Oxidative Iodination of Deactivated Arenes in Concentrated Sulfuric Acid with I_2/$NaIO_4$ and KI/$NaIO_4$ Iodinating Systems[1]

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Abstract: Deactivated arenes were mono- or diiodinated with strong electrophilic I^+ reagents, which were prepared from $NaIO_4$ and either I_2 or KI in concentrated H_2SO_4 (minimum 95% by weight). In general a small excess of the dark brown iodinating solution was used (1.1/1.5 equivalents, for nitrobenzene two equivalents was required). The iodinations were conducted at 25–30 °C with a reaction time of 1–2 hours using either a 'direct' or an 'inverse' method of aromatic iodination to give mono- or diiodinated pure products in 31–91% optimized yields.

Key words: iodoarenes, deactivated arenes, iodine, potassium iodide, sodium periodate, direct oxidative iodination

Aromatic iodides are generally more reactive, albeit more costly, than their respective bromides and chlorides. There are many different methods, direct and indirect, for their synthesis;[2] they are widely used in laboratory scale organic synthesis and to a lesser extent in industry. Moreover, they are able to form a variety of aromatic hypervalent iodine derivatives, which have found increasing application in modern organic synthesis.[3] Our two reviews[4,5] relate and explain a variety of aromatic iodination methods suitable for both activated and deactivated aromatics, devised in our laboratory since 1990, as well as our novel methods for preparing several classes of aromatic hypervalent iodine compounds, easily synthesized from aromatic iodides; our most recent work is in relation to the oxidative iodination of various aromatics.[6,7]

In our previous work,[7] two 'model' deactivated arenes, benzoic acid and nitrobenzene, dissolved in concentrated H_2SO_4 (90%) were monoiodinated with strongly electrophilic I^+ reagents prepared from diiodine and various oxidants (CrO_3, $KMnO_4$, active MnO_2, HIO_3, $NaIO_3$, or $NaIO_4$) in concentrated H_2SO_4 (90%, 30 min at 25–30 °C), to give a stable dark brown iodinating solution containing I^+ (i.e. $IOSO_3H$) intermediates; 1.1 equivalents were required for the monoiodination of benzoic acid, while two equivalents were required for the monoiodination of nitrobenzene. Only the $I_2/NaIO_3/H_2SO_4$ liquid system was next used to effectively mono- or diiodinate a considerable number of more or less deactivated arenes, according to the following stoichiometries:

$5\ ArH + 2\ I_2 + NaIO_3 + H_2SO_4 \rightarrow 5\ \mathbf{ArI} + NaHSO_4 + 3\ H_2O$ (monoiodination)

$2.5\ H\text{-}Ar\text{-}H + 2\ I_2 + NaIO_3 + H_2SO_4 \rightarrow 2.5\ \mathbf{I\text{-}Ar\text{-}I} + NaHSO_4 + 3\ H_2O$ (diiodination)

Generally, the arenes reacted with the previously prepared iodinating solution at 25–30 °C for 1–2 hours giving the desired products in 33–85% yield, by two different methods.[7] For nitrobenzene, benzoic acid and other deactivated arenes, which can be partly diiodinated only by a large excess of iodinating solution, a 'direct' method of aromatic monoiodination was applied: the arenes were added in one portion to the iodinating solution and stirred at 25–30 °C for one hour. However, some mildly deactivated arenes readily formed mixtures of mono- and diiodinated products, which were difficult to separate, for example, methoxy or methyl *para*-substituted benzoic acids and nitrobenzenes. An 'inverse' method of monoiodination was preferred to obtain pure monoiodinated crude products: the mildly deactivated arenes were suspended in 90% H_2SO_4, the iodinating solution was added very slowly (45 min) at 25–30 °C, and stirring was continued at the same temperature for a further 15 minutes to complete the reactions. The simpler 'direct' method of aromatic iodination was preferable for the diiodination of arenes.[7]

In order to further extend and improve our iodination procedures,[7] herein we describe numerous oxidative iodination reactions, employing $I_2/NaIO_4/H_2SO_4$ and, for the sake of comparison, $KI/NaIO_4/H_2SO_4$, with a variety of more or less deactivated arenes, including nitrobenzene (Tables 1– 3). It was convenient to change the concentration of H_2SO_4 from 90% to the commercially available 95% to avoid the hazardous dilution of 95% H_2SO_4. Increasing the concentration of H_2SO_4 to 95%, has resulted in a greater oxidizing ability at 25–30 °C, however, in only a few cases it has had some negative consequences (vide infra). According to Merkushev,[2] the replacement of elemental iodine, usually requiring careful grinding before use, by readily accessible and cheap alkali iodides, is often convenient, although larger quantities of the oxidants are required in such oxidative iodination reactions. However, in the application of periodic acid, iodic acid, or their alkali salts as the oxidants in the oxidative aromatic iodination reactions[8] nearly all the iodine atoms present in the oxidant are incorporated into the iodinated final products (an eco-friendly factor);[8] hence, the said disadvan-

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Table 1 'Direct' Monoiodination[a]

Substrate	Product	Equiv I^+	Yield (%)[b]		Mp (°C)	Lit. mp (°C)
			$I_2/NaIO_4$	$KI/NaIO_4$		
C_6H_5COOH	$3\text{-}IC_6H_4COOH$	1.1	80	82	186–188 (CCl_4)	187–188[10]
$4\text{-}ClC_6H_4COOH$	$4\text{-}Cl\text{-}3\text{-}IC_6H_3COOH$	1.1	82	84	214–215 (aq AcOH)	216–217[10]
$4\text{-}BrC_6H_4COOH$	$4\text{-}Br\text{-}3\text{-}IC_6H_3COOH$	1.1	91	89	243–244 (aq AcOH)	243–245[10]
$4\text{-}IC_6H_4COOH$	$3,4\text{-}I_2C_6H_3COOH$	1.1	67	65	267–268 (EtOH)	265–266[7], 258–259[10]
$4\text{-}RC_6H_4COOH$[c]	$3\text{-}I\text{-}4\text{-}RC_6H_3COOH$[c]	1.5	64	65	228–230 (aq EtOH)	230[10]
$C_6H_5COOCH_3$	$3\text{-}IC_6H_4COOCH_3$	1.5	80	78	51–52 (PE)	50–52[8]
$C_6H_5CONH_2$	$3\text{-}IC_6H_4CONH_2$	1.1	69	70	186–187 (EtOH–H_2O)	186.5[10]
$C_6H_5SO_2NH_2$	$3\text{-}IC_6H_4SO_2NH_2$	1.1	72	71	152–153 (H_2O)	152–153[11]
C_6H_5CHO	$3\text{-}IC_6H_4CHO$	1.5	63[d]	62[d]	54–55 (PE)	53–54,[7] 57[10]
$4\text{-}FC_6H_4CHO$	$4\text{-}F\text{-}3\text{-}IC_6H_3CHO$[e]	1.1	54	56	63–64 (EtOH–H_2O)	–[12]
$4\text{-}ClC_6H_4CHO$	$4\text{-}Cl\text{-}3\text{-}IC_6H_3CHO$	1.1	61	63	113–116 (EtOH)	117[10]
$C_6H_5NO_2$	$3\text{-}IC_6H_4NO_2$	2	87	89	35–36 (EtOH)	37–38,[8] 38[10]

[a] Unless otherwise stated 95% H_2SO_4 was used.

[b] Satisfactory microanalyses obtained for the purified products I ±0.3. Product formation and purity confirmed by TLC and NMR spectroscopy (not shown here). The yields given are optimized.

[c] R = acetylamino group.

[d] Benzaldehyde was 'directly' monoiodinated with 90% H_2SO_4.

[e] Anal. Calcd for C_7H_4FIO: C, 33.62; H, 1.61; I, 50.76. Found: C, 33.5; H, 1.5; I, 50.6.[12]

tage of replacing the diiodine by alkali iodides is lessened in part.

In the present work we have followed the same experimental procedure as previously reported.[7] The iodinating solutions were prepared by stirring $NaIO_4$ (an oxidizing and iodinating reagent) with either I_2 or KI in warm (25–30 °C) 95% H_2SO_4 for 30 minutes. The 'direct' method of aromatic iodination was mostly used for the mono- or diiodination of arenes shown in Tables 1 and 3, while the 'inverse' method of aromatic iodination was used for the monoiodination of arenes shown in Table 2. As previously,[7] the reaction mixtures were poured into ice water when the reaction was complete. The isolated mono- or diiodinated crude solid products were recrystallized to give the pure iodinated products in 31–91% optimized yields (Tables 1– 3).

'Direct' monoiodination gave aromatic iodides in 54–91% yields. It is remarkable that the both iodinating systems afforded practically the same final yields within the limits of experimental error (ca. ±2%). The stoichiometry of these monoiodination reactions is shown in Scheme 1.[7]

$$3\,I_2 + I(VII) \longrightarrow 7\,\mathbf{I}^+ \text{ (preliminary stoichiometry)}$$

$$NaIO_4 + H_2SO_4 \longrightarrow NaHSO_4 + HIO_4 \text{ (true oxidant in this system)}^{8}$$

$$3\,I_2 + HIO_4 + 7\,H_2SO_4 \longrightarrow 4\,H_2O + 7\,IOSO_3H \text{ (iodinating agent)}^{7,8}$$

$$7\,ArH + 7\,IOSO_3H \longrightarrow 7\,ArI + 7\,H_2SO_4 \text{ (arenium ion mechanism, } S_E2)^{2}$$

$$7\,ArH + 3\,I_2 + NaIO_4 + H_2SO_4 \xrightarrow[\text{25–30 °C, 1 h}]{\text{concd } H_2SO_4} 7\,\mathbf{ArI} + NaHSO_4 + 4\,H_2O$$

$$3\,I^- + I(VII) \longrightarrow 4\,\mathbf{I}^+ \text{ (preliminary stoichiometry)}$$

$$NaIO_4 + H_2SO_4 \longrightarrow NaHSO_4 + HIO_4 \text{ (true oxidant in this system)}^{8}$$

$$3\,KI + 3\,H_2SO_4 \longrightarrow 3\,KHSO_4 + 3\,HI$$

$$3\,HI + HIO_4 + 4\,H_2SO_4 \longrightarrow 4\,H_2O + 4\,IOSO_3H \text{ (iodinating agent)}^{7,8}$$

$$4\,ArH + 4\,IOSO_3H \longrightarrow 4\,ArI + 4\,H_2SO_4 \text{ (arenium ion mechanism, } S_E2)^{2}$$

$$4\,ArH + 3\,KI + NaIO_4 + 4\,H_2SO_4 \xrightarrow[\text{25–30 °C, 1 h}]{\text{concd } H_2SO_4} 4\,\mathbf{ArI} + 3\,KHSO_4 + NaHSO_4 + 4\,H_2O$$

Scheme 1

Table 2 'Inverse' Monoiodination[a]

Substrate	Product	Equiv I^+	Yield[b] (%)		Mp (°C)	Lit. mp (°C)
			$I_2/NaIO_4$	$KI/NaIO_4$		
4-$CH_3C_6H_4COOH$	3-I-4-$CH_3C_6H_3COOH$	1.1	79	78	210–212 (EtOH)	208–212[10]
4-$CH_3OC_6H_4COOH$	3-I-4-$CH_3OC_6H_3COOH$	1.1	80	81	247–249 (EtOH)	242–243,[7] 233–234[10]
4-$CH_3OC_6H_4COOCH_3$	3-I-4-$CH_3OC_6H_3COOCH_3$	1.1	65[c]	67[c]	96–98 (EtOH)	95–97[10]
4-$CH_3C_6H_4CHO$	3-I-4-$CH_3C_6H_3CHO$	1.1	56	57	112–113 (EtOH)	112–114[10]
4-$CH_3C_6H_4NO_2$	3-I-4-$CH_3C_6H_3NO_2$	1.1	72	70	53–55 (EtOH)	55–56,[7] 61[10]
4-$CH_3OC_6H_4NO_2$	3-I-4-$CH_3OC_6H_3NO_2$	1.1	81	82	98–99 (EtOH)	97[10]
2-$CH_3OC_6H_4NO_2$	5-I-2-$CH_3OC_6H_3NO_2$	1.1	67	66	92–93 (EtOH)	93–97[10]

[a] Unless otherwise stated 95% H_2SO_4 was used.

[b] Satisfactory microanalyses obtained for the purified products I ±0.3. Product formation and purity confirmed by TLC and NMR spectroscopy (not shown here). The yields given are optimized.

[c] Methyl anisate was 'inversely' monoiodinated with 90% H_2SO_4.

As previously,[7] we assume that the water present in H_2SO_4 acts as a stronger base than the acid, considerably increasing the general polarity of the prepared iodinating solution according to:

$$H_2O\ (\text{base}) + H_2SO_4\ (\text{excess}) \rightarrow (H_3O)^+ + (HSO_4)^-$$

This strongly favors the full ionization of the iodinating intermediates; $IOSO_3H$ forms the more reactive solvated species I^+ and HSO_4^-. Hence, such iodinating solutions would react as a superelectrophilic iodinating reagent, I^+, capable of readily iodinating various deactivated arenes, including nitrobenzene, under the mild reaction conditions.

All the deactivated arenes were, at first, reacted with iodinating solutions containing 1.1 equivalents and then 1.5 equivalents of the I^+ intermediate (Table 1). For methyl benzoate, 4-acetylaminobenzoic acid, and benzaldehyde, much higher yields were obtained with 1.5 equivalents of the I^+ intermediate, while for the remaining arenes the yields were not increased. Nitrobenzene gave 1-iodo-3-nitrobenzene in optimized 87% and 89% yields when

Table 3 'Direct' Diiodination[a]

Substrate	Product	Equiv I^+	Yield[b] (%)		Mp (°C)	Lit. mp (°C)
			$I_2/NaIO_4$	$KI/NaIO_4$		
4-$CH_3C_6H_4COOH$	3,5-I_2-4-$CH_3C_6H_2COOH$	1.5	80	82	333–334 (EtOH)	334–335[10]
4-$CH_3OC_6H_4COOH$	3,5-I_2-4-$CH_3OC_6H_2COOH$	1.5	72[c]	71[c]	254–256 (EtOH)	253–255[7], 255–256[10]
4-ClC_6H_4COOH	4-Cl-3,5-I_2-C_6H_2COOH	1.1	71	72	289–290 (EtOH)	288–290[7], 303–304[10]
4-BrC_6H_4COOH	4-Br-3,5-I_2-C_6H_2COOH[d]	1.5	71	72	317–318 (EtOH)	–
4-IC_6H_4COOH	3,4,5-$I_3C_6H_2COOH$	1.5	55	56	301–302 (EtOH)	300–302[7], 289–290[10]
4-$CH_3C_6H_4CHO$	3,5-I_2-4-$CH_3C_6H_2CHO$[e]	1.5	64	64	305–307 (EtOH–H_2O)	–
4-$CH_3C_6H_4NO_2$	3,5-I_2-4-$CH_3C_6H_2NO_2$	1.5	88	87	117–118 (EtOH)	115–116[10]
4-$CH_3OC_6H_4NO_2$	3,5-I_2-4-$CH_3OC_6H_2NO_2$	1.5	82	83	131–132 (EtOH)	133–135[10]
$C_6H_5COC_6H_5$	3-$IC_6H_4COC_6H_4I$-3′	1.1	31[f]	32[f]	150–152 (Me_2CO)	152–153[10]
$C_6H_5COCOC_6H_5$	3-$IC_6H_4COCOC_6H_4I$-3′	1.1	45	45	125–127 (EtOH)	124–128[7]
$C_6H_5SO_2C_6H_5$	3-$IC_6H_4SO_2C_6H_4I$-3′	1.1	46	47	121–122 (EtOH)	122–123[7]

[a] Unless otherwise stated 95% H_2SO_4 was used.

[b] Satisfactory microanalyses obtained for the purified products I ±0.3. Product formation and purity confirmed by TLC and NMR spectroscopy (not shown here). The yields given are optimized.

[c] Anisic acid was 'directly' diiodinated with 90% H_2SO_4.

[d] Anal. Calcd for $C_7H_3BrI_2O_2$: C, 18.57; H, 0.67; I, 56.05. Found: C, 18.7; H, 0.7; I. 56.2.

[e] Anal. Calcd for $C_8H_6I_2O$: C, 25.83; H, 1.63; I, 68.24. Found: C, 25.7; H, 1.6; I, 68.4.

[f] Benzophenone was diiodinated at 0–5 °C by the 'inverse' method.

$$3.5\ \text{H-Ar-H} + 3\ I_2 + NaIO_4 + H_2SO_4 \xrightarrow[25\text{–}30\ °C,\ 2\ h]{\text{concd } H_2SO_4} 3.5\ \textbf{I-Ar-I} + NaHSO_4 + 4\ H_2O$$

$$2\ \text{H-Ar-H} + 3\ KI + NaIO_4 + 4\ H_2SO_4 \xrightarrow[25\text{–}30\ °C,\ 2\ h]{\text{concd } H_2SO_4} 2\ \textbf{I-Ar-I} + 3\ KHSO_4 + NaHSO_4 + 4\ H_2O$$

Scheme 2

monoiodinated with an iodinating solution containing two equivalents of the I^+ intermediate. The concentration of H_2SO_4 for monoiodination of benzaldehyde was reduced to 90%; 95% H_2SO_4 afforded a mixture of 3-iodobenzaldehyde and 3-iodobenzoic acid (TLC, NMR spectroscopy). It is probably due to the fact that warming (25–30 °C) the more concentrated H_2SO_4 resulted in a stronger oxidizing ability.

All mildly deactivated arenes (Table 2) were monoiodinated only by 'inverse' methodology in iodinating solutions containing 1.1 equivalents of the I^+ intermediate. The final iodination yields varied from 56%/57% up to 81%/82%. When the 'direct' iodination method was applied, the crude products thus obtained were strongly contaminated by diiodinated side products (TLC, NMR spectroscopy), and the repeated recrystallizations required considerably lowered the yields of the aryl iodide product.

Finally, several deactivated arenes, as well as benzil and diphenyl sulfone (Table 3) were 'directly' diiodinated at 25–30 °C (120 min). The stoichiometry of these diiodination reactions is shown in Scheme 2.

For 4-toluic acid, anisic acid, 4-bromobenzoic acids, 4-iodobenzoic acids, 4-methylbenzaldehyde, 4-nitrotoluene, and 4-nitroanisole, higher yields were obtained with iodinating solutions containing 1.5 equivalents of the I^+ intermediate, while for the remaining arenes the yields were not increased. For anisic acid, diiodination with 90% H_2SO_4 gave more uniform crude diiodinated products, which were then recrystallized from ethanol to afford pure 3,5-diiodoanisic acid in 71% and 72% yields. Only benzophenone should be diiodinated by the 'inverse' iodinating method at 0–5 °C (120 min), with an iodinating solution containing 1.1 equivalents of I^+ intermediates; otherwise a number of isomeric diiodinated products were formed as side products (TLC, NMR spectroscopy), which were difficult to remove from the desired 3,3′-diiodobenzophenone.[7]

The good yields, mild and easy experimental conditions, and low cost of the commercially available inorganic reagents used for the preparation of stable iodinating solutions are attractive features of the iodination methods presented herein. We have found $NaIO_4$ to be a more efficient oxidant than the $NaIO_3$ formerly applied:[7] $3\ I_2 + I(VII) \rightarrow 7\ \mathbf{I^+}$ as compared with $2\ I_2 + I(V) \rightarrow 5\ \mathbf{I^+}$. The use of commercially available concentrated H_2SO_4 (95%) as the solvent (and reactant) of choice has allowed hazardous dilutions of concentrated H_2SO_4 to be avoided.[7] Also, the possibility of replacing the $I_2/NaIO_4$ iodinating system by the alternative $KI/NaIO_4$ system, while preserving the same iodination yields, is both practical and convenient. Organic solvents are used only for the purification of the crude iodinated products. The strongly acidic waste products can be neutralized, diluted with water, and disposed of without a problem, hence, such iodination reactions are environmentally benign,[8] and in our opinion can be safely scaled up.

In the present work, as previously,[7] we excluded the use of costly *N*-iodoimides, silver salts, and triflic acid, as well as the hazardous use of F_2/N_2 gaseous mixtures, hot oleum, and toxic ICl, formerly recommended in the literature for the effective iodination of deactivated arenes.[7]

The structures of the purified mono- or diiodinated products were confirmed by comparison with known data in the literature (TLC, mp, and ^1H and ^{13}C NMR spectra[9]). Mps (uncorrected) of freshly purified mono- or diiodinated products were within the limits of experimental error (±0.5 °C). Purified iodinated products should be stored in the dark, preferably at 0–5 °C. Satisfactory microanalyses obtained for the purified products, I ±0.3. Theoretical ^1H and ^{13}C NMR spectra were calculated for unknowns and they were in agreement with those obtained. Elemental analyses were carried out at the Institute of Organic Chemistry, the Polish Academy of Sciences, Warsaw. ^1H and ^{13}C NMR spectra were obtained at the Department of Physical Chemistry, Medical University of Warsaw. Commercial reagents and solvents (Aldrich, Lancaster) were used without further purification. Petroleum ether used had a bp range 35–60 °C. Molecular iodine (diiodine) should be finely powdered in order to facilitate its dissolution.

Iodination solutions containing 11 mmol (1.1 equiv), 15 mmol (1.5 equiv), or 20 mmol (2 equiv) of I^+ were used (Tables 1– 3). All iodinations were carried out according to the procedures described; for specific concentrations of iodinating solutions required see Tables 1– 3.

Iodinating Solution; Typical Procedure

Powdered I_2 (1.20 g, 4.73 mmol) and then $NaIO_4$ (0.34 g, 1.59 mmol) [or alternatively: $NaIO_4$ (0.59 g, 2.75 mmol) and KI (1.37 g, 8.25 mmol)] were added slowly portionwise to stirred 95% H_2SO_4 (30 mL). Stirring was continued for 30 min at 25–30 °C to give a dark brown iodinating solution containing ca. 11 mmol (1.1 equiv) of the I^+ intermediate. Iodinating solutions containing ca. 15 mmol or 20 mmol of I^+ were prepared in a similar manner; cf. Ref. 7.

'Direct' Monoiodination of Benzoic Acid; Typical Procedure

Benzoic acid (1.22 g, 10 mmol, 1 equiv) was added in one portion to the iodinating solution containing the I^+ intermediate (1.1 equiv) and the resulting solution was stirred for 1 h at 25–30 °C. Then the reaction mixture was slowly poured into stirred ice water (300 g). The crude solid products were collected by filtration, washed with cold water until the filtrates were neutral, dried preliminarily on the sintered-glass filter by suction, then air-dried in the dark, and recrystallized from CCl_4 (60 mL) to give pure 3-iodobenzoic acid.

'Inverse' Monoiodination of 4-Toluic Acid; Typical Procedure
4-Toluic acid (1.36 g, 10 mmol, 1 equiv) was suspended in stirred 95% H_2SO_4 (10 mL) at 25–30 °C. The iodinating solution (1.1 equiv) was added dropwise over 45 min, while maintaining the temperature at 25–30 °C. Stirring was continued for a further 15 min and the iodination reaction was quenched by slowly pouring the final reaction mixture into stirred ice water (300 g). The reaction was worked up as above and the crude solid was recrystallized from EtOH (12 mL) to give pure 3-iodo-4-toluic acid.

'Direct' Diiodination of 4-Chlorobenzoic Acid; Typical Procedure
4-Chlorobenzoic acid (0.78 g, 5 mmol, 1 equiv) was added in one portion to the iodinating solution (1.1 equiv) and the resulting solution was stirred for 2 h at 25–30 °C. Then the reaction mixture was slowly poured into stirred ice water (300 g). The reaction was worked up as above and the crude solid was recrystallized from EtOH (25 mL) to give pure 4-chloro-3,5-diiodobenzoic acid.

'Inverse' Diiodination of Benzophenone; Typical Procedure
Benzophenone (0.96 g, 5 mmol, 1 equiv) was suspended in cold (0–5 °C) 95% H_2SO_4 (10 mL), then the iodinating solution (1.1 equiv) was added dropwise with stirring over 45 min. The resulting solution was stirred for a further 75 min while keeping the temperature at 0–5 °C. Then the reaction mixture was slowly poured into stirred ice water (300 g). The reaction was worked up as above and the crude solid was recrystallized from acetone (19 mL) to give pure 3,3′-diiodobenzophenone.

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