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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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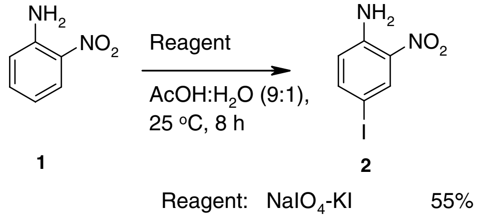
Abstract—A new reagent system consisting of $NaIO_4$/KI/NaCl in aq AcOH has been found to be effective in iodinating a variety of activated aromatic substrates via in situ-generated iodine monochloride, to furnish iodoaromatics in excellent yields. This iodination procedure has been applied successfully 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)



Reagent:		
	$NaIO_4$-KI	55%
	$NaIO_4$-KI-NaCl	98%
	$NaIO_4$-I_2-NaCl	95%

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

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_4NI	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.