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

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Received 23 June 2006; revised 6 July 2006

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/$NaNO_2$/*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.

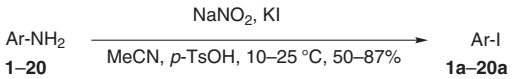
Key words: aromatic iodides, aromatic amines, diazotization, potassium iodide, sodium nitrite

Aromatic iodides are important building blocks in modern organic synthesis for carbon–carbon bond formation.[1] 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.[2]

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).[3] 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 nitrite 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.[3] As an alternative to these traditional methods, more expensive methods involving alkyl nitrites in the presence of diiodomethane or other sources of iodine have been reported.[4] Recently, a one-step method for introducing iodine into an aromatic substrate by a sequence involving diazotization-iodination of the corresponding amines with HI/KNO_2 in DMSO was suggested.[5]

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 nitrite 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, 16, 17). This deactivation effect was especially strong with di-*ortho*-substituted derivatives to the extant 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

SYNTHESIS 2007, No. 1, pp 0081–0084
Advanced online publication: 12.12.2006
DOI: 10.1055/s-2006-958936; Art ID: Z13006SS
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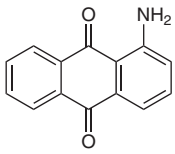
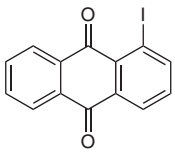
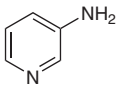
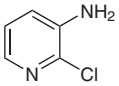
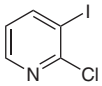
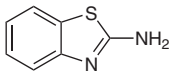
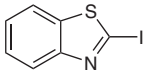
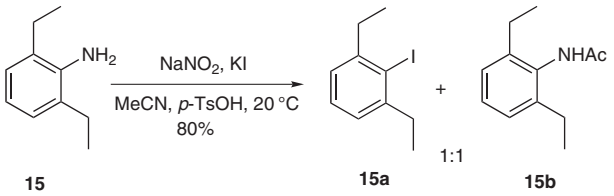
Table 1 Iodination of Aromatic Amines with $NaNO_2$/KI/*p*-TsOH in Acetonitrile, at Room Temperature[a]

Entry	$ArNH_2$ (**1–20**)	Time (min)	Product (**1a–20a**)	Yield (%)	mp (°C)	Lit. mp (°C)
1	4-$NO_2C_6H_4NH_2$	30	4-$NO_2C_6H_4I$	84	172–173	171[6]
2	2-$NO_2C_6H_4NH_2$	50	2-$NO_2C_6H_4I$	81	52–53	47–49[7]
3	4-$MeCOC_6H_4NH_2$	30	4-$MeCOC_6H_4I$	87	84–85	85[6]
4	2-$MeCOC_6H_4NH_2$	60	2-$MeCOC_6H_4I$	85	oil	–
5	2-$NH_2C_6H_4CO_2H$	30	2-$IC_6H_4CO_2H$	50	161–162	162[6]
6	4-$NH_2C_6H_4NH_2$	30	1,4-$I_2C_6H_4$	50	130–131	129[6]
7	4-$IC_6H_4NH_2$	30	1,4-$I_2C_6H_4$	78	130–131	–
8	2,4,6-$Cl_3C_6H_2NH_2$	30	2,4,6-$Cl_3C_6H_2I$	80	53–54	54[8]
9	2-$IC_6H_4NH_2$	60	1,2-$I_2C_6H_4$	73	oil	–
10	2,4,6-$I_3C_6H_2NH_2$	120	1,2,4,6-$I_4C_6H_2$	50	162–164	162–165[9]
11	2,4-$(NO_2)_2C_6H_3NH_2$	135	2,4-$(NO_2)_2C_6H_3I$	48	88.5–89	88.5[10]
12	4-$PhC_6H_4NH_2$	30	4-PhC_6H_4I	80	112–113	109–111[11]
13	4-$NH_2C_6H_4C_6H_4$-4′-NH_2	30	4-$IC_6H_4C_6H_4$-4′-I	78	203–204	204–205[11]
14	4-$MeOC_6H_4NH_2$	30	4-$MeOC_6H_4I$	90	51–52	52[6]
15	2,6-$Et_2C_6H_4NH_2$	60	2,6-$Et_2C_6H_4I$	75[b]	oil	–
16	2-I-4-$NO_2C_6H_3NH_2$	60	1,2-I_2-4-$NO_2C_6H_3$	78	110–111	109–110[12]
17		60		83	203–204	204–205[13]
18		60		76	52–53	52.3–53[14]
19		50		80	93.5–95	91–93[15]
20		210		78	79–80	79–81[16]

[a] Molar ratio of reagents Ar-NH_2–$NaNO_2$–KI–*p*-TsOH = 1:2:2.5:3.
[b] *t*-BuOH was used as solvent.

mixture of 1,3-diethyl-2-iodobenzene (**15a**) and *N*-(2,6-diethylphenyl)acetamide (**15b**) in a 1: 1 ratio.



Scheme 2

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 *N*-(5-bromo-2-pyridyl)acetamide (**21a**) and 5-bromo-2-(4-methylphenyl-

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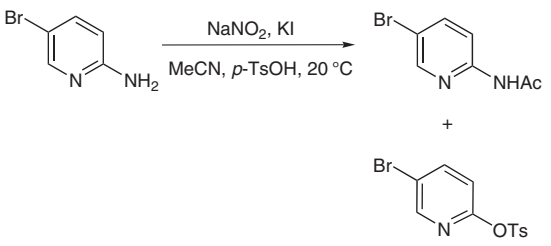
sulfonyloxy)pyridine (**21b**) could be isolated in 30% and 15% yield, respectively. Similar problems were encountered with 2- and 4-aminopyridine and 2-pyrazinamine (GC-MS data).



Scheme 3

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.

All starting materials were purchased from commercial sources and used without further purification. Acetonitrile was used as HPLC-quality from VWR. *t*-BuOH was distilled over CaH_2. Yields refer to isolated yields of compounds estimated to be > 95% pure as determined by ^{1}H NMR and capillary GC.

Synthesis of Aromatic Iodides (1a–20a); General Procedure

To a solution of *p*-TsOH·H_2O (1.719 g, 9 mmol) in MeCN (12 mL) was added the aromatic amine (3 mmol). The resulting suspension of amine salt was cooled to 10–15 °C and to this was added, gradually, a solution of $NaNO_2$ (0.414 g, 6 mmol) and KI (1.245 g, 7.5 mmol) in H_2O (1.8 mL). The reaction mixture was stirred for 10 min then allowed to come to 20 °C and stirred until the total time indicated in Table 1 had elapsed. To the reaction mixture was then added H_2O (50 mL), $NaHCO_3$ (1 M; until pH = 9–10) and $Na_2S_2O_3$ (2 M, 6 mL). The precipitated aromatic iodide was filtered or extracted either with Et_2O or EtOAc and purified by flash chromatography (pentane–Et_2O, 1:3 or pentane–CH_2Cl_2, 5:1).

2-Iodacetophenone (4a)

The synthesis and workup was carried out as described in the general procedure. The reaction mixture was extracted with Et_2O (3 × 20 mL) and concentrated under vacuum and the resultant yellow oil was purified by chromatography (pentane–Et_2O, 1:3).

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

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, $COCH_3$), 7.0–7.3 (m, 3 H), 7.8 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.1, 90.7, 128.0, 131.6, 140.5, 143.5, 200.1.

1,2-Diiodobenzene (9a)

Purified by column chromatography (pentane–CH_2Cl_2, 5:1).

Yield: 0.72 g (73%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.03 (ddd, *J* = 8.0, 1.5, 0.3 Hz, 2 H), 7.88 (ddd, *J* = 8.0, 1.5, 0.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.9, 128.8, 138.9.

1,3-Diethyl-2-iodobenzene (15) and *N*-(2,6-Diethylphenyl)acetamide (15b)

The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to yield the crude product. Pentane (30 mL) was added and the insoluble material was filtered off and recrystallized from hexane to give **15b**.

15b

Yield: 0.24 g (42%); colorless crystals; mp 140–141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1 (t, *J* = 7.5 Hz, 6 H, CH_2CH_3), 2.1 (s, 3 H, $COCH_3$), 2.5 (q, *J* = 7.5 Hz, 4 H, CH_2CH_3), 7.0–7.1 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 23.5, 25.2, 127.0, 128.6, 142.0, 142.7, 174.0.

The remaining hexane solution was purified by flash chromatography on silica gel (pentane) to give **15a**.

15a

Yield: 0.3 g (38%); pale oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1 (t, *J* = 7.5 Hz, 6 H), 2.7 (q, *J* = 7.5 Hz, 4 H), 6.96 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 36.0, 107.6, 126.3, 128.5, 147.7.

***N*-(5-Bromo-2-pyridyl)acetamide (21) and 5-Bromo-2-(4-methylphenylsulfonyloxy)pyridine (21b)**

The reaction mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under vacuum to yield an oily product which was purified by flash chromatography (pentane–Et_2O, 1:3) to give **21a** and **21b**.

21a

Yield: 0.2 g (30%); colorless crystals; mp 181–182 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.1 (s, 3 H, $COCH_3$), 7.7 (dd, *J* = 7.8, 2.1 Hz, 1 H), 8.09 (d, *J* = 7.8 Hz, 1 H), 8.2 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 114.6, 115.4, 141.0, 148.5, 150.2, 168.8.

21b

Yield: 0.15 g (15%); pale oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 3 H), 7.0–7.3 (m, 3 H), 7.7–7.8 (m, 3 H), 8.2 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 117.3, 118.6, 128.5, 129.7, 132.6, 142.6, 145.6, 149.1, 155.6.

Acknowledgment

E.A.K. thanks D. A. A. D. for a research grant in 2006 allowing a stay at the Ludwig-Maximilians-University of Munich.

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