibromide in 74% isolated yield (Scheme 2).



Scheme 2 Gram-scale bromination reaction of 1-decene in water by using $Bu_4NBr/TFA/H_2O_2$ system.

In conclusion, a combination of tetrabutylammonium bromide as a bromide source, trifluoroacetic acid as an acid, and hydrogen peroxide as an oxidant has been demonstrated to induce metal-free oxidative bromination reactions in aqueous media under mild conditions. This oxidative bromination system could be applied to the oxidative bromination of alkenes, alkynes, arenes, and 3,4-dihydronaphthalen-1(2*H*)-one. A gram-scale brominaton reaction was also performed successfully. Future work will concentrate on synthetic versatility and application of this practical method to other reactions.

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Supporting Information is available on http://dx.doi.org/.

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