Iodination of nitroarenes by a superactive reagent based on iodine chloride

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Iodine chloride reacts with Ag_2SO_4 in H_2SO_4 to give a new superelectrophilic reagent capable of iodinating nitrobenzene, halogenated nitrobenzenes, nitrotoluenes, and aromatic compounds with two nitro groups in the ring. Mononitroarenes are easily iodinated at 0-20 °C, while dinitroarenes require heating to 100-170 °C.

Key words: iodination, iodine chloride, electrophilic iodine, nitroarenes.

The nitro group is known to belong to the substituents significantly hindering electrophilic substitution reactions in an aromatic ring, including iodination. Out of the great number of the currently existing iodinating systems, only a few can generate electrophilic iodine capable of interacting with nitroarenes. These are NIS in TfOH,¹ iodine—mixture of H₂SO₄ and HNO₃ in AcOH,² electrochemical iodination,³ iodine in oleum,⁴ iodine in the presence of fluorine as an oxidant,⁵ and iodine—Ag₂SO₄ in H₂SO₄.^{6,7} The last method, which has been successfully used by chemists already for 50 years, allows one to iodinate some deactivated arenes, including nitrobenzene (1a), within 2–3 h at 100 °C to give 3-iodonitrobenzene (1b) in 55% yield.

Previously,⁸ we reported that the reaction of iodine chloride with Ag_2SO_4 in H_2SO_4 results in a solution capable of very effectively iodinating nitrobenzene **1a** and some other deactivated arenes. The goal of the present work is to study in more detail the preparative potentialities of this new system for iodination of strongly deactivated nitroarenes and obtain primary information on the absorption spectra of the reagent.

When iodine chloride is mixed with Ag_2SO_4 in a 2 : 1 molar ratio in 90% H₂SO₄ at ~20 °C, a rapid reaction between ICI and Ag₃SO₄ takes place. The resulting transparent solution in sulfuric acid (in which both components, taken separately, are poorly soluble) rapidly forms a precipitate of AgCl (up to 80-90% with respect to the initial amount of Ag₃SO₄). After the precipitate is filtered off, the remaining homogeneous dark brown solution proves to exhibit very strong iodinating properties. Of critical importance is the fact that the behavior of ICI and Ag₂SO₄ mixture strongly differs from that of iodine and Ag₂SO₄ in H₂SO₄. For example, a mixture of I_2 and Ag_2SO_4 is soluble in 90% H_2SO_4 and no precipitate of Agl is formed even at 100 °C for 12 h.7 The formation of silver iodide in a sulfuric acid solution begins only upon addition of an aromatic substrate to be iodinated.⁷ Similar behavior of a mixture of I_2 and Ag_2SO_4 is also observed in 100% H_2SO_4 , which is explained⁹ by the formation of soluble AgI_2^+ . In turn, AgI_2^+ is believed⁹ to function as an active iodinating agent because of generation of I_3^+ in the presence of an aromatic substrate.

Inasmuch as the composition of the solution obtained and the form of its electrophilic iodinating species remain unknown, hereinafter, let us designate it as reagent " 1^+ ".

When nitrobenzene (1a) is mixed with a solution of reagent "I⁺" at 20 °C, nearly 50% of nitrobenzene is converted within 2 min, and only traces of the starting compound are detected after 8—9 min (Table 1). The temperature of the reaction mixture increases by 1.5-2 °C upon mixing the reagent and the substrate. Moreover, nitrobenzene (1a) can be successfully iodinated even at 0 °C, but this requires a longer reaction time (2.5 h) (see Table 1).

For complete conversion of nitroarene 1a to 1-iodo-3-nitrobenzene (1b), a twofold molar excess of reagent "I⁺" is needed (hereinafter, the molar substrate/reagent ratio is given with respect to ICl). More active iodinating reagents were not reported in the literature. It is of interest that even bromination of nitrobenzene with a Br_2 --Ag₂SO₄-H₂SO₄ system at ~20 °C proceeds much more slowly (16 h).¹⁰

Table 1. Conversion of nitrobenzene 1a in the reaction with reagent "I⁺" at different temperatures

τ∕min	Conversi	on (%)	τ/min	Conversion (%)	
	20 °C	0 °C		20 °C	0 °C
2	49		30		74
5	80	36	40		79
8	96		60		86
10	100	51	90		93
20		67	120		97
			150		100

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At room temperature, the iodination rate of p-iodonitrobenzene (2a) is much lower than that of nitrobenzene. The product, 1,2-diiodo-4-nitrobenzene (2b), is formed within 3.5-4 h (Table 2). However, compound 2a reacts with an excess of reagent "1⁺" at 100 °C within 30 min (substrate/reagent ratio 1 : 6) to give 1,2,3-triiodo-5-nitrobenzene (2c) in 36% yield. It should be noted that a comparison of the results of iodination of p-chloro-, p-bromonitrobenzenes (3a, 4a), and compound 2a by the proposed method allows one to conclude that their reactivity increases as the halogen size, rather than its electron-accepting character, decreases. Thus, compounds 3a and 4a are iodinated at ~20 °C within 1 and 2 h, respectively, to give 6-chloro-1-iodo-3-nitrobenzene (3b) and 1-bromo-2-iodo-4-nitrobenzene (4b) (Table 2).

Depending on the reactivity of substrates, two variants for the preparative iodination with reagent "I*" were developed. In the case of low-activity substrates 1a, 2a, 3a, and 4a, the corresponding aromatic compound was added in one portion with stirring to a solution of reagent "I⁺" (method A). However, because of the very high reactivity of reagent "I+", we faced problems when iodinating para- (5a) and orthonitrotoluenes (6a) by this method. For these compounds, slow addition of reagent "I+" to a stirred suspension of a substrate in H₂SO₄ was found to be more effective (method B). Nevertheless, even under these conditions, attempts to introduce one iodine atom into compounds 5a and 6a at ~20 °C resulted in the formation of a difficult-to-separate mixture of mono- and diiodosubstituted products and the initial compounds. Only iodination of these compounds at 0 to +3 °C and slow addition of an iodinating mixture allowed us to obtain 2-iodo-4-nitrotoluene (5b) and 4-iodo-2-nitrotoluene (6b) (see Table 2).

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1-Nitronaphthalene (7a) was chosen as a representative of polycyclic nitro compounds. It turned out that the reagent ratio commonly used for monocyclic nitroarenes is not suitable for its iodination. At a molar substrate/reagent ratio of 1: 1.5-2.0, incomplete conversion of 7a takes place. But, at a ratio of 1: 2.5, when an iodinating mixture was gradually added at 0 °C for 1 h (variant B), we could obtain 1-iodo-5-nitronaphthalene (7b) in satisfactory yield (see Table 2). However, we failed to iodinate another representative of polycyclic arenes, 5-nitroacenaphthene.

Introduction of a substituent into an aromatic ring containing two nitro groups by electrophilic substitution is difficult even for electrophiles as strong as the nitronium or Cl⁺ cation. However, the proposed reagent "I⁺" successfully iodinates 2,4-dinitrotoluene (8a) and 1,3-dinitrobenzene (9a), albeit it needs higher temperatures and longer reaction times (see Table 2). 6-Iodo-2,4-dinitrotoluene (8b) was obtained at 100 °C within

Substrate (mmol)	V_{t+}/mL	• Method	<i>T/</i> °C	Product	τ/min**	Yield	M.p./°C	
	of synthesis					(%)	Experimental (solvent)	Literature data
la (10)	50	A	20	16	10	74	34-36 (EtOH)	36-37 1
1a (10)	50	А	0	16	150	64	34-36 (EtOH)	
2a (10)	50	Α	20	2b	240	43	109—111 (Pr'OH)	112.5 14
2a (5)	62.5	А	100	2c	30	36	165—166 (Pr ⁱ OH)	166-167 4
3a (10)	50	A	20	36-	60	67	73-74 (EtOH)	74-75
4a (10)	50	A	20	4b	120	53	94—96 (EtOH)	9899 1
5a (10)	37.5	В	0	5b	50 (40)	65	54-56 (EtOH)	58 13
5a (5)	50	А	20	5c	60	41	115-116 (EtOH)	117-118 4
6a (10)	37.5	B	0	6b	90 (80)	45	58-60 (McOH)	6061 13
6a (5)	37.5	В	Ü	6c	120 (60)	34	73-74 (EtOH)	73-74 4
7a (10)	62.5	В	0	7b	90 (60)	35	161-163 (Pr'OH)	163-164 ¹³
8a (5)	50	Ā	100	8b	390	47	77-78 (EtOH)	78 4
9a (5)	85		170	9b	150 (20)***	37	97–98 (Pr ⁱ OH)	99-100 4

Table 2. Iodination of nitroarenes with reagent "I+"

V₁+ is the amount of reagent "I^{*}".

** The time during which the reagent was added is given in parentheses.

*** Addition of the reagents was carried out at 170 °C (see Experimental part).

Although the preparation of polyiodinated products was not a specific task of this investigation, we studied the influence of the amount of reagent "I+" on the course of the process with nitrotoluenes 5a and 6a as examples. As the amount of reagent "1⁺" increases by a factor of 2.6 (as compared to that in the synthesis of compounds 5b and 6b), para-isomer 5a is smoothly diiodinated at ~20 °C within 1 h to give 2,6-diiodo-4-nitrotoluene (5c) (method A). Attempts to diiodinate ortho-nitrotoluene (6a) under the same conditions and with the same reagent/substrate ratio resulted in three products: monoiodo derivative 6b, 4,6-diiodo-2-nitrotoluene (6c), and, probably, 4,5,6-triiodo-2-nitrotoluene. Diiodo derivative 6c with a significant impurity of monoiodide 6b was obtained by careful addition of the reagent to the substrate at 0 °C with subsequent purification of the reaction mixture by chromatography.

6.5 h. Under these condition, dinitrobenzene 9a was resistant to iodination. Even at 150 °C, its conversion did not exceed 50%, yielding a mixture of the initial substrate and 1-iodo-3,5-dinitrobenzene (9b). For this reason, compound 9a was iodinated as follows. Half the amount of reagent "1+" was mixed with the substrate at 20 °C, and the rest of the reagent was added to the reaction mixture at 170 °C (see Experimental). The iodination of dinitroarenes 8a and 9a was carried out with a four- or sixfold excess of the reagent, respectively.

Reagent "I⁺" was usually used by us within a week after its preparation. Note, however, that its iodinating ability remained virtually unchanged even after storage for four to five months in the dark at ~20 °C. The AgCI that precipitates can be transformed into Ag_2SO_4 by the known procedures and reused in the iodination process.

It is noteworthy that, along with evident preparative advantages, reagent "I⁺" has a disadvantage, namely, side chlorination. Thus, after the first recrystallization from EtOH the obtained iodonitrobenzene Ib contained compound 1b (94.2%), I-chloro-3-nitrobenzene (2.1%), and a mixture of isomeric chloroiodonitrobenzenes (3.7%) (GC/MS analysis). This reduces the preparative yields of iodination products because at least threefold recrystallization is needed to remove chlorination products from them. At present, the causes for side chlorination remain to be elucidated. Probably, it is due to the presence of impurities of molecular chlorine in the iodine chloride used.

So far, we can only suppose the composition and structure of reagent "1+". Attempts to determine the type of electrophilic iodine particles by electronic absorption spectroscopy gave ambiguous results. The spectrum of the reagent solution exhibits only a residual band at 439 nm coinciding with an absorption band for ICl in H₂SO₄, which may be evidence for the presence of impurities of free ICI. When the solution of reagent "I+" in sulfuric acid is extracted with carbon tetrachloride, its colored component passes into CCl₄. The extract is devoid of iodinating ability and cannot iodinate toluene even at 70-80 °C. The electronic absorption spectrum of the extract shows a visible band with the maximum at 490 nm, which is very close to that for a solution of iodine chloride in CCl₄ (500 nm). At the same time, the solution of reagent "I+" in sulfuric acid that remains after the extraction is light yellow and absorbs only slightly in the visible region, but retains its iodinating properties. It iodinates nitrobenzene (1a) at ~20 °C, though, for complete conversion of the substrate, the volume of this solution should be twice as large as that of freshly prepared reagent "I+". It is of importance that its spectral characteristics do not correlate with those of the known electrophilic iodinating particles. Thus, a solution of 1^+ cation prepared from 1_2 or ICI in oleum, FSO₃H, or 100% H₂SO₄ is light blue and absorbs at 640, 500, and 410 nm \mathbf{n} Solutions of \mathbf{I}_3^+

and I_5^+ cations in sulfuric acid absorb in the visible region at 460 nm,^{9,11} while AgI₂⁺ absorbs at 520 and 900 nm.⁹ Only oxygen-containing derivatives with covalently bonded electrophilic iodine, *e.g.*, H₂IO₃⁺, IO₂⁺, IO⁺, IO(HS₂O₇)₂⁺, (IO)₂SO₄, or IO(HSO₄), are colorless or light yellow without intense absorption in the visible region.⁹ However, these derivatives are not as strong iodinating agents as reagent "I⁺". Thus, further specific investigations are needed to determine the nature of the electrophilic iodine species contained in reagent "I⁺".

Experimental

The course of the reactions was monitored, and the purity of the reaction products was checked, by TLC on Silufol UV-254 plates with benzene—CCl₄ (1 : 4) as the cluent. ¹H NMR spectra were recorded on a Tesla BS-497 spectrometer (100 MHz) in CDCl₃. Electronic absorption spectra were recorded on a Specord UV-VIS instrument. IR spectra were obtained with a UR-20 instrument. GC/MS analysis was performed on HP 5972 and HP 5890 instruments (EI, 70 eV, HP-5 quartz capillary column (30 m × 0.25 mm), copolyner of 95% dimethylsiloxane and 5% diphenylsiloxane as stationary phase (0.25 mm thick)). Reagent grade substrates were used. Iodine chloride was prepared according to the known procedure.¹² The structures of iodination products were determined from their spectral characteristics, analytical data, and a comparison with authentic samples.

Preparation of reagent "I⁺". Ag_2SO_4 (6.24 g, 20 mmol) was added to a mixture of conc. H_2SO_4 (90 mL) and water (10 mL) at ~20 °C. The suspension was stirred for 0.5 h, and then ICI (6.48 g, 40 mmol) was added. Stirring was continued for 1 h, and the AgCl that precipitated was filtered off. The resulting homogeneous dark brown solution was kept at ~20 °C and used for subsequent iodination.

Method A. An amount of an aromatic substrate was added in one portion with stirring to a solution of reagent "I⁺" at 0 or 20 °C. The reaction temperatures and the reaction times are given in Table 2. Regardless of the variant of iodination procedure, an additional 5-10% of AgCl precipitated during the reaction. The reaction mixture was poured into water, and the products were extracted with CHCl₃. The AgCl was filtered off, and the organic layer was separated, dried with CaCl₂, and concentrated. The reaction products were recrystallized from the solvents listed in Table 2.

Method B. Reagent "1+" was added gradually (dropwise) to a suspension of a substrate (1 mmol of the substrate per 1 ml. of 90% H_2SO_4) at a given temperature for 20-80 min. The reaction mixture was treated as described in method A.

1-Iodo-3,5-dinitrobenzene (9b). 1,3-Dinitrobenzene (9a) (1.68 g, 10 mmol) was added with stirring to reagent "I⁺" (40 mL) at 20 °C. The reaction mixture was heated to 170 °C, and an additional 45 mL of reagent "I⁺" was added dropwise for 20 min. After two hours, the reaction mixture was treated as described in method A to give compound 9b (1.09 g, 37%), m.p. 97–98 °C (PriOH) (Ref. 4: 99–100 °C).

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