Superactive Iodination Reagent on a Base of Iodine Chloride and Silver Sulfate

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Abstract: After reaction of ICl and Ag_2SO_4 in sulfuric acid and separation of resulting AgCl a stable solution is formed, containing very active forms of electrophilic iodine. This solution has a powerful iodination ability with respect to aromatic compounds. Deactivated arenes are iodinated easily and in mild conditions by action of this new reagent in generally good yields of the iodoarenes.

Key words: iodination, iodine chloride, aromatic compounds

Iodoarenes are valuable, versatile synthetic intermediates and have found wide applications in medicine and biochemistry. But the electrophilic nature of iodine is weaker than bromine and chlorine. For this and other reasons there are few methods for direct iodination of deactivated aromatics known.[1] Some arenes having electron-withdrawing substituents can be iodinated by the I_2/Ag_2SO_4 system in sulfuric acid. Under these conditions nitrobenzene (**1a**) is transformed into 3-iodonitrobenzene (**2a**) at 100 °C within 2–3 hours.[2] The use of iodine in 20% fuming sulfuric acid (oleum) for iodination of a range of aromatic nitro compounds was described.[3] In these conditions nitrobenzene (**1a**) can be iodinated to 3-iodonitrobenzene (**2a**) at room temperature and within 20 hours with 52% yield. Specific iodination of some deactivated arenes was achieved by using iodine with fluorine as the oxidant.[4] Probably nowadays the most active iodination agent is *N*-iodosuccinimide in CF_3SO_3H.[5] Deactivated arenes were found to react easily with this reagent giving iodoarenes with good yields. So, for example, nitrobenzene (**1a**) gives iodonitrobenzene **2a** (86%) within two hours at room temperature.[5]

Recently we have shown that ICl in H_2SO_4 is a convenient reagent for iodination of activated as well as mildly deactivated arenes.[6] However nitrobenzene was not iodinated under these conditions.

$$\mathrm{ICl} + \mathrm{Ag_2SO_4} \xrightarrow{\mathrm{H_2SO_4}} \text{"I}^{+}\text{"} + \mathrm{AgCl}$$

$$\mathrm{ArH} + \text{"I}^{+}\text{"} \xrightarrow[\text{53-77\%}]{\substack{\mathrm{H_2SO_4} \\ \text{0-20 °C, 15-150 min}}} \mathrm{ArI}$$

ArH = $C_6H_5NO_2$, 4-$MeC_6H_4NO_2$, 4-$ClC_6H_4NO_2$, 4-$BrC_6H_4NO_2$, C_6H_5CHO , C_6H_5COOH , PhCOCOPh

As an extension of our attempts in search of the most active and available iodination reagents we concentrated attention on ICl and a silver salts system. It was long ago reported that with heating a mixture of I_2 and Ag_2SO_4 in sulfuric acid under 100 °C a precipitation of AgI is not formed within 12 hours. Silver iodide is formed only after the addition of an aromatic substrate.[7] In other words only in the presence of the substrate does generation of electrophilic iodine from I_2 and Ag_2SO_4 occur (an alternative explanation of this phenomenon consists of the assumption that iodination agent in this case is AgI_2^+,[8] but there are not clear experimental confirmations of this assumption). Contrary to this fact we have found that addition of two equivalents of ICl into the suspension of one equivalent of Ag_2SO_4 in sulfuric acid (90 wt% in water) at room temperature leads to the immediate precipitation of AgCl. The weight of the precipitation is an average of 90% from the calculated. After the separation of AgCl by means of filtration a stable dark-brown solution is formed. The composition of this solution to the best of our knowledge is unknown and further studies are in progress in our laboratory. Probably the solution contains sulfate and (or) bisulfate of iodine or solvated I^+ ions. Whatever the real composition and structure of this solution is, it has an extremely strong ability for iodination of various deactivated aromatics **1a–g** (Table). Conditionally we will designate this iodination reagent here as “I^+”.

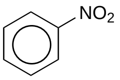
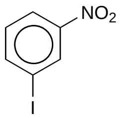
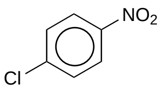
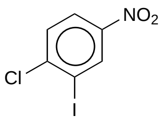
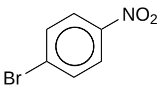
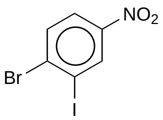
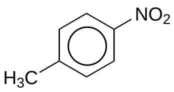
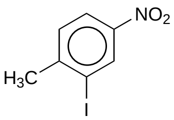
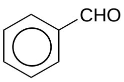
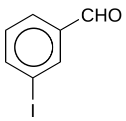
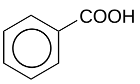
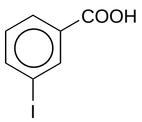
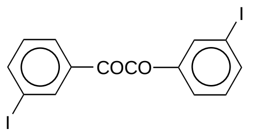
Two variants of the iodination using reagent “I^+” were worked out. In Method A one equivalent of the substrate immediately adds to the solution of two equivalents of reagent “I^+” (calculated on the basis of the starting ICl). Method B consists of dropwise addition of 1.5 equivalents of reagent “I^+” to the stirred suspension of the substrate in sulfuric acid. Method A is more appropriate for the most strong deactivated arenes **1a–c**. On the other hand Method B provides better results in the case of the iodination of substrates **1d–g** (Table).

After addition of nitrobenzene **1a** to reagent “I^+” at 20 °C sizeable amounts of iodonitrobenzene **2a** arise in 1–2 min, and in 7–10 min starting substrate **1a** remains only in trace amounts in the reaction mixture (TLC). Iodination of nitrobenzene **1a** can be realized even at 0 °C but the reaction time is longer for the completion of the reaction (Table). In this context it is significant to mention that bromination of nitrobenzene **1a** by action of $Br_2/Ag_2SO_4/H_2SO_4$ system is accomplished at room temperature in 16 hours.[9] Thus the electrophilic activity of reagent “I^+” is at least not smaller than of the bromination.

The activity of reagent “I^+” is so high that it can be used for a successful iodination of nitrotoluene **1d** only at 0 °C (Method B). Much higher temperature iodination of the substrate **1d** leads to a complicated mixture of isomers of iodo- and diiodonitrotoluenes.

Synthesis of iodobenzils by a direct iodination of benzil **1g** is not a simple task. Many common reagents are used usually in an oxidative iodination of arenes ($I_2/HNO_3/H_2SO_4$, I_2/HIO_3, I_2/H_5IO_6, I_2/oleum, I_2/O_2, KI/$Tl(OCOCF_3)_3/CF_3COOH$) lead to destruction of CO–CO bond of benzil **1g.**[10] Earlier benzil **1g** was iodinated by $I_2/Ag_2SO_4/H_2SO_4$ system at 90 °C within 2 hours with general yield of a mixture of 2,2'- diiodobenzil, 4,4'-diiodobenzil and 3,3'-diiodobenzil **2g** 84%.[10] In the case of the iodination of benzil **1g** by using one equivalent reagent

Table Iodination of arenes **1a-g** with reagent "I^+"

Substrate **1**	Product **2**	Time (min)	Temp. (°C)	Yield (%)[a]	mp (°C) (solvent)	Lit. mp (°C)
 a	 a	15	20	74[b]	34–36 (EtOH)	36–37[5]
a	a	150	0	64[b]	34–36 (EtOH)	
 b	 b	50	20	67[b]	73–74 (EtOH)	74–75[5]
 c	 c	120	20	53[b]	94–96 (EtOH)	98–99[5]
 d	 d	40	0	65[c]	54–56 (EtOH)	53–54[2]
 e	 e	40	20	61[c]	54–56 (ethanol)	57[2]
e	e	60	0	67[c]	55–57	
 f	 f	60	0	57[c]	184–186 (50% isopropanol)	186–187[7]
PhCOCOPh g	 g	60	0	77[c]	127–128 (EtOH)	128–129[10]

[a] Yield of pure, isolated product
[b] Method A
[c] Method B

"I^+" per one equivalent of the substrate (Method B) mixture consisting of starting compounds **1g**, 3-iodobenzil and compound **2g** is formed. At the same time with using double the amount of reagent "I^+" at 0 °C mild diiodination of benzil **1g** occurred with good yield of diiodobenzil **2g** (Table).

As a rule we used reagent "I^+" within two–three days of the preparation. But one can keep it for a longer period of time. So the iodination of nitrobenzene **1a** with reagent "I^+" which was kept for one month at room temperature provided iodonitrotoluene **2a** with 53% yield. It should be also noticed that not only reagent "I^+" but a simple mixture of $ICl–Ag_2SO_4–H_2SO_4$ is able to iodinate arenes **1a–g**. However in this case the reaction is longer and the product contains, besides iodo compounds **2a–g,** sizeable amounts of the corresponding chloroarenes.

Thus the proposed reagent "I^+" is probably the most reactive known reagent in iodination of aromatic compounds. The proposed method is also not too expensive because it allows the recovery of 90–95% of the exploitable silver. Another advantage of the proposed method is the absence of strong oxidizers which are employed in most cases in iodination processes.[1] As a result of this, compounds **1d,e** are exposed only to iodination without casual oxidation of CH_3 and even CHO groups. However we must say that along with the iodination a chlorination process takes place to a small extent. So the crude product of the iodination of nitrobenzene **1a** before the purification contains 94.2% of iodnitrobenzene **2a**, 2.1% of 3-chloronitrobenzene and 3.7% of isomers of chloroiodonitrobenzenes (GS-MS data). We believe that the minor chlorination is a result of a presence impurity of chlorine in ICl.

IR spectra were taken on a UR-20 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer. GC-MS analyses were performed on a HP 5890 gas chromatograph equipped with a 12 m x 0.2 mm methyl silicone gum capillary column, coupled with an HP 5972 mass selective detector. The substrates used in this study are commercially available. The structures of the products **2a–g** were determined by IR, ^1H, ^{13}C NMR spectra and by comparisons with authentic samples.

Preparation of the Iodination Reagent "I^+"

A suspension of Ag_2SO_4 (3.12 g, 10 mmol) in concd H_2SO_4 (45 ml) and H_2O (5 ml) was stirred at r.t. for 15 min. Then ICl was added and the mixture was stirred at r.t. for 1 h. The precipitated AgCl (2.58 g) was removed by filtration. The resultant dark-brown solute was kept in darkness and used for iodination.

3-Iodonitrobenzene (2a) (Method A)

Nitrobenzene (**1a**; 1.23 g, 10 mmol) was added in one portion to a well-stirred solution of reagent "I^+" (50 mL) at r.t. The mixture was then stirred for 15 min at r.t. In this period 0.15 g AgCl was precipitated additionally. The mixture was poured into H_2O (150 mL). Product **2a** was extracted with $CHCl_3$ (2 x 20 mL). The solvent was removed in vacuo to efford a yellow oil, which was cooled to –10 °C, washed with EtOH (5 mL) at the same temperature, and recrystallized from EtOH to give 3-iodonitrobenzene (**2a**); yield: 1.84 g (74%); mp 34–36 °C (Lit.[5], mp 36–37 °C).

2-Iodo-4-nitrotoluene (2d) (Method B)

To a mixture of 4-nitrotoluene (**1d**; 1.37 g, 10 mmol) in 90% concd H_2SO_4 (10 ml) was added reagent "I^+" (37.5 ml) dropwise with stirring at 0 °C over 40 min. The mixture was poured into H_2O (100 ml), product **2d** was removed by filtration, dried, and recrystallized from EtOH to give 2-iodo-4-nitrotoluene **2d**; yield: 1.71 g (65%); mp 54–56 °C (Lit.[2], mp 53–54 °C).

3-Iodobenzoic Acid (2f) (Method B)

To a mixture of benzoic acid (**1f**; 1.22 g, 10 mmol) in 90% conc. H_2SO_4 (10 mL) was added reagent "I^+" (37.5 ml) dropwise with stirring at 0 °C over 40 min. The resulting mixture was stirred for 20 min at the same temperature and poured into H_2O (100 mL). The solid product was filtered and solvated in hot 50% isopropanol. After filtration the hot solution from a residue AgCl and cooling crystals of compound **2f** were filtered; yield: 1.27 g (57%); mp 185–186 °C (Lit.,[7] mp 187–188 °C).

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