

Easy, inexpensive and effective oxidative iodination of deactivated arenes in sulfuric acid

Lukasz Kraszkiewicz, Maciej Sosnowski and Lech Skulski*

Chair and Laboratory of Organic Chemistry, Faculty of Pharmacy, Medical University of Warsaw, 1 Banacha Street, 02-097 Warsaw, Poland

Received 2 April 2004; revised 5 July 2004; accepted 28 July 2004

Available online 28 August 2004

Abstract—Two ‘model’ deactivated arenes, benzoic acid and nitrobenzene, were effectively monoiodinated within 1 h at 25–30 °C, with strongly electrophilic I⁺ reagents, prior prepared from diiodine and various oxidants (CrO₃, KMnO₄, active MnO₂, HIO₃, NaIO₃, or NaIO₄) in 90% (v/v) concd sulfuric acid (ca. 75 mol% H₂SO₄). Next, an I₂/NaIO₃/90% (v/v) concd H₂SO₄ exemplary system was used to effectively mono- or diiodinate a number of deactivated arenes. All former papers dealing with the direct iodination of deactivated arenes are briefly reviewed.

© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

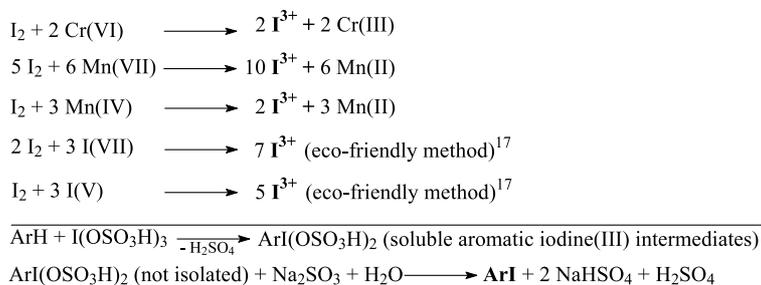
Aromatic iodides are widely used in organic synthesis; hence many different synthetic methods (direct and indirect), or their improvements, have been reported for their effective preparation.¹ Moreover, they are able to form a large variety of stable aromatic iodine(III or V) compounds, which have found increasing applications in modern organic synthesis.² Our two latest reviews^{3,4} 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 attainable from aromatic iodides.

There is a large number of synthetic methods for the direct iodination of activated aromatics, but those suitable for the deactivated ones are less numerous. Initially, diiodine in hot 50–65% oleum, in which the electrophile is probably I₂⁺, has been used to polyiodinate strongly deactivated molecules, but it is difficult to use such systems for partial iodination under controlled conditions.¹ Masson⁵ remarked that I₃⁺ in concentrated sulfuric acid would monoiodinate nitrobenzene and triiodinate chlorobenzene, but his observations were not exploited. Barker and Waters⁶ showed that diiodine and silver sulfate in ca. 90% concd sulfuric acid (in

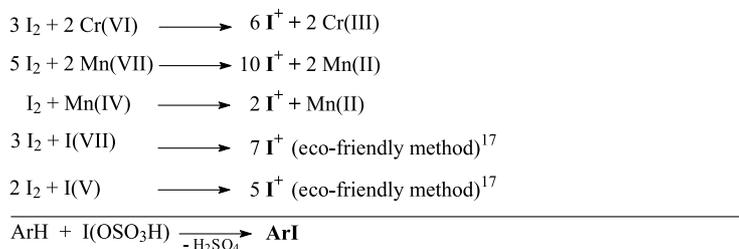
which the iodinating agent is believed to be AgI₂⁺) monoiodinated e.g. nitrobenzene in 55% yield at 100 °C and within ca. 1 h. Arotzky and co-workers⁷ used diiodine in 20% oleum for the iodination of a range of aromatic nitrocompounds. The iodination of nitrobenzene for 19.5 h at room temperature gave 3-iodonitrobenzene in 52% crude yield; at 100 °C with 3 equiv of iodinating agent, 1,3,5-triiodobenzene was obtained in 26% crude yield, similar reaction at 180 °C gave hexaiodobenzene in only 3% crude yield—these were the first examples of iodo-denitration. They also monoiodinated 1,3-dinitrobenzene in 89% crude yield, and diiodinated 1,2-dinitrobenzene in 57% crude yield, at 170–180 °C during 105 min, but they failed to likewise iodinate 1,4-dinitrobenzene. Olah and co-workers⁸ iodinated several deactivated aromatics with *N*-iodosuccinimide (NIS) in trifluoromethanesulfonic acid (triflic acid); it is believed that the active agent is ‘superelectrophilic’ protosolvated iodine(I) triflate, which is generated in situ. For example, at room temperature and within 2 h, 3-iodonitrobenzene was formed from nitrobenzene in 86% yield. Kobayashi and co-workers⁹ reacted various aromatics with diiodine in the presence of silver triflate; it gave e.g. 3-iodonitrobenzene in 45% yield based on the silver salt, when an excess of nitrobenzene was reacted at 150 °C for 1.5 h. Chambers and co-workers¹⁰ passed F₂/N₂ mixtures through the systems containing diiodine and various deactivated arenes suspended in concd H₂SO₄ mixed with various inert co-solvents, at room temperature. In this way, e.g. nitrobenzene afforded 3-iodonitrobenzene in 58–82% crude yields, while 1,3- and 1,4-dinitrobenzenes were unaffected; the details of the said process are still uncertain. Chaikovski, Filimonov and co-workers^{11–13} reported on the

Keywords: Iodoarenes; Deactivated arenes; Iodine; Direct oxidative iodination; Oxidation.

* Corresponding author. Fax: +48-22-5720643;
e-mail: lskulski@farm.amwaw.edu.pl



Scheme 1.



Scheme 2.

effective iodination of numerous deactivated arenes with some very active I^+ species. The superelectrophilic iodinating reagent (reagent ' I^+ ') was primarily prepared¹¹ in the reaction of iodine(I) chloride with silver sulfate in 90% (v/v) concd H_2SO_4 ; mononitroarenes were easily iodinated at 0–20 °C within 15–150 min, while dinitroarenes required heating to 100–170 °C and longer reaction times. Along with the iodination, a side chlorination process also took place to a certain extent. Later, the same Russian chemists¹² effectively iodinated various deactivated arenes, also in 90% (v/v) concd H_2SO_4 , with a new powerful reagent, 2,4,6,8-tetraiodo-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (2,4,6,8-tetraiodoglycoluril, TIG) at 0 °C and within 30–90 min, to obtain 40–82% yields of the purified mono- or diiodinated products. Finally,¹³ they monoiodinated only nitrobenzene (in 79% yield) with NIS in 90% (v/v) concd H_2SO_4 , at room temperature for 20 min. It is known,^{8,14} that *N*-iodoimides can be a useful source of a positive iodine, I^+ , when their reactions proceed in strongly polar and/or acidic media. Lulinski et al.¹⁵ monoiodinated several deactivated arenes, however not nitrobenzene, with sodium periodate used alone as the iodinating reagent. They failed to isolate the expected (and still hypothetical) periodyl intermediates, ArIO_3 . After completing the reactions, carried out in the $\text{NaIO}_4/\text{AcOH}/\text{Ac}_2\text{O}/\text{concd } \text{H}_2\text{SO}_4$ system, they were quenched with aq Na_2SO_3 solutions to give the expected iodoarenes in 45–78% yields.

Previously, we reported (see Ref. 3, pp 1332–1345) on the oxidative iodination of a number of deactivated arenes, including nitrobenzene, always in anhydrous solvent mixtures, $\text{AcOH}/\text{Ac}_2\text{O}/\text{concd } \text{H}_2\text{SO}_4$ (a catalyst and reagent; other inorganic acids were less effective), by using the following oxidants for this purpose: CrO_3 , KMnO_4 , active MnO_2 , NaIO_3 , NaIO_4 , and quite recently a urea-hydrogen peroxide adduct (UHP).¹⁶ In order to

generate in the iodinating mixtures some strongly electrophilic I^{3+} intermediates to afford the effective iodination of some halobenzenes and deactivated arenes, the appropriate combinations of the reactants were used (see Scheme 1).[†] The reactions took place in warm iodinating mixtures containing iodine(III) sulfate or more reactive iodine(III) hydrogensulfate.³ The cooled reaction mixtures were quenched with excess aq Na_2SO_3 solutions to destroy unreacted diiodine and any oxidized species (Scheme 1). After simple workups (see experimental sections in our former papers),^{3,16} the purified iodoarenes were obtained in 18–95% yields. On the other hand, our oxidative iodinations of benzene, some halobenzenes and activated arenes were the most effective by generating in anhydrous solvent mixtures, $\text{AcOH}/\text{Ac}_2\text{O}/\text{concd } \text{H}_2\text{SO}_4$, some less electrophilic I^+ intermediates. The appropriate combinations of the reactants were used (see Scheme 2).¹⁸ The reactions took place in warm iodinating mixtures containing iodine(I) sulfate or more reactive iodine(I) hydrogensulfate³ (Scheme 2). The reactions were quenched with excess aq Na_2SO_3 solutions. After simple workups, the purified iodoarenes were obtained in 22–92% yields.

Taking into account all the aforesaid literature reports, we have tried to achieve the effective oxidative iodination of deactivated arenes, including nitrobenzene, with some strongly electrophilic I^+ intermediates, simply generated from diiodine and various oxidants according to Scheme 2, but in 90% (v/v) concd H_2SO_4 . In our opinion, water present there in a deficit, ca. 25 mol% H_2O , acts as a stronger base, considerably increasing the general polarity of so prepared

[†] See the following review in which such stable, though strongly hygroscopic, compounds as $\text{I}_2(\text{SO}_4)_3$, $\text{I}(\text{OSO}_3\text{H})_3$, ArISO_4 , and $\text{ArI}(\text{OSO}_3\text{H})_2$ are discussed and referred to the literature: Kasumov, T. M.; Koz'min, A. S.; Zefirov, N. S. *Usp. Khim.* **1997**, *66*, 936–952; *Russ. Chem. Rev.* **1997**, *66*, 843–857.

iodinating systems: H_2O (a base) + H_2SO_4 (in excess) \rightarrow $(\text{H}_3\text{O})^+(\text{HSO}_4)^-$. This favors the full ionization of the iodinating intermediates, IOSO_3H , to form more reactive solvated species, I^+ and HSO_4^- . We have expected that such iodinating solutions would react as the super-electrophilic iodinating reagents, I^+ , capable to iodinate various deactivated arenes. Our expectations have indeed been fulfilled to a great extent (vide infra).

2. Results and discussion

At first, we carried out the preliminary oxidative iodination reactions as follows: finely powdered diiodine was suspended in 90% (v/v) concd H_2SO_4 , followed by an oxidant added portionwise with stirring and keeping the temperature below 30 °C; altogether, seven various inorganic oxidants (Table 1) were checked out by us experimentally. The stirring was continued for 30 min at 25–30 °C to afford dark brown solutions having very strong iodinating properties—which remained virtually unchanged, even after their storing for several days in the dark at room temperature. We have found that for the most effective monoiodination of benzoic acid (a ‘model’ moderately deactivated arene), the I^+ intermediates generated in the previously prepared iodinating solution should be used in ca. 10% excess, whereas for the most effective monoiodination of nitrobenzene (a ‘model’ strongly deactivated arene) they should be used in ca. 100% excess; see Table 1 for the definite amounts of diiodine and particular

oxidants, as well as for the volumes of 90% (v/v) concd H_2SO_4 , used by us in each of the preliminary iodination reactions. Next, using a ‘direct’ method of aromatic iodination, either benzoic acid or nitrobenzene (10 mmol; 0% excess) was added to the appropriate iodinating solution, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixtures were poured into ice-water, the crude products were collected by filtration, washed with cold water, air-dried in the dark, and recrystallized from appropriate organic solvents (Table 1). These experiments confirmed our former expectations (vide supra). We extended the said ‘direct’ iodination method onto a number of deactivated arenes; for more details see the experimental section, and the yields given in Table 2 (in brackets).

Furthermore we selected, just for example, only one of the above iodinating systems, viz. $\text{I}_2/\text{NaIO}_3/90\%$ (v/v) concd H_2SO_4 (Table 1), to effectively mono- or diiodinate a number of more or less deactivated arenes (Table 2). However, we have established experimentally that more uniform crude products were obtained from mildly deactivated arenes, forming readily the hardly separable mixtures of mono- and diiodinated products, when an ‘inverse’ method of aromatic iodination was applied; see Section 4.2.6. in the experimental section. Next, this method was consequently used for all substrates shown in Table 2. In this case, the appropriate iodinating solutions were very slowly added dropwise to the stirred suspensions of iodinated arenes in given volumes of 90% (v/v) concd H_2SO_4 . After completing the reactions within 1 h, mostly at 25–30 °C, the reaction mixtures were poured into ice-water, and the precipitated monoiodinated products were worked up as above. When some arenes were purposely diiodinated (Table 2), we used only half of their amounts, i.e. 5 mmol, with respect to those used for their monoiodination, i.e. 10 mmol, and the diiodination reaction times were prolonged to 2 h. Generally, all the iodinated arenes, taken in strictly stoichiometric amounts (0% excess), were always reacted with the iodinating solutions used in the excesses: 10, 50, or 100%. For more details see the Section 4.

It is possible to put forward some plausible reaction paths for the oxidative iodination of deactivated arenes with the applied $\text{I}_2/\text{NaIO}_3/90\%$ (v/v) concd H_2SO_4 liquid system, as well as to derive the resulting stoichiometries (Scheme 3). For the other iodinating systems shown in Table 1, a similar reasoning is applicable; see Ref. 3, pp 1332–1345.

In Scheme 3 we suggest that the apparently less reactive I_2SO_4 intermediates (in our opinion, 2I^+ and SO_4^{2-} are there more tightly bound together than I^+ and HSO_4^- in iodine(I) hydrogensulfate)³ would react with excess H_2SO_4 to give the more reactive IOSO_3H intermediates, which are fully ionized in very strongly polar iodinating solutions. This is why all the iodinating solutions applied in this work do represent, in fact, the super-electrophilic iodinating reagents, I^+ , capable to iodinate various deactivated arenes, including nitrobenzene, under relatively mild conditions, in good yields, and within short times; see our results shown in Tables 1 and 2, as well as the reaction conditions reported in the experimental section.

Table 1. Monoiodination of benzoic acid or nitrobenzene: reaction conditions and final yields of pure products, using the ‘direct’ method of aromatic iodination

90% concd H_2SO_4 (mL)	Diiodine (g; mmol)	Oxidant (g; mmol)	Yield ^a (%)
(a) Oxidative iodination of PhCOOH (1.22 g; 10 mmol; 0% excess) to give pure 3-iodobenzoic acid, mp 187–188 °C (from CCl_4) ^b ; lit. ¹² mp 185–186 °C (from 50% aq <i>i</i> -PrOH)			
37.5	1.40; 5.5	CrO_3 ; 0.37; 3.7	78
37.5	1.40; 5.5	KMnO_4 ; 0.35; 2.2	80
37.5	1.40; 5.5	MnO_2 (85%); 0.56; 5.5	68
37.5	1.40; 5.5	MnO_2 (90%); 0.53; 5.5	85
30.0	1.12; 4.4	HIO_3 ; 0.39; 2.2	80
30.0	1.12; 4.4	NaIO_3 ; 0.44; 2.2	80
32.0	1.20; 4.7	NaIO_4 ; 0.34; 1.6	80
(b) Oxidative iodination of PhNO_2 (1.23 g; 10 mmol; 0% excess) to give pure 3-iodonitrobenzene, mp 37–38 °C (from petroleum ether); lit. ¹³ mp 35–36 °C (from EtOH)			
68.0	2.54; 10.0	CrO_3 ; 0.67; 6.7	77
68.0	2.54; 10.0	KMnO_4 ; 0.63; 4.0	61
68.0	2.54; 10.0	MnO_2 (85%); 1.0; 10.0	69
68.0	2.54; 10.0	MnO_2 (90%); 0.96; 10.0	76
55.0	2.03; 8.0	HIO_3 ; 0.70; 4.0	75
55.0	2.03; 8.0	NaIO_3 ; 0.79; 4.0	85
58.0	2.18; 8.6	NaIO_4 ; 0.61; 2.8	70

^a The given yields were optimized.

^b From our repeated crystallization experiments with crude 3-IC₆H₄-COOH we have established that CCl_4 was a most effective and selective solvent as compared with 50% aq *i*-PrOH¹² or CHCl_3 ; the respective crystallization losses were as follows: 17, 25, and 22%, and the product recrystallized once from CCl_4 showed a higher purity (mp, TLC).

Table 2. Final yields and melting points (uncorrected) of pure monoiodinated or diiodinated products, with using the I₂/NaIO₃/90% (v/v) concd H₂SO₄ iodinating systems. These results were obtained by the ‘inverse’ method of aromatic iodination. For comparison, also the yields obtained by the ‘direct’ iodination method are given below (in brackets), while the corresponding melting points were practically the same

Substrate	Product	Yield ^a (%)	Mp (°C)/S ^b	Lit. mp (°C)
(a) Oxidative monoiodination of some deactivated arenas				
C ₆ H ₅ NO ₂ ^c	3-IC ₆ H ₄ NO ₂	83 (85)	37–38/P	35–36 ¹³
4-CH ₃ C ₆ H ₄ NO ₂	3-I-4-CH ₃ C ₆ H ₃ NO ₂	74	55–56/E	54–56 ^{11a}
2-CH ₃ OC ₆ H ₄ NO ₂	5-I-2-CH ₃ OC ₆ H ₃ NO ₂	76	97–99/E	97 ²⁰
4-CH ₃ OC ₆ H ₄ NO ₂	3-I-4-CH ₃ OC ₆ H ₃ NO ₂	84	93–96/E	97 ²⁰
4-IC ₆ H ₄ NO ₂ ^d	3,4-I ₂ C ₆ H ₃ NO ₂	56 (58)	108–110/E	109–111 ^{11b}
C ₆ H ₅ COOH	3-IC ₆ H ₄ COOH	78 (80)	187–188/C	185–186 ¹²
4-ClC ₆ H ₄ COOH	4-Cl-3-IC ₆ H ₃ COOH	82 (83)	215–216/B	216–217 ²⁰
4-IC ₆ H ₄ COOH	3,4-I ₂ C ₆ H ₃ COOH	46 (46)	265–266/E	258–259 ²⁰
4-CH ₃ C ₆ H ₄ COOH	3-I-4-CH ₃ C ₆ H ₃ COOH	77 ^e	208–210/E	210–212 ²⁰
4-CH ₃ OC ₆ H ₄ COOH	3-I-4-CH ₃ OC ₆ H ₃ COOH	80 ^e	242–243/E	233–234 ²⁰
C ₆ H ₅ COOCH ₃	3-IC ₆ H ₄ COOCH ₃	76 (78)	50–51/P	50–52 ¹⁷
4-CH ₃ OC ₆ H ₄ COOCH ₃	3-I-4-CH ₃ OC ₆ H ₃ COOCH ₃	67	97–98/E	95–97 ²⁰
C ₆ H ₅ CONH ₂ ^d	3-IC ₆ H ₄ CONH ₂	74 (74)	185–187/E	186.5 ²⁰
C ₆ H ₅ SO ₂ NH ₂ ^d	3-IC ₆ H ₄ SO ₂ NH ₂	77 (79)	151–152/W	152–153 ²¹
C ₆ H ₅ CHO ^d	3-IC ₆ H ₄ CHO	57 (56)	53–54/E	54–56 ¹²
4-ClC ₆ H ₄ CHO	4-Cl-3-IC ₆ H ₃ CHO	73 (73)	114–116/E	117 ²⁰
C ₆ H ₅ I	1,4-I ₂ C ₆ H ₄	50 ^e	125–126/E	128–129 ¹²
(b) Oxidative diiodination of some deactivated arenes				
4-CH ₃ C ₆ H ₄ NO ₂ ^d	3,5-I ₂ -4-CH ₃ C ₆ H ₂ NO ₂	77 (77)	111–113/E	115–116 ^{11b}
4-CH ₃ OC ₆ H ₄ NO ₂ ^d	3,5-I ₂ -4-CH ₃ OC ₆ H ₂ NO ₂	78 (78)	130–132/E	133–135 ²⁰
4-ClC ₆ H ₄ COOH ^d	4-Cl-3,5-I ₂ C ₆ H ₂ COOH	73 (74)	288–290/E	303–304 ²²
4-IC ₆ H ₄ COOH ^d	3,4,5-I ₃ C ₆ H ₂ COOH	54 ^f (57)	300–302/E	289–290 ²⁰
4-CH ₃ C ₆ H ₄ COOH ^d	3,5-I ₂ -4-CH ₃ C ₆ H ₂ COOH	68 (71)	330–332/D	334–335 ²³
4-CH ₃ OC ₆ H ₄ COOH ^d	3,5-I ₂ -4-CH ₃ OC ₆ H ₂ COOH	66 (66)	253–255/E	255–256 ²⁰
C ₆ H ₅ COC ₆ H ₅	3-IC ₆ H ₄ COC ₆ H ₄ I-3'	33 ^e	151–153/A	152–153 ²⁰
C ₆ H ₅ SO ₂ C ₆ H ₅ ^d	3-IC ₆ H ₄ SO ₂ C ₆ H ₄ I-3'	61 (61)	122–123/E	122–123 ²⁴
C ₆ H ₅ COCOC ₆ H ₅	3-IC ₆ H ₄ COCOC ₆ H ₄ I-3'	54	124–126/E	127–128 ^{11a}

^a The given yields were optimized. Satisfactory microanalyses obtained for the purified products: I ± 0.3%; their purities and homogeneities were checked by TLC and ¹H NMR spectra (not shown here).¹⁹

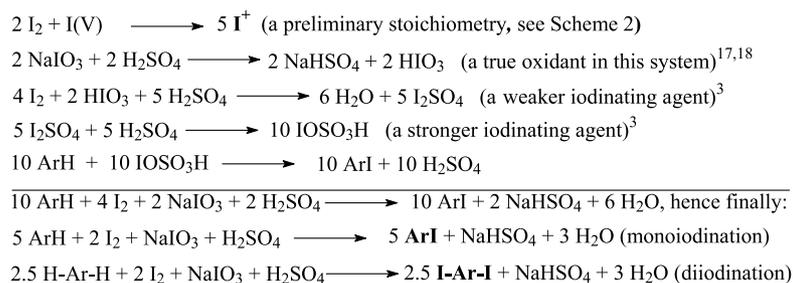
^b Solvent (S) used for crystallization: A—Me₂CO; B—aq AcOH; C—CCl₄; D—extracted with boiling EtOH and hot-filtered; E—EtOH; P—petroleum ether, bp 35–60 °C; W—water.

^c Nitrobenzene was monoiodinated with the previously prepared iodinating solution containing the I⁺ intermediates in ca. 100% excess.

^d The respective deactivated arenes were iodinated with the previously prepared iodinating solutions containing the I⁺ intermediates in ca. 50% excess. Except of nitrobenzene, the remaining ones were iodinated with the previously prepared iodinating solutions containing the I⁺ intermediates in ca. 10% excess.

^e The respective iodination reactions were carried out at 0–5 °C, whereas the remaining ones were carried out at 25–30 °C.

^f When we increased the preparative scale 10-fold, the same purified product was obtained in 55% yield, mp 302–303 °C. It can be used as the substrate for preparing X-ray contrasts.



Scheme 3.

3. Conclusions

The good yields, mild and easy experimental conditions, and low prices of the commercial inorganic reagents used for preparing the fairly stable iodinating solutions are attractive features of this novel oxidative iodination method. In our work, we excluded the use of costly *N*-iodoimides, silver salts, and triflic acid, formerly applied (vide supra) for the effective iodination of deactivated arenes. We also

excluded the hazardous uses of F₂/N₂ gaseous mixtures, fuming sulfuric acid (oleum), or toxic iodine(I) chloride. Organic solvents are used only for purification of the crude iodinated products. The strongly acidic wastes left after some of the iodination reactions, i.e. after those with using HIO₃, NaIO₃ or NaIO₄ as the oxidants, can be neutralized, diluted with water, and disposed of without problem—hence, such iodination reactions are environmentally benign,¹⁷ and in our opinion can be safely scaled up.

4. Experimental

4.1. General

The structures of the purified mono- or diiodinated products (their purities and homogeneities were prior checked with TLC), all reported in the literature, were supported by their melting points (uncorrected) compared with the literature data (Tables 1 and 2). The structures were also supported by correct elemental analyses (%I) and ^1H NMR solution spectra (not shown here) compared with the respective spectra of authentic samples.¹⁹ Elemental analyses were carried out at the Institute of Organic Chemistry, The Polish Academy of Sciences, Warsaw. ^1H NMR spectra were run at the Department of Physical Chemistry, Medical University of Warsaw. The commercial reagents and solvents (Aldrich) were used without further purification. Molecular iodine should be finely powdered in order to facilitate its dissolution in the reaction mixtures.

4.2. General procedures, with using the $\text{I}_2/\text{NaIO}_3/90\%$ (v/v) concd H_2SO_4 system

4.2.1. Preparations of three various iodinating solutions.

Definite amounts of finely powdered diiodine and next NaIO_3 were suspended in given volumes of 90% (v/v) concd H_2SO_4 (Table 1). The mixtures were stirred for 30 min at 25–30 °C to give the dark brown iodinating solutions, containing either ca. 11 mmol (10% excess) of the I^+ intermediates [used for the iodination of benzoic acid and several substrates shown in Table 2] or ca. 20 mmol (100% excess) of the I^+ intermediates [used only for the monoiodination of nitrobenzene, Tables 1 and 2]. For the mono- or diiodination of the remaining substrates (Table 2), the iodinating solution containing ca. 15 mmol (50% excess) of the I^+ intermediates was prepared, as above, from diiodine (1.52 g, 6.0 mmol) and NaIO_3 (0.60 g, 3.0 mmol) suspended in 90% (v/v) concd H_2SO_4 (41 mL).

4.2.2. ‘Direct’ monoiodination of benzoic acid; cf. Table 1.

Benzoic acid (1.22 g, 10 mmol, 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 10% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The crude solid product was collected by filtration, washed with cold water until the filtrates were neutral, air-dried in the dark, and recrystallized from CCl_4 (60 mL) to give pure 3-iodobenzoic acid in 80% yield; 1.98 g.

Quite similarly, also 4-chlorobenzoic acid, 4-iodobenzoic acid, methyl benzoate, and 4-chlorobenzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.3. ‘Direct’ monoiodination of benzamide. Benzamide (1.21 g, 10 mmol; 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 50% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized

from ethanol (15 mL) to give pure 3-iodobenzamide in 74% yield; 1.83 g.

Quite similarly, also benzenesulfonamide, benzaldehyde, and 4-iodonitrobenzene (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.4. ‘Direct’ monoiodination of nitrobenzene; cf. Table 1.

Nitrobenzene (1.23 g, 10 mmol; 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 100% excess, and the stirring was continued for 1 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from petroleum ether, bp 35–60 °C (30 mL) to give pure 3-iodonitrobenzene in 85% yield; 2.12 g.

4.2.5. ‘Direct’ diiodination of anisic acid.

Anisic acid (0.76 g, 5 mmol, 0% excess) was added to the iodinating solution containing the I^+ intermediates in ca. 50% excess, and the stirring was continued for 2 h at 25–30 °C. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (16 mL) to give pure 3,5-diiodoanisic acid in 66% yield; 1.34 g.

Quite similarly, also 4-nitrotoluene, 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, 4-toluic acid, and diphenyl sulfone (5 mmol, 0% excess) were diiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (in brackets).

4.2.6. ‘Inverse’ monoiodination of benzoic acid.

Benzoic acid (1.22 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H_2SO_4 (20 mL) at 25–30 °C. While keeping the same temperature, we slowly added dropwise, with stirring and within 45 min, the iodinating solution containing the I^+ intermediates in ca. 10% excess, and the stirring was continued at 25–30 °C for a further 15 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from CCl_4 (60 mL) to give pure 3-iodobenzoic acid in 78% yield; 1.94 g.

Quite similarly, also 4-nitrotoluene, 2- and 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, methyl benzoate, methyl anisate, and 4-chlorobenzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

Note. 4-Toluic acid, anisic acid, and iodobenzene (10 mmol, 0% excess) were similarly monoiodinated, but their iodination reactions were carried out at 0–5 °C to give more uniform crude products as compared with those obtained at 25–30 °C (TLC).

Some mildly deactivated arenes, viz. 4-nitrotoluene, 2- and

4-nitroanisole, 4-toluic acid, anisic acid, and its methyl ester, and iodobenzene were effectively monoiodinated only by the ‘inverse’ method (Table 2). When the same substrates were monoiodinated by the ‘direct’ method, then the corresponding crude products were heavily contaminated by undesirable diiodinated side products (TLC); though their repeated recrystallizations gave the same pure monoiodinated products (mp, %I), but the unavoidable crystallization losses lowered the yields by ca. 20–50%.

4.2.7. ‘Inverse’ monoiodination of benzamide. Benzamide (1.21 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H₂SO₄ (20 mL) at 25–30 °C. While keeping the same temperature, we slowly added dropwise, with stirring and within 45 min, the iodinating solution containing the I⁺ intermediates in ca. 50% excess, and the stirring was continued at 25–30 °C for a further 15 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (15 mL) to give pure 3-iodobenzamide in 74% yield; 1.83 g.

Quite similarly, also 4-iodonitrobenzene, benzenesulfonamide, and benzaldehyde (10 mmol, 0% excess) were monoiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

4.2.8. ‘Inverse’ monoiodination of nitrobenzene. The best result was attained as follows: nitrobenzene (1.23 g, 10 mmol, 0% excess) was suspended in 90% (v/v) concd H₂SO₄ (20 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I⁺ intermediates in ca. 100% excess was added at once, in one portion, and the stirring was continued at 25–30 °C for 1 h. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from petroleum ether, bp 35–50 °C (30 mL) to give pure 3-iodonitrobenzene in 83% yield; 2.07 g.

4.2.9. ‘Inverse’ diiodination of benzil. Benzil, diphenylethanedione (1.05 g, 5 mmol, 0% excess) was suspended in 90% (v/v) concd H₂SO₄ (10 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I⁺ intermediates in ca. 10% excess was slowly added dropwise, with stirring and within 45 min. The stirring was continued at 25–30 °C for a further 75 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (15 mL) to give pure 3,3'-diiodobenzil in 54% yield; 1.25 g. cf. Ref. 25.[‡]

Note. Benzophenone (0.91 g, 5 mmol, 0% excess) was similarly diiodinated, but its iodination reaction was carried

out at 0–5 °C to give a fairly uniform crude product, which was recrystallized from acetone to give pure 3,3'-diiodobenzophenone in only 33% yield; 0.72 g. At 25–30 °C, the final crude product was notably contaminated with hardly separable isomeric admixtures, and with a trace of a triiodinated benzophenone (TLC, %I).

4.2.10. ‘Inverse’ diiodination of 4-nitrotoluene. 4-nitrotoluene (0.68 g, 5 mmol, 0% excess) was suspended in 90% (v/v) concd H₂SO₄ (10 mL) at 25–30 °C. While keeping the same temperature, the iodinating solution containing the I⁺ intermediates in ca. 50% excess was slowly added dropwise, with stirring and within 45 min. The stirring was continued at 25–30 °C for a further 75 min. The final reaction mixture was poured, with stirring, into ice-water (300 g). The following workup was the same as above; see Section 4.2.2. The crude solid product was recrystallized from ethanol (27 mL) to give pure 2,6-diiodo-4-nitrotoluene in 77% yield; 1.50 g.

Quite similarly, also 4-nitroanisole, 4-chlorobenzoic acid, 4-iodobenzoic acid, 4-toluic acid, anisic acid, and diphenyl sulfone (5 mmol, 0% excess) were diiodinated. After recrystallizations from appropriate solvents, the respective yields are given in Table 2 (without brackets).

These results were partly presented at the XLVIth Annual Meeting of the Polish Chemical Society, Lublin, 15–18 September, 2003.

References and notes

- (a) Roedig, A. *Houben-Weyl, Methoden der organischen Chemie* **1960**, Vol. V/4, 517–678. (b) Merkushev, E. B. *Synthesis* **1988**, 923–937.
- (a) Varvoglis, A. *The Organic Chemistry of Polycordinated Iodine*; VCH: Weinheim, 1992. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, 96, 1123–1178. (c) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, 102, 2523–2584. (e) Stang, P. J. *J. Org. Chem.* **2003**, 68, 2997–3008. (f) *Hypervalent Iodine Chemistry Topics in Current Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2003; Vol. 224.
- Skulski, L. *Molecules* **2000**, 5, 1331–1371 <http://www.mdpi.org/molecules>.
- Skulski, L. *Molecules* **2003**, 8, 45–52 <http://www.mdpi.org/molecules>.
- Masson, I. *J. Chem. Soc.* **1938**, 1708–1712.
- Baker, I. R. L.; Waters, W. A. *J. Chem. Soc.* **1952**, 150–153.
- Arotzky, J.; Butler, R.; Darby, A. C. *J. Chem. Soc. (C)* **1970**, 1480–1485.
- Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, 58, 3194–3195.
- Kobayashi, Y.; Kumadaki, I.; Yoshida, T. *J. Chem. Res. (S)* **1997**, 215.
- Chambers, R. D.; Skinner, C. J.; Atherton, M. J.; Moilliet, J. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1659–1664.
- (a) Chaikovski, V. K.; Kharlova, T. S.; Filimonov, V. D.; Saryucheva, T. A. *Synthesis* **1999**, 748–750. (b) Chaikovski,

[‡] The diiodination of benzil, at 90 °C for 2 h, with an I₂/Ag₂SO₄/90% H₂SO₄ system, gave the crude product (84%) containing 85.1% 3,3'-, 14.7% 2,2'-, and only 0.2% 4,4'-diiodobenzil. It shows that on increasing the iodination temperatures, the undesirable admixtures of isomeric side products are enlarged.

- V. K.; Kharlova, T. S.; Filimonov, V. D. *Russ. Chem. Bull.* **1999**, *48*, 1291–1294. (c) Chaikovski, V. K.; Filimonov, V. D.; Kharlova, T. S.; Chernova, T. N.; Sharapova, E. S. *Russ. J. Org. Chem.* **2000**, *36*, 666–670.
12. Chaikovski, V. K.; Filimonov, V. D.; Yagovkin, Yu. A.; Kharlova, T. S. *Tetrahedron Lett.* **2000**, *41*, 9101–9104.
13. Chaikovski, V. K.; Skorokhodov, V. I.; Filimonov, V. D. *Russ. J. Org. Chem.* **2001**, *37*, 1503–1504.
14. Koval', I. V. *Russ. J. Org. Chem.* **2002**, *38*, 301–337. A review on *N*-haloimides.
15. Lulinski, P.; Sosnowski, M.; Skulski, L. Paper A013 presented at the 7th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-7), Nov 1–30, 2003; <http://www.mdpi.net/ecsoc-7>.
16. Lulinski, P.; Kryska, A.; Sosnowski, M.; Skulski, L. *Synthesis* **2004**, 441–445. Benzoic acid was monoiodinated in 81% yield, while nitrobenzene was unaffected.
17. Lulinski, P.; Skulski, L. *Bull. Chem. Soc. Jpn* **2000**, *73*, 951–956.
18. Wirth, H. O.; Koenigstein, O.; Kern, W. *Liebigs Ann. Chem.* **1960**, *634*, 84–104, see footnote in p 90.
19. Lulinski, P. Ph.D. Thesis (in Polish), Faculty of Pharmacy, Medical University of Warsaw, Poland, 2002.
20. *Dictionary of Organic Compounds*, 6th ed.; Chapman & Hall: London, 1996.
21. Langmuir, A. C. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 90–96.
22. Borrows, E. T.; Clayton, J. C.; Hems, B. A. *J. Chem. Soc., (S)* **1949**, 185–190.
23. Arotzky, J.; Butler, R.; Darby, A. C. *Chem. Commun.* **1966**, 650.
24. Burchfield, H. P.; Storrs, E. E.; Wheeler, R. J.; Bhat, V. K.; Green, L. L. *Anal. Chem.* **1973**, *45*, 916–920.
25. Novikov, A. N.; Grigor'ev, M. G. *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **1977**, *20*, 1716–1717. *Chem. Abstr.* **1978**, *88*, 89293.