A New, One-Step, Effective Protocol for the Iodination of Aromatic and Heterocyclic Compounds via Aprotic Diazotization of Amines

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Abstract: We have developed a convenient one-step preparation of aromatic and some heterocyclic iodides by the sequential diazotization-iodination of the aromatic amines with a KI/NaNO2/p-TsOH system in acetonitrile at room temperature. This method has general character and allows aryl iodides with either donor or acceptor substituents in various positions to be obtained from the corresponding amines in 50–90% yield.

Keywords: aromatic iodides, aromatic amines, diazotization, potassium iodide, sodium nitrite

Aromatic iodides are important building blocks in modern organic synthesis for carbon–carbon bond formation. In addition, many iodoarenes are biologically active molecules that are used as drugs or diagnostic aids, as contactors and radioactively labeled markers in radioimmunoassay studies and in nuclear magnetic imaging.

One of the first and the most commonly used methods for preparing aromatic iodides is the substitution of a diazo group by iodine (often called the Sandmeyer reaction). The fundamental advantage of this reaction over other methods involving a direct electrophilic iodination of aromatic compounds, is the selective introduction of iodine into a specified position of the aromatic ring; direct electrophilic iodination frequently gives mixtures of isomers.

The process of diazotization-iodination is usually carried out with sodium nitrate at low temperatures in two steps: diazotization of the amine in hydrochloric or sulfuric acid and a subsequent reaction with iodine and KI, sometimes in the presence of copper salts. As an alternative to these traditional methods, more expensive methods involving alkyl nitrates in the presence of diiodomethane or other sources of iodine have been reported. Recently, a one-step method for introducing iodine into an aromatic substrate by a sequence involving diazotization-iodination of the corresponding amines with HI/KNO2 in DMSO was suggested.

Herein, we describe a convenient, alternative method for the preparation of aromatic iodides by a diazotization-iodination sequence of the corresponding aromatic amines. The sequential diazotization-iodination occurs in one stage in acetonitrile solution, in the presence of p-toluenesulfonic acid. There is no need to maintain a low temperature for these reactions as the process generally occurs between 10–25 °C, to furnish the iodoarenes in high yields (Scheme 1).

Scheme 1

Under optimal reaction conditions, the amine is added to p-toluenesulfonic acid in acetonitrile. An aqueous solution of sodium nitrate and potassium iodide is then added dropwise to the ammonium salt, causing a vigorous emission of nitrogen. The mixture is stirred until the gas evolution completely stops. The progress of the reaction can be followed by TLC analysis and by testing for the presence of the diazonium salt with 2-naphthol. As a rule, full conversion of the starting amine takes 30–60 minutes (Table 1).

This method has rather a general character and allows the preparation of aromatic iodides containing either donor or acceptor groups at various positions relative to the amino group, in good yields. The method also allows diiodoarenes to be obtained from the corresponding diamines. As by-products, the corresponding hydroxy-containing derivatives are formed in 3–5% (as indicated by GC-MS analysis) and are readily separated from the desired aromatic iodides by chromatographic separation. Adding the solution of sodium nitrite and potassium iodide whilst cooling the reaction mixture to 10–15 °C for the first 10 minutes, however, can minimize the amount of phenol formed.

Electron donor and electron acceptor functional groups, which do not occupy an ortho-position to the amine group, had relatively little influence on the reaction time and yields (see entries 1, 3, 6, 7, 14). However, steric effects of ortho-substituents significantly retarded the reaction rate and decreased the yields of the corresponding aromatic iodides (entries 2, 4, 9, 10, 11, 15, 17). This deactivation effect was especially strong with di-ortho-substituted derivatives to the extent that the reaction with 2,6-dinitroaniline did not occur at all, even after prolonged heating for 12 h. 2,6-Diethylaniline (15) gave a
mixture of 1,3-diethyl-2-iodobenzene (15a) and \( \text{N}-(2,6\text{-diethylphenyl})\text{acetamide} \) (15b) in a 1:1 ratio.

Replacing acetonitrile by tert-butanol under the same reaction conditions did, however, allow the desired 1,3-diethyl-2-iodobenzene (15a) to be obtained with 75% yield (Table 1, entry 15).

Among the heterocyclic amines studied, the reaction proved to be suitable for obtaining 3-iodopyridines and 1,3-benzothiazol-2-amine (entries 18–20). However, 2-amino-5-bromopyridine (21) did not furnish the corresponding iodide. In this case, the reaction gave a complex mixture of products from which \( \text{N}-(5\text{-bromo-2-pyridyl})\text{acetamide} \) (21a) and 5-bromo-2-(4-methylphenyl-...
sulfonyloxy)pyridine (21b) could be isolated in 30% and 15% yield, respectively. Similar problems were encountered with 2- and 4-aminopyridine and 2-pyrazinamine (GC-MS data).

![Scheme 3](image)

Scheme 3

In summary, we have developed a novel method for preparing aromatic iodides. It is simple to perform and suitable for a wide range of aromatic and some heterocyclic amines. We have also studied its scope and limitations and conclude that this methodology should be of value for the preparation of functionalized unsaturated iodides.

2-Iodacetophenone (4a)
The synthesis and workup was carried out as described in the general procedure. The reaction mixture was extracted with Et2O (??× ?? mL) and concentrated under vacuum to yield a yellow oil.

Yield: 0.63 g (85%); yellow oil.

1H NMR (300 MHz, CDCl3): δ = 2.47 (s, 3 H, COCH3), 7.0–7.3 (m, 3 H), 7.7–7.8 (d, J = 7.5 Hz, 1 H).

13C NMR (300 MHz, CDCl3) = 14.7, 23.5, 25.2, 127.0, 128.6, 138.9.

The reaction mixture was extracted either with Et2O or EtOAc and purified by flash chromatography (pentane–Et2O, 1:3) to give 21a and 21b.

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References

(3) Bellina, F.; Carpita, A.; Rossi, R. Synthesis 2004, 2419.


