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Iodination of aryl amines in a water-paste form via stable aryl diazonium tosylates

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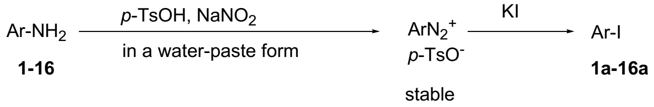
Abstract

The diazotization of aryl amines at room temperature in paste form with $NaNO_2$, *p*-TsOH and a small amount of water, followed by treatment with KI provides a new, simple, and effective route for the preparation of various aryl iodides. The water-paste and strong acid-free reaction conditions are environmentally friendly and compatible with acid-sensitive functional groups.

Aromatic diazonium salts have drawn increased attention as important intermediates in many organic reactions.[1] Aromatic iodides are important building blocks in modern organic synthesis, especially for carbon–carbon bond formation via cross-coupling reactions.[2] In addition, many aryl iodides are biologically active molecules that are used as drugs or diagnostic aids. For example, some aryl iodides are used as X-ray contrast agents or radioactively labeled markers in radioimmunoassays.[3]

One of the most commonly used methods for preparing aromatic iodides is the substitution of a diazonium group by iodine, the so-called Sandmeyer reaction.[1] The fundamental advantage of this reaction, over other methods involving the direct electrophilic iodination[4] of aromatic compounds, is the selective introduction of iodine atoms into a specific position of the aromatic ring. Direct electrophilic iodination, on the other hand, frequently gives a mixture of regioisomers. The process of diazotization–iodination is usually carried out in two steps: diazotization of the amine with sodium nitrite at low temperatures in hydrochloric or sulfuric acid, and a subsequent reaction with iodine and KI, sometimes in the presence of copper salts.[1] As an alternative to this traditional method, acid-free conditions involving alkyl nitrites in the presence of diiodomethane or other sources of iodine have been reported.[5] Recently, progressive one-step methods for the introduction of iodine into an aromatic substrate have been suggested; these methods use a sequence involving diazotization–iodination of the corresponding amines with HI/KNO_2 in DMSO or $KI/NaNO_2$/*p*-TsOH in CH_3CN.[6] However, most iodination methods developed thus far have drawbacks, such as increased waste or require organic solvents.

In this Letter, we report a facile and environmentally friendly one-pot method for the diazotization and subsequent iodination of aryl amines **1–16** (Scheme 1).



Scheme 1. One-pot iodination of aryl amines via aryl diazonium tosylates.

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The essence of this method involves carrying out the diazotization and subsequent iodination in a water-paste form. Reaction details are as follows: An aromatic amine (2 mmol) was ground with 0.2 mL of water and solid *p*-TsOH hydrate (6 mmol) in an agate mortar for a few minutes. The diazotizating reagent, $NaNO_2$ (5 mmol), was added. The diazotization reaction lasted approximately 10 min with periodic grinding using a pestle. The formation of diazonium salt was verified using the color-test with β-naphthol.[1a] Then, commercially available KI (5 mmol) was added to the diazonium salt paste, and grinding continued for 10–20 min. The iodination reaction began immediately after KI addition, and the paste volume increased due to the evolution of nitrogen gas. The whole process of diazotization and iodination took 20–30 min. The crude product paste was treated with water and aqueous Na_2SO_3 (10%, 15 mL). Precipitated aromatic iodide products were filtered and dried. Only when the product was liquid was the reaction mixture extracted with diethyl ether (3 × 15 mL). The product aryl iodides were purified by recrystallization or flash chromatography.

This new, simple method can be successfully applied for the synthesis of a wide range of aryl iodides starting from the corresponding aryl amines. Various aromatic amines, **1**–**14**, with electron-withdrawing groups as well as electron-donating groups, were transformed into aromatic iodides, **1a**–**14a**, in good yields (Table 1). Iodination of two substrates: weakly-basic 2,4-dinitroaniline and 5-aminouracil provided only moderate yields of the corresponding iodo derivatives **15a** and **16a**.

We have also successfully applied this new method on a larger scale. For example, up to 15 mmol of anthranilic acid (**9**) could be converted into 2-iodobenzoic acid (**9a**) without any loss of efficiency.

Table 1
Syntheses of aryl iodides by means of the diazotization–iodination of aromatic amines in a water-paste form at room temperature (substrate: $NaNO_2$/KI/*p*-TsOH = 1:2.5:2.5:3 molar ratio)

Entry	Substrate	Product	Isolated yield (%)
1	$4\text{-}NO_2C_6H_4NH_2$	$4\text{-}NO_2C_6H_4I$	72
2	$2\text{-}NO_2C_6H_4NH_2$	$2\text{-}NO_2C_6H_4I$	72
3	$4\text{-}CH_3COC_6H_4NH_2$	$4\text{-}CH_3COC_6H_4I$	75
4	$2\text{-}CH_3COC_6H_4NH_2$	$2\text{-}CH_3COC_6H_4I$	87
5	$4\text{-}IC_6H_4NH_2$	$1,4\text{-}I_2C_6H_4$	87
6	$2\text{-}IC_6H_4NH_2$	$1,2\text{-}I_2C_6H_4$	79
7	$2,4,6\text{-}Cl_3C_6H_2NH_2$	$2,4,6\text{-}Cl_3C_6H_2I$	63
8	$2\text{-}NH_2C_6H_4CO_2H$	$2\text{-}IC_6H_4CO_2H$	67
9	$4\text{-}NH_2C_6H_4CO_2H$	$4\text{-}IC_6H_4CO_2H$	80
10[a]	$4\text{-}NH_2,2\text{-}OH\text{–}C_6H_3CO_2Na$	$4\text{-}I,2\text{-}OH\text{-}C_6H_3CO_2H$	77
11	$3\text{-}NCC_6H_4NH_2$	$3\text{-}NCC_6H_4I$	85
12	$4\text{-}NCC_6H_4NH_2$	$4\text{-}NCC_6H_4I$	79
13	$4\text{-}MeOC_6H_4NH_2$	$4\text{-}MeOC_6H_4I$	70
14	$4\text{-}PhC_6H_4NH_2$	$4\text{-}PhC_6H_4I$	81
15	$2,4\text{-}(NO_2)_2C_6H_3NH_2$	$2,4\text{-}(NO_2)_2C_6H_3I$	38
16	5-Aminouracil	5-Iodouracil	41

[a] Molar ratio of reagents $Ar\text{–}NH_2/NaNO_2/KI/p\text{-}TsOH = 1:2:2.5:4$.

It should be emphasized that the reaction requires a small amount of water for the formation of the water-paste and must be carried out in a stepwise fashion for a successful outcome. When KI was added together with $NaNO_2$, a complex product mixture was produced with much lower yields of aryl iodides. This indicates that the iodination reaction in a water-paste form occurs differently than the diazotization–iodination in an aprotic solvent, where sodium nitrite and KI are treated together with aromatic amines.[6b]

It is known that the co-grinding of dry diazonium nitrate salts with KI results in the formation of aryl iodides in quantitative yield.[7] However, Kaupp's method[7] requires cumbersome gas phase reagents for the preparation of diazonium salts and a lengthy reaction time for iodination. Furthermore, neat reactions with dry diazonium salts may be more dangerous and explosive than wet reactions or those that take place in solution. Our diazotization–iodination method was safer in this sense, as the reactions were carried out in a water-paste. Besides, it is known that diazonium salts, such as $ArN_2^+Ar'SO_3^-$, are relatively stable and non-explosive.[8a] Previously, these kinds of salts were prepared only for analytical purposes by ion exchange between aryl diazonium chlorides and aryl sulfonates.[8b,c]

The aryldiazonium tosylates, $ArN_2^+p\text{-}TsO^-$, that we prepared were sufficiently stable to be kept at room temperature either in a paste form or dried state. For example, *p*-nitrophenyldiazonium *p*-tosylate (NPAT)[9] was prepared in crude form as described here and kept at room temperature in a desiccator. After one month, the addition of water and KI to the stored tosylate salt provided almost the same yield of *p*-iodonitrobenzene (**1a**) as that from freshly-prepared salt (Table 1). Besides, NPAT did not reveal any explosive character. The thermal stability of NPAT in pure or crude form was verified by DSC under a nitrogen atmosphere and did not show any exothermic reactions up to 150 °C.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.192.

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9. Off-white solid, mp 134–136 °C dec (lit. mp 141–142 °C[8c]), IR(Nujol) cm^{-1} 2306, 1543, 1225, 1173, 1122, 1030. ^{1}H NMR (CD_3OD, 500 MHz) δ 8.88 (d, $J = 9.0$ Hz, 2H), 8.65 (d, $J = 9.0$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 2H), 2.33 (s, 3 H). ^{13}C NMR (CD_3OD, 125 MHz) δ 155.2, 143.5, 141.7, 135.6, 129.8, 127.3, 126.9, 122.7, 21.3.