

1,3-Diiodo-5,5-dimethylhydantoin—An Efficient Reagent for Iodination of Aromatic Compounds

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Abstract—1,3-Diiodo-5,5-dimethylhydantoin in organic solvents successfully iodates alkylbenzenes, aromatic amines, and phenyl ethers. The reactivity of electrophilic iodine is controlled by acidity of the medium. Superelectrophilic iodine generated upon dissolution of 1,3-diiodo-5,5-dimethylhydantoin in sulfuric acid readily reacts with electron-deficient arenes at 0 to 20°C with formation of the corresponding iodo derivatives in good yields. The structure of electrophilic iodine species generated from 1,3-diiodo-5,5-dimethylhydantoin in sulfuric acid is discussed.

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More than 40 years ago Orazi et al. [1] made an attempt to effect iodination of phenol derivatives, aromatic amines, and some electron-rich heterocycles with 1,3-diiodo-5,5-dimethylhydantoin (**I**, 1,3-diiodo-5,5-dimethylimidazolidine-2,4-dione). Most syntheses were carried out in acetone as solvent. We showed that acetone is capable of reacting with compound **I** to give some amount of lacrimatory iodoacetone. Presumably, this is the reason why the developed procedure has not found subsequent application despite quite satisfactory results.

The goal of the present work was to study in detail preparative potential of 1,3-diiodo-5,5-dimethylhydantoin in iodination of aromatic compounds in organic solvents and in sulfuric acid, as well as to elucidate the nature of electrophilic iodine species generated in sulfuric acid.

1,2,4,5-Tetramethylbenzene (**IIa**, durene) was selected as model compound for studying the efficiency of solvents (methanol, ethanol, acetic acid, dioxane,

tetrachloromethane, and acetone) in the iodination of arenes with donor substituents. Sulfuric acid was used as catalyst (H₂SO₄, 2 ml per 10 mmol of **I**). The reactions were carried out at 20°C. In most solvents, iododurene (**IIb**) separated from the reaction mixture even in 1–2 min after addition of H₂SO₄; however, the product often contained impurities that hindered its isolation or reduced its melting point. When the reaction was performed in acetone, the products were clearly lacrimatory, so that the isolation and purification procedures were complicated. Using dioxane as solvent, we obtained a mixture consisting of initial arene **IIa** and mono- and diiododurenes **IIb** and **IIc**. Quite satisfactory results were obtained in methanol and ethanol, but the most effective was the system **I**–AcOH–H₂SO₄ (yield 85%, mp 75–76°C). This system also ensured successful preparation of diiododurene (**IIc**) in 75% yield (reaction time 30 min). By varying the substrate-to-reagent ratio in acetic acid, we succeeded in synthesizing di- and triiodomesitylenes **IIb**

Scheme 1.

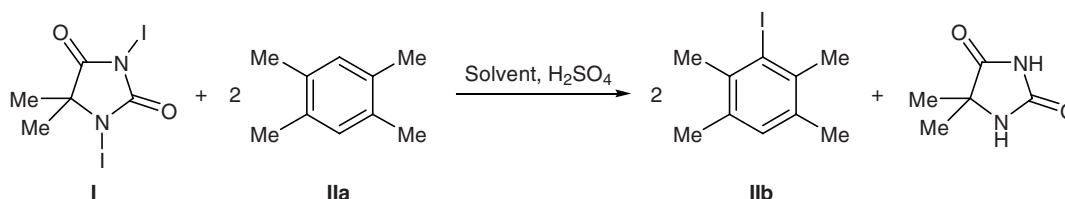


Table 1. Iodination of aromatic compounds with the system 1,3-diiodo-5,5-dimethylhydantoin–organic solvent–H₂SO₄

Substrate (no.)	Solvent	Temperature, °C	Reaction time, min	Product	Yield, %	mp, °C (solvent); published data
Durene (IIa)	EtOH	20	20	Iododurene (IIb)	71	78–79 (EtOH); 78–79 [2]
	AcOH	20	30	1,4-Diiododurene (IIc)	75	137–138 (EtOH); 139 [2]
Mesitylene (IIIa)	AcOH	20	30	1,3-Diiodo-2,4,6-trimethylbenzene (IIIb)	71	74–75 (EtOH); 74–75 [3]
	AcOH	20	30	1,3,5-Triiodo-2,4,6-trimethylbenzene (IIIc)	72	207–208 (DMF); 207–209 [3]
Biphenyl (IVa)	AcOH	20	120	4,4'-Diiodobiphenyl (IVb)	65	202–203 (PrOH); 204 [2]
Fluorene (Va)	Dioxane	20	40	2,7-Diiodofluorene (Vb)	75	208–210 (toluene); 210 [2]
Phenol (VIa)	EtOH	20	30	2,4,6-Triiodophenol (VIb)	80	158–159; 159 [4]
Anisole (VIIa)	EtOH	20	10	4-Iodoanisole (VIIb)	97	51–52 (MeOH); 51–52 [4]
Diphenyl ether (VIIIa)	EtOH	20	15	4,4'-Diiododiphenyl ether (VIIIb)	30	138–139 (EtOH); 140 [2]
Aniline (IXa)	EtOH	0	20	4-Iodoaniline (IXb)	40	67–68 (hexane); 67–68 [4]
	EtOH	20	15	2,4,6-Triiodoaniline (IXc)	90	183–185 (EtOH); 185.5 [4]
4-Iodoaniline (IXb)	EtOH	20	15	2,4,6-Triiodoaniline (IXc)	93	183–185 (EtOH); 185.5 [4]
4-Nitroaniline (Xa)	EtOH	20	30	2-Iodo-4-nitroaniline (Xb)	76	114–115 (EtOH); 115 [4]
Acetanilide (XIa)	EtOH	20	30	4-Iodoacetanilide (XIb)	65	182–183 (EtOH); 183–184 [4]
Diphenylamine (XIIa)	EtOH	0	10	4,4'-Diiododiphenylamine (XIIb)	55	122–124 (80% EtOH); 122–124 [5]

and **IIIc** from mesitylene. It is advisable to use 50% excess of reagent **I** over the theoretical amount to raise the yield of triiodomesitylene (**IIIc**). The reaction of biphenyl (**IVa**) with the system **I**–AcOH–H₂SO₄ gave up to 65% of 4,4'-diiodobiphenyl (**IVb**). The iodination of fluorene (**Va**) in acetic acid leads to the formation of 2,7-diiodofluorene (**Vb**), but its yield does not exceed 40%. The yield of diiodide **Vb** increases to 75% in going from acetic acid to dioxane (Table 1). As in the reaction with **Va**, the iodination of other aromatic compounds required individual solvent selection to improve the yield of iodine-containing products. For example, ethanol turned out to be the most effective solvent in the preparation of iodo-substituted derivatives of phenol (**VIa**), anisole (**VIIa**), diphenyl ether (**VIIIa**), and aromatic amines (Table 1).

The iodination of phenol (**VIa**) in ethanol (even under the conditions corresponding to the synthesis of its monoiodo derivative) was accompanied by formation of some amount of 2,4,6-triiodophenol (**VIb**) which immediately separated from the reaction mixture; in the reaction with equimolar amounts of the reactants, up to 80% of triiodide **VIb** was formed.

Unlike phenol (**VIa**), the iodination of anisole (**VIIa**) selectively afforded 4-iodoanisole (**VIIb**) in high yield. From diphenyl ether (**VIIIa**) we obtained the corresponding diiodo derivative, 4,4'-diiododiphenyl ether (**VIIIb**), in a poor yield, and the yield did not change upon increase of the reaction time to 1.5 h. The reasons for such a behavior of **VIIIa** are unclear.

Aromatic amines readily reacted with the system **I**–EtOH–H₂SO₄ in the temperature range from 0 to 20°C. The iodination of aniline (**IXa**) at 0°C gave 4-iodoaniline (**IXb**), and both aniline (**IXa**) and 4-iodoaniline (**IXb**) at 20°C were converted in 15–20 min into 2,4,6-triiodoaniline (**IXc**) provided that the amount of electrophilic iodine was sufficient. Under analogous conditions, 4-nitroaniline (**Xa**) and acetanilide (**XIa**) were iodinated to 2-iodo-4-nitroaniline (**Xb**) and 4-iodoacetanilide (**XIb**), respectively, in 30 min. Diphenylamine (**XIIa**) turned out to be very reactive. The reaction with **XIIa** as substrate at room temperature was accompanied by strong tarring, but at 0°C the yield of 4,4'-diiododiphenylamine (**XIIb**) reached 55% in 10 min (Table 1). Introduction of each subsequent iodine atom into a substrate molecule requires increase

of the acidity of the medium via addition of appropriate amount of sulfuric acid.

Some moderately deactivated benzene derivatives also reacted with 1,3-diiodo-5,5-dimethylhydantoin in acetic acid containing H_2SO_4 and in trifluoroacetic acid. However, sulfuric acid was the most effective solvent for the iodination of aromatic compounds with electron-withdrawing substituents.

We and other authors previously showed that compounds having an N–I bond, e.g., *N*-iodosuccinimide [6–9] and tetraiodoglycoluril [10], can be successfully used for the iodination of electron-deficient aromatic compounds in strongly acidic media. By removing organic solvent from the system and using only 90% sulfuric acid ($d = 1.815 \text{ g/cm}^3$) as solvent we obtained a medium which ensured ready iodination of arenes having electron-withdrawing groups. The best results were obtained when compound **I** was preliminarily dissolved in sulfuric acid. As a rule, dissolution of **I** in sulfuric acid at 0 to 3°C takes 15–20 min and produces a dark brown homogeneous solution. This solution was then used as iodinating agent. Unlike organic solvents, the iodination in 90% sulfuric acid required twofold molar excess of **I** to complete the conversion of aromatic substrate.

The iodination of nitrobenzene (**XIIIa**) with the above reagent at 20°C in 15–20 min gave 76% of 3-iodonitrobenzene (**XIIIb**). The reaction at 0°C was complete in 60 min, and the yield of **XIIIb** was approximately the same. 2-Iodo-4-nitrotoluene (**XIVb**) was obtained by iodination of finely powdered 4-nitrotoluene (**XIVa**) at 0°C under vigorous stirring. If these conditions were not met, a mixture of initial 4-nitrotoluene (**XIVa**), 2-iodo-4-nitrotoluene (**XIVb**), and 1,3-diiodo-2-methyl-5-nitrobenzene (**XIVc**) was formed (according to the GC–MS data), which was difficult to separate. Raising the temperature to 20°C with 2 equiv of the iodinating reagent resulted in the formation of only diiodo derivative **XIVc**.

The iodination of liquid *o*-nitrotoluene (**XVa**) gave a mixture of isomeric iodonitrotoluenes in an overall yield of 89%. According to the GC–MS data, the product mixture contained 77% of 4-iodo-2-nitrotoluene (**XVb**) and 23% of 6-iodo-2-nitrotoluene (**XVc**). Isomer **XVb** was isolated in 47% yield by freezing-out and recrystallization from ethanol.

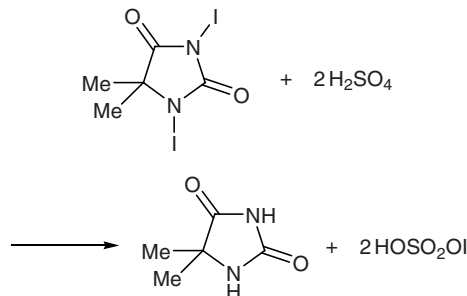
Benzoic and 4-fluorobenzoic acids **XVIa** and **XVIIa** were iodinated to 3-iodobenzoic and 3-iodo-4-fluorobenzoic acids **XVIb** and **XVIIb**, respectively,

but the reaction at 0°C was slower than analogous transformation of nitroarenes. Presumably, the reason is protonation of the carboxy group in sulfuric acid, which makes it even stronger electron acceptor. Compounds with one or two carbonyl groups, such as benzaldehyde (**XVIIIa**) and benzil (**XIXa**) readily underwent iodination at 0°C in 0.5–1 h to give 3-iodobenzaldehyde (**XVIIIb**) and 3,3'-diiodobenzil (**XIXb**), respectively. Phenanthrenequinone (**XXa**) was converted into 2,7-diiodophenanthrenequinone (**XXb**), but the reaction was accompanied by formation of by-products whose structure was not determined; therefore, the yield of expected product **XXb** was appreciably reduced.

In the iodination of iodobenzene (**XXIa**) with 2 equiv of compound **I** in H_2SO_4 we obtained a mixture of iodobenzenes with different degrees of substitution. The reaction with increased amount of **I** (8 equiv) gave 1,2,4,5-tetraiodobenzene (**XXIb**) in 55% yield (Table 2).

Analysis of the ^{13}C NMR spectra of solutions of compound **I** showed that its dissolution in sulfuric acid is accompanied by replacement of both iodine atoms by hydrogen. Even in a few minutes after dissolution in sulfuric acid, the ^{13}C NMR spectrum contained only signals at δ_{C} 159.5 and 182.6 ppm from two carbonyl carbon atoms of protonated unsubstituted 5,5-dimethylhydantoin (the same chemical shifts are typical of 5,5-dimethylhydantoin dissolved in sulfuric acid). These data indicate that the iodination is preceded by iodine transfer from compound **I** to sulfuric acid (Scheme 2). Presumably, both iodine atoms are replaced simultaneously, for no signals assignable to monoiodohydantoin were observed in the spectra.

Scheme 2.



It is known [11, 12] that blue solutions of iodine-containing species in sulfuric acid (λ_{max} 640, 500, 410 nm) contain I^+ ions and that dark brown solutions (λ_{max} 460, 290 nm) possessing enhanced electrophilic-

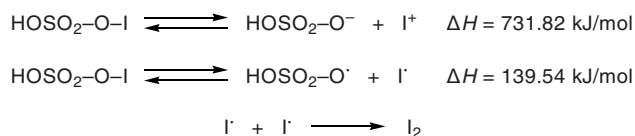
Table 2. Iodination of deactivated aromatic compounds with 1,3-diiodo-5,5-dimethylhydantoin in 90% sulfuric acid

Substrate	Temperature, °C	Reaction time, min	Product	Yield, %	mp, °C (solvent); published data
Nitrobenzene (XIIIa)	0	60	3-Iodonitrobenzene (XIIIb)	75	35–36 (EtOH); 36–37 [8]
	20	15	3-Iodonitrobenzene (XIIIb)	76	35–36 (EtOH); 36–37 [8]
4-Nitrotoluene (XIVa)	0	80	2-Iodo-4-nitrotoluene (XIVb)	61	56–57 (EtOH); 58 [2]
	20	80	2,5-Diiodo-4-nitrotoluene (XIVc)	72	116–117 (EtOH); 117–118 [2]
2-Nitrotoluene (XVa)	0	45	4-Iodo-2-nitrotoluene (XVb)	47	60–61 (50% <i>i</i> -PrOH); 60–61 [2]
Benzoic acid (XVIa)	0	120	3-Iodobenzoic acid (XVIb)	70	185–187 (50% <i>i</i> -PrOH); 185–187 [2]
4-Fluorobenzoic acid (XVIIa)	0	90	3-Iodo-4-fluorobenzoic acid (XVIIb)	75	174–176 (EtOH); 174–176 [11]
Benzaldehyde (XVIIIa)	0	30	3-Iodobenzaldehyde (XVIIIb)	62	54–56 (EtOH); 57 [2]
Benzil (XIXa)	0	40	3,3'-Diiodobenzil (XIXb)	75	126–127 (EtOH); 128–129 [9]
Phenanthrenequinone (XXa)	0	60	2,7-Diiodophenanthrenequinone (XXb)	40	305–307 (toluene); 310–311 [2]
Iodobenzene (XXIa)	0	30	2,3,5,6-Tetraiodobenzene (XXIb)	55	248–250 (DMF); 254 [4]

ity contain I_3^+ ions. In the electronic absorption spectrum of a solution of **I** in sulfuric acid, which was used as iodinating agent, we observed maxima at λ 451, 289, and 240 nm. Therefore, it is highly probable that the solution contains no free I^+ ions and that some amount of I_3^+ is present therein.

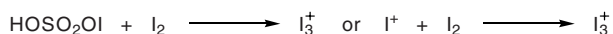
DFT calculations at the B3LYP/6-311G* level [13, 14] of the enthalpies of dissociation of iodine hydrogen sulfate $HOSO_2OI$ showed that homolytic cleavage of the O–I bond is thermodynamically more favorable than heterolytic dissociation, so that molecular iodine can be formed in the system (Scheme 3).

Scheme 3.



Iodine molecules are capable of reacting with neutral and especially protonated $HOSO_2OI$ molecules, as well as with I^+ ions, to produce some equilibrium amount of I_3^+ in solution (Scheme 4).

Scheme 4.



The formation of I_3^+ is likely to be responsible for the necessity of using twofold excess of the reagent (calculated on electrophilic iodine) to attain complete conversion in the iodination in sulfuric acid.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates (detection under UV light). The electronic absorption spectra in the UV and visible regions were measured on a Uvicon-943 spectrophotometer. The ^{13}C NMR spectra were obtained on a Bruker AS-300 spectrometer using D_2O as external reference. Compound **I** was prepared according to the procedure described in [1].

Iodination of compounds IIa–Va (general procedure). Compound **I**, 5 mmol (1.9 g), was added to a solution of 10 mmol of aromatic substrate **IIa–Va** in 15 ml of acetic acid or dioxane (in the iodination of **Va**). The mixture was cooled with an ice–water mixture, 2 ml of concentrated sulfuric acid was added under stirring, and the mixture was stirred for 10–180 min at 20°C. In the synthesis of di- and triiodo derivatives, the amount of the substrate was twice or thrice as low. The progress of the reaction was monitored by TLC using hexane as eluent. When the reaction was complete, the mixture was diluted with 30 ml of water, and

the precipitate was filtered off, dried, and recrystallized if necessary. The yields, melting points, solvents for recrystallization, and reaction times are given in Table 1.

1,4-Diiodo-2,3,5,6-tetramethylbenzene (IIc). Compound **I**, 5 mmol (1.9 g), was added to a solution of 5 mmol (0.67 g) of durene (**IIa**) in 15 ml of acetic acid, 2 ml of concentrated sulfuric acid was then added under stirring and cooling with cold water, and the mixture was stirred for 30 min at 20°C and diluted with 30 ml of water. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield of **IIc** 1.45 g (75%).

Iodination of compounds VIa–XIIa (general procedure). Sulfuric acid, 2 ml, was added under stirring and cooling to a solution of 10 mmol of compound **VIa–XIIa** in 15 ml of ethanol, and 5 mmol (1.9 g) of compound **I** was then added in 3 portions over a period of 2–3 min. In the synthesis of di- and triiodo derivatives, the substrate amount was reduced twice and thrice, respectively. When the reaction was complete, the mixture was diluted with 50 ml of a 3% solution of Na₂SO₃ (to isolate iodinated products **VIIb–VIIIb**) or with 40 ml of a 10% solution of NaOH (to isolate iodinated amines **IXb–XIb** and **IXc**), and the precipitate was filtered off, washed with water (**IXb–XIb**, **IXc**), dried, and recrystallized from appropriate solvent. For other details, yields, and solvents for recrystallization, see Table 1.

4,4'-Diiododiphenylamine (XIb). Sulfuric acid, 2 ml, was added under stirring and cooling with an ice–water mixture to a solution of 0.5 mmol (0.85 g) of diphenylamine (**XIIa**) in 15 ml of ethanol, and 5 mmol (1.9 g) of compound **I** was then added in 3 portions over a period of 2–3 min. After 10 min, 40 ml of a 10% solution of sodium hydroxide was added, and the precipitate was filtered off, washed with water, dried, and recrystallized from 80% ethanol. Yield 1.16 g (55%).

Iodination of deactivated aromatic compounds XIIIa–XXIa with 1,3-diiodo-5,5-dimethylhydantoin (I) in sulfuric acid (general procedure). Sulfuric acid (90%, $d = 1.825 \text{ g/cm}^3$), 15 ml, was cooled to 0–3°C and added to 5 mmol (1.9 g) of compound **I**, and the mixture was stirred for 15–20 min at room temperature until it became homogeneous. To introduce one iodine atom into an aromatic substrate molecule, 5 mmol of arene **XIIIa–XXIa** was added to the resulting dark brown solution, and the mixture was vigorously stirred for 20–120 min. To introduce two iodine atoms, the

substrate amount was reduced by half. The progress of the reaction was monitored by TLC using carbon tetrachloride (nitro compounds **XIII–XV** and **XXI**), hexane–acetic acid (10:1) (carboxylic acids **XVI–XXVII**), or benzene (**XVIII–XX**) as eluent. When the reaction was complete, the mixture was poured into 100 ml of an ice–water mixture and treated with a solution of Na₂SO₃. Compounds **XIIIb–XVb** were extracted into methylene chloride, the extract was dried over CaCl₂, and the solvent was removed. Compounds **XVIb** and **XVIIb** precipitated from the mixture and were filtered off, dried, and (if necessary) recrystallized from appropriate solvent (Table 2). Compound **XXb** was dissolved in benzene, the solution was filtered through a layer of silica gel, and the solvent was distilled off from the filtrate. The yields, melting points, solvents used for recrystallization, and reaction times are given in Table 2.

3-Iodonitrobenzene (XIIIb). Sulfuric acid (90%, $d = 1.825 \text{ g/cm}^3$), 15 ml, was cooled to 0–5°C and added to 5 mmol (1.9 g) of compound **I**, and the mixture was stirred for 20–30 min at room temperature until it became homogeneous. The solution was cooled to 0°C, 5 mmol (0.62 g) of nitrobenzene (**XIIIa**) was added, and the mixture was stirred for 60 min at 0°C, poured into 50 ml of water containing ice, treated with an aqueous solution of Na₂SO₃, and extracted with methylene chloride. The extract was dried over CaCl₂, the solvent was distilled off, and the residue was recrystallized from ethanol. Yield 0.93 g (75%). The iodination of **XIIIa** at 20°C was performed in a similar way. Yield 0.96 g (77%).

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