

Practical Electrochemical Iodination of Aromatic Compounds

Kazuhide Kataoka,[†] Yuji Hagiwara,[‡] Koji Midorikawa,[‡] Seiji Suga,[§] and Jun-ichi Yoshida*^{,§}

JST Innovation Plaza Kyoto, Kyoto 615-8245, Japan, Technology Laboratory, Nippon Chemicals Co., Ltd., Chiba 298-0104, Japan, and Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Abstract:

A practical method for electrochemical iodination of aromatic compounds was developed. The method involves the generation of I⁺ by electrochemical oxidation of I₂ in CH₃CN using H₂SO₄ as supporting electrolyte followed by the reaction with aromatic compounds. The para/ortho selectivity for the reaction of mono-substituted benzenes was significantly improved using dimethoxyethane as cosolvent in the second step. The reaction with highly reactive aromatic compounds led to the formation of significant amounts of diiodo compounds in a macrobatch reactor. This problem was solved by fast 1:1 mixing of I⁺ with an aromatic compound using a microflow system consisting of a T-shaped micromixer and a microtube reactor.

Introduction

Aromatic iodides are valuable and versatile intermediates in the synthesis of functional materials and biologically active compounds such as medical drugs and agricultural chemicals.¹ In particular, aromatic iodides serve as excellent substrates for transition metal-catalyzed homo- and cross-coupling reactions,² which are used for the synthesis of complex molecules. Thus, various aromatic iodides have been produced commercially and have been used in laboratory and industrial synthesis. Some aromatic iodides that are industrially produced are listed in Figure 1.

Currently, some aromatic iodides such as iodobenzene and iodotoluene have been produced in industry using the Sandmeyer reaction of diazonium salts.³ For example, benzene is converted into aniline, which is diazotized with hydrochloric acid and sodium nitrite (Scheme 1). The resulting diazonium chloride is allowed to react with KI to obtain iodobenzene. Iodotoluene is also produced in a similar manner via toluidine. Because this multistep process involves a potentially explosive diazonium salt as an intermediate, development of a much safer method has been highly desirable.

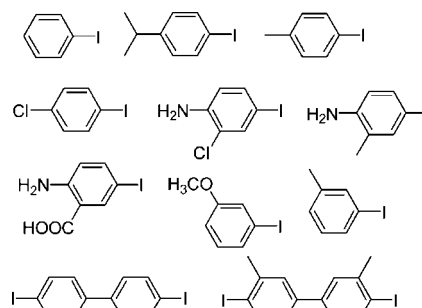
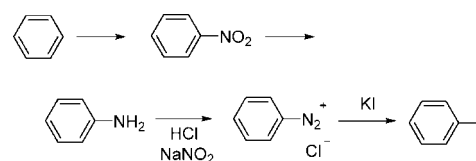
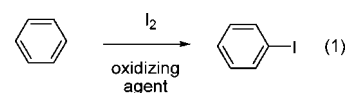


Figure 1. Some aromatic iodides produced in industry.

Scheme 1. Synthesis of iodobenzene from benzene via benzenediazonium salt



Although various methods for the synthesis of aromatic iodides have been developed so far,⁴ direct iodination of aromatic compounds using I₂ seems to be one of the most straightforward ways.⁵ This reaction usually requires additional reagents. For example, the reaction of benzene with I₂ requires an oxidizing reagent⁶ (eq 1). Presumably I⁺ or its equivalent, which is produced by the oxidation of I₂ serves as a highly reactive iodinating agent. However, this process suffers from a problem of a large amount of wastes derived from such chemical oxidants, causing serious limitations in industrial applications.⁷



Therefore, development of an environmentally benign method has been highly needed.

* Author for correspondence. E-mail: yoshida@sbchem.kyoto-u.ac.jp.

[†] JST Innovation Plaza Kyoto.

[‡] Technology Laboratory, Nippon Chemicals Co., Ltd.

[§] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University.

(1) For examples: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For example: (a) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, 2000. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

(3) Lucas, H. J.; Kennedy, E. R. *Organic Syntheses*; Wiley & Sons: New York, 1943; Vol. 2, p 351.

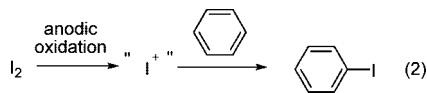
(4) Merkushev, E. B. *Synthesis* **1988**, 923.

(5) For recent examples: (a) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047. (b) Ghorbani-Vaghei, R. *Tetrahedron Lett.* **2003**, *44*, 7529. (c) Jereb, M.; Zupan, M.; Stavber, S. *Chem. Commun.* **2004**, 2614. (d) Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657. (e) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

(6) (a) Nitric acid: Dains, F. B.; Brewster, R. Q. *Organic Syntheses*; Wiley & Sons: New York, 1941; Vol. 1, p 323. (b) Periodic acid: Suzuki, H. *Organic Syntheses*; Wiley & Sons: New York, 1988; Vol. VI, p 700. (c) Peroxyacetic acid: Ogata, Y.; Nakajima, K. *Tetrahedron* **1964**, *20*, 2751. (d) Ogata, Y.; Aoki, K. *J. Am. Chem. Soc.* **1978**, *90*, 6187.

(7) In fact, various aromatic iodides are produced in industrial scales using chemical oxidants, and in those processes large amounts of wastes are produced.

The electrochemical methods^{8,9} have received significant research interest from both academia and industry¹⁰ because they serve as environmentally benign processes¹¹ for organic synthesis. It is particularly noteworthy that the electrochemical reactions serve as excellent methods for the generation of reactive species under mild conditions.¹² In the 1970s Miller and co-workers reported that the electrochemical oxidation of iodine gave "I⁺", which reacted with a wide range of aromatic compounds to give the corresponding aromatic iodides (eq 2).¹³



Recently, we reported that selective monoiodination of highly reactive aromatic compounds with the electrochemically generated "I⁺"¹⁴ could be achieved using extremely fast 1:1 mixing using a micromixer.¹⁵

With such information in hand, we initiated our study on a practical method of electrochemical iodination of aromatic compounds that is suitable for industrial production of aromatic iodides. Herein we report the results of this study.

Results and Discussion

The in Situ Method or the Sequential Method. Miller and co-workers reported that the sequential method involving anodic oxidation of I₂ to form reactive I⁺ followed by the addition of

an aromatic compound gave much a better yield of the corresponding aromatic iodide than the electrolysis of a mixture of I₂ and an aromatic compound (in situ method).¹³ This is presumably because of undesirable side reactions such as the side-chain oxidation caused by direct electron transfer from the aromatic compound.

The sequential method has another advantage over the in situ method. The polyiodination problem for highly reactive aromatic compounds based on disguised chemical selectivity¹⁶ could also be avoided by extremely fast 1:1 micromixing¹⁷ of a solution of preformed I⁺ and a solution of an aromatic compound.¹⁵

For these reasons, we decided to employ the one-pot sequential method for developing a practical electrochemical iodination of aromatic compounds.

Supporting Electrolyte/Solvent System. The choice of a supporting electrolyte/solvent system is very important for the success of the reaction because it determines the nature of a reactive intermediate generated by the electrolysis. The choice of a supporting/electrolyte system is also important from a practical point of view, such as cost, ease of product separation, and wastes.

Miller and co-workers reported that the use of LiClO₄/CH₃CN requires an excess amount of electricity (greater than 2.0 F/mol based on I₂) presumably because of the contamination of water in *anhydrous* LiClO₄. They also reported that the use of Et₄NClO₄/CH₃CN gave better results and that Bu₄NBF₄/CH₂Cl₂ could be also used for the oxidation of I₂.

Quaternary ammonium salts such as Bu₄NBF₄ are commonly used for laboratory electroorganic synthesis because of good solubility in organic solvents. However, the use of such quaternary ammonium salts is problematic from a viewpoint of industrial applications, because of high costs and difficulty in separation from products after electrolysis. Recovery and reuse of quaternary ammonium salts are also difficult.

Inorganic salts are usually much cheaper than quaternary ammonium salts. However, low solubility of inorganic salts in common organic solvents causes severe limitation in electroorganic synthesis. It is noteworthy that I₂ dissolves in organic solvents and that solubility of I₂ in water is very low.

Therefore, we initiated our study with searching for supporting electrolyte that is suitable for industrial applications. We focused on protic acids (HX) as supporting electrolyte, because reduction of proton is expected to serve as a good cathodic reaction as a counterpart of the anodic oxidation of I₂ as shown in Figure 2. I₂ loses two electrons at the anode to generate two I⁺. X⁻ that is derived from HX serves as a counteranion of I⁺. At the cathode two H⁺ that are derived from HX receive two electrons to generate H₂. Therefore, HX is expected to serve as both a proton source and supporting electrolyte.

Thus, the electrochemical oxidation reactions of I₂ (0.5 mmol) were carried out in CH₃CN using various protic acids as supporting electrolyte. An H-type divided cell (4G glass filter) equipped with a platinum plate anode (25 mm × 30 mm) and

- (8) (a) Lund, H.; Hammerich, O. *Organic Electrochemistry*, 4th ed.; Marcel Dekker: New York, 2001. (b) Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer: Berlin, 1984. (c) Fry, A. J. *Electroorganic Chemistry*, 2nd ed.; Wiley: New York, 2001. (d) Shono, T. *Electroorganic Synthesis*; Academic Press: London, 1990. (e) Little, R. D., Weinberg, N. L., Eds.; *Electroorganic Synthesis*; Marcel Dekker: New York, 1991. (f) Shono, T. In *The New Chemistry*; Hall, N., Ed; Cambridge University Press: Cambridge, 2000; p 55. (g) Grimshaw, J. *Electrochemical Reactions and Mechanisms in Organic Chemistry*; Elsevier: Amsterdam, 2000. (h) Sainsbury, M., Ed.; *Roddl's Chemistry of Carbon Compounds*; Elsevier: Amsterdam, 2002. (i) Torii, S. *Electroorganic Reduction Synthesis*; Kodansha: Tokyo, 2006; Vols. 1 and 2.
- (9) Selected reviews: (a) Schäfer, H. *J. Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 911. (b) Shono, T. *Tetrahedron* **1984**, *40*, 811. (c) Utley, J. *Chem. Soc. Rev.* **1997**, *26*, 157. (d) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (e) Lund, H. *J. Electrochem. Soc.* **2002**, *149*, S21. (f) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (g) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.
- (10) Industrial applications of electroorganic reactions. For examples: (a) Hoormann, D.; Kubon, C.; Jörissen, J.; Kröner, L.; Pütter, H. *J. Electroanal. Chem.* **2001**, *517*, 215. (b) Pletcher, D.; Walsh, F. C. *Industrial Electrochemistry*, 2nd ed.; Chapman and Hall: London, 1990. (c) Beck, F. *J. Appl. Electrochem.* **1972**, *2*, 59. (d) Baizer, M. M. *J. Appl. Electrochem.* **1980**, *10*, 285.
- (11) Mathews, M. A. *Pure Appl. Chem.* **2001**, *73*, 1305.
- (12) Recently we have developed a one-pot sequential method involving electrochemical generation of highly reactive organic cations followed by the reaction with a nucleophile (the cation-pool method). (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Yoshida, J.; Suga, S. *Chem. Eur. J.* **2002**, *8*, 2650. (d) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (e) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (f) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 6930. (g) Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (h) Suga, S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710.
- (13) (a) Miller, L. L.; Kujawa, E. P.; Compbell, C. B. *J. Am. Chem. Soc.* **1970**, *92*, 2821. (b) Miller, L. L.; Watkins, B. F. *J. Am. Chem. Soc.* **1976**, *98*, 1515.

(14) CSI-MS studies suggested that I⁺ is mainly existing as (CH₃CN)₂I⁺ and that CH₃CN is partially liberated to give CH₃CNI⁺. Hereafter, reactive iodine species generated by electrochemical oxidation is simply designated as I⁺ in this paper.

(15) Midorikawa, K.; Suga, S.; Yoshida, J. *Chem. Commun.* **2006**, 3794. (16) (a) Rys, P. *Acc. Chem. Res.* **1976**, *10*, 345. (b) Rys, P. *Angew. Chem., Int. Ed. Engl.* **1977**, *12*, 807.

(17) For example: (a) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (b) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (c) Yoshida, J.; Nagaki, A.; Iwasaki, T.; Suga, S. *Chem. Eng. Technol.* **2005**, *28*, 259.

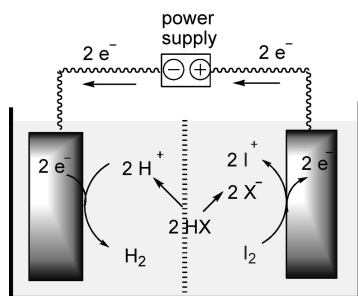


Figure 2. Schematic diagram of electrolysis of I_2 to generate I^+ using HX as supporting electrolyte and a proton source.

a platinum plate cathode (25 mm × 30 mm) was used, and the constant current electrolysis (20 mA) was conducted at 0 °C with magnetic stirring. The thus-generated solution of I^+ (2.0 F/mol of electricity based on I_2) in the anodic chamber was allowed to react with an excess amount of toluene (2.0 mmol) for 30 min at 0 °C, and the amount of iodotoluene was determined by GC.

As shown in Table 1, $C_6H_5SO_3H$, CF_3SO_3H , and H_2SO_4 were each found to be effective as supporting electrolyte, although the yield was not high. In the case of other protic acids such as CF_3CO_2H , CH_3SO_3H , and H_3PO_4 conductivity of the solution was very low and an appreciable amount of current did not flow. From an industrial point of view, we chose to use H_2SO_4 as a proton source and supporting electrolyte.

Other organic solvents such as CH_3OH and CH_3CO_2H were also examined using H_2SO_4 as supporting electrolyte. In CH_3OH , electric current flew smoothly, but only a small amount of iodotoluene was obtained, although the reason is not clear at present. In CH_3CO_2H an appreciable amount of current did not flow.

Concentration of Supporting Electrolyte. H_2SO_4 was found to be quite effective as supporting electrolyte. However, after the electrolysis, the amount of the cathodic solution increased as shown in Table 2. It is also important to note that the cathodic solution was colored. These observations indicate that I^+ generated at the anode moved to the cathodic chamber through the separator as a charge carrier (Figure 3). The dark brown color of the cathodic solution seemed to be attributed to I_2 , which is produced by electrochemical reduction of I^+ at the cathode. This undesirable phenomenon should be responsible for relatively low efficiency of the electrochemical generation and accumulation of I^+ .

To avoid the movement of I^+ as a charge carrier and to improve the efficiency of I^+ accumulation, an increase in the

Table 1. Electrochemical oxidation of I_2 using various protic acids as supporting electrolyte

supporting electrolyte ^a	solvent	% yield of iodotoluene ^b
Bu_4NBF_4	CH_3CN	78
CF_3CO_2H	CH_3CN	c
CH_3SO_3H	CH_3CN	c
$C_6H_5SO_3H$	CH_3CN	19
CF_3SO_3H	CH_3CN	46
H_3PO_4 ^d	CH_3CN	c
H_2SO_4	CH_3CN	56
H_2SO_4	CH_3OH	2
H_2SO_4	CH_3CO_2H	c

^a Reactions were carried out with 0.3 M of supporting electrolyte. ^b Determined by GC. ^c Conductivity of the solution was very low. ^d 85% aqueous solution.

Table 2. Effect of H_2SO_4 concentration on the efficiency of accumulation of I^+

H_2SO_4 concentration (M)	a picture of the cell after electrolysis anodic chamber (right) cathodic chamber (left)	% yield of iodotoluene
0.10		42
0.30		56
0.50		77
1.00		88
2.00		90

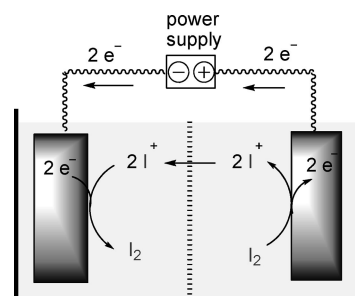


Figure 3. Schematic diagram of the movement of I^+ as a charge carrier and cathodic reduction of I^+ to generate I_2 .

concentration of H^+ should be effective. At much higher concentration of H^+ in comparison with that of I^+ , H^+ should become the major charge carrier. Based on this hypothesis, the effect of H_2SO_4 concentration was examined.

As shown in Table 2, an increase in the H₂SO₄ concentration causes a decrease in color intensity of the cathodic solution. At higher H₂SO₄ concentrations, the movement of I⁺ from the anodic chamber to the cathodic chamber seemed to be suppressed.

Iodination of Aromatic Compounds with Electrochemically Generated I⁺. Using the optimized electrolytic conditions (2.0 M H₂SO₄/CH₃CN), the reaction of electrochemically generated I⁺ with various aromatic compounds (1.0 equiv) were examined. The results are summarized in Table 3.

Alkylbenzenes such as toluene and cumene gave the corresponding monoiodination products in good yields as a mixture of para and ortho isomers. The present method can be applicable to biphenyl, and the corresponding monoiodination product was obtained in good yield. Disubstituted benzenes such as xylenes and methoxytoluenes also reacted to give the corresponding monoiodination products.

Control of Regioselectivity. As stated in the previous section, electrochemically generated I⁺ reacted with toluene to give iodotoluene in good yield. However, a mixture of para and ortho isomers was obtained, and the selectivity was not high. The regioselectivity should be improved from an industrial point of view. The regioselectivity strongly depends on the nature of I⁺. In fact, the selectivity for I⁺ generated in LiClO₄/CH₃CN system was para/ortho = 50/50 according to Miller's paper,¹³ whereas the selectivity for I⁺ generated in H₂SO₄/CH₃CN system was 57/43. Shono and co-workers reported that I⁺ generated in LiClO₄/HC(OMe)₃ system reacted with toluene to give *p*- and *o*-iodotoluenes in 70/30 ratio.¹⁸

To improve the regioselectivity, the use of an oxygen-containing compound that may coordinate I⁺ as a cosolvent was examined in the second step. Thus, a solution of I⁺ in CH₃CN (2.0 mL), which was electrochemically generated in H₂SO₄/CH₃CN was added to a cosolvent (1.6 mL) at 0 °C. After stirring at the same temperature for 30 min, the resulting solution was added dropwise to a solution of toluene in a cosolvent (0.4 mL) at 0 °C, and the mixture was stirred at the same temperature for 30 min.

It can be seen from Table 4 that the use of dimethoxyethane (DME) as a cosolvent gives rise to the best selectivity among the solvents examined. The two oxygen atoms of DME seem to coordinate I⁺ to make the iodinating species more bulky and less reactive, facilitating the reaction at the sterically less demanding para position, although the detailed mechanism is not clear at present.

Para/ortho selectivity increases with a decrease in the temperature as shown in Table 4. Using DME as a cosolvent, the para/ortho selectivity increased to 77/23 at -40 °C. However, this temperature is not suitable for industrial production. Therefore, we chose to carry out the reaction at 0 °C, because this temperature can be easily used in industrial production.

The reaction using DME as a cosolvent could be carried out in a gram scale.¹⁹ Thus, 3.06 g (12 mmol) of I₂ was electrochemically oxidized in 2.0 M H₂SO₄/CH₃CN (60 mL) under constant current conditions (100 mA, 2.0 F/mol) at 0 °C. DME (30 mL) was added to the resulting solution of I⁺. A

Table 3. Iodination of aromatic compounds with electrochemically generated I⁺ ^a

aromatic compound	product	% yield	isomer ratio
		88	57/43
		86	71/29
		90	86/14
		56	93/7
		72	93/7
		82	96/4
		87	83/17
		86	93/7
		69	-
		91	-
		92	-

^a I⁺ generated by anodic oxidation (2.0 F/mol) of I₂ (0.50 mmol) in 2.0 M H₂SO₄/CH₃CN was allowed to react with 1.0 mmol of an aromatic compound in CH₃CN at 0 °C for 30 min.

solution of toluene (2.23 g, 24 mmol) in 24 mL of DME was added, and the mixture was stirred at 0 °C for 0.5 h. After workup with water, extraction with hexane and ethyl acetate followed by removal of volatile materials under reduced pressure gave iodotoluene (4.47 g, 85% yield) as a mixture of para and ortho isomers (para/ortho = 73/27).






(18) Shono, T.; Matsumura, Y.; Katoh, S.; Ikeda, K.; Kamada, T. *Tetrahedron Lett.* **1989**, *30*, 1649.

Table 4. Effect of cosolvent in the iodination of toluene with electrochemically generated I^+ ^a

cosolvent	temperature (°C)	% yield of iodotoluene	para/ortho
none	0	90	57/43
HC(OCH ₃) ₃	0	79	64/36
C ₂ H ₅ OC ₂ H ₅	0	89	64/36
tetrahydrofuran	0	66	68/32
tetrahydropyran	0	72	69/31
dimethoxyethane (DME)	0	88	71/29
diethyleneglycol dimethyl ether	-40	77	77/23
tetraethyleneglycol dimethyl ether	0	83	70/30
1,4-dioxane	0	82	67/33
	0	90	66/34

^a Reactions were carried out with I^+ generated from 0.50 mmol of I_2 (2 F/mol of electricity based on I_2) and 2.0 mmol of toluene.

Table 5. Iodination of aromatic compounds with electrochemically generated I^+ using DME as cosolvent^a

aromatic compound	% yield of aromatic iodide	para/ortho
	88	71/29
	82	82/18
	85	91/9
	89	98/2
	82	97/3

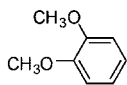
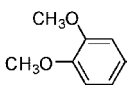
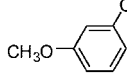
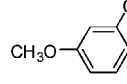
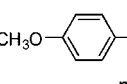
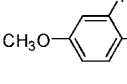
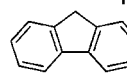
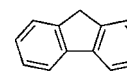
^a Reactions were carried out with I^+ generated from 0.5 mmol of I_2 (2 F/mol of electricity based on I_2) and 1.0 mmol of an aromatic compound.

It should be noted that the improvement of para/ortho selectivity by the use of DME as a cosolvent enabled easy recrystallization to obtain the para isomer in high purity. Recrystallization of the mixture obtained by the reaction (para/ortho = 71/29) from methanol led to significant improvement of para/ortho ratio (para/ortho = 95/5). The second recrystallization from methanol gave *p*-iodotoluene in high purity (para/ortho = 99/1) with acceptable yield (52% based on the initial mixture).

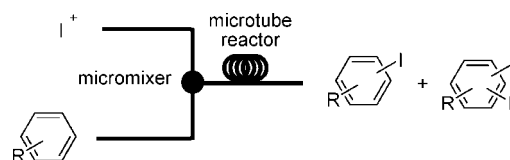
Iodination reactions of various aromatic compounds with electrochemically generated I^+ in CH₃CN using DME as cosolvent were examined. As summarized in Table 5, the para/ortho selectivity increased in all cases (see also Table 3).

Reactions of electrochemically generated I^+ with highly reactive aromatic compounds, such as dimethoxybenzenes, led to the formation of significant amounts of diiodo compounds as shown in Table 6. Monoiodo compounds should be less reactive than the parent compounds because the iodo group is an electron-withdrawing group. Therefore, the formation of the

Table 6. Iodination of electron-rich aromatic compounds with electrochemically generated I^+ ^a

aromatic compound	method	product % yield ^b
	macrobatch	38
	micro-flow	85
	macrobatch	24
	micro-flow	4
	macrobatch	29
	micro-flow	81
	macrobatch	26
	micro-flow	7
	macrobatch	36
	micro-flow	57
	macrobatch	29
	micro-flow	8
	macrobatch	49
	micro-flow	66
	macrobatch	17
	micro-flow	8

^a Reactions were carried out with I^+ generated from 0.5 mmol of I_2 (2 F/mol of electricity based on I_2) and 0.9 mmol of an aromatic compound. ^b Yields based on the aromatic compounds.

**Figure 4.** Microflow system for the reaction of electrochemically generated I^+ with electron-rich aromatic compounds.

diiodo compound is ascribed to disguised chemical selectivity.¹⁶ When a reaction is faster than mixing, the selectivity of the reaction is not determined by kinetics but by the manner of mixing, because it is not possible to obtain a homogeneous solution before a significant amount of reaction takes place in such cases. This problem can be solved using extremely fast 1:1 mixing using micromixers. Therefore, we examined the effect of 1:1 micromixing using a microflow system shown in Figure 4.

As shown in Table 6, the use of the microflow system gave rise to significant improvement of the selectivity for dimethoxybenzenes and fluorene. The corresponding monoiodo compounds were produced in high selectivity, whereas the reactions in a macrobatch reactor gave significant amounts of diiodo compounds.

Conclusions

It was found that the anodic oxidation of I_2 took place effectively in CH₃CN using H₂SO₄, which served as both

(19) Scaling-up of the electrochemical process. For examples: (a) Steckhan, E.; Arns, T.; Heineman, W. R.; Hilt, G.; Hoormann, D.; Jörissen, J.; Kröner, L.; Lewall, B.; Pütter, H. *Chemosphere* **2001**, *43*, 63. (b) Zollinger, D.; Griesbach, U.; Pütter, H.; Comminellis, C. *Electrochem. Commun.* **2004**, *6*, 600. See also Chapter 31 of ref 8a. See also ref 10.

supporting electrolyte and a proton source for cathodic generation of H₂. The thus-generated I⁺ species reacted with various aromatic compounds to give the corresponding aromatic iodides. It was also found that para/ortho selectivity could be improved using DME as a cosolvent in the iodination step. The use of the cosolvent enabled the synthesis of *p*-iodotoluene in high purity after recrystallization. For highly reactive aromatic compounds, diiodination takes place even if I⁺ and the aromatic compound were allowed to react in 1:1 molar ratio. This problem could be solved by extremely fast 1:1 mixing using a micromixer. These observations indicate that iodination of aromatic compounds using the electrochemically generated I⁺ (the sequential method) serves as an efficient and practical method for industrial production of a wide range of aromatic iodides. Further studies on improvement and scaling-up of the process are currently in progress.

Experimental Section

General Remarks. GC analysis was performed on a Shimadzu GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Varian Gemini 2000 (¹H 300 MHz, ¹³C 75 MHz), Varian Mercury plus-400 (¹H 400 MHz, ¹³C 100 MHz). HPLC analysis was carried out with Hitachi High-Technologies LaChrom Elite equipped with a diode-array detector using a reversed phase packed column (Cosmosil Cholesterol Φ 4.6 mm × 150 + 10 mm). The mobile phase was a mixture of acetonitrile and water (50:50 v/v). Thin-layer chromatography (TLC) was carried out by using Whatman precoated silica gel F₂₅₄ plates (thickness 0.25 mm). Flash chromatography was carried out on a column of silica gel (Nacalai, Silica Gel 60, spherical, neutral, 150–325 mesh). All reactions were carried out under N₂ atmosphere unless otherwise noted.

Materials. Bu₄NBF₄ was purchased from TCI, and dried at 50 °C/mmHg overnight before use. Methanesulfonic acid, trifluoromethanesulfonic acid (TfOH), acetic acid, benzenesulfonic acid monohydrate, trifluoroacetic acid, and H₂SO₄ were purchased from Wako, and were used without purification. Dehydrated grade of acetonitrile (CH₃CN) and methanol were purchased from Wako, and were used as obtained. Diethyleneglycol dimethyl ether, and dimethoxyethane (DME) were purchased from Wako, were distilled from metal sodium, and were stored over sodium metal.

Dehydrated grade of toluene was purchased from Nacalai and was used without purification. Ethylbenzene was purchased from Kishida and was used without purification. Phenol, anisole biphenyl, *o*-xylene, *m*-xylene, *p*-methoxytoluene, and 1,3-dimethoxybenzene were purchased from Wako and were used without purification. Cumene, *p*-xylene, *o*-methoxytoluene, 1,2-dimethoxybenzene, 1,4-dimethoxybenzene, and fluorene were purchased from TCI and were used without purification.

General Procedure for Optimization of Reaction Conditions of Electrochemical Generation and Accumulation of I⁺. The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a platinum plate anode (25 mm × 30 mm) and a platinum plate cathode (25 mm × 30 mm). In the anodic chamber were placed I₂ (127 mg, 0.5 mmol) and a solution of a supporting electrolyte in acetonitrile (10 mL).

In the cathodic chamber was placed a solution of a supporting electrolyte in acetonitrile (10 mL). The constant current electrolysis (20 mA) was carried out at 0 °C with magnetic stirring until 2.00 F/mol of electricity was consumed. The anodic solution was added to a solution of toluene (184 mg, 2.0 mmol) in CH₃CN (4 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The amount of iodotoluene produced was determined by GC analysis using decane as an internal standard.

General Procedure for Iodination of Aromatic Compounds with Electrochemically Generated I⁺ in H₂SO₄/CH₃CN. The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a platinum plate anode (25 mm × 30 mm) and a platinum plate cathode (25 mm × 30 mm). In the anodic chamber were placed I₂ (127 mg, 0.5 mmol) and a solution of H₂SO₄ (2.0 M) in acetonitrile (10 mL). In the cathodic chamber was placed a solution of H₂SO₄ (2.0 M) in acetonitrile (10 mL). The constant current electrolysis (20 mA) was carried out at 0 °C with magnetic stirring until 2.00 F/mol of electricity was consumed. The anodic solution was added to a solution of an aromatic compound (1.0 mmol) in CH₃CN (4 mL, cooled at 0 °C). After being stirred at 0 °C for 30 min, the reaction mixture was neutralized by aq NaOH solution and was diluted with ether. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and were dried over MgSO₄. After filtration, the solvent was removed under reduced pressure.

1-Iodo-2-methylbenzene (*o*-iodotoluene),²⁰ 1-iodo-4-methylbenzene (*p*-iodotoluene),²⁰ 1-iodo-4-ethylbenzene,²¹ 1-iodo-4-isopropylbenzene,²² 2-iodophenol,²³ 4-iodophenol,²⁴ 1-iodo-2-methoxybenzene,²⁰ 1-iodo-4-methoxybenzene,²⁰ 2-iodobiphenyl,²⁵ 4-iodobiphenyl,²⁴ 4-iodo-1,2-dimethylbenzene,²⁰ 1-iodo-2,4-dimethylbenzene,²⁰ 2-iodo-1,3-dimethylbenzene,²⁶ 2-iodo-1,4-dimethylbenzene,²⁷ 4-iodo-1-methoxy-2-methylbenzene,²⁷ 2-iodo-1-methoxy-4-methylbenzene,²⁷ 4-iodo-1,2-dimethoxybenzene,²⁸ 4,5-diiodo-1,2-dimethoxybenzene,²⁸ 4-iodo-1,3-dimethoxybenzene,²⁸ 4,6-diiodo-1,3-dimethoxybenzene,²⁸ 2-iodo-1,4-dimethoxybenzene,²⁸ 2,5-diiodo-1,4-dimethoxybenzene,²⁸ 2-iodofluorene,²⁹ and 2,7-diiodofluorene²⁰ were identified by comparison of their spectral data with those reported in the literature. 1-Iodo-2-ethylbenzene, 1-iodo-2-isopropylbenzene, 1-iodo-2,3-dimethylbenzene are also known compounds^{13,23} and were identified as a mixture with the corresponding regioisomers by NMR analysis.

General Procedure for Iodination of Aromatic Compounds with Electrochemically Generated I⁺ in H₂SO₄/

- (20) Spectral Database for Organic Compounds (SDBS); National Institute of Advanced Industrial Science and Technology (AIST): Japan.
- (21) Abe, T.; Yamaji, T.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2175.
- (22) Bachkil, A.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5139.
- (23) Kitagawa, H.; Shibata, T.; Matsuo, J.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 229.
- (24) Branytska, O. V.; Neumann, R. *J. Org. Chem.* **2003**, *68*, 9510.
- (25) Dektar, J. L.; Hacker, N. P. *J. Org. Chem.* **1990**, *55*, 639.
- (26) Fujihara, H.; Chiu, J.-J.; Furukawa, N. *J. Am. Chem. Soc.* **1988**, *110*, 1280.
- (27) Wan, S.; Wang, S. R.; Lu, W. *J. Org. Chem.* **2006**, *71*, 4349.
- (28) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. *Synthesis* **1995**, 1273.
- (29) Kajigeshi, S.; Kakinami, T.; Mokiwaki, M.; Tanaka, T.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 439.

CH₃CN Using DME as Cosolvent. The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a platinum plate anode (25 mm × 30 mm) and a platinum plate cathode (25 mm × 30 mm). In the anodic chamber were placed I₂ (3.06 g, 12.1 mmol) and a solution of H₂SO₄ (2.0 M) in acetonitrile (60 mL). In the cathodic chamber was placed a solution of H₂SO₄ (2.0 M) in acetonitrile (60 mL). The constant current electrolysis (100 mA) was carried out at 0 °C with magnetic stirring until 2.00 F/mol of electricity was consumed.

The anodic solution was added to 1,2-dimethoxyethane (DME) (30 mL) at 0 °C. The resulting mixture was added to a solution of toluene (2.23 g, 24.2 mmol) in DME (30 mL, cooled at 0 °C). After being stirred at 0 °C for 30 min, the reaction mixture was neutralized by aq NaOH solution (3 N, 80 mL) and was diluted with hexane (150 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (150 mL × 2). The combined organic extracts were washed with brine and were dried over MgSO₄. After filtration, the solvent was removed under reduced pressure to give iodotoluene (4.47 g, 85%, para/ortho = 73/27).

General Procedure for Iodination of Aromatic Compounds with Electrochemically Generated I⁺ Using a Microflow System. A solution of an aromatic compound (0.909 mmol) in CH₃CN (10 mL) and the I⁺ solution (10 mL, cooled

at 0 °C), electrochemically generated from I₂ (127 mg, 0.500 mmol), were introduced into a T-shaped micromixer (Φ 250 μm) using syringe pumps (flow rate is 6.0 mL/min) at 0 °C. The mixture was allowed to react in a microtube reactor (Φ 250 μm × 2 m). The outlet solution was introduced in water (40 mL) at 0 °C. The reaction mixture was neutralized by 2 N aq NaOH (20 mL) and was diluted with ether. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine and were dried over MgSO₄. After filtration, the solvent was removed under reduced pressure to give a crude product. Yields of products were determined by HPLC analysis.

Acknowledgment

This research has been carried out as the project entitled “Development of environmentally benign electrochemical process for production of functional organoiodine compounds” under the contract of Japan Science and Technology Agency (JST), Kyoto University, and Nippon Chemicals Co., Ltd.

Received for review June 29, 2008.

OP800155M