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Practical and regioselective brominations of aromatic compounds using tetrabutylammonium peroxydisulfate

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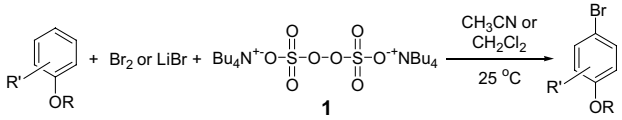
Abstract—Direct bromination of wide range of aromatic compounds substituted with electron donating groups such as methoxy, hydroxy, or amino groups have been achieved with high regioselectivity by the reaction with Br_2 in the presence of tetrabutylammonium peroxydisulfate **1** under mild conditions in acetonitrile in excellent yields. The use of lithium bromide as a bromination reagent afforded high yields of monobromo compounds with complete regioselectivity under neutral and mild reaction conditions in acetonitrile.

Halogenated aromatic compounds have been used as intermediates for a number of natural products and bioactive materials[1] and also proved as important and useful reagents in organic syntheses by functionalization through carbon–carbon bond formation of diarenes, ethylenic, or acetylenic condensations using transition metals.[2] Especially during the past decade, numerous methods for the direct introduction of halogen atom into aromatic molecules have been intensively developed. Aryl bromides are often used in the syntheses of aryl esters, aryl olefins, and other useful classes of compounds. There are many published cases. It is well known that bromine is more reactive than iodine in aromatic halogenation. But it is difficult to control monobromination using elemental bromine which only depend on the reaction conditions[3] especially for the electron-rich aromatic compounds. Thus, there have been numerous reported bromination reagents such as NBS (*N*-bromosuccinimide),[4] HBr/TBHP (*t*-butylhydroperoxide),[5] quaternaryammonium tribromide,[6] PHP (pyridinium hydrobromide perbromide),[7] $KBr/NaBO_3$,[8] $NaBr/NaClO_2/Mn(acac)_3$/moist montmorillonite,[9] LiBr/CAN (ceric ammoniumnitrate),[10] BuOBr/zeolite,[11] benzyltriphenyl phosphonium tribromide,[12] NaBr/dimethyl dioxirane,[13] and $HBr/NaBO_3$.[14] However, many of them suffer from regioselectivity of bromination of activated aromatic compounds, so the control over the degree of bromination and the regioselectivity is still needed.

Here, we describe a new practical and regioselective bromination of activated aromatic and heterocyclic compounds under mild reaction conditions as shown in Scheme 1.

The peroxide **1** turned out to be a useful source of tetrabutylammonium sulfate radical, which shows oxidizing ability and can be readily converted to sulfate anion by one electron transfer from substrate.[15] In contrast to $K_2S_2O_8$, $Na_2S_2O_8$, or $(NH_4)_2S_2O_8$, **1** is easily soluble in various organic solvents such as acetonitrile, acetone, methanol, and methylene chloride and therefore it can be easily used in general organic reactions. Aromatic bromination with complete regioselectivity by preventing polybromination under mild conditions has been



Scheme 1. Bromination of aromatic compounds with tetrabutylammonium peroxydisulfate.

Keywords: Bromination; Bromonium cation; Regioselectivity; Tetrabutylammonium peroxydisulfate; Oxidation.
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accomplished by lithium bromide in the presence of **1**. The results obtained are reported herein.

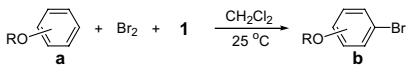
Compound **1** was successfully prepared by mixing two equivalents of tetrabutylammonium hydrogen sulfate and potassium persulfate in water. After stirring for 30 min at 25 °C, the desired product was extracted with methylene chloride, washed with distilled water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give the pure precipitate solid, which met elemental analysis.[15a] The white solid **1** is stable for a couple of months at 25 °C and can be stored in the refrigerator almost permanently.

Various electron-rich aromatic compounds were brominated with bromine in the presence of **1** at 25 °C in methylene chloride to give monobrominated products with high regioselectivity. The results obtained are summarized in Table 1.

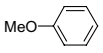
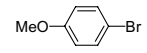
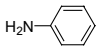
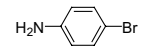
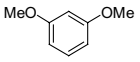
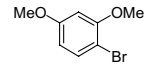
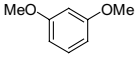
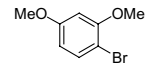
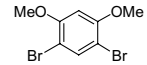
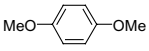
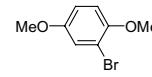
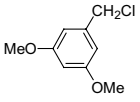
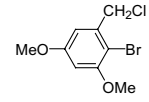
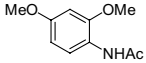
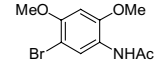
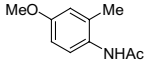
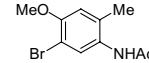
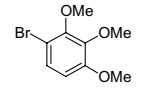
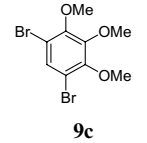
Monobrominations exclusively occurred at the *p*-position of methoxy or amino group (Table 1, entries 1, 2, 3, 5, and 6). When *p*-position of methoxy group was blocked with a substituent, only *o*-bromination occurred (Table 1, entries 4 and 7). Since bromination of aniline and methoxybenzene proceeded more slowly compared with that of dimethoxybenzene, the reaction appears to be related to the electron density of the aromatic compounds. In bromination also, we may conclude that *p*-orientation is more favorable than *o*-orientation from the fact that 1,3-dimethoxybenzene was more readily brominated than 1,4-dimethoxybenzene (Table 1, entries 3 and 4). In order to compare the regioselectivities in the absence of **1**, when **4a** was reacted with Br_2 in AcOH, a mixture of monobrominated product **4b** and dibrominated product **4c** was obtained (Table 1, entry 3′).

While, complete regioselectivity of monobromination of 1,2,3-trimethoxybenzene (**9a**) with bromine and **1** failed: a mixture of mono- (**9b**) and dibrominated (**9c**) products was obtained in the ratio of 6:1. The elongated reaction time (6 h) with **4a** also caused the formation of a small amount of dibrominated product (monobrominated **4b**: ca. 90%, dibrominated product **4c**: ca. 10%). To overcome this problem, a milder bromination system was designed using lithium bromide and **1**. The direct use of hazardous molecular bromine can be avoided by the use of neutral salt of LiBr. Various activated aromatic compounds reacted with lithium bromide in the presence of **1** in acetonitrile at 25 °C to give the corresponding monobrominated products in excellent yields with complete regioselectivity. In a representative experimental, lithium bromide (261 mg, 3 mmol) and **1** (2.03 g, 3 mmol) were added to a solution of **4a** (139 mg, 1.0 mmol, CH_3CN: 20 mL) at 25 °C with stirring. When the reaction was complete, the reaction mixture was quenched into distilled water (20 mL) and extracted with ethylether (3×10 mL). The organic layer was washed with distilled water (20 mL), dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure to give the crude product, which was purified by a silica gel column chromatography (silica gel 60: 0.040–0.063 mm, eluent: ethyl acetate/*n*-hexane = 1/10,

Table 1. Bromination reaction of aromatic compounds with bromine and tetrabutylammonium peroxydisulfate



a b

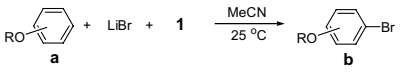
	Substrate	Time (h)	Product	Yield[a] (%)
1	 **2a**	1	 **2b**	96
2	 **3a**	1	 **3b**	86
3	 **4a**	0.5	 **4b**	87
3′	 **4a**	0.1	 **4b**  **4c**	69[b] 17[b] **4b** + **4c** (**4b**/**4c** = 4:1)
4	 **5a**	1	 **5b**	93
5	 **6a**	1	 **6b**	82
6	 **7a**	0.5	 **7b**	93
7	 **8a**	2	 **8b**	86
8	 **9a**	3	 **9b**  **9c**	Ca. 90[c]

[a] Isolated yield.
[b] In the absence of **1**, the reaction was carried out in AcOH.
[c] The yield of mixture of **9b** and **9c**: the ratio of **9b** and **9c** (6:1) was determined by ^1H NMR and the intensity of them **9b** (*m*/*e*; 245.99)/**9c** (*m*/*e*; 323.90) = ca. 6:1.

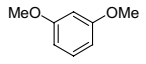
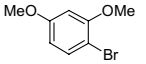
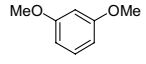
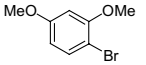
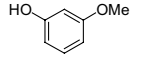
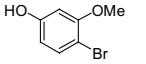
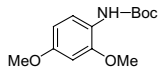
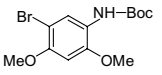
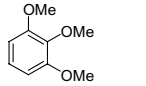
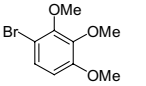
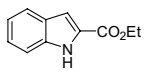
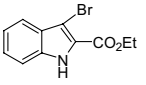
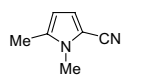
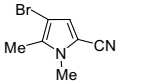
4b: 213 mg, 98%). The results obtained are summarized in Table 2.

In comparison with the system using bromine and **1**, the LiBr system needed longer reaction time but resulted in high yields and complete regioselectivity in monobrominations. *m*-Methoxyanisole (**4a**) gave *o*-bromo-*m*-methoxyanisole (**4b**) in quantitative yield (98%). A large scale bromination reaction (**9a**: 4.33 g, 25.7 mmol, **1**: 43.5 g, 64.2 mmol, LiBr: 5.6 g, 64.2 mmol) was performed for the practical purpose to give **9b** in high yield (82%). The bromination occurred at only *p*-position of electron donating group: *o*-brominated isomers were not detected. In the case of *m*-methoxyphenol (**10a**), only *p*-bromo-*m*-methoxyphenol (**10b**, *p*-position was brominated toward OH group) was obtained. When the reaction of **4a** with LiBr–H_2SO_4 in the absence of **1** was carried out, no bromination occurred: starting material **4a** was recovered quantitatively. These results indicate that **1** takes an important role in these bromination reactions. Some heterocycles (**13a** and **14a**) were also successfully brominated with lithium bromide and **1** at 25 °C in acetonitrile in high yields. However, less activated aromatic compounds such as anisole or toluene did not give brominated products under the same reaction conditions.

Table 2. Bromination of aromatic compounds with lithium bromide and tetrabutylammonium peroxydisulfate



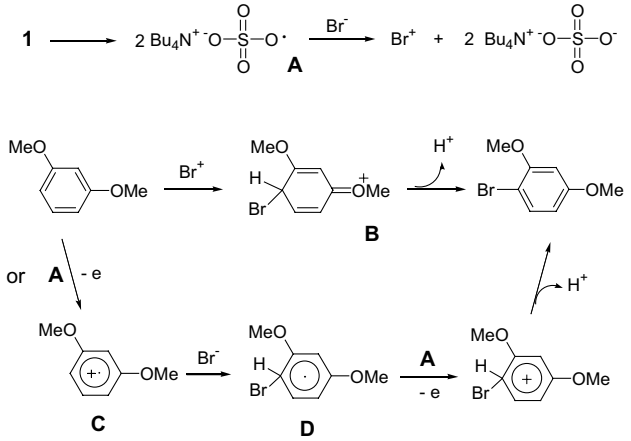
a **b**

	Substrate	Time (h)	Product	Yield[a] (%)
1	 **4a**	8	 **4b**	98
1′	 **4a**	8	 **4b**	0[b]
2	 **10a**	8	 **10b**	75
3	 **11a**	24	 **11b**	71[c]
4	 **12a**	24	 **12b**	85
5	 **9a**	36	 **9b**	83 (82[d])
6	 **13a**	8	 **13b**	95
7	 **14a**	8	 **14b**	86

[a] Isolated yield.
[b] In the absence of **1**, but with 1 equiv of H_2SO_4.
[c] Excess amount of **1** (3 equiv) was used.
[d] Large scale (**9a**: 4.33 g, 25.7 mmol; **1**: 43.5 g, 64.2 mmol; LiBr: 5.6 g, 64.2 mmol).

Although the mechanism for the bromination with lithium bromide and **1** is not clear but the reaction appears to be initiated via formation of tetrabutylammonium sulfate radical **A** by homolysis of **1**. The sulfate radical **A** may oxidize bromide anion to bromonium cation.[10] The electrophilic attack of bromonium cation at *p*-position of activated aromatic compounds produces the intermediate **B**, which is readily converted to brominated product. However, there is an alternative possibility to form a radical cation **C**[16] by one electron transfer, which may convert to a radical intermediate **D** (Scheme 2).

In conclusion, we have developed a complete regioselective bromination of activated aromatic compounds under the mild conditions using **1** as an oxidant. The stable peroxydisulfate **1** can be readily prepared, which can be handled easily and safely. Thus, it can be practically used for oxyhalogenation reaction. Bromination with bromine in the presence of **1** gave the monobrominated products, respectively, in high to excellent yields as the major products in short reaction time. In contrast to using bromine, bromination with lithium bromide resulted in only monobrominated products with complete regioselectivity in good to excellent yields under neutral and mild conditions. In this reaction,



Scheme 2. Proposed mechanism for the bromination with lithium bromide and tetrabutylammonium peroxydisulfate.

lithium bromide proves a better alternative to hazardous molecular bromine.

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