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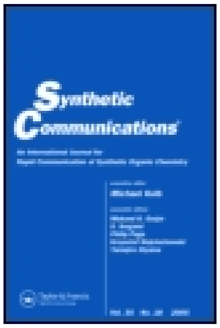

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A Bromination of Arenes Using I_2O_5-KBr in Water

Jieping Hou[1], Zejiang Li[2], Xiao-Dong Jia[1], Zhong-Quan Liu[2]

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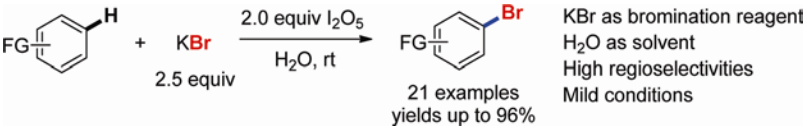
Abstract

An efficient and environmentally-benign bromination of various aromatic compounds using aqueous I_2O_5-KBr system at room temperature has been developed in this work. A series of aromatic compounds such as acetophenones, benzaldehydes, benzoic acids, anilines, amides, and aminopyridine have been successfully brominated in excellent regioselectivities and high yields under the typical reaction conditions. The features of KBr as brominating reagent, water as solvent, and mild conditions make this system an attractive synthetic procedure.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: Arene, Bromination, KBr

INTRODUCTION

Aromatic bromides represent a large class of useful compounds in the synthesis of pharmaceuticals, natural products, and agrochemicals, etc.[1] The most general and convenient access to these compounds are direct bromination of aromatic compounds.[2] Although numerous strategies for bromination of aromatic compounds using elemental bromine have been developed in the past decades,[3] more efficient, avoid to use bromine, and organic solvent free systems are highly desirable due to clean production. Recently, a few attractive procedures using KBr and NH_4Br as the bromine source and the Oxone, *tert*-butyl hydroperoxide (TBHP), and hydrogen peroxide as oxidant have been established. [4] However, most of these systems suffer from acid assistance and using organic solvent. Herein we wish to report an efficient and metal-free bromination of various aromatic compounds using I_2O_5-KBr in water (Scheme 1).

EXPERIMENTAL

Initially, we chose 4-methoxyacetophenone as the model substrate to optimize suitable conditions for this reaction (Table 1). It was found that the desired product **1a** was isolated in moderate to nearly quantitative yields by using I_2O_5-KBr in a mixture of acetonitrile and water (Table 1, entries 1-8). We found that the yields increase with the increasing volume of water in the mixed solvent (Table 1, entries 6-8). Interestingly, the corresponding aromatic bromide was isolated in a yield of 96% in water (Table 1, entry 9). The yield decreased very slightly when 1.5 equivalent of KBr was used as the bromination reagent in water (Table 1, entry 10).

To examine the scope of this system, the bromination of various aromatic compounds using I_2O_5-KBr were studied (Table 2). A variety of aromatic compounds such as acetophenones, benzaldehydes, benzoic acids, amides, anilines, and aminopyridine have been smoothly brominated in moderate to high yields with excellent regioselectivities under the typical reaction conditions. Arenes bearing one electron-donating group and one electron-withdrawing group in ortho or para relationship, such as 4-methoxyacetophenones, 4-methoxybenzaldehyde, 4-methoxybenzoic acid, 2-methoxybenzaldehyde, and methyl 2-methoxybenzoate gave good to excellent yields of the corresponding aromatic bromides **1a**-**6a** (Table 2, entries 1-6). 3-Methoxybenzaldehyde gave the monobrominated product **7a** in 83% yield and the dibrominated product **7b** in 10% yield (Table 2, entry 7), 3-methoxyacetophenone gave dibrominated product **8a** as the only product, but in 24% yield, and no mono-brominated products were obtained (Table 2, entry 8). In addition, amides were also effective substrates in this system (Table 2, entries 9 and 10). A dibrominated product **11a** was obtained in 90% yield using 4-nitroaniline (Table 2, entry 11). Anisole gave 72% yield of 2,4-dibromoanisole (Table 2, entry 12). Bromination of 2,3-dihydrobenzofuran and

2,3-dihydro-1,4-benzodioxane produced the corresponding dibrominated products **13a** and **14a** in 89% and 78% yields, respectively (Table 2, entries 13 and 14). When phenols were used as substrates, a complex mixture was produced, which involved oxidized compounds due to the high reactivity of phenol. For example, *p*-dihydroxybenzene gave a very low yield of the corresponding bromide **15a** (Table 2, entry 15). Mesitylene also acts as effective substrate and gives the dibrominated product **16a** in 76% yield (Table 2, entry 16). A 33% yield of the bromide **17a** was obtained using 2,4,6-trimethylbenzoic acid (Table 2, entry 17). Piperonyl aldehyde gave 85% yield of the mono-brominated product **18a**. Acetophenone and 4-methylacetophenone gave the methyl group brominated products in 36% and 62% yields, respectively (Table 2, entries 19 and 20). It is noteworthy that 2-aminopyridine also gave good yield of a dibrominated product (Table 2, entry 21). Although highly electron-deficient arenes such as nitrobenzene and polyfluorinated benzenes did not provide satisfactory yield in this system, the features of commercial available oxidant, KBr as brominating reagent, water as solvent, and mild conditions make this strategy an attractive synthetic procedure.

Furthermore, under the typical conditions, this bromination reaction could be scaled up (Scheme 2). A mixture of 4-methoxyacetophenone (1.0 g, 6.67 mmol), I_2O_5 (4.45 g, 13.33 mmol), and KBr (1.97 g, 16.67 mmol) was dissolved in 50 mL of H_2O. The reaction was complete after stirring for 22.5 hours at room temperature. The mixture was extracted by ethyl acetate (3 × 100 mL), concentrated under reduced pressure, and the mixture was purified by flash column chromatography (petroleum ether/ethyl acetate=40:1) to afford the desired product **1a** as a pale yellow solid (1.44 g, 95% isolated yield).

The possible mechanism [5] of this process may involve oxidation of the KBr by hypervalent iodine to generate an electrophilic bromine molecule, [6] which then brominates the arenes, the aromatic bromide is formed followed by elimination of a proton.

In summary, we have developed an efficient, mild and environmentally-benign protocol for preparation of aromatic bromides using I_2O_5-KBr in water. Various aromatic compounds such as benzaldehydes, benzoic acids, acetophenones, anilines, amides, and aminopyridine etc. can be successfully brominated to generate the corresponding aromatic bromides. Finally, this procedure can be conveniently scaled up to gram-scale level which might be useful to its application in industry.

General Method

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ with TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz and referenced to the internal solvent signals (center peak is 77.0 ppm in $CDCl_3$ or 39.9 ppm in DMSO-d_6). Mass spectroscopy data were collected on HRMS-ESI and MS-EI instruments. All products were identified by ^1H and ^{13}C NMR, MS, and/or HRMS. The starting materials were purchased from common commercial sources and used without further purification.

Typical Procedure For The Bromination Of Aromatic Compounds By Using I_2O_5-Kbr In Water

A mixture of arene (0.5 mmol), I_2O_5 (334 mg, 1.0 mmol), and KBr (148 mg, 1.25 mmol) was dissolved in 2 mL of H_2O. The reaction was complete after stirring for the indicated time at room temperature. The mixture was extracted by ethyl acetate, concentrated under reduced pressure, and the mixture was purified by flash column chromatography (silica gel) to afford the desired product.

*1-(3-bromo-4-methoxyphenyl)ethanone (**1a**):* A light yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 40/1). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 2.0 Hz, 1H), 7.91 (dd, J = 8.8, 2.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 3.96 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 159.5, 133.7, 131.1, 129.4, 111.8, 111.0, 56.4, 26.2. MS(EI): m/z(%): 230(34.1, M^++2), 228(35.5, M^+), 215(96.3), 213(100.0), 187(14.0), 185(14.5), 172(8.6), 170(10.1), 157(10.0), 155(9.0), 78(15.8), 63(11.8).

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REFERENCES

1. (a) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937. (b) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335.

2. For selected reviews, see: (a) Djerassi, C. *Chem. Rev.* **1948**, *48*, 271. (b) Skell, P. S.; Traynham, J. G. *Acc. Chem. Res.* **1984**, *17*, 160. (c) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131. (d) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH, New York, 2nd edn, 1999. (e) Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8424. (f) Bora, U.; Chaudhuri, M. K.; Dey, D.; Dhar, S. S. *Pure Appl. Chem.* **2001**, *73*, 93.

3. For selected reviews, see: (a) De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press, Cambridge, UK, 1976, Chapter 5. (b) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley, Chichester, UK, 1990. For selected examples, see: (a) Schmid, H. *Helv. Chim. Acta* **1946**, *29*, 1144. (b) Jacquesy, J.; Jouannetaud, M.; Makani, S. *J. Chem.*

Soc., Chem. Commun. **1980**, 110. (c) Clark, J. H.; Ross, J. C.; Macquarrie, D. J.; Barlow, S. J.; Bastock, T. W. *Chem. Commun.* **1997**, 1203. (d) Smith, K.; El-Hiti, G. A.; Hammond, M. E.W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2745. (e) Firouzabadi, H.; Iranpoor, N.; Amani, K. *J. Mol. Catal. A: Chem.* **2003**, *195*, 289. (f) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **2005**, *46*, 4465. (g) Menzel, K.; Fisher, E. L.; DiMichele, L.; Frantz, D. E.; Nelson, T. D.; Kress, M. H. *J. Org. Chem.* **2006**, *71*, 2188. (h) Al-Zoubi, R. M.; Hall, D. G. *Org. Lett.* **2010**, *12*, 2480. (i) Kumar, L.; Mahajan, T.; Agarwal, D. D. *Green Chem.* **2011**, *13*, 2187.

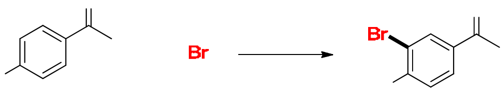
4. For a very recent review, see: Kandepi, V. V. K. M.; Narender, N. *Synthesis* **2012**, *44*, 15. For selected examples, see: (a) Choudary, B. M.; Sudha, Y.; Reddy, P. N. *Synlett* **1994**, 450. (b) Dinesh, C. U.; Kumar, R.; Pandey, B.; Kumar, P. *J. Chem. Soc., Chem. Commun.* **1995**, 611. (c) Walker, J. V.; Morey, M.; Carlson, H.; Davidson, A.; Stucky, G. D.; Butler, A. *J. Am. Chem. Soc.* **1997**, *119*, 6921. (d) Mestres, R.; Palenzuela, J. *Green Chem.* **2002**, *4*, 314. (e) Das, D. P.; Parida, K. *Catal. Commun.* **2006**, 68. (f) Tsoukala, A.; Liguori, L.; Occhipinti, G.; Bjørsvik, H. R. *Tetrahedron Lett.* **2009**, *50*, 831. (g) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron* **2009**, *65*, 4429. (h) Kumar, M. A.; Rohitha, C. N.; Kulkarni, S. J.; Narender, N. *Synthesis* **2010**, 1629. (i) Wang, G.-W.; Gao, J. *Green Chem.* **2012**, *14*, 1125.

5. (a) Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S. Vairamani, M. *Tetrahedron* **2001**, *57*, 7417. (b) Moriuchi, T.; Yamaguchi, M.; Kikushima, K.; Hirao, T. *Tetrahedron Lett.* **2007**, *48*, 2667.

6. Khazaei, A.; Zolfigol, M. A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Komaki, F.

Synthesis **2009**, 3672.

Table 1. Optimization of the typical reaction conditions[a]



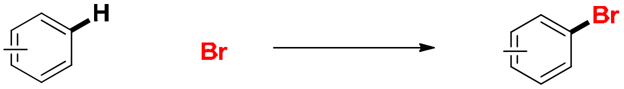
1a

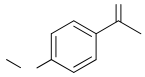
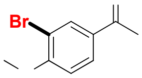
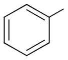
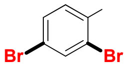
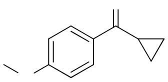
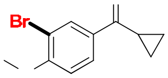
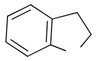
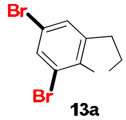
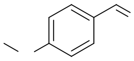
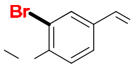
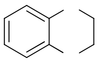
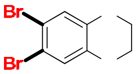
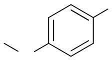
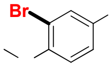
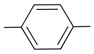
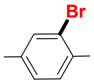
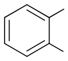
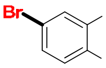
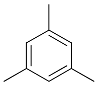
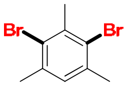
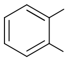
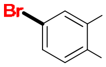
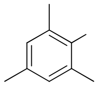
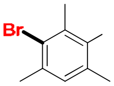
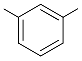
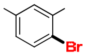
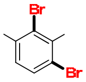
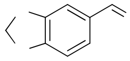
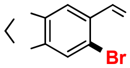
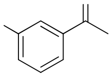
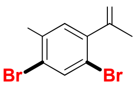
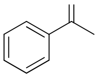
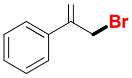
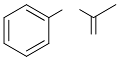
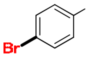
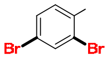
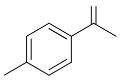
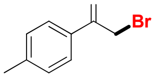
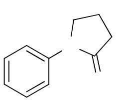
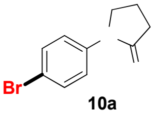
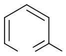
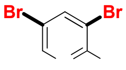
Entry	I_2O_5 (eq)	KBr (eq)	Solvent	Yield (%) [b]
1	1	2.5	$CH_3CN:H_2O$ (1:1)	57
2	2	2.5	$CH_3CN:H_2O$ (1:1)	79
3	2.5	2.5	$CH_3CN:H_2O$ (1:1)	98
4	2	2	$CH_3CN:H_2O$ (1:1)	88
5	2	3	$CH_3CN:H_2O$ (1:1)	78
6	2	2.5	$CH_3CN:H_2O$ (1:1.5)	96
7	2	2.5	$CH_3CN:H_2O$ (1:2)	97
8	2	2.5	$CH_3CN:H_2O$	99

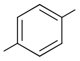
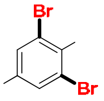
			(1:4)	
9	**2**	**2.5**	**H_2O**	**96**
10	2	1.5	H_2O	95

[a] Reaction conditions: 4-methoxyacetophenone (0.5 mmol, 1 eq.), solvent (2 mL), stirred at room temperature for 10 h. [b] Isolated yield.

Table 2. Bromination of aromatic compounds by using I_2O_5-KBr in water[a]

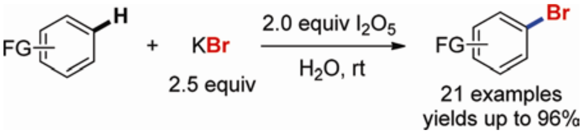


Entry	Arene	Product	Time (h)	Yield (%)[b]	Entry	Arene	Product	Time (h)	Yield (%)[b]
1		 1a	10	96	12		 12a	20	72
2		 2a	6	90	13		 13a	23	89
3		 3a	20	82	14		 14a	23	78
4		 4a	23	68	15		 15a	23	27
5		 5a	23	94	16		 16a	20	76
6		 6a	20	92	17		 17a	23	33
7		 7a  7b	23	83/10	18		 18a	23	85
8		 8a	66	24	19		 19a	20	36
9		 9a  9b	20	78/18	20		 20a	23	62
10		 10a	23	82	21		 21a	23	75

11		 **11a**	23	90					

[a] Reaction conditions: aromatic compound (0.5 mmol, 1 eq.), I_2O_5 (1.0 mmol, 2 eq.), KBr (1.25 mmol, 2.5 eq.), H_2O (2 mL), stirred at room temperature for the indicated time. [b] Isolated yield.

Scheme 1. Bromination of aromatic compounds by using I_2O_5-KBr in water.



Scheme 2. Scaled-up experiment.