SELEETIVE IODODEAMINATION OF ELECTRON-DEFICIENT ANILINES USING TASK-SPECIFIC NITRITE- AND IODIDE-BASED IONIC LIQUIDS

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GRAPHICAL ABSTRACT

Abstract  A convenient and rapid method for the synthesis of aryliodides via the sequential diazotization–iodination of electron-deficient anilines using IL-ONO/[bmim]I is described. IL-ONO and [bmim]I were used as a nitrosonium source for diazotization of anilines and as a iodide ion source for subsequent iodination respectively. Electron-deficient anilines were efficiently and selectively iododeaminated in the presence of other anilines in good to excellent yields. This reaction can be regarded as a new method for the preparation of synthetically and pharmaceutically important iodoarens. Selectively iododeamination of electron-poor anilines in the presence of electron-rich anilines is one of the synthetically important advantages of this new method.

Keywords  Arylamine; aryliodide; iodide ionic liquid; iododeamination; nitrite ionic liquid

INTRODUCTION

Ionic liquids (ILs) have some particular properties, such as wide liquid range, undetectable vapor pressure, and ease of recovery and reuse. Because of these
properties, ILs have attracted chemists’ interest and these compounds have been used increasingly in synthetic organic chemistry.\[1\] In advanced ionic liquid research, task-specific ionic liquids (TSILs) have been used as solvents, reagents, and/or catalysts.\[2\]

Aromatic iodides are valuable and versatile synthetic intermediates and are used increasingly in synthetic organic chemistry, especially for carbon–carbon bond formation.\[3\] Many aryl iodides are also biologically active compounds and are used as drugs or diagnostic aids.\[4\] Some aryl iodides are used as x-ray contrast agents or radioactively labeled markers in radioimmunoassay.\[5\] Although many reports have been published about the synthesis of iodoarenes, preparation of these compounds via direct iodination has some limitations. For example, only electron-rich aromatics can be directly iodinated via electrophilic substitution reaction because iodine is a weaker electrophile in comparison to bromine and chlorine.\[6\] For electron-poor aromatics, direct electrophilic iodination is carried out under harsh reaction conditions.\[7\] Because of the lack of regioselectivity of this reaction, electrophilic iodination reaction usually gives a mixture of isomers. The Sandmeyer reaction can be a useful procedure for the preparation of aromatic iodides, which sometimes is carried out in the presence of copper salts.\[8\] As alternative methods, reports involving alkyl nitrites in the presence of diiodomethane or other sources of iodine have been published.\[9\] Furthermore, one-pot methods for the sequential diazotization–iodination of amines have been reported.\[10\] Chi et al. reported the diazotization of aryl amines at room temperature in water-paste form with NaNO₂ and p-TsOH followed by treatment with KI.\[11\] When KI was added together with NaNO₂, a complex product mixture was produced with much lower yields of aryl iodides in their reported method. Recently we reported the synthesis of azo dyes using task-specific nitrite ionic liquids (TSILs) in synthetic organic chemistry.\[12\] In continuation of our interest in using task-specific ionic liquids in synthetic organic chemistry,\[13\] we report here a convenient and rapid one-pot method for the iododeamination of electron-deficient anilines. The sequential diazotization–iodination takes place in the presence of nitrite- and iodide-based ionic liquids under mild conditions (Scheme 1).

RESULTS AND DISCUSSION

As a typical experiment, 4-nitroaniline (10 mmol) was added into a vessel containing 37% HCl (3 eq) and mixed thoroughly in an ice bath. While mixing, a
solution of IL-ONO (0.5 mL) in water (2 mL) was added dropwise for a few minutes. Formation of the corresponding diazonium salt was verified using the color test with 2-naphthol. The progress of the diazotization reaction was monitored by thin-layer chromatography (TLC), and mixing was continued until disappearance of 4-nitroaniline. Next, [bmim]I (0.5 mL) was added to the mixture, the reaction temperature was slowly increased up to 45 °C, and mixing was continued for 1 h. The iodination reaction began immediately by increasing the reaction temperature, and the evolution of nitrogen gas was observed. This one-pot diazotization–iodination process takes 70 min to complete. Product 2a was isolated in 80% yield under these conditions. With the encouraging initial result, optimization of the reaction conditions was studied using various combinations of the reactants under different conditions (Table 1). It was found that the best yield of the product were obtained using 2/3 molar ratios of 4-nitroaniline/IL-ONO in the presence of HCl (20 mol %) at 60 °C in aqueous media. Despite alkyl nitrites, which generally can diazotize aromatic amines only in organic solvents (e.g., Et2O, MeCN, tetrahydrofuran [THF]), nitrite ionic liquid (IL-ONO) diazotize these compounds in water. When the reaction was finished, cold distilled water (5 mL) was added gradually, and the reaction mixture was extracted with ethylacetate (3 × 5 mL). The extract was evaporated in vacuo and the aromatic iodides were purified by flash chromatography (n-hexane–EtOAc, 7:1). At the end of the reaction, ionic liquids, [bmim]Cl and IL-OH, were extracted from the mixture into cool aqueous solution. We also studied the effect of the organic solvents such as MeCN, EtOH, CH2Cl2, THF, and dimethylformamide (DMF) on these reactions. Use of these solvents under the optimized conditions led to much lower yields of the expected iodoarenes whereas the yields of phenol by-products were greater. We also examined this process in water at reflux conditions and the result is shown in Table 1 (Table 1, entry 6).

The scope of this methodology was further extended by reaction of various arylamines under optimal conditions. Various highly deactivated anilines were smoothly transformed to iodoarenes in good to excellent yields (Table 2). However, electron-rich anilines were only led to the related diazonium salts and the iodination step of

| Entry | Solvent | HCl (mol%) | Iodination step | Temperature (°C) | Time (min) | Product 2b yield (%) |
|-------|---------|------------|----------------|------------------|------------|----------------------|
| 1     | H2O     | 10         |                 | 45               | 45         | 68                   |
| 2     | H2O     | 15         |                 | 45               | 45         | 70                   |
| 3     | H2O     | 20         |                 | 45               | 45         | 75                   |
| 4     | H2O     | 20         |                 | 55               | 60         | 78                   |
| 5     | H2O     | 20         |                 | 60               | 60         | 80                   |
| 6     | H2O     | 20         | Reflux          | 60               | 60         | 80                   |
| 7     | CH2Cl2  | 20         | Reflux          | 60               | <20        | <20                  |
| 8     | DMF     | 20         | Reflux          | 60               | <25        | <25                  |
| 9     | EtOH    | 20         | Reflux          | 60               | <25        | <25                  |
| 10    | CH3CN   | 20         | Reflux          | 60               | <25        | <25                  |

*Isolated yields.*
the procedure was not accrued for these compounds under different conditions. Formation of the diazonium salt from the reaction of electron-rich anilines in this process was confirmed by addition of 1-naphthoxide to the reaction mixture and isolation of the prepared azo dye. We examined the reaction of the mixture (1 : 1) of 4-nitroaniline and 4-methylaniline in this procedure and only 4-nitroiodobenzene was isolated as iodinated product. Examination of some electron-donor substituted anilines (such as 4-OMe, 4-OH, 4-OEt, and 2-OMe) showed that these anilines were not converted to the related iodo arenes under the described reaction conditions. These results show that electron-poor anilines were selectively converted to relative iodo arenes in this process. Probably electron-withdrawing substituent in diazonium salt facilitated the replacement of N₂ with iodide ion.

A wide range of electron-deficient aryl iodides can be successfully synthesized via this new one-pot method starting from the corresponding aryl amines (Table 2). All of products (2a – s) were characterized by their spectroscopic data (FT-IR, ¹H and ¹³C NMR), elemental analysis, and comparison of their melting point with reported melting points in literature. We conducted these reactions on a 20-mmol scale and found that they underwent a smooth transformation to the iodoarenes in good yields. For example, up to 40 mmol of 4-nitroaniline (1b) could be converted into 4-nitroiodobenzene (2b) without any loss of efficiency. Thus, the present procedure is amenable for scaling up.

A plausible mechanism for the iododeamination of electron-deficient arylamines in the present research is shown in Scheme 2. In the first step, nitrosonium ion is resulted from the reaction of IL-ONO with HCl 37%. Intermediate 2 was generated from the reaction of aniline with nitrosonium ion. Then via the two

| Table 2. Diazotization-iodination of aromatic amines 1a – s using iodide-based and nitrite ionic liquid |
| --- |
| Entry | Substrate (1a – s) | Reaction time (min) | Product (2a – s) | Yield * (%) |
| 1 | Aniline | 180 | — | — |
| 2 | 4-NO₂-aniline | 60 | 4-NO₂-iodobenzene | 80 |
| 3 | 3-Cl-aniline | 180 | 3-Cl-iodobenzene | 15 |
| 4 | 2,6-Diethylaniline | 180 | — | — |
| 5 | 4-Cyanylaniline | 65 | 4-Cyanoiodobenzene | 78 |
| 6 | 4-Aminoacetophenone | 70 | 4-Iodoacetophenone | 80 |
| 7 | 4-Aminobenzophenone | 75 | 4-Iodobenzophenone | 82 |
| 8 | 4-Aminobenzoic acid | 65 | 4-Iodobenzoic acid | 84 |
| 9 | 2-Methylaniline | — | — | — |
| 10 | 4-OMe-aniline | 180 | — | — |
| 11 | 2-Aminobenzoic acid | 80 | 2-Iodobenzoic acid | 81 |
| 12 | 2,4,6-Cl₃C₆H₂NH₂ | 120 | 2,4,6-Cl₃C₆H₂I | 35 |
| 13 | 4-Ph-aniline | 180 | — | — |
| 14 | 2-Chloro-3-aminopyridine | 120 | 2-Chloro-3-iodopyridine | 79 |
| 15 | 3-Aminopyridine | 75 | 3-Iodopyridine | 75 |
| 16 | 4-NH₂C₆H₄C₆H₄-4-NH₂ | 180 | — | — |
| 17 | 2,4-(NO₂)₂-aniline | 60 | 2,4-(NO₂)₂-iodobenzene | 86 |
| 18 | 2,4,6-I₃-aniline | 150 | 2,4,6-I₃-iodobenzene | 38 |
| 19 | 2-I-aniline | 180 | — | — |

* Yield of isolated product.
successive rearrangements, diazonium salt (compound 3) is formed. In the last step, the N₂ group in diazonium salt is replaced with iodide ion to produce the related aryl iodide product (compound 4).

In summary, we have developed an efficient and experimentally simple method for the selective iododeamination of electron-deficient arylamines using IL-ONO/[bmim]I. The resulting diazonium salts at 5 °C are stable and react rapidly with iodide anion to produce aryl iodides at 60 °C in good to excellent yields. IL-ONO and [bmim]I play the role of nitrosonium and iodode anion sources respectively. This reaction can be regarded as a new method for the preparation of synthetically and pharmaceutically important iodoarens, and the use of organic solvents was not necessary in any stage of the diazotization iodination process. Selective iododeamination of electron-poor anilines in the presence of electron-rich anilines is one of the synthetically important advantages of this new method.

EXPERIMENTAL

1-(4-Nitritobutyl)-3-methylimidazolium chloride was prepared according the literature. All other reagents were purchased from Merck and used without further purification. Infrared spectra were recorded in KBr and were determined on a Perkin-Elmer FT-IR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance AC, 400 and 300 MHz, using CDCl₃ as a deuterated solvent and TMS as an internal standard. All melting points are uncorrected and measured in open glass-capillaries using a Stuart melting-point apparatus.
Typical Procedure for Iododeamination of Arylamines Using Nitrite- and Iodide-Based Ionic Liquids

The aniline derivative (20 mmol) was dissolved in 37% HCl (20 mol%) and stirred thoroughly at 0–5 °C for 5 min. While stirring the mixture, IL-ONO (30 mmol) was added over 5 min. The diazonium salt product was assayed by well-known azo-coupling reaction with naphthalene. For the iodination reaction, [bmim]I (0.5 mL) was added, the temperature of the reaction mixture was increased slowly up to 60 °C, and the mixture was stirred for the times shown in Table 1. After completion of the reaction, the mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layer was washed with a 10% aqueous Na2SO3 solution and then dried over anhydrous Na2SO4. The extracts were concentrated on a rotary evaporator and the crude mixture was purified by recrystallization or by flash chromatography using a 1:7 ethyl acetate/n-hexane mixture as eluent to give pure products 2a–t, which were characterized by their (IR,1H and13C NMR) spectra and comparison of their melting points with melting points reported in the literature.

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SUPPORTING INFORMATION

FT-IR and 1H and 13C NMR spectral data for this article can be accessed on the publisher’s website.

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