Sulfonic Acid Based Cation-Exchange Resin: A Novel Proton Source for One-Pot Diazotization–Iodination of Aromatic Amines in Water

Victor D. Filimonov,*[a] Nadya I. Semenischeva,[a] Elena A. Krasnokutskaya,[a] Alexei N. Tretyakov,[a] Ho Yun Hwang,[b] Ki-Whan Chi*[b]

[a] Department of Organic Chemistry, Tomsk Polytechnic University, 634050 Tomsk, Russia
Fax +7(3822)563637; E-mail: filimonov@tpu.ru

[b] Department of Chemistry, University of Ulsan, 680-749 Ulsan, Republic of Korea
E-mail: kwchi@ulsan.ac.kr

Abstract: A convenient and simple one-pot method for the preparation of iodoarenes at room temperature has been developed, by sequential diazotization–iodination of aromatic amines with $NaNO_2$/KI in the presence of a sulfonic acid based cation-exchange resin in water. This inexpensive, noncorrosive and eco-friendly synthetic route is general in nature and allows for the preparation of iodoarenes with an electron-donating or -withdrawing group in various positions from the corresponding amines in 50–98% yields.

Key words: iodoarenes, aromatic amines, diazotization, potassium iodide, sodium nitrite, cation-exchange resin

Iodoaromatic compounds are useful synthetic building blocks in organic synthesis. They are valuable, versatile synthetic intermediates and have wide applications in medicine and biochemistry.[1,2] One of the first and most commonly used methods for the preparation of iodoarenes is the substitution of a diazo group by iodine (often called the Sandmeyer reaction).[3] The fundamental advantage of this reaction, over other methods involving direct electrophilic iodination of aromatic compounds, is the selective introduction of iodine into a specific position of the aromatic ring, whereas direct electrophilic iodination frequently gives a mixture of isomers.

The process of diazotization–iodination is usually carried out with sodium nitrite at low temperature in two steps: diazotization of the amine in aqueous hydrochloric or sulfuric acid and a subsequent reaction with iodine and KI, sometimes in the presence of copper salts.[3] As an alternative to these traditional methods, more expensive methods involving alkyl nitrites in the presence of diiodomethane or other sources of iodine have been reported.[4] Recently, a one-pot method for introducing iodine into an aromatic substrate was suggested which involves a sequence including diazotization-iodination of the corresponding amines with HI/KNO_2 in DMSO or $KI/NaNO_2$/PTSA in acetonitrile.[5] These one-pot methods, however, require organic solvents as a reaction medium.

We discovered that diazotization–iodination reactions easily and successfully proceed at room temperature in

aqueous medium if sulfonic acid based resins are used as an acid source. The reaction proceeds in two stages in the one-pot method: firstly, amines **1–11** are diazotized by mixing with $NaNO_2$ and cation-exchange resins[6] for 25–420 min, then KI is sequentially added to the resulting mixture followed by continuous stirring for 50–600 minutes (Scheme 1).
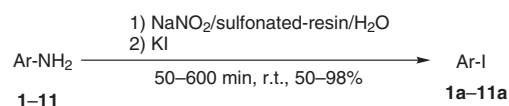
Scheme 1 Diazotization–iodination of aromatic amines

The advantages of this new synthetic method also include monitoring simplicity: at the first stage the diazotization proceeds till the starting amines disappear as verified by TLC, and the iodination stage is carried out until the reaction mixture reveals a negative result with the β-naphthol test. This reaction can be applied to a wide range of amines with either electron-donating or -withdrawing substituents in various positions in relation to the amino group. There is no clear dependence between electronic properties or position of substituents and reaction rate along with yields of iodorenes. For example, *para*-isomers of nitroaniline **1** and aminobenzoic acid **7** provide higher yields of iodorenes than *ortho*-isomers **2** and **8**, although for the *para*-isomer **7**, the iodination stage takes more time than **8**. On the other hand, 4-iodoaniline (**4**) reacts more slowly than the *ortho*-isomer **5** and provides much less iodoarene **4a**. A slow reaction rate in the diazotization stage was clearly observed with 2,4,6-trichloroaniline (**9**) which has two *ortho*-substituents. It is likely that the results of the reactions studied are influenced by a number of factors – amine basicity, water solubility, reagent diffusion rate into the polymeric matrix, product diffusion rate from the polymeric matrix, strength of interaction between starting arylammonium (and/or formed aryldiazonium) cations, and the polymeric matrix.

Reactions with all the studied amines proceeded smoothly at room temperature except for 4-methoxyaniline (**6**). Diazotization–iodination of **6** was successful only at 7–10 °C. Higher temperatures decreased the yield of 4-iodoanisole (**6a**) due to resinification and a high degree of volatility of **6a**.

Although water is safer, more convenient, and meets the 'Green Chemistry' requirements as a reaction medium, we also studied the possibility of using organic solvents such as DMSO and acetonitrile in this diazotization–iodination method. We found out that in these organic solvents, in contrast to aqueous medium, the diazotization stage for amines **1–11** proceeds with low conversion of the starting amines. This may be attributed to the hydrophilic nature of the cation-exchange resins used and their nonswelling ability in aprotic media.

Another attempt at carrying out the diazotization–iodination in water with cation-exchange resins in one stage, that is, with simultaneous treatment of NaNO$_2$ and KI, was in vain. During this procedure, we observed the release of elemental iodine and the formation of product mixtures with an incomplete conversion of the starting amines.

The yields of iodoarenes **1a–11a** obtained by the developed method can be compared with the results of traditional diazotization-iodination methods,[7] although the reactions proceed at a slower rate due to the polymeric nature of the acidic agent (Table 1). After iodination was completed, providing products **1a–11a**, the sulfonic acid-based resin could be recycled without any significant loss

in reactivity by washing with acetone, water, and then treating with aqueous hydrochloric acid.

It should be noted that the aryldiazonium cations, ArN$_2^+$, prepared at the first stage have strong interactions with the polymeric resin matrix and the salts can be isolated by filtration. For example, after the diazotization stage the polymer-supported diazonium salt of amine **1** was filtered, washed with water, and then allowed to stand open at room temperature for nine days. After this period of time, the salt reacts with KI in an aqueous solution to give 4-iodonitrobenzene (**1a**) in a 71% yield, which is only a little less than that obtained under normal one-pot conditions (Table 1).

Previously, diazonium salts supported on sulfonic resins were obtained via the ion exchange of preliminarily synthesized aryldiazonium chlorides, ArN$_2^+$Cl$^-$, with the sodium form of sulfonic resin (Amberlyst A-15), and also revealed high storage stability and reactivity in obtaining an azo dye library.[9]

In summary, we have demonstrated for the first time that, in the presence of sulfonic acid based cation-exchange resins, diazotization of aromatic amines successfully proceeds at room temperature in water. The resulting diazo-

Table 1 The Diazotization–Iodination of Aromatic Amines **1–11** with NaNO$_2$ and Cation-Exchange Resins in Water at Room Temperature

Molar ratio of reagents Substrate:NaNO$_2$:KI[a] (mmol)	Substrate	Reaction time (min) Diazotization/Iodination	Product	Yield (%)[b]	Mp (°C)
1:2:2.5	4-NO$_2$C$_6$H$_4$NH$_2$ **1**	25/65	4-NO$_2$C$_6$H$_4$I **1a**	81	172–173 (171–173)[c]
1:2:2.5	2-NO$_2$C$_6$H$_4$NH$_2$ **2**	30/60	2-NO$_2$C$_6$H$_4$I **2a**	71	52-53 (49–51)[c]
1:2:2.5	4-MeCOC$_6$H$_4$NH$_2$ **3**	40/50	4-MeCOC$_6$H$_4$I **3a**	75	84–85 (82–84)[c]
1:2:2.5	4-IC$_6$H$_4$NH$_2$ **4**	55/300	1,4-I$_2$C$_6$H$_4$ **4a**	50	128–129 (131–133)[c]
1:2:2.5	2-IC$_6$H$_4$NH$_2$ **5**	45/95	1,2-I$_2$C$_6$H$_4$ **5a**	90	oil (oil)[c]
1:2:2.5[d]	4-MeOC$_6$H$_4$NH$_2$ **6**	40/60	4-MeOC$_6$H$_4$I **6a**	61	51–52 (50–53)[c]
1:2:2.5	4-NH$_2$C$_6$H$_4$CO$_2$H **7**	140/600	4-IC$_6$H$_4$CO$_2$H **7a**	98	269–270 (270–273)[c]
1: 2: 2.5	2-NH$_2$C$_6$H$_4$CO$_2$H **8**	180/190	2-IC$_6$H$_4$CO$_2$H **8a**	65	161–162 (160–162)[c]
1:2:2.5	2,4,6-Cl$_3$C$_6$H$_2$NH$_2$ **9**	420/100	2,4,6-Cl$_3$C$_6$H$_2$I **9a**	53	50–51 (53–54)[5b]
1:4:2.5	4-CNC$_6$H$_4$NH$_2$ **10**	100/80	4-CNC$_6$H$_4$I **10a**	56	125–127 (124–128)[c]
1:2:2.5	4-PhC$_6$H$_4$NH$_2$ **11**	100/85	4-PhC$_6$H$_4$I **11a**	50	112–113 (110–114)[c]

[a] An amount of 5 g of cation-exchange resin was used with 2 mmol of the substrate.
[b] Yield of isolated product.
[c] Reference 8.
[d] The reaction proceeded at 7–10 °C.

nium salts are generally stable and readily react with KI to form iodoarenes in moderate to high yields. This new method has a number of advantages over traditional diazotization–iodination methods with sodium nitrite. These advantages include the use of water as solvent, strong acid-free conditions, mild reactions at room temperature, ease of separation of the intermediates and products from the reaction mixture, and the possibility of recycling the resins.

Commercially available reagents and solvents were used as received without further purification. Column chromatography was performed using silica gel 60 (40–60 μm mesh). Merck silica gel 60 F_{254} aluminum sheets were used for analytical TLC. ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$ on a Bruker AC 300 MHz spectrometer. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Commercially available sulfonic acid-based cation-exchange resins KU-2-8 (Russia) and Trilite SPC-160H (South Korea) with exchange capacity of 4.9–5.1 mg equiv/g were treated in the following way for subsequent reactions.

Cation Exchange Resins
KU-2-8 Resin: At first the resin (200 g) was allowed to swell in sat. aq NaCl (250 mL). Then, the crude cation exchange resin KU-2-8 in the Na-form (200 g) was treated with aq 5% NaOH (250 mL) for 3–4 h with frequent shaking. Treatment with a 5% solution of NaOH was repeated until the color of the solution faded. After the alkaline treatment, the cation exchange resin was washed with 10 volumes of distilled H$_2$O and then aq HCl: first, 5 volumes of a 5% solution, then 5 volumes of a 10% solution, and finally, by a 15% solution until the complete absence of ferrous ions in the solution (test by ammonium thiocyanate). After the acid treatment, the cation exchange resin was thoroughly washed with distilled H$_2$O until the pH reached 6–7 in order to remove traces of acid. Finally, the processed cation exchange resin was collected by filtration and dried in the open air.

Trilite SPC-160H Resin: The cation exchange resin Trilite SPC-160H (South Korea) in H-form was washed with distilled H$_2$O until the pH reached 6–7.

Iodoarenes 1a–11a; General Procedure
The respective aromatic amine **1–11** (2.0 mmol) was added to the cation-exchange resin (5.0 g) in H$_2$O (50 mL). After stirring for 10 min, NaNO$_2$ (4.0 mmol, 0.276 g) was added to the mixture. Then, the mixture was stirred for the time specified in Table 1, and the process was accompanied by the substrate dissolution. The reaction was followed by monitoring the complete disappearance of starting aromatic amine by TLC. Then, KI (5.0 mmol, 0.830 g) was added to the mixture and stirred for the time specified in Table 1. The reaction was monitored by the β-naphthol color test. The formation of iodoarene precipitates was observed in most reactions. After the iodination was complete, the reaction mixture was treated with aq 10% Na$_2$SO$_3$ (15 mL). The solid products and cation-exchange resins were filtered and washed with H$_2$O, and then treated with acetone (10 mL). To this acetone solution was added H$_2$O to precipitate the iodoarene products, which were then collected by filtration and dried. In the case of liquid products, the mixture extracted with Et$_2$O (3 × 15 mL) and worked up in the usual way. All the products were characterized by comparison of melting points with the literature values (Table 1).

References

(1) (a) Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2001**, *42*, 2949. (b) Soderberg, B. C. *Coord. Chem. Rev.* **2004**, *248*, 1085. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (e) Guiry, P.; Kiely, D. *Curr. Org. Chem.* **2004**, *8*, 781. (f) Prajapati, D.; Gohain, M. *Tetrahedron* **2004**, *60*, 815. (g) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086. (h) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613.

(2) (a) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269. (b) Yu, S.-B.; Watson, A. D. *Chem. Rev.* **1999**, *99*, 2353.

(3) (a) *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, **1978**. (b) Godovikova, T. I.; Rakitin, O. A.; Khmelnitskii, L. I. *Russ. Chem. Rev.* **1983**, *52*, 440. (c) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(4) (a) Friedman, L.; Chlebowsky, J. F. *J. Org. Chem.* **1968**, *33*, 1636. (b) Smith, W. B.; Ho, O. C. *J. Org. Chem.* **1990**, *55*, 2543.

(5) (a) Baik, W.; Luan, W.; Lee, H. J.; Yoon, C. H.; Koo, S.; Kim, B. H. *Can. J. Chem.* **2005**, *83*, 213.
(b) Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis* **2007**, 81.

(6) KU-2-8 (Russia) and Trilite SPC-160H (South Korea) were used as cation-exchange resins. No significant difference was found in the result of reactions with these two resins.

(7) Previous reaction conditions and yields: **1a**: *tert*-BuSNO$_2$/KI/C$_6$H$_6$, 80%;^{10} NaNO$_2$/HBF$_4$/KI/DMSO, 90%;^{11} NaNO$_2$/HBF$_4$/Me$_3$SiI/MeI, 91%;^{12} *i*-C$_5$H$_{11}$NO$_2$/CH$_2$I$_2$, 90%;^{13} NO$_2$ (liq)/NaI/MeCN/–20 °C, 98%;^{14} *i*-C$_5$H$_{11}$NO$_2$/*o*-benzene-disulfonimide/Bu$_4$NI/MeCN, 92%;^{15} NaNO$_2$/KI/MeCN, 82%.^{5b} **2a**: KNO$_2$/HI/DMSO, 89%;^{5a} NaNO$_2$/KI/MeCN, 81%.^{5b} **7a**: NO$_2$ (liq)/anhyd KI, 100% (potentially explosive!).^{16} **8a**: NaNO$_2$/HCl/KI, 67%;^{17} NaNO$_2$/KI/MeCN, 50%.^{5b} **9a**: NaNO$_2$/KI/MeCN, 80%.^{5b}

(8) *Aldrich Handbook of Fine Chemicals and Laboratory Equipment*; Aldrich: Milwaukee, **2006-2007**.

(9) Merrington, J.; James, M.; Bradley, M. *Chem. Commun.* **2002**, 140.

(10) Oae, S.; Shinhama, K.; Kim, Y. H. *Chem. Lett.* **1979**, 939.

(11) Citterio, A.; Arnoldi, A. *Synth. Commun.* **1981**, *11*, 639.

(12) Keumi, T.; Umeda, T.; Inoue, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 89.

(13) Smith, W. B.; Ho, O. C. *J. Org. Chem.* **1990**, *50*, 2543.

(14) Suzuki, H.; Nonoyama, N. *Tetrahedron Lett.* **1998**, *39*, 4533.

(15) Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *J. Org. Chem.* **1999**, *64*, 3448.

(16) Kaupp, G.; Herrmann, A.; Schmeyers, J. *Chem. Eur. J.* **2002**, *8*, 1395.

(17) Tietze, L. F.; Eicher, T. *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*; Thieme-Verlag: Stuttgart, **1991**.