

A Simple and Effective Protocol for One-Pot Diazotization-Iodination of Aromatic Amines by Acidic Ionic Liquid [H-NMP]HSO₄ at Room Temperature

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ABSTRACT: A simple and efficient one-pot method for the preparation of aromatic iodides has been developed by sequential diazotization–iodination of aromatic amines employing sodium nitrite and sodium iodide in the presence of acidic ionic liquid *N*-methyl-2-pyrrolidonium hydrosulfate ([H-NMP]HSO₄). The diazonium salts that are formed by this ionic liquid are stable at room temperature and react rapidly with sodium iodide to produce aryl iodides in moderate to good yields. The mild reaction conditions, straightforward procedure, inexpensive and green method make these transformations superior to the reported

KEY WORDS: Iodoarenes, Aromatic amines, Diazotization, Sodium iodide, Sodium nitrite, Acidic ionic liquid.

INTRODUCTION

Aromatic iodides are widely used in organic synthesis [1,2]. In addition to using iodoaromatic compounds in classic chemistry, these building blocks are useful in modern organic synthesis. They are important synthetic intermediates and can be functionalized readily through C–C bond formation via cross-coupling reactions and have wide applications in medicine and biochemistry [3,4]. Some aryl iodides can be used as X-ray contrast agents or radioactively-labeled markers in radioimmunoassay [5]. Number methods have been suggested for introducing iodine into an aromatic substrate. Some of these methodologies illustrate the direct iodination of aromatic compounds [6-9] and others involves a sequence

including diazotization-iodination of the corresponding amines with the various sources for diazotization of aryl amines and iodide ion such as NaNO₂ /sulfonated-resin /KI in H₂O [10], NaNO₂ /PTSA /KI in water–paste form [11], NaNO₂ /silica sulfuric acid /KI in solvent-free conditions [12]. Direct iodination has some limitations such as weak electrophilicity of molecular iodine [13] and giving a mixture of isomers due to the lack of regioselectivity of this reaction. Replacement of the diazonium group of arenediazonium salts by iodine is one of the usual and effective methods for the preparation of aromatic iodides (the Sandmeyer reaction) [14,15]. The process of diazotization-iodination is usually carried out

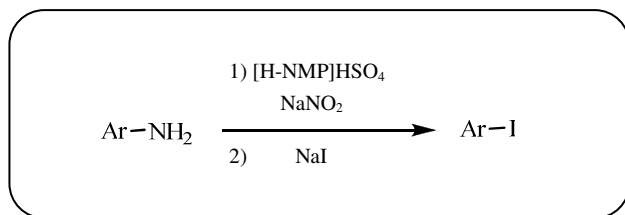
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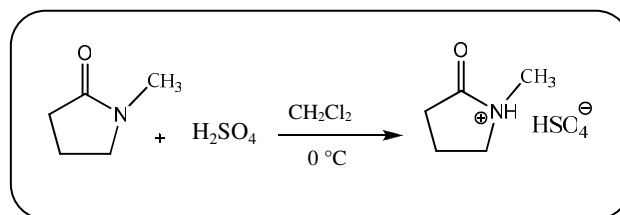
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7/\$/2.70



Scheme 1



Scheme 2

with sodium nitrite at low temperatures in two steps: diazotization of the amine in hydrochloric or sulfuric acid and a subsequent reaction with iodine ion, sometimes in the presence of copper salts [14,15]. Some diazotization methodologies are harsh and involve use of strong inorganic acids. Development of quick, inexpensive, widely applicable, and environmentally green iodinating agents is therefore still an active area of research.

Ionic Liquids (ILs), and particularly room-temperature ILs, have gained wide popularity in recent years, and many new applications of these compounds as reaction media for a wide variety of synthetic processes have been reported [16]. Brønsted acidic ILs are important class of ionic liquids and form by the transfer of a proton between a Brønsted acid and a Brønsted bases. The key property of these ILs is their Brønsted acidity, and much research has been conducted into this [17, 18]. They have been used as catalysts and/or media instead of inorganic acids in many conventional synthetic reactions. Since the most organic compounds can dissolve in ionic liquids, acidic ILs can be used both as reaction medium and solvent [16].

In continuation of our effort to develop efficient methods in organic synthesis [19-22], we are also interested in the applications of functionalized acidic ionic liquids in organic reactions [23,26] and in this paper we show that diazotization-iodination reactions easily and successfully proceed at room temperature in the presence of acidic ionic liquid *N*-methyl-2-pyrrolidonium hydrosulfate ([H-NMP] HSO₄) as a novel and mild proton source for diazotization of aromatic amines (Scheme 1). Diazotization process was easily carried out by grinding of appropriate aryl amine, acidic ionic liquid and NaNO₂ in the presence of little water and at room temperature and there is no need to maintain a low temperature. The mild reaction conditions make these transformations superior to the previous reported.

EXPERIMENTAL SECTION

Melting points measured with a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT-IR-680 PLUS spectrometer. The ¹H NMR spectra were recorded on a Bruker 500 MHz spectrometer at 500 MHz with chemical shift (δ) values reported in ppm relative to an internal standard (Me₄Si).

Preparation of acidic ionic liquid

In a 25-mL round bottom flask a mixture containing 0.97 mL (10 mmol) of 1-Methyl-2-pyrrolidone in dichloromethane (15 mL) was cooled in an ice bath and while stirring. Then 0.53 mL of sulfuric acid 98% (10 mmol) was added dropwise to the reaction mixture within 10 min and was stirred for 4 h at room temperature. The dichloromethane was removed under reduced pressure using a rotary evaporator and product was dried at 70 °C under vacuum for 30 min in a vacuum oven. FT-IR (KBr, cm⁻¹): 2300–3600, 1660, 1509, 1302, 1114, 962, 610 cm⁻¹. ¹H NMR (500 MHz, D₂O): δ 1.4 (2H, m, CH₂), 1.8 (2H, t, CH₂), 2.2 (3H, s, CH₃), 2.9 (2H, t, CH₂). ¹³C NMR (500 MHz, D₂O): δ 22.22 (CH₂), 35.09 (CH₂), 42.10–43.51 (CH₂, CH₃), 180 (C=O) ppm.

General procedure for preparation of aryl iodides

An aromatic amine (1 mmol) was ground with acidic ionic liquid (4 mmol, 0.79 g) and 1 ml of water in an mortar for a few minutes. The NaNO₂ (2.5 mmol, 0.175 g), was added to the reaction mixture and was ground 15-20 min with periodic grinding using a pestle. Then, NaI (2.5 mmol, 0.375 g) was added to the diazonium salt, and grinding continued for 5-10 min until gas evolution was completely stopped. The iodination reaction began immediately after NaI addition, and the reaction mixture volume increased due to the evolution of nitrogen gas. This one-pot diazotization-iodination process takes 20-30 min to complete. The product was extracted with

EtOAc (3 × 12 mL) and the combined organic layers were washed with a 10% aq Na₂SO₅ solution and then dried with Na₂SO₄. The solvent was evaporated to afford the product and if necessary, was purified by recrystallization or via column chromatography (ethyl acetate- cyclohexane 1:5). Selected spectral data are given below for representative products.

1,4-Diiodobenzene (Table 1, Entry 6)

mp 124–126 °C (lit. mp 128–130 °C [12]), ¹H NMR (500 MHz, CDCl₃): δ 7.44 (4H, s) ppm. IR (KBr, cm⁻¹): 2922, 1624, 1461, 994, 799.

1-Cyano-4-iodobenzene (Table 1, Entry 4)

mp 124–126 °C (lit. mp 123–125 °C [12]), ¹H NMR (500 MHz, CDCl₃): δ 7.83 (2H, d, J = 8.45 Hz), 7.35 (2H, d, J = 8.44 Hz) ppm. IR (KBr, cm⁻¹): 2959, 2226, 1721, 1577, 1474, 818, 699.

4-Iodoacetophenone (Table 1, Entry 9):

mp 74–76 °C (lit. mp 82–84 °C [12]), ¹H NMR (500 MHz, CDCl₃): δ 7.86 (2H, d, J = 8.53 Hz), 7.69 (2H, d, J = 8.53 Hz), 2.6 (3H, s) ppm. IR (KBr, cm⁻¹): 2926, 1669, 1581, 1389, 1057, 819, 604.

4-Iodobenzophenone (Table 1, Entry 10)

mp 98–100 °C (lit. mp 99–101 °C [12]), ¹H NMR (500 MHz, CDCl₃): δ 7.88 (2H, d, J = 8.54 Hz), 7.8 (2H, d, J = 8.3 Hz), 7.6 (1H, m), 7.55 (2H, d, J = 8.43 Hz), 7.52 (2H, t, J = 7.83 Hz) ppm. IR (KBr, cm⁻¹): 3035, 2920, 1605, 1578, 1285, 1107, 1005, 927, 851, 817, 744, 660.

RESULTS AND DISCUSSION

We have developed a new and efficient method for the diazotization–iodination sequential process in the presence of acidic ionic liquid [H-NMP] HSO₄ as mild acidic agent and solvent. This ionic liquid was employed successfully for the synthesis of various aryl diazonium salts starting from the corresponding aryl amines. The prepared aryl diazonium salts were stable and transformed in good yields to aryl iodides in the presence of iodide ion (Table 1). The reactions were accomplished at room temperature without phenol formation as by-product in aqueous media. The optimal molar ratio for amine/sodium nitrite/[H-NMP]HSO₄ and NaI was found to be 1: 2.5 : 4 : 2.5 in general. Our diazotization-iodination

method is safe and the grinding of these aryldiazonium salts in a mortar is not hazardous under laboratory conditions. When sodium iodide was added together with sodium nitrite, obtained mixture of products and lower yields of the expected aryl iodides, therefore NaI was added after formation of corresponding diazonium salt. The reaction mixture becomes more dilute in the presence of water. Therefore, water plays co-solvent role in this reaction and helps to the better interaction of the reaction components.

The present protocol was compared with the some procedures reported in the literatures and the results have been shown in Table 2. The most important advantages of this diazotization-iodination method are mild and strong acid-free conditions, availability, simplicity, short reaction times and good yields. The Brønsted acidic IL [H-NMP]HSO₄ has been used as reagent and solvent in this work, and promoted the diazotization/iodination process successfully. This IL is inexpensive and available. Because of using excess NaNO₂ and NaI in the reaction mixture and formation of the some by-product, reusability of IL was not examined.

We also studied the stability of the intermediates aryldiazonium salts prepared using [H-NMP]HSO₄ and found that keeping of them at room temperature for long time (4 days) led to lower yields of aryl iodide, however, any decrease in yields was not observed by storing these compounds under aqueous conditions at 0 °C temperature for long period (a week).

CONCLUSIONS

We have developed a novel and simple method for preparing aromatic iodides. The sequential diazotization–iodination takes place in the presence of acidic ionic liquid [H-NMP] HSO₄ as a mild and new proton source. The produced diazonium salts are stable and react rapidly with sodium iodide to produce aryl iodides in moderate to good yields.

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Table 1: Synthesis of aryl iodides from aryl amines in the presence of $[H-NMP]HSO_4$ at room temperature^a.

Entry	Substrate	Product	Yield (%)
1			80
2			80
3			85
4			75
5			70
6			81
7			80
8			50
9			60
10			80

^a The products were characterized from their spectral (IR, ¹H NMR).

Table 2: Comparison of the results for the preparation of 2-Iodonitrobenzene (Table 1, entry 3) through the various procedures in the literatures including the sequential diazotization-Iodination of the aromatic amines (2mmol) with the various sources for diazotization and iodide ion.

Entry	Reaction Conditions	Yield (%)	[Ref.]
1	NaNO ₂ / <i>p</i> -TsOH /KI in water-paste form (5: 6: 5 molar ratio), r.t, 20–30 min	72	[11]
2	NaNO ₂ /sulfonated-resin in H ₂ O /KI (4 mmol: 5 g: 5 mmol), r.t, 90 min	71	[10]
3	NaNO ₂ /NaHSO ₄ /KI, aqueous paste (5: 6: 5 molar ratio), 18–20°C, 20–30 min	68	[27]
4	NaNO ₂ / <i>p</i> -TsOH /KI in acetonitrile (5: 6: 5 molar ratio), r.t, 20–30 min	81	[8]
5	Present work	85	-

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