http://dx.doi.org/10.5012/bkcs.2012.33.8.2619

A Green Protocol for the Bromination and Iodination of the Aromatic Compounds using H_5IO_6/NaBr and H_5IO_6/NaI in the Water

Jaber Yousefi-Seyf, Kazem Tajeian, Eskandar Kolvari,†,* Nadiya Koukabi,†,*
Ardeshir Khazaei, and Mohammad Ali Zolfigol

Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran
†Department of Chemistry, Semnan University, Semnan 3535119111, Iran
**E-mail: kolvari@semnan.ac.ir (Kolvari, E.); n.koukabi@semnan.ac.ir (Koukabi, N.)*
Received January 25, 2012, Accepted May 10, 2012

Bromination and iodination of the aromatic compounds have efficiently been carried out at room temperature and 70 °C, respectively, in short reaction times using orthoperiodic acid/sodium bromide (1:2) and orthoperiodic acid/sodium iodide (1:2) in water to prepare the corresponding halo compounds with excellent yields.

Key Words : Iodination, Bromination, Orthoperiodic acid, Water

Introduction

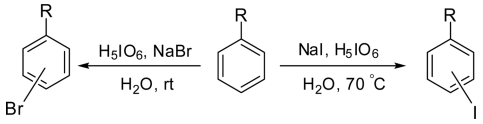
Organic halides are an important class of intermediates as they can be converted efficiently into other functional groups by simple chemical transformations.[1,2] Due to the potential utilization of aryl bromides and iodides in the synthesis of aryl esters, aryl olefins and other useful compounds and their wide applications in medicine and biochemitry,[3-18] bromination and iodination of aromatic compounds have been the subject of numerous studies. Recently, the oxidative halogenation of organic compounds by halides have emerged as an important alternative for the synthesis of such halo-derivatives.[19-30] Despite the broad choice of options, however, many bromination and iodination methodologies are cumbersome, costly and harsh or involve the use of toxic heavy metals, volatile organic solvents, or elemental halogenes which are highly corrosive, toxic or self-sublimating. In addition, there are some environmental hazards with respect to handling them.

From this point of view, the development of quick, inexpensive, widely applicable and environmentally benign iodinating and brominating agents is still an active area of research. The uses of water as the reaction medium have several benefits that are briefly pointed out. Water is a cheap, ample, nontoxic non-flammable solvent. In addition, because the polarity of water and organic materials are completely different, we can easily isolate the products from the mixture.

Results and Discussions

Herein we wish to report a new environmentally friendly method for the efficient halogenation of aromatic compounds using orthoperiodic acid[31-32] as the oxidant. The reactions for bromination and iodination are carried out at room temperature and 70 °C, respectively.

In this study, we report halogenations of structurally different arenes (Scheme 1) in the water using orthoperiodic acid as a mild and safe solid oxidant and NaI or NaBr as safe sources of iodide and bromide without any organic cosolvent.

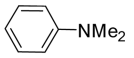
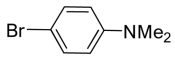
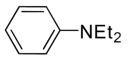
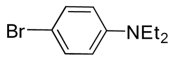
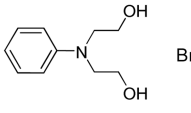
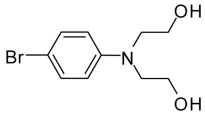
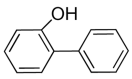
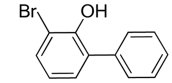
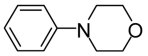
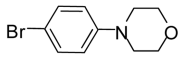
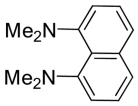
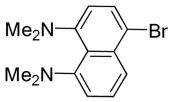
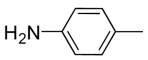
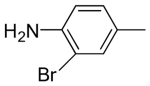
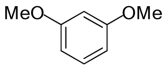
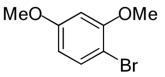
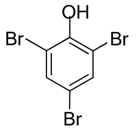
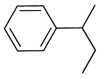
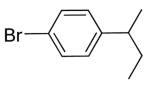
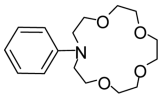
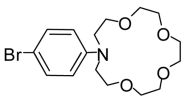
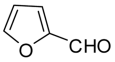


Scheme 1. Iodination and bromination of aromatic compounds in water.

To optimize bromination reaction conditions, we first studied oxidative bromination of *N,N*-dimethylaniline (DMA) as a model compound using NaBr in the presence of orthoperiodic acid in water at room temperature. We found that the optimized molar ratio of NaBr/DMA/orthoperiodic acid was 1:1:0.5 mmol in 2 mL of water. The reaction proceeded well with excellent para selectivity within 5 min (TLC). After work up of the reaction mixture, the 4-bromo-*N,N*-dimethylaniline was isolated in 96% yield. After optimization, in model condensation reaction, the scope and the generality of the present method were demonstrated by the bromination of various aromatic comounds such as phenols, aromatic amines, and arenes. As can be seen in Table 1, the results indicate that aromatic electrophilic bromination proceeds well at room temprature in water using orthoperiodic acid/sodium bromide (1:2) system for electron -rich aromatic compounds. Yields are good to excellent, and selective mono bromo products have been obtained. Phenol gives sluggish reaction under this condition, but increasing amount of orthoperiodic acid to 1.5 and NaBr to 3 equivalent leads to obtain 2,4,5-tribromophenol in 70%.

Other unactivated aromatic compounds such as benzonitrile and furfural not react even after prolong reaction time (48 hours). Using the difference of the reactivity's we could achieve chemoselective bromination of activated aromatic compounds in the presence of unactivated ones could be achieved. Even though orthoperiodic acid/sodium bromide

Table 1. Bromination of aromatic compounds using orthoperiodic acid/sodium bromide (1:2) in water at room temperature[a]

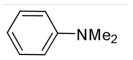
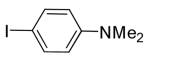
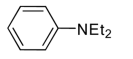
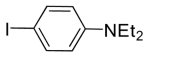
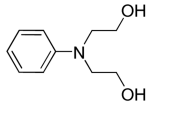
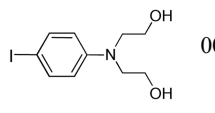
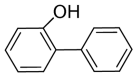
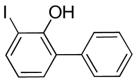
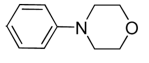
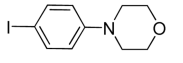
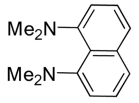
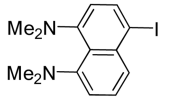
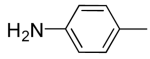
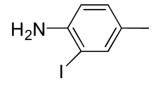
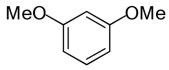
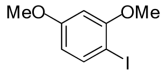
Entry	Substrate	Product	Time (h:min)	Yield (%)[b]
1			00:05	96
2			00:05	95
3			00:10	93
4			00:04	89
5			00:40	91
6			01:00	80
7			00:05	90
8			00:05	95
9			05:00	69[c]
10			05:00	52
11			00:30	95
12		-	48:00	-
13		-	48:00	-

[a]All products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic data, and melting points. [b]Yields refer to isolated products. [c]Reaction coditions: orthoperiodic acid (1.5 mmol), NaBr (3 mmol), phenol (1 mmol) in water at rt.

(1:2) is capable of oxidizing alcohol,[33] it remains intact during the bromination of aromatic nucleus (Entry 3).

To extend the application of this method in organic reactions and transformations, we have also studied iodination of aromatic compounds with orthoperiodic acid/sodium iodide (1:2) in H_2O as solvent (Table 2). We first studied oxidative iodination of *N,N*-dimethylaniline (1 mmol) as a model compound using NaI (1 mmol) in the presence of orthoperiodic acid (0.5 mmol) in water at room temperature. In contrast with our expectation, the product yield was low (15%) within a long reaction time (4 h). To increase the yield, the reaction was tested under heating at 70 °C.

Table 2. Iodination of aromatic compounds using orthoperiodic acid/sodium iodide (1:2) in water at 70 °C[a]

Entry	Substrate	Product	Time (h:min)	Yield (%)[b]
1			00:05	93
2			00:05	93
3			00:45	92
4			00:07	85
5			00:55	90
6			01:15	70
7			00:05	85
8			00:05	84
9			06:00	25, 20
10			00:45	90
11		-	48:00	-
12		-	48:00	-

[a]All products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic data, and melting points. [b]Yields refer to isolated products.

Increasing the temperature caused the reaction to proceed very well and 4-iodo-*N,N*-dimethylaniline was isolated in 93% yield within 5 min.

To generalize this application, we have used various materials with the different structure arenes of such as *N*-phenylmorpholine, N^1,N^1,N^8,N^8-tetramethylnaphthalene-1,8-diamine, phenol, 1,3-dimethoxybenzene, *N*-phenyl-1-*aza*-15-crown-5 subjected to iodination reaction using orthoperiodic/sodium iodide (1:2). The results are tabulated in Table 2. One of the most important results was the iodination of phenol which produced two products that were separated by plate chromatography technique to achieve the desired

Scheme 2. Mechanism for the formation of haloarenes.

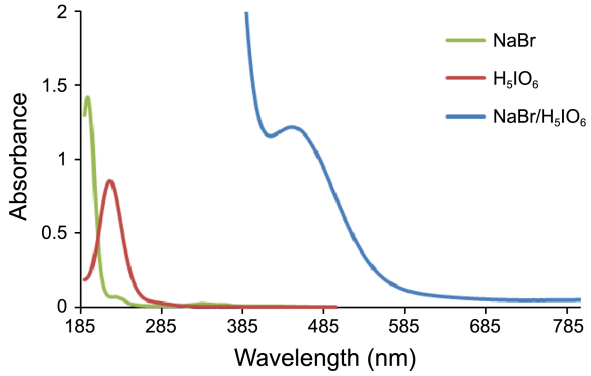


Figure 1. UV-Vis spectra of sodium bromide, orthoperiodic acid, orthoperiodic acid/sodium bromide (1:2) in aqueous media.

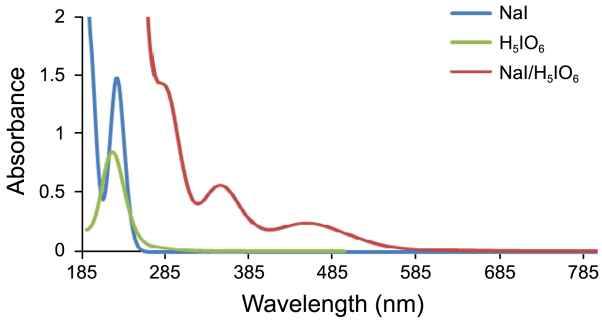


Figure 2. UV-Vis spectra of sodium iodide, orthoperiodic acid, orthoperiodic acid/sodium iodide (1:2) in aqueous media.

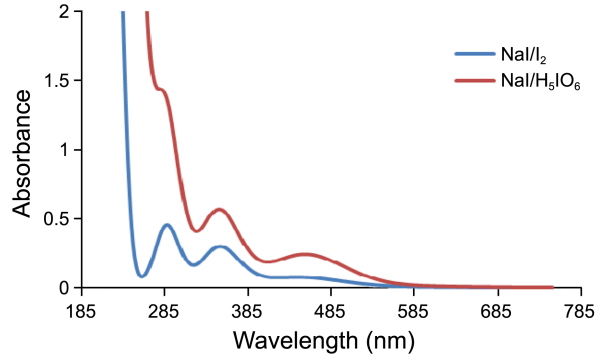


Figure 3. UV-Vis spectra of sodium iodide/iodine, orthoperiodic acid /sodium iodide (1:2) in aqueous media.

products. They were verified to be 2-iodophenol and 2,6-iodophenol by ^{1}H and ^{13}C NMR techniques. The results were compared with credible sample.[34]

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2.

To obtain more evidence in support of the proposed mechanism, we conducted the following experiments. The UV-visible spectra of NaX and orthoperiodic acid showed strong absorption bands < 285 nm (Figures 1 and 2). After the addition of 0.5 mmol of orthoperiodic acid to 1.0 mmol of NaX in water, the colorless solution of X^- was immediately changed to a colored solution of X_2 (brown and orange for I_2 and Br_2 solutions, respectively) and the UV-visible spectra of mixtures did not show any absorption at < 285 nm. This is very strong evidence for the *in situ* generation of X_2 species in the mixtures (Figures 1 and 2). Also, comparing UV-visible spectra of the solutions of NaI/I_2 (1:1) and orthoperiodic acid/sodium iodide (1:2) demonstrated that all λ_{max} of the two solutions are identical (Figure 3).

Conclusion

Finally, we have presented a green protocol for iodination and bromination of aromatic compounds in the water medium without any organic cosolvent using NaBr or NaI/H_5IO_6/water system instead of organic solvent medium and the iodination of phenol without oxidation. Singular regioselective product is one of the good characteristics of this protocol.

Experimental Section

General Procedure for Bromination or Iodination and of the Arenes with NaBr or NaI. To a soultion of NaBr or NaI (2 mmol) in water (4 mL), arene (2 mmol) and orthoperiodic acid (1 mmol) were added at room temperature or 70 °C, respectively. After sufficient reaction time (Table 2), the resulting reaction mixture was treated with $Na_2S_2O_3$ solution (10 mol %, 5 mL) and the mixture was extracted with Et_2O (3 × 10 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, crude product was obtained. Further purification was carried out by crystallization in suitable solvent like *n*-hexane.

Typical procedure for bromination of *N*-phenyl morpholine using NaBr and orthoperiodic acid in waer at room temprature

To get a solution of NaBr (1 mmol, 103 mg) in water (2 mL), added *N*-methylmorpholine (1 mmol, 163 mg) and orthoperiodic acid (0.5 mmol, 228 mg) were added at room temperature- and the mixture was stirred vigorously for 55 min. After the completion of reaction that was indicated by TLC, the reaction mixture was transferred to a separatory funnel and aqaous $Na_2S_2O_3$ (10%, 5 mL) was added. The aqueous fraction was extracted with Et_2O (3 × 10 mL). The organic layer was dried with Na_2SO_4 and the mixture was filtereated. The solvent was removed by simple distillation to give a crude product (225 mg, 93%). Further purification was carried out by crystallization from cold hexane to afford a pale yellow crystalline product (217 mg; 91%), mp 110-112 °C, which showed satisfactory analytical and spectroscopic properties.

Acknowledgments. The authors acknowledge Semnan University Research council, Bu-Ali Sina University Research Council (Grant Number 32-1716), and Center of Excellence in Development of Chemical Methods (CEDCM).

References

1. Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609.
2. Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*,

11657.
3. Richardson, T. I.; Clarke, C. A.; Yu, K. L.; Yee, Y. K.; Bleisch, T. J.; Lopez, J. E.; Jones, S. A.; Hughes, N. E.; Muehl, B. S.; Lugar, C. W.; Moore, T. L.; Shetler, P. K.; Zink, R. W.; Osborne, J. J.; Montrose-Rafizadeh, C.; Patel, N.; Geiser, A. G.; Galvin, R. J. S.; Dodge, J. A. *ACS Med. Chem. Lett.* **2011**, *2*, 148.
4. Karczmarzyk, Z.; Wolinska, E.; Fruzinski, A. *Acta Crystallogr. Sect. E.-Struct Rep. Online* **2011**, *67*, O651.
5. Bolliger, J. L.; Oberholzer, M.; Frech, C. M. *Adv. Synth. Catal.* **2011**, *353*, 945.
6. Rafat, M. M.; Schatz, J. *Bioorg. Med. Chem.* **2011**, *19*, 2707.
7. Schumacher, R. F.; Rosario, A. R.; Souza, A. C. G.; Acker, C. I.; Nogueira, C. W.; Zeni, G. *Bioorg. Med. Chem.* **2011**, *19*, 1418.
8. Firouzabadi, H.; Iranpoor, N.; Ghaderi, A.; Ghavami, M.; Hoseini, S. J. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 100.
9. Macickova-Cahova, H.; Pohl, R.; Horakova, P.; Havran, L.; Spacek, J.; Fojta, M.; Hocek, M. *Chem.-Eur. J.* **2011**, *17*, 5833.
10. Yagi, S.; Nakasaku, Y.; Maeda, T.; Nakazumi, H.; Sakurai, Y. *Dyes Pigment.* **2011**, *90*, 211.
11. Doring, K.; Ballav, N.; Zharnikov, M.; Lang, H. *Eur. J. Inorg. Chem.* **2010**, 3952.
12. Vishnumurthy, K.; Makriyannis, A. *J. Comb. Chem.* **2010**, *12*, 664.
13. Lee, P. H.; Mo, J.; Kang, D.; Eom, D.; Park, C.; Lee, C. H.; Jung, Y. M.; Hwang, H. *J. Org. Chem.* **2011**, *76*, 312.
14. Qi, J. P.; Deng, H. Z.; Cao, D. R. *Sci. China-Chem.* **2010**, *53*, 2547.
15. Hassan, Z.; Hussain, M.; Langer, P. *Synlett* **2011**, 1827.
16. Wang, Z. H.; Chi, Y. S.; Harris, A. R.; Gray, D.; Davoren, J. E. *Synthesis-Stuttgart* **2011**, 1529.
17. Khan, T. A.; Kumar, S.; Venkatesh, C.; Ila, H. *Tetrahedron* **2011**, *67*, 2961.
18. Rieke, R. D.; Kim, S. H. *Tetrahedron Lett.* **2011**, *52*, 244.
19. Leveque, J.-M.; Fujita, M.; Bosson, A.; Sohmiya, H.; Petrier, C.; Komatsu, N.; Kimura, T. *Ultrason. Sonochem.* **2011**, *18*, 753.
20. Podgorsek, A.; Iskra, J. *Molecules* **2010**, *15*, 2857.
21. Kolvari, E.; Ghorbani-Choghamarani, A.; Salehi, P.; Shirini, F.; Zolfigol, M. A. *J. Iran. Chem. Soc.* **2007**, *4*, 126.
22. Chen, A.-J.; Chen, X.-R.; Mou, C.-Y. *J. Chin. Chem. Soc.* **2010**, *57*, 820.
23. Wischang, D.; Hartung, J.; Hahn, T.; Ulber, R.; Stumpf, T.; Fecher-Trost, C. *Green Chem.* **2011**, *13*, 102.
24. Boehmdorfer, S.; Patel, A.; Hofinger, A.; Netscher, T.; Gille, L.; Rosenau, T. *Eur. J. Org. Chem.* **2011**, 3036.
25. Zhang, G.; Wang, Y.; Ding, C.; Liu, R.; Liang, X. *Chin. J. Org. Chem.* **2011**, *31*, 804.
26. Ju, J.; Li, Y. J.; Gao, J. R.; Jia, J. H.; Han, L.; Sheng, W. J.; Jia, Y. X. *Chin. Chem. Lett.* **2011**, *22*, 382.
27. Ghiaci, M.; Sedaghat, M. E.; Ranjbari, S.; Gil, A. *App. Catal. A-Gen.* **2010**, *384*, 18.
28. Chen, A.-J.; Wong, S.-T.; Hwang, C.-C.; Mou, C.-Y. *ACS Catal.* **2011**, *1*, 786.
29. Khazaei, A.; Zolfigol, M. A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Bayani, L. S. *Synth. Commun.* **2010**, *40*, 2954.
30. Zolfigol, M. A.; Khazaei, A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Behjunia, M.; Khakyzadeh, V. *Arkivoc* **2009**, 200.
31. Khazaei, A.; Zolfigol, M. A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Komaki, F. *Synthesis* **2009**, 3672.
32. Zolfigol, M. A.; Khazaei, A.; Kolvari, E.; Koukabi, N.; Soltani, H.; Behjunia, M. *Helvetica Chim. Acta* **2010**, *93*, 587.
33. Zolfigol, M. A.; Shirini, F.; Chehardoli, G.; Kolvari, E. *J. Mol. Catal. A: Chem.* **2007**, *265*, 272.
34. Characterization of the products. Table 2, Entry 7: white solid, mp 39-41 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.58-7.40 (m, 3H), 3.96 (s, 2H), 2.10-2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.84, 84.31, 114.68, 129.53, 130.05, 139.02, 144.33. Entry 4: orange liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.74-7.72 (m, 8H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 86.25, 122.77, 128.13, 128.94, 129.11, 129.54, 131.21, 137.45, 138.26, 151.78. Entry 8: yellow solid, mp 37-39 °C; ^{1}H NMR ($CDCl_3$, 75 MHz): δ 7.51-7.54 (d, 1H), 6.21-6.35 (m, 2H), 3.70-3.73 (s, 3H), 3.76-3.79 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz): δ 55.58, 56.29, 74.80, 99.23, 107.07, 139.16, 158.85, 161.40. Entry 6: dark brown solid; mp 197-200 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.91-7.33 (m, 5H), 2.78-2.88 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 44.49, 112.87, 120.24, 121.83, 125.16, 127.91, 137.32, 150.70. Entry 3: blue solid, mp 66-71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.43-6.45 (d, 2H), 7.43-7.46 (d, 2H), 4.47 (s, 2H), 3.74 (t, 4H), 3.50 (t, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.21, 60.30, 77.76, 114.80, 137.79, 147.23. Entry 1: blue solid, mp 67-71 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.54-6.51 (m, 2H), 7.46-7.43 (m, 2H), 2.94 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.51, 77.69, 114.60, 137.58, 149.89. Entry 2: brown liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.49 (d, 2H), 7.46 (d, 2H), 3.34 (q, 4H), 1.31 (t, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.40, 44.46, 77.69, 114.33, 137.77, 147.24. Entry 5: brown solid, mp 151-154 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.71 (d, 2H), 7.57 (d, 2H), 3.80 (t, 4H), 3.11 (t,4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.90, 66.67, 81.64, 117.70, 137.80, 150.97. Entry 10: brown liquid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.48 (d, 2H), 7.36 (d, 2H), 3.64 (t, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.198, 71.172, 72.64, 74.04, 79.63, 120.16, 140.48, 150.11. Table 1, Entry 3: brown solid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73-3.50 (m, 10H), 6.59 (m, 2H), 7.22 (m, 2H). Entry 5: brown solid; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80 (d, 2H), 7.29 (d, 2H), 3.09 (t, 4H), 3.78 (t, 4H).