A Green Procedure for the Diazotization–Iodination of Aromatic Amines under Aqueous, Strong-Acid-Free Conditions

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Abstract: A convenient and mild one-pot method for the synthesis of iodoarenes in high yields by the sequential diazotization–iodination of aromatic amines with a reusable polymeric diazotization agent in the presence of *p*-toluenesulfonic acid at room temperature in water was developed. The method is general and is the greenest alternative of the known diazotization–iodination methods. The method is also effective for the preparation of 1*H*-benzo[*d*][1,2,3]triazole and benzo[*d*][1,2,3]thiadiazole.

Key words: diazotization, halogenation, iodination, heterocycles, amines

Aromatic iodides are versatile reagents that can be converted into a wide variety of materials.[1] Many iodoarenes are biologically active molecules that are used in medicine and biochemistry.[2] Although significant developments have been achieved in the synthesis of iodoarenes, their preparation via direct iodination has some limitations.[3] Direct electrophilic iodination is often carried out under harsh reaction conditions in the presence of toxic oxidants and frequently gives a mixture of isomers due to the lack of regioselectivity for this reaction. Since aromatic amines are generally available, most methods for the preparation of substituted aromatic iodides have focused on improving the diazotization–iodination reaction.

Usually diazotization–iodination of aromatic amines is carried out in two steps by means of sodium nitrite in a strongly acidic medium (H_2SO_4, HCl) at low temperature or by means of alkyl nitrites in organic solvents[4] followed by reaction with iodine or potassium iodide, often in the presence of copper salts. Both of these approaches to the diazotization step do not meet the requirements of green chemistry for the following reasons. First, the use of sodium nitrite as the diazotizing agent is almost always accompanied by the release of nitrogen oxides, an issue particularly with industrial-scale reactions. Second, the isolation of iodination products from strongly acidic solution requires a neutralization stage, which generates large quantities of salts. In addition, a strongly acidic environment for the diazotization cannot be tolerated by amines containing acid-sensitive functional groups. The alternative reagents, alkyl nitrites, are not very suitable for diazotization on an industrial scale, since they are expensive, decompose during storage, and are corrosive. Moreover, alkyl nitrites generally can diazotize aromatic amines only in organic solvents (e.g., Et_2O, MeCN, THF), but not in water. It should also be taken into account that diazonium salts obtained under classical conditions are potentially explosive substances.

Little work on the diazotization of aromatic amines in a weakly acidic medium using nontoxic, nonflammable, and explosive-free conditions has been reported. Tundo et al.[5] reported a diazotization–iodination with sodium nitrite and potassium iodide in a liquid carbon dioxide/water solvent system at 65 bar for a small number of anilines; however, in some of the cases, diazotization was accompanied by the formation of triazenes and biphenyls. A convenient and rapid method for the synthesis of iodoarenes in good yields has recently been developed; it involves the sequential diazotization–iodination of aromatic amines with sodium nitrite, solid silica sulfuric acid, and potassium iodide by grinding in a mortar.[6] This method proved to be applicable to various aromatic amines, but the grinding of the reaction components in a mortar cannot presently be implemented on a large scale, and the diazotization stage was accompanied by the release of nitrogen oxides, as is common with other diazotization conditions using sodium nitrite.

Recently we have shown that a sulfonic cation-exchange resin, *p*-toluenesulfonic acid (*p*-TsOH), or sodium hydrogensulfate are mildly acidic agents for the diazotization–halogenation of aromatic amines with sodium nitrite or *tert*-butyl nitrite in acetonitrile, water, or water pastes.[7] However, the use of sodium nitrite or alkyl nitrite in these methods makes the release of gaseous nitrogen oxides difficult to avoid, and the above-mentioned problems with scaling up the process would still be an issue. Thus, the development of a new method to circumvent these problems is necessary.

We have also recently shown that anion-exchange resins saturated with nitrite ions from sodium nitrite are convenient and mild polymer-supported diazotization reagents (‘Resin NO_2^-’) for the synthesis of stable arenediazonium tosylates from aromatic amines and *p*-toluenesulfonic acid in acetic acid.[8] A similar polymer-supported reagent has been used to generate a few arenediazonium chlorides

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in aqueous hydrogen chloride.[9] 'Resin NO_2^-' is readily obtained and is stable to storage at room temperature in a moist state for at least one month (see experimental section). Until now, this reagent has not been used for the diazotization of aromatic amines in water or for one-pot diazotization–iodination reactions.

We have found that simply stirring 'Resin NO_2^-' with the aromatic amines **1–13** in water in the presence of *p*-toluenesulfonic acid at room temperature for 20–30 minutes leads to complete conversion of the starting amines (Scheme 1, Table 1). In these reactions, the release of nitrogen oxides or other gaseous substances was never observed. After filtration of the resin, a pure and stable aqueous solution of the corresponding arenediazonium tosylate ($ArN_2^+TsO^-$) was obtained.[10] Next, potassium iodide was added to the solution, and the solution was stirred at room temperature for the period of time specified in Table 1. After the addition of potassium iodide, nitrogen bubbling was immediately observed, and aryl iodides **1a–13a** precipitated from the water.

$$\underset{\mathbf{1\text{–}13}}{ArNH_3} \xrightarrow{\substack{\text{1) 'Resin } NO_2^-\text{', } p\text{-TsOH, } H_2O\text{, r.t.} \\ \text{2) KI, r.t.}}} \underset{\mathbf{1a\text{–}13a}}{ArI} + N_2$$

Scheme 1 Preparation of aryl iodides **1a–13a** by the aqueous, one-pot diazotization–iodination method

Table 1 Diazotization–Iodination of Aromatic Amines **1–13** by Using the Polymeric Diazotization Agent 'Resin NO_2^-'[a]

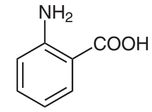
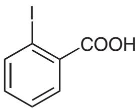
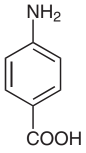
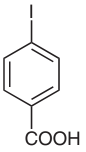
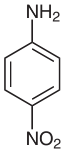
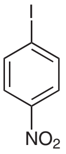
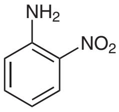
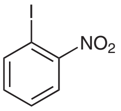
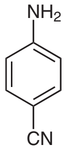
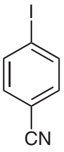
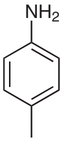
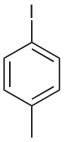
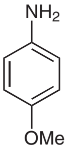
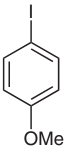
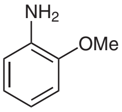
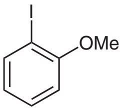
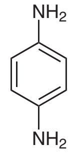
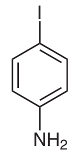
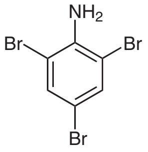
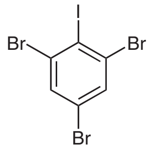
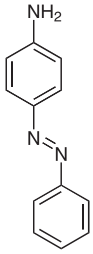
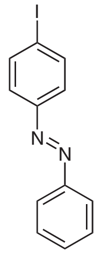
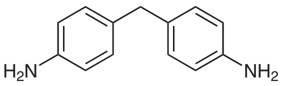
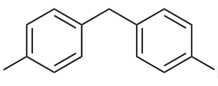
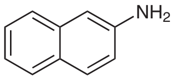
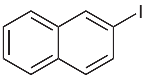
Aromatic amine		Time (min)	Product		Yield (%)	Mp (°C)
1		300	**1a**		74 (50[b])	161–163 (162)[11]
2		270	**2a**		85 (52[b])	266–268 (270)[11]
3		90	**3a**		95 (89[a])	170 (171)[11]
4		90	**4a**		91	52 (52–53)[7a]
5		90	**5a**		88	122–124 (124–128)[14]
6		75	**6a**		91	oil
7		70	**7a**		91	53–55 (52)[11]
8		75	**8a**		94	oil

Table 1 Diazotization–Iodination of Aromatic Amines **1**–**13** by Using the Polymeric Diazotization Agent 'Resin NO$_2^-$'[a] (continued)

Aromatic amine		Time (min)	Product		Yield (%)	Mp (°C)
9		90	**9a**		98	64 (63–65)[15]
10		120	**10a**		81	103–104 (104–105)[16]
11		60	**11a**		55	88–90 (89–90)[17]
12		120	**12a**		80	92–94 (93–94)[12]
13		90	**13a**		84	52–54 (53)[11]

[a] Reaction conditions: 1. Amine **1**–**13** (1 equiv), 'Resin NO$_2^-$' (2 equiv), *p*-TsOH (3 equiv), H_2O, 20 °C; 2. KI (2.5 equiv), 20 °C.

[b] Reactions in the presence of HCl instead of *p*-TsOH.

An optimal ratio of reactants was found to be aromatic substrate/'Resin NO$_2^-$'/KI/*p*-TsOH = 1:2:2.5:3. The solid products **3a**, **4a**, **5a**, and **9a**–**13a** were easily filtered from the aqueous medium, then washed with water, and dried. For isolation of the oily products **1a**, **2a**, **6a**, **7a**, and **8a**, ethyl acetate was used for extraction. Analysis of the water reaction solutes by gas chromatography and thin-layer chromatography did not show phenolic compounds, triazenes, or biphenyls as possible side products. The running of both stages of the diazotization–iodination process was very easy to control. Thus, thin-layer chromatography was a convenient method for determining the end of the first stage of the diazotization reaction, because the disappearance of the starting amine spot could be observed. The iodination step was carried out until the intermediate diazonium tosylate was exhausted; this was simply determined by the negative probe with b-naphthol.

It is important to note that the solid aryl iodides **3a**, **4a**, **5a**, and **9a**–**13a** have fairly high NMR and GC-MS purity and can be used in further reactions without additional purification; i.e., in these cases, the use of organic solvents was not necessary in any stage of the diazotization iodination process. This approach would be especially suitable for combinatorial chemistry.

After the diazotization reaction, the filtered resin was washed with acetone and alkaline solution and could be reused for the preparation of 'Resin NO$_2^-$'. The diazotization activity of this recycled 'Resin NO$_2^-$' did not decrease after at least three cycles of regeneration.

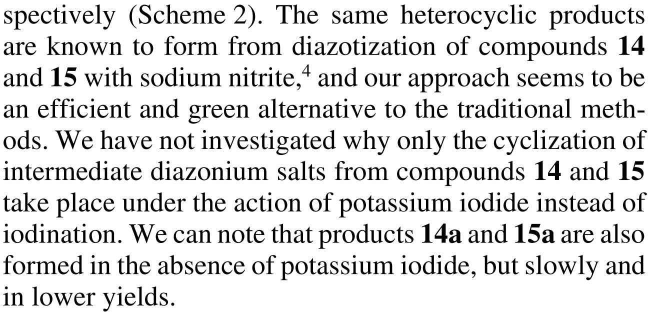
Another advantage of this method is its relative safety, since it uses aqueous solutions of arenediazonium tosylates, which have been shown to be stable even in the dry state.[8]

It should be noted that performing a single-step diazotization–iodination reaction of aromatic amines with 'Resin NO$_2^-$' and *p*-toluenesulfonic acid in the presence of potassium iodide in water leads to incomplete conversions of the starting amines and the formation of iodine and gaseous products. This is presumably due to active diazotizating intermediates (probably HNO_2, NO^+, or TsONO) being partially consumed in the oxidation of iodide ion to iodine.

Typically, the diazotization–iodination reactions were run with two mmol of starting amine, but in the case of 4-aminobenzonitrile (**5**), scaling up to six mmol did not reduce the yield of 4-iodobenzonitrile (**5a**).

The procedure proved to be applicable to aromatic amines of various structures **1**–**13**, both strongly and weakly basic, polycyclic, and also sterically crowded (tribromoaniline **10**) amines; i.e., the method is generally applicable (for exceptions, see below). In general, we did not observe any clear correlations between reaction time, electronic and steric effects of substituents on the aromatic ring, and aryl iodide yield (Table 1). This occurrence is rather common for the reactivity of aromatic arenediazonium salts in which substituents often produce opposing effects at different stages of the reaction mechanism.[4] Yields of isolated iodoarenes were good or excellent, except for 4-iodoazobenzene **11a** (Table 1). Although we cannot yet fully explain this exception, part of the starting 4-aminoazobenzene probably interacts with the 'Resin NO_2^-' in the diazotization step and/or gives water-soluble byproducts.

In the case of *o*-phenylenediamine (**14**) and *o*-sulfanylaniline (**15**), the diazotization reaction with 'Resin NO_2^-' in water and subsequent reaction with potassium iodide provides only the cyclization products, 1*H*-benzo[*d*][1,2,3]triazole (**14a**) and benzo[*d*][1,2,3]thiadiazole (**15a**), which were isolated in yields of 97% and 96%, respectively (Scheme 2). The same heterocyclic products are known to form from diazotization of compounds **14** and **15** with sodium nitrite,[4] and our approach seems to be an efficient and green alternative to the traditional methods. We have not investigated why only the cyclization of intermediate diazonium salts from compounds **14** and **15** take place under the action of potassium iodide instead of iodination. We can note that products **14a** and **15a** are also formed in the absence of potassium iodide, but slowly and in lower yields.



Scheme 2 Preparation of 1*H*-benzo[*d*][1,2,3]triazole (**14a**) and benzo[*d*][1,2,3]thiadiazole (**15a**) by diazotization with 'Resin NO_2^-'

It is important to note that only the combination of the polymer diazotizing agent 'Resin NO_2^-' and *p*-toluenesulfonic acid provides the above results. Thus, the use of sodium nitrite instead of 'Resin NO_2^-' in the presence of *p*-toluenesulfonic acid leads to an appreciable release of nitrogen oxides during the process of diazotization of anilines **1**–**15**. On the other hand, the diazotization of aromatic amines **1**–**3** by 'Resin NO_2^-' in the presence of hydrogen chloride instead of *p*-toluenesulfonic acid requires at least 10–11 equivalents of hydrogen chloride for complete conversion of the starting amines and provides lower yields of the iodinated products **1a**–**3a** in the subsequent reaction with potassium iodide (see Table 1).

In conclusion, we have developed an efficient and experimentally simple one-pot method for the diazotization–iodination of aromatic amines that utilizes the polymeric diazotization reagent 'Resin NO_2^-' in the presence of *p*-toluenesulfonic acid in water at room temperature. The resulting water solutes of arenediazonium tosylates gently react with potassium iodide to provide pure iodoarenes, which do not need further purification. In the case of *o*-phenylenediamine and *o*-thioaniline, the products benzotriazole and benzothiadiazole form in excellent yields. In general, this method, which features the use of a weakly acidic, aqueous medium, is run at room temperature, is characterized by ease of isolation of sufficiently pure products and the absence of side products, and allows recycling of the diazotization reagent, meets the requirements of a green chemistry process when compared with other known diazotization–iodination methods.

All starting reagents were ACS grade and were employed without further purification. Melting points were determined with a Boetius melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 instrument. GC-MS spectra were obtained on an Agilent 7890/5975C instrument.

Polymeric Diazotization Reagent 'Resin NO_2^-'

Anion-exchange resin AV-17-8 (Russia) or Amberlist A26 (Aldrich) (3.5 g) was added to a soln of $NaNO_2$ (2.07 g, 30 mmol) in H_2O (30 mL). The mixture was stirred at r.t. for 10 min. 'Resin NO_2^-' was filtered and washed with H_2O until the pH of the filtrate became neutral. The ion-exchange capacity of prepared samples of 'Resin NO_2^-' was 2.6–3.6 mmol of NO_2^-/g and did not decrease during storage in a moist state for at least one month.

Diazotization–Iodination of Aromatic Amines 1–13; General Procedure

'Resin NO_2^-' (2.3 g, 6 mmol of NO_2^-) was added to a soln of *p*-TsOH·H_2O (1.14 g, 6 mmol) in H_2O (5 mL), and the reaction mixture was stirred for 1–2 min. Then aromatic amine **1**–**13** (2 mmol) was slowly added, the reaction mixture was stirred for 20–30 min at r.t. until disappearance of the starting amine (by TLC), and the resin was removed by filtration. Next, KI (0.83 g, 5 mmol) was added to the resulting aqueous soln, and stirring was continued until N_2 bubble evolution ceased, for the period of time specified in Table 1. The aqueous soln was decolorized with Na_2SO_3. Solid products (**3a**, **4a**, **5a**, **9a**–**13a**) were filtered, washed with H_2O, and dried. Oily products (**1a**, **2a**, **6a**, **7a**, **8a**) were extracted with EtOAc (3 × 15 mL), and the organic layer was washed with H_2O (3 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo; this afforded the corresponding iodoarenes.

4-Iodobenzoic Acid (2a)

Yield: 85%; mp 266–268 °C (Lit.[11] 270 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.94 (d, J = 7.8 Hz, 2 H), 7.81 (d, J = 7.8 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.8, 130.0, 128.1, 99.4.

Bis(4-iodophenyl)methane (12a)

Yield: 80%; mp 92–94 °C (Lit.[12] 93–94 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.60 (d, J = 7.8 Hz, 4 H), 6.91 (d, J = 7.8 Hz, 4 H), 3.87 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.2, 137.7, 131.2, 91.9, 41.0.

1*H*-Benzo[*d*][1,2,3]triazole (14a) and Benzo[*d*][1,2,3]thiadiazole (15a)

'Resin NO_2^-' (2.3 g, 6 mmol of NO_2^-) was added to a soln of *p*-TsOH·H_2O (1.14 g, 6 mmol) in H_2O (5 mL), and the reaction mixture was stirred for 1–2 min. Then aromatic amine **14** or **15** (2 mmol) was slowly added, the reaction mixture was stirred for 30 min at r.t. until disappearance of the starting amine (by TLC), and the resin was removed by filtration. Next, KI (0.83 g, 5 mmol) was added to the resulting aqueous soln, and stirring was continued for 15 min. The aqueous soln was decolorized with Na_2SO_3 and extracted with CH_2Cl_2 (3×15 mL), the organic layer was washed with H_2O (3×10 mL) and dried ($MgSO_4$), and the solvent was evaporated in vacuo; this afforded the corresponding product **14a** or **15a**.

1*H*-Benzo[*d*][1,2,3]triazole (14a)
Yield: 97%; mp 95–97 °C (Lit.[13a] 98 °C).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.21 (d, *J* = 7.8 Hz, 2 H), 7.61 (d, *J* = 7.8 Hz, 2 H), 8.24 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 138.09, 121.71, 115.31.

Benzo[*d*][1,2,3]thiadiazole (15a)
Yield: 96%; mp 35 °C (Lit.[13b] 35 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (m, 2 H), 7.94 (d, *J* = 6.0 Hz, 1 H), 8.47 (d, *J* = 9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.84, 126.52, 123.37, 118.82.

MS: *m/z* (%) = 136 (100), 108 (80), 82 (60), 69 (51).

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