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# $NaIO_4$/KI/NaCl: a new reagent system for iodination of activated aromatics through in situ generation of iodine monochloride

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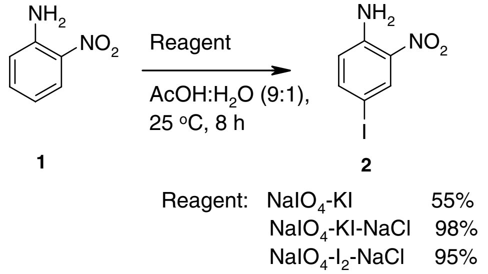
**Abstract**—A new reagent system consisting of $NaIO_4$/KI/NaCl in aq AcOH has been found to be effective in iodinating a variety of activated aromatic substrates via in situ-generated iodine monochloride, to furnish iodoaromatics in excellent yields. This iodination procedure has been applied successfully for a cost-effective synthesis of 3,3′-diaminobenzidine, a key intermediate for preparing proton conducting membranes for fuel cell applications, with high yield and a purity of 99.7%.

## 1. Introduction

Aromatic iodo compounds are versatile building blocks for the preparation of organometallic reagents and some are potential intermediates for the synthesis of pharmaceutical and bioactive molecules.[1] They are also useful in metal-catalyzed (e.g., Heck, Stille and Negishi) cross-coupling reactions, which are widely employed in C–C, C–N, etc., bond forming reactions.[2] Aryl iodides are usually more difficult to prepare than the other corresponding aryl halides due to the low electrophilic strength of iodine. Hence, synthetic methods involving a source of $I^+$ as the reactive species seem to be the most convenient procedures for the direct iodination of arenes. Generally, arenes can be iodinated by iodine in the presence of a Lewis acid, a hydrogen iodide trap or most commonly in the presence of an oxidizing agent. Several reagents reported for iodination of aromatic compounds include iodine–HgO,[3] iodine–tetrabutylammonium peroxydisulfate,[4] *n*-BuLi–$CF_3CH_2I$,[5] NIS–$CF_3SO_3H$,[6] NIS,[7] ICl,[8] $NH_4I$–oxone®,[9] etc.[10] In addition, iodination is carried out under harsh conditions in the presence of powerful oxidants[11] such as nitrogen dioxide, diiodine pentoxide, $Ag_2SO_4$, HgO, $NaIO_4$, $HIO_4$, $KIO_3$, $CrO_3$, $KMnO_4$, lead acetate, NaOCl, ammonium hexanitrocerate, nitric acid, or liquid $SO_3$. Since most of these reagents are complex, costly or involve toxic heavy metals, it is desirable to provide a quick, inexpensive, easy and environmentally benign method of iodination. In this letter, we wish to report an efficient, new and milder procedure for the iodination of activated aromatics under ambient conditions, using the $NaIO_4$/KI/NaCl/aq AcOH reagent system.

In connection with our ongoing program on $NaIO_4$ mediated oxidations[12] as well as our interest in providing a cheaper method for producing 3,3′,4,4′-tetraaminobiphenyl (**4**, TAB),[13] a monomer for fuel cell applications, we envisioned a simple route, which might involve iodination of 2-nitroaniline (**1**) to give 4-iodo-2-nitroaniline (**2**), followed by an Ullmann-type homocoupling of **2** and subsequent reduction (Schemes 1 and 3).

When iodination of 2-nitroaniline (**1**) was carried out with alkali metal iodides (KI or NaI) as the iodine source and $NaIO_4$ as the oxidant in aq AcOH, acting both as solvent and acid source, iodination occurred to give **2** in 55% yield. Surprisingly, when NaCl (2 equiv)



**Scheme 1.** Iodination using the $NaIO_4$–KI–NaCl system.

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*Keywords*: $NaIO_4$; Iodination; Aryl halides; Amines; Phenols.

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**Table 1.** Iodination of 2-nitroaniline (**1**)[a]

| Entry | Oxidant | Iodine source | Additive | Yield[b] of **2** (%) |
|---|---|---|---|---|
| 1 | $NaIO_4$ | KI | — | 55 |
| 2 | $NaIO_4$ | KI | NaCl | 98 |
| 3 | $KIO_3$ | KI | NaCl | 98 |
| 4 | $KBrO_3$ | KI | NaCl | 71 |
| 5 | Oxone | KI | NaCl | 47 |
| 6 | $HIO_4$ | KI | NaCl | 87 |
| 7 | *m*-CPBA[c] | KI | NaCl | 56 |
| 8 | $V_2O_5$ | KI | NaCl | 32[d] |
| 9 | $NaIO_4$ | NaI | NaCl | 84 |
| 10 | $NaIO_4$ | *n*-$Bu_4$NI | NaCl | 82 |
| 11 | $NaIO_4$ | $I_2$ | NaCl | 95[e] |
| 12 | $NaIO_4$ | KI | NaF | 58 |
| 13 | $NaIO_4$ | KI | LiBr | 100[f] (16:84)[g] |
| 14 | $NaIO_4$ | KI | NCS[c] | 73 |

[a] Reaction conditions: Molar equivalents of oxidant:iodine source:additive = 1:1:2 unless otherwise stated, 10 ml of AcOH:$H_2O$ (9:1), 25 °C, 8 h.

[b] Isolated yield by column chromatography.

[c] *m*-CPBA = 3-chloroperbenzoic acid; NCS = *N*-chlorosuccinimide.

[d] The reaction was carried out at 60 °C; the yield at 25 °C was 5%.

[e] 0.5 equiv of molecular iodine were used.

[f] The conversion was determined by GC–MS.

[g] 4-Iodo-2-nitroaniline: 4-bromo-2-nitroaniline in the ratio 1:6 were formed.

was added to the reaction mixture, both the reactivity as well as the yield of **2** (98%) increased significantly. Encouraged by this observation, we screened several other oxidants which are known to oxidize alkali metal halides liberating iodine, and the results are shown in Table 1. The use of a catalytic amount of $NaIO_4$ (30 mol %) and NaCl (30 mol %) was not fruitful and when LiBr was employed as the additive, nuclear bromination was a competitive reaction resulting in the formation of 4-iodo-2-nitroaniline and 4-bromo-2-nitroaniline in the ratio of 1:6.

To establish the scope of the methodology, we subjected a variety of activated aromatic compounds to nuclear iodination and the results are shown in Table 2. As can be seen, activated aromatic compounds were converted to mono or poly-iodoaromatics in quantitative yields within a short period of time at 25 °C. The reaction of phenol with one molar equivalent of KI led to a mixture of mono and poly-iodinated products. The degree of poly-iodination is temperature dependent, but attempts to control iodination by conducting the reaction at 0 °C resulted in low conversion (23%; entry 18) probably because the NaCl was not oxidized at 0 °C. Similarly, aniline and substituted anilines were extremely active and gave excellent yields of iodoaromatics. When anilines with deactivating groups such as $NO_2$, $CO_2H$, Cl and I were subjected to the iodination, mono-iodination took place. The reaction was exothermic, often the temperature of the reaction reached 50–55 °C during the addition of KI. Easily oxidizable groups such as hydroxy, aldehyde or amine were not affected, but sulfides and *o*-phenylenediamine, when subjected to the oxidation, gave sulfoxides and ring opened product, respectively. Also the method failed in the case of deactivated and weakly activated aromatic systems such as arenes and alkyl arenes.

The proposed reaction pathway for the iodination is shown in Scheme 2. It was established in our earlier studies[12] that $NaIO_4$ oxidizes metal halides (e.g., KI, NaCl) in the presence of acid to liberate halogens ($I_2$, $Cl_2$) (Eqs. 1–2). Iodine monochloride,[14] presumably formed from the liberated halogens may act as the electrophile (Eqs. 3–4). The formation of I–Cl was confirmed by the fact that styrene, under the same reaction conditions, yielded a mixture of 1-(1-chloro-2-iodoethyl)benzene (23%) and 2-iodo-1-phenylethyl acetate (35%).

**Table 2.** $NaIO_4$/KI/NaCl-mediated iodination of activated arenes[a]

| Entry | Substrate | KI (equiv) | Product | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Aniline | 2 | 2,4-Diiodoaniline | 2 | 97 |
| 2 | 2-Iodoaniline | 1 | 2,4-Diiodoaniline | 2 | 89 |
| 3 | 4-Iodoaniline | 1 | 2,4-Diiodoaniline | 2 | 94 |
| 4 | 2-Nitroaniline | 1 | 4-Iodo-2-nitroaniline | 8 | 98[c] |
| 5 | 2-Chloroaniline | 1 | 4-Iodo-2-chloroaniline | 3 | 95 |
| 6 | 4-Chloroaniline | 1 | 2-Iodo-4-chloroaniline | 3 | 96 |
| 7 | 2-Aminobenzoic acid | 1 | 2-Amino-5-iodobenzoic acid | 8 | 96 |
| 8 | 1*H*-Benzo[*d*]imidazole-2(3*H*)-one | 1 | 5-Iodo-*H*-benzo[*d*]imidazole-2(3*H*)-one | 8 | 90 |
| 9 | Anisole | 1 | 4-Iodoanisole | 12 | 87 |
| 10 | 1,3-Diethoxybenzene | 2 | 1,5-Diethoxy-2,4-diiodobenzene | 0.5 | 98 |
| 11 | 1-Methoxynaphthalene | 1 | 2-Iodo-1-methoxynaphthalene | 8 | 95 |
| 12 | Phenol | 3 | 2,4,6-Triiodophenol | 0.5 | 99[d] |
| 13 | 2-Chlorophenol | 2 | 2-Chloro-4,6-diiodophenol | 0.25 | 98 |
| 14 | 2,4-Dichlorophenol | 1 | 2,4-Dichloro-6-iodophenol | 6 | 95 |
| 15 | 1-(2-Hydroxyphenyl)–ethanone | 2 | 1-(2-Hydroxy-3,5-diiodophenyl)ethanone | 1 | 97 |
| 16 | Methyl 2-hydroxybenzoate | 2 | Methyl 2-hydroxy-3,5-diiodobenzoate | 2 | 96 |
| 17 | 4-Bromophenol | 2 | 4-Bromo-2,6-diiodophenol | 0.5 | 95 |
| 18 | 4-Hydroxybenzaldehyde | 2 | 4-Hydroxy-3,5-diiodobenzaldehyde | 0.25 | 95[e] |

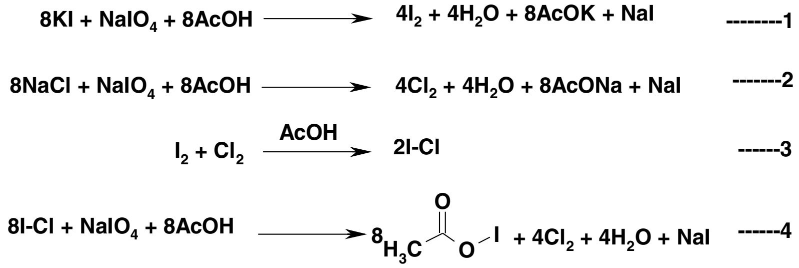
[a] Reaction conditions for monoiodination: Substrate (3 mmol), KI (3 mmol), $NaIO_4$ (3 mmol), NaCl (6 mmol), 10 ml of AcOH: $H_2O$ (9:1), 25 °C.

[b] Isolated yield after column chromatographic purification.

[c] Diiodination was not observed even with 1.2 equiv of KI.

[d] KI was added portionwise to maintain the temperature around 50 °C.

[e] The yield was 23% when the reaction was conducted at 0 °C.



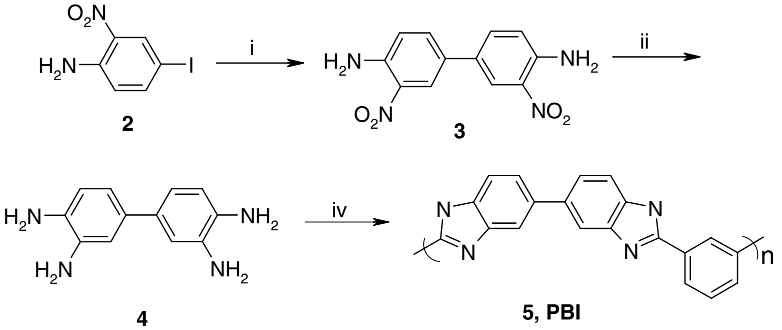
$$8KI + NaIO_4 + 8AcOH \longrightarrow 4I_2 + 4H_2O + 8AcOK + NaI \quad \text{--------1}$$

$$8NaCl + NaIO_4 + 8AcOH \longrightarrow 4Cl_2 + 4H_2O + 8AcONa + NaI \quad \text{-------2}$$

$$I_2 + Cl_2 \xrightarrow{AcOH} 2I\text{-}Cl \quad \text{------3}$$

$$8I\text{-}Cl + NaIO_4 + 8AcOH \longrightarrow 8\,CH_3C(=O)O\text{-}I + 4Cl_2 + 4H_2O + NaI \quad \text{------4}$$

**Scheme 2.** Proposed mechanistic pathway for the iodination.



**Scheme 3.** Reagents and conditions: (i) $Pd_2(dba)_3$, $Et_3N$, toluene, 110 °C, 12 h, 89%; (ii) $SnCl_2 \cdot 2H_2O$, HCl, 25–40 °C, 2 h, 73%; (iii) isophthalic acid, polyphosphoric acid, 120–220 °C, 19 h, 92%.

Finally, the procedure has been applied to the synthesis of poly-benzimidazole (**5**, PBI), a polymer used for making proton conducting membranes in fuel cell applications. Thus, 4-iodo-2-nitroaniline (**2**) underwent homocoupling[15] in the presence of a Pd-catalyst to afford 3,3′-dinitrobenzidine (**3**) in 89% yield. Reduction of the nitro groups in **3**, followed by polymerization of the tetramine **4** with isophthalic acid produced PBI (**5**) in a 92% yield; the inherent viscosity of **5** was found to be 1.9 dL/g (Scheme 3).

In conclusion, we have developed a simple procedure for the iodination of activated aromatic compounds under ambient conditions using $NaIO_4/KI/NaCl$ as a mild, inexpensive and selective iodinating agent. The methodology involves the in situ generation of I–Cl which acts as the electrophile for the iodination. A remarkable feature of this system, is that even acid sensitive functionalities like anilines can be iodinated quantitatively. The present procedure was successfully employed for an efficient, cost-effective synthesis of 3,3′-diaminobenzidine (**4**), an important monomer for fuel cell applications, with an overall yield of 64% and of 99.7% purity.

## 2. General procedure for the mono-iodination of activated aromatics

To a mixture of the activated aromatic compound (3 mmol), $NaIO_4$(3 mmol) and NaCl (6 mmol) in 10 ml of $AcOH:H_2O$ (9:1) was added KI (3 mmol) slowly so that the temperature of the reaction mixture did not exceed 50 °C. The reaction mixture was stirred at 25 °C for the period mentioned in Table 2 then poured over ice-cold water. The solid was extracted with dichloromethane, washed twice with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography.

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