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Research note

Green and efficient diazotization-iodination of aryl amines using cellulose sulfuric acid as a biodegradable and recyclable proton source under solvent-free condition

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Abstract This article describes simple and efficient method for the diazotization and iodination of different aromatic amines over cellulose sulfuric acid, sodium nitrite and potassium iodide under solvent-free conditions at room temperature. Various aryl amines possessing electron-withdrawing groups or electron-donating groups are converted into the corresponding aryl iodides in 54%–97% yields. Advantages of this methodology are the use of mild reaction conditions, avoiding the use of harmful acids and toxic solvents and short reaction time.

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1. Introduction

Iodoaromatic compounds are useful synthetic building blocks in organic synthesis for carbon–carbon bond formation [1]. They are valuable and versatile synthetic intermediates and they have wide applications in medicine such as radioactivity label markers in radio-immunoassays or in nuclear magnetic imaging [2,3]. Since some reactions, such as Ullman [4–6], Suzuki [7–10], are facile for iodoarenes, a simple and reliable preparation method is still under investigation. One of the first and useful procedures for the preparation of the iodoarenes is the Sandmeyer reaction [11,12]. This reaction is usually carried out with sodium nitrite at low temperature in two steps: diazotization of the aryl amin in hydrochloric or sulfuric acid and then reaction with iodine or KI sometimes in the presence of copper salts [11]. The Sandmeyer reaction is complicated because of numerous competing reactions [13]. Recently, some new versions are reported for introducing iodine into an aromatic substrate by a sequence involving diazotization-iodination of

corresponding amines, such as HI/KNO₂ in DMSO [14], KI/NaNO₂/PTSA in MeCN [15], NaNO₂/sulfonated-resin/KI in H₂O [16], PTSA/NaNO₂/KI in water-paste form [17] and Resin NO₂, *p*-TsOH, H₂O [18]. Although there are specific merits to each of these methods, different kinds of drawbacks including long reaction times, highly expensive reagents and use of toxic solvents are commonly required. Hence, there is still considerable high interest in developing simple methods for synthesis of aryl iodides that requires a low manufacturing cost while minimizing environmental pollution are preferable. To broaden the scope of arenediazonium salt applications, recently, the synthesis of new and highly stable arenediazonium tosylate salts and arenediazonium silica sulfates with various applications are reported [19,20]. It is well-known that arenediazonium tosylate salts are highly stable and non-explosive because of the close and multiple contacts between the N atom in the diazonium cation and the O atoms of tosylate anion [21].

Considering the new trends of science and technology to use natural materials, and because of environmental hazards of some current methods, researches are improved about green and eco-friendly methods. One of the recent investigated methods which could conform to standards of green chemistry is natural biopolymers and specially cellulose which could be used as a support for sulfuric acid [22,23].

2. Material and methods

Chemicals were purchased from the Fluka, Merck, and Aldrich chemical companies. Melting points were determined

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Table 1: Iodination of Aromatic Amines with wet CSA/NaNO₂/KI/ at room temperature.

Entry	ArNH ₂	Time (min.) diazotization/iodination	Product ^a	Yield (%) ^b	Mp (°C)	Lit. mp (°C)
1	4-NO ₂ C ₆ H ₄ NH ₂	10/2	4-NO ₂ C ₆ H ₄ I	87	171–172	172–173 [20]
2	2-NO ₂ C ₆ H ₄ NH ₂	10/2	2-NO ₂ C ₆ H ₄ I	82	51–53	52–53 [15]
3	4-MeC ₆ H ₄ NH ₂	6/5	4-MeC ₆ H ₄ I	57	34–35	35–37 [20]
4	4-MeOC ₆ H ₄ NH ₂	5/5	4-MeOC ₆ H ₄ I	61	49–51	49–52 [15]
5	4-BrC ₆ H ₄ NH ₂	7/3	4-BrC ₆ H ₄ I	78	88–89	89–91 [28]
6	4-ClC ₆ H ₄ NH ₂	7/3	4-ClC ₆ H ₄ I	81	55–56	55–56 [20]
7	3, 4-Cl ₂ C ₆ H ₃ NH ₂	8/3	3, 4-Cl ₂ C ₆ H ₃ I	73	Oil	27–29 [28]
8	2, 4-Cl ₂ C ₆ H ₃ NH ₂	8/3	2, 4-Cl ₂ C ₆ H ₃ I	54	Oil	bp: 262 [28]
9	4-NH ₂ C ₆ H ₄ COOH	6/4	4-IC ₆ H ₄ COOH	97	268–270	269–270 [20]
10	3-NH ₂ C ₆ H ₄ COOH	7/4	3-IC ₆ H ₄ COOH	92	183–184	185–189 [29]
11	2-NH ₂ C ₆ H ₄ COOH	7/4	2-IC ₆ H ₄ COOH	85	161–162	161–162 [20]
12	2-IC ₆ H ₄ NH ₂	5/4	1, 2-I ₂ C ₆ H ₄	65	Oil	Oil [15]
13	C ₆ H ₅ NH ₂	5/5	C ₆ H ₅ I	71	Oil	Oil [20]

^a The products were characterized from their spectral data (IR, ¹H NMR) or mp, by comparison with reported samples.

^b The yields refer to isolated products.

by an Electrothermal 9100 and are not corrected. TLC on commercial aluminum-backed plates of silica gel 60 F254 was used to monitor the progress of reactions. ¹H NMR spectra were recorded on Bruker Avance3 400 MHz spectrometers with 7–10 mM solutions in CDCl₃ in the presence of tetramethyl silan as internal standard.

2.1. Preparation and recycling of Cellulose sulfuric acid

CSA was prepared according to Ahmad Shaabani et al.'s procedure [23]. The catalyst was recovered by filtration and washed with EtOAc and MeOH thoroughly and dried in vacuum oven at 70 °C for 24 h to give recycled CSA. The diazotization-iodination of 4-nitroaniline was repeated with recycled catalyst. The results indicate that the catalyst was recyclable three times without any significant loss of activity.

2.2. General experimental procedure for synthesis of iodoaromatic compounds

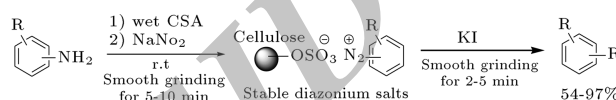
An aromatic amine (2 mmol), CSA (1.5 g) and 0.1 mL of water were ground in a mortar with a pestle to afford a homogeneous mixture, then NaNO₂ (4 mmol, 0.138 g) was added. The reaction mixture was ground *mildly* for 5–10 min. Then, KI (5 mmol, 0.41 g) was added to the mixture and grinding continued for 2–5 min. The reaction mixture was monitored by the β-naphthol test. After completion of the reaction, mixture was diluted with EtOAc (10 mL) and after stirring, it was filtered. The filtrate was extracted with EtOAc (3 × 10 mL) and combined organic layer was treated with aq. 10% Na₂SO₃ (15 mL), then dried over anhyd. Na₂SO₄. The solvent was evaporated in vacuo and the aromatic iodides were purified by flash chromatography (*n*-hexane-EtOAc, 95:5).

2.3. Some spectroscopic data

2-Nitro-1-Iodo benzene (Table 1, entry 2): ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (*t*, *d*, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz), 7.52 (*t*, *d*, 1H, *J* = 8 Hz, *J* = 1.2 Hz), 7.88 (*d*, *d*, 1H, *J* = 8 Hz, *J* = 1.2 Hz), 8.07 (*d*, *d*, 1H, *J* = 8 Hz, *J* = 0.8 Hz);

1, 2-Dichloro-4-iodobenzene (Table 1, entry 7): ¹H NMR (CDCl₃, 400 MHz) δ 7.19 (*d*, 1H, *J* = 8.4 Hz), 7.54 (*dd*, 1H, *J* = 8.4 Hz, *J* = 2 Hz), 7.80 (*d*, 1H, *J* = 2 Hz);

3-Iodobenzoic acid (Table 1, entry 10): ¹H NMR (CDCl₃, 400 MHz) δ 7.28 (*d*, 1H, *J* = 3.2 Hz), 7.98 (*d*, 1H, *J* = 8 Hz), 8.10 (*d*, 1H, *J* = 8 Hz), 8.48 (*s*, 1H).



Scheme 1: The diazotization-iodination of aromatic amines.

3. Results and discussion

In our pursuit of improved synthetic method for the preparation of organic compounds [24–26] hereby, we report a facile, environmentally friendly, one-pot method for the diazotization-iodination reaction of aryl amines under solvent-free condition. The reaction occurs in two steps in the presence of Cellulose Sulfuric Acid (CSA) [23] (Scheme 1).

The sequential diazotization-iodination reactions occur at room temperature and are monitored easily. At the first stage, aryl amines were homogenized by mixing with CSA and 0.1 mL of water. Then NaNO₂ was added, and the diazotization proceeded in 5–10 min. The amines with electron-donating groups need shorter grinding time. In this period of time, the starting amines disappear. The iodination stage is carried out until the reaction mixture exhibits a negative result with the β-naphthol test. We found that when the reaction mixture is ground strongly, only the N-nitroso amines would produce [27].

Thus, under the reaction conditions, we evaluated the general applicability of this procedure for several aromatic amines and the results are presented in Table 1. Various aromatic amines including electron-deficient or electron-rich groups were converted into the aryl iodides in excellent to moderate yields. As it was indicated in Table 1, the yields of reaction with electron-rich amines were modest (entries 2, 4). Thus, the present method is especially agreeable for anilines bearing electron-withdrawing groups. Steric effects of *ortho*-substituents decreased the yields of the corresponding iodoarenes (entries 2, 8, 11, 12). In addition, conversion of aromatic diamines to the corresponding diiodo products was unsatisfactory. However, the present method was effective for preparing highly halogen-substituted benzenes (entries 7, 8, 12).

It should be noted that the aryldiazonium salts supported on cellulose sulfuric acid were stable to be kept at room temperature and could be stored for 48 h in a desiccator without any loss of activity.

In Table 2, the efficiency of our method for the diazotization-iodination of aromatic amines is compared with some other published works in literature. Each of these methods have

Table 2: Comparison of results using Cellulose sulfuric acid/ NaNO_2/KI with results obtained by other works for the diazotization-iodination of 2-nitro aniline.

Entry	Reagents	Conditions	Time (min)	Yield (%)	Ref.
1	HI/KNO_2	$\text{DMSO}/35\text{ }^\circ\text{C}$	15	89	[14]
2	$\text{KI}/\text{NaNO}_2/\text{PTSA}$	$\text{MeCN}/10\text{--}25\text{ }^\circ\text{C}$	50	81	[15]
3	$\text{NaNO}_2/\text{sulfonated-resin}/\text{KI}$	$\text{H}_2\text{O}/\text{RT}$	90	71	[16]
4	$\text{PTSA}/\text{NaNO}_2/\text{KI}$	Water-paste form	20–30	72	[17]
5	$\text{Wet SSA}/\text{NaNO}_2/\text{KI}$	Solvent free/RT	30	83	[21]
6	Resin NO_2^- , $p\text{-TsOH}$, H_2O	$\text{KI}/\text{R T}$	90	91	[20]
7	$[\text{H-NMP}]\text{HSO}_4$, NaNO_2 , NaI	Solvent-free/RT	20–30	85	[30]
8	$[\text{P4-VP}]^a\text{NO}_2/\text{H}_2\text{SO}_4/\text{KI}$	Water/ $0\text{--}60\text{ }^\circ\text{C}$	100	74	[31]
9	$\text{Wet CSA}/\text{NaNO}_2/\text{KI}$	Solvent-free/RT	12	82	This work

^a Poly(4-vinylpyridine).

their own advantages, but they often suffer from some troubles including the use of organic solvent, necessity of temperature control (entries 1, 2 and 8), long reaction time (entries 2, 3, 5 and 6) and employ of non-recyclable catalyst (entry 4).

3.1. Conclusion

In summary, we have developed a simple, green, cost-effective and practical method for synthesis of aromatic iodides in the presence of cellulose sulfuric acid as a biodegradable proton source. The resulting diazonium salts are typically stable and could react with KI to form iodoarenes. This procedure offers several advantages including the short reaction time, use of mild reaction condition and avoiding the use of harmful acids and toxic solvents.

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