Superelectrophilic Iodination of Deactivated Arenes with Triiodoisocyanuric Acid

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Abstract: The reaction of triiodoisocyanuric acid (TICA) with deactivated arenes in acidic medium led to the efficient and regioselective formation of the corresponding iodoarenes, in 55–88% isolated yield. The acidity of the medium was found to be the most important factor influencing the electrophilic iodination of weakly nucleophilic substrates by TICA.

Key words: triiodoisocyanuric acid, iodination, deactivated aromatic compound, iodoarene, electrophilic halogenation

Several important compounds that exhibit biological activity, e.g. thyroid hormones (like thyroxine), dakaramine, and fialuridine, have a C–I bond in their structure (Figure 1).

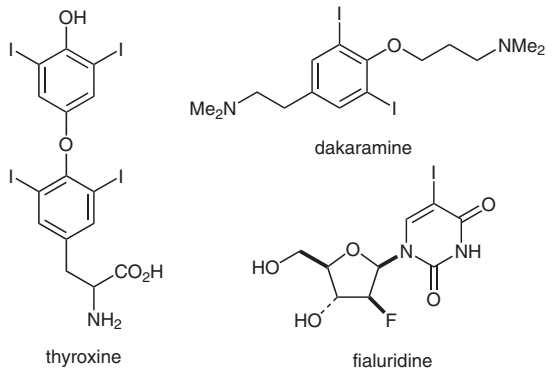


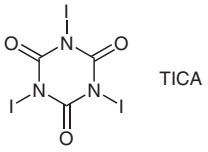
Figure 1 Organoiodo compounds with biological activity

Iodoarenes are also compounds of high practical utility as precursors of a variety of active pharmaceutical ingredients, such as camptothecin,[1a] dehydrotubifoline,[1b] morphine,[1c] sangliferine A,[1d] ecteinascidine 743,[1e] etc. Furthermore, iodoarenes have been extensively used in aromatic bond formation reactions such as Heck arylation[2a] and Stille,[2b] Negishi,[2c] Suzuki,[2d] Buchwald,[2e] and Sonogashira[2f] couplings. In some of these reactions, even with another halide present on the aromatic ring, the coupling occurs selectively at the iodo group.[3] Another important application of organoiodo compounds is in radiopharmaceuticals. Radioactively labeled iodoarene compounds have been extensively used in radioimmunoassay studies and in nuclear magnetic imaging.[4]

Aryl iodides are usually more difficult to prepare than the corresponding aryl chlorides and bromides due to the low electrophilicity of iodine which requires the presence of an activating agent in order to produce a strongly electrophilic 'I^+' species. Direct iodination is also hampered by the formation of hydrogen iodide, which is both a strong reducing agent and a strong acid that can cause protolytic cleavage of sensitive compounds.[5]

A large number of synthetic methods are available for the iodination of activated arenes, but there are only a limited number of methods for the direct iodination of deactivated aromatics.[6] Some arenes with electron-withdrawing substituents can be iodinated by $I_2/HNO_3/H_2SO_4/AcOH$,[7a] $I_2/SbCl_5$,[7a] $I_2/Ag_2SO_4/H_2SO_4$,[7b] I_2/oleum,[7c] $ICl/Ag_2SO_4/H_2SO_4$,[7d] $I_2/AgOTf$,[7e] and $IPy_2BF_4/TfOH$,[7f] and PyICl,[7g] I_2 or $KI/NaIO_4/H_2SO_4$,[7h] I_2/IBX,[7i] and $I_2/K_2S_2O_8$ in strong acid.[7j,k] However, some of these reactions involve corrosive reagents, the use of heavy metal oxidants, or the formation of byproducts that are sometimes difficult to separate. Potent iodination agents such as *N*-iodosuccinimide in triflic acid,[8a] and 2,4,6,8-tetraiodoglycoluril in sulfuric acid[8b] are capable of iodinating strongly deactivated arenes, but the former is limited on a large preparative scale by the expense of triflic acid, while the second affords iodoarenes in generally moderate yields when using two equivalents of the 'active iodine'.

Triiodoisocyanuric acid (TICA, Figure 2), was recently reported by us as an efficient reagent for the co-iodination of alkenes with oxygenated nucleophiles,[9] and the iodination of activated arenes.[10] In addition, TICA has the advantage of transferring three equivalents of iodine atom to the substrate, that is of up to 75% of its mass. As an extension of our search for more potent and practical electrophilic halogenation reagents,[11] in the present work we describe our results on the iodination of deactivated aromatic rings using triiodoisocyanuric acid in acidic medium, as the source of superelectrophilic iodine.[12]



TICA

Figure 2

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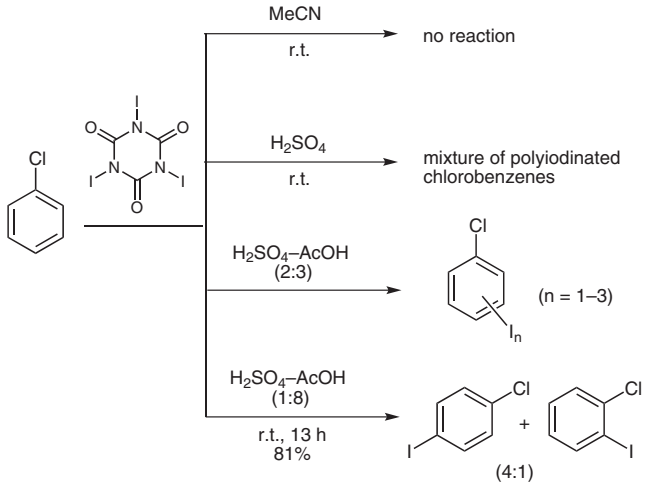
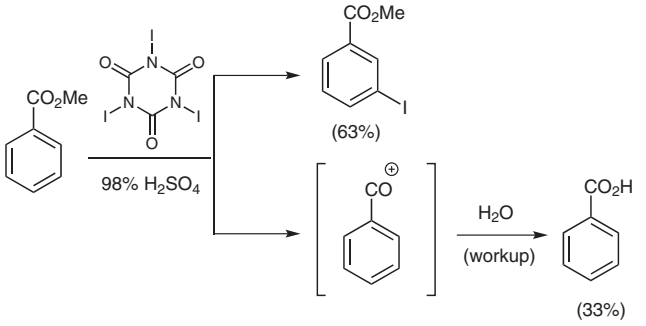
The iodination of chlorobenzene with TICA in acetonitrile was not observed after 72 hours at room temperature. However changing the solvent to 98% sulfuric acid led to the formation of several polyiodinated products, while using sulfuric acid diluted with acetic acid gave a cleaner reaction; the monoiodinated products were obtained using H_2SO_4–AcOH 1:8 (Scheme 1).

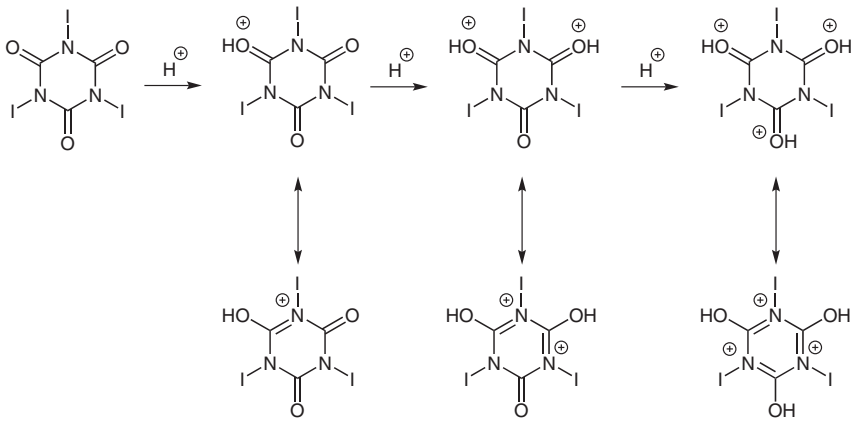
Based on the above results, we studied the reaction of deactivated arenes with TICA in acidic media with the aim of forming the monoiodinated products and the results are shown in Table 1. The reactions were performed by stirring the arene with 0.34 molar equivalents of TICA at different temperatures and acid strengths. Weakly deactivated arenes (entries 1–4) were smoothly monoiodinated using sulfuric acid diluted in acetic acid at room temperature, while more deactivated arenes needed higher sulfuric acid concentrations. On the other hand, highly deactivated arenes (entries 11–13) were iodinated by TICA in 65% oleum (65% SO_3 in H_2SO_4) at higher temperatures. Unfortunately, 1,3,5-trinitrobenzene was unreactive under these conditions.



Scheme 1



Scheme 2



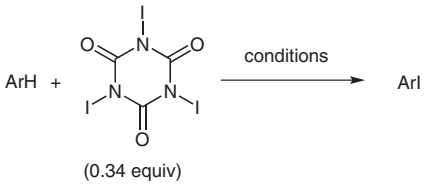
Scheme 3

The products were characterized by their melting points and/or spectrometric techniques. The regioselectivity of the reactions was very high and no regioisomers were detected by the analytical procedures employed (HRGC, ^1H and ^{13}C NMR spectroscopy). However, exceptions were observed in the reactions of chloro-, bromo-, and iodobenzene which produced both *o*- and *p*-iodo-substituted haloarenes in which the *p*-regioisomers predominated (entries 2–4). In these cases, the identities of the products were determined by NMR spectra which were in good agreement with those previously reported.[7j,13] Curiously, the reaction of methyl benzoate with TICA in 98% sulfuric acid (entry 9) produced the expected *m*-iodinated ester (63%) along with benzoic acid (33%). The unexpected formation of the carboxylic acid without incorporating iodine can be explained by a partial reaction of the ester with sulfuric acid to produce the benzoyl cation, which is too deactivated to be iodinated by TICA in 98% sulfuric acid. Further treatment with water during the workup process leads to benzoic acid, as shown in Scheme 2.

As observed in the reactions of deactivated arenes with trichloroisocyanuric[14] and tribromoisocyanuric[15] acids in acidic media, we believe that sulfuric acid promotes O-protonation of TICA forming a polyprotonated or protosolvated superelectrophilic species[16] (Scheme 3). This species can act as an efficient iodenium-transfer agent due to the intramolecular charge–charge repulsion and it is possible to regulate the reactivity of the reagent by modulation of the acid strength of the media. The increase of the degree of protonation of the TICA can lead to higher reactivity of such species, since the reactant is destabilized by the charge–charge repulsion in relation to the transition

state for I^+ release, decreasing the activation barrier. Hence, iodination of phenyl halides was observed in less acidic conditions whereas polyiodination was more prominent in more acidic media. Not surprisingly, the highly reactive powerful electrophile obtained by the system TICA/oleum was able to attack even relatively unreactive strongly deactivated arene nucleophiles (1,3-dinitrobenzene, 2,6-dinitrotoluene).

Table 1 Iodination of Deactivated Arenes



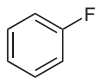
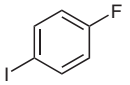
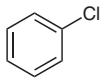
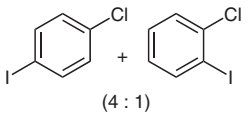
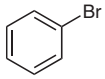
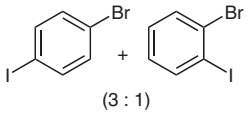
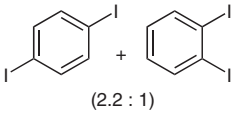
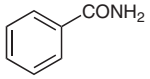
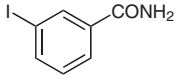
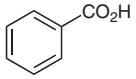
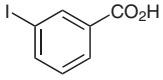
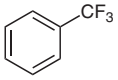
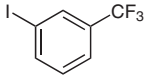
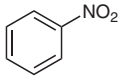
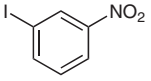
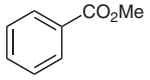
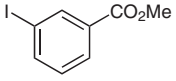
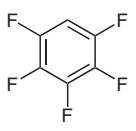
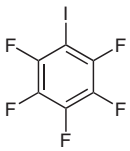
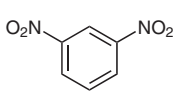
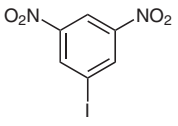
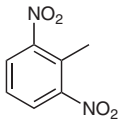
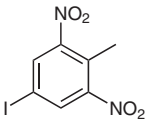
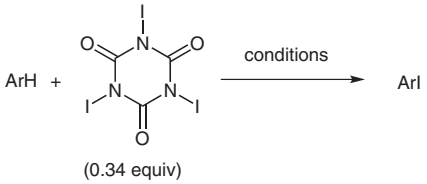
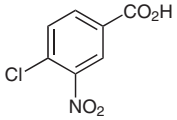
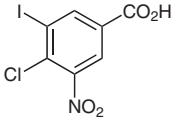
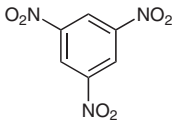
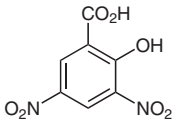
Entry	Substrate	Product	Conditions	Yield (%)[a]
1			H_2SO_4–AcOH (1:10), r.t., 14 h	83
2		 (4 : 1)	H_2SO_4–AcOH (1:8), r.t., 13 h	81[b]
3		 (3 : 1)	H_2SO_4–AcOH (1:8), r.t., 13 h	80[b]
4		 (2.2 : 1)	H_2SO_4–AcOH (1:8), r.t., 13 h	86[b]
5			H_2SO_4–AcOH (1:1), r.t., 144 h	88[c]
6			H_2SO_4–AcOH (3:2), r.t., 24 h	55
7			H_2SO_4–AcOH (3:2), r.t., 24 h	80
8			H_2SO_4–AcOH (4:1), r.t., 24 h	78
9			98% H_2SO_4, r.t., 2 h	63[d]
10			98% H_2SO_4, r.t., 18 h	74
11			65% oleum, 70 °C, 17 h	80
12			65% oleum, 70 °C, 17 h	58

Table 1 Iodination of Deactivated Arenes (continued)



Entry	Substrate	Product	Conditions	Yield (%)[a]
13			65% oleum, 70 °C, 19 h	80
14		–	65% oleum, 80 °C, 46 h	–
15		–	65% oleum, 80 °C, 46 h	–

[a] Yield of pure product, based on arene.
[b] Product ratio determined by HRGC.
[c] TICA used: 0.68 equiv.
[d] Formed together with benzoic acid (33%).

In conclusion, we have shown that the use of acidic medium increases the reactivity of TICA, allowing the iodination of deactivated aromatic rings. We favor an explanation in which there is probably participation of the polyprotonated form of TICA in this process.

Triiodoisocyanuric acid (TICA) was prepared from trichloroisocyanuric acid as previously described.[9] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ or DMSO-d_6 solutions with TMS as an internal standard. High-resolution GC was performed on a HP-5890-II gas chromatograph with FID using a 30 m (length), 0.25 mm (i.d.), and 25 μm (phase thickness) RTX-5 capillary column and H_2 (flow rate 50 cm/s) as carrier gas (split: 1:10). HRGC-MS analyses were performed on a Shimadzu GCMS-QP2010S gas chromatograph with electron impact (70 eV) by using a 30 m DB-5 silica capillary column.

Iodination of Deactivated Arenes with TICA; General Procedure

To a stirred soln of the arene (2 mmol) in acidic medium (5 mL, according to Table 1), was added TICA (0.67 mmol) at r.t. (in the case of 1,3-dinitrobenzene, 2,6-dinitrotoluene, and 4-chloro-3-nitrobenzoic acid the reaction was performed at 70 °C) and in the absence of light. The reaction was monitored by HRGC-MS and after the specified time (Table 1) the mixture was poured onto crushed ice (100 g). The aqueous layer was washed with EtOAc (3 × 15 mL), cyanuric acid was filtered off, and the combined organic layers were treated with 10% aq Na_2SO_3 (50 mL) and carefully neutralized with 10% Na_2CO_3 (except carboxylic acids which were washed with concd NaCl). The organic layer was dried (anhyd Na_2SO_4) and filtered. The solvent was evaporated on a rotary evaporator and the product collected. Selected analytical data follow.

1-Fluoro-4-iodobenzene[7j]

^{1}H NMR ($CDCl_3$): δ = 6.84 (t, *J* = 8.9 Hz, 2 H), 7.63 (dd, *J* = 8.9, 5.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 87.13 (d, *J* = 3.5 Hz), 118.0 (d, *J* = 22.2 Hz), 139.2 (d, *J* = 7.7 Hz), 160.5 (d, *J* = 247.3 Hz).

1-Chloro-4-iodobenzene[7j]

^{1}H NMR ($CDCl_3$): δ = 7.07 (d, *J* = 8.8 Hz, 2 H), 7.60 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 91.2, 130.6, 134.3, 138.8.

1-Chloro-2-iodobenzene[13]

^{1}H NMR ($CDCl_3$): δ = 6.94 (t, *J* = 7.9 Hz, 1 H), 7.27 (t, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 7.85 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 98.2, 127.9, 129.5, 138.6, 140.3.

1-Bromo-4-iodobenzene[7j]

^{1}H NMR ($CDCl_3$): δ = 7.24 (d, *J* = 8.5 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 92.2, 122.4, 133.7, 139.3.

1-Bromo-2-iodobenzene[13]

^{13}C NMR ($CDCl_3$): δ = 101.4, 128.6, 129.6, 133.0, 133.3, 140.5.

1,4-Diiodobenzene[7j]

^{1}H NMR ($CDCl_3$): δ = 7.42 (s, 4 H).

^{13}C NMR ($CDCl_3$): δ = 93.5, 139.5.

1,2-Diiodobenzene[13]

^{13}C NMR ($CDCl_3$): δ = 108.0, 129.3, 139.6.

3-Iodobenzamide[17]

Mp 183–185 °C (Lit.[17] 185–186 °C).

^{1}H NMR (DMSO-d_6): δ = 7.25 (t, *J* = 7.9 Hz, 1 H), 7.47 (br s, 1 H), 7.87 (dd, *J* = 7.9, 1.4 Hz, 2 H), 8.09 (br s, 1 H), 8.20 (t, *J* = 1.4 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 94.7, 127.1, 130.7, 136.2, 136.4, 140.1, 166.8.

3-Iodobenzoic Acid[7j]
Mp 181–183 °C (Lit.[7j] 185–186 °C).

^{1}H NMR (DMSO-d_6): δ = 7.31 (t, *J* = 7.9 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 8.22 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 95.2, 129.2, 131.4, 133.4, 138.2, 141.9, 166.5.

1-Iodo-3-(trifluoromethyl)benzene[7j]
^{1}H NMR ($CDCl_3$): δ = 7.23 (t, *J* = 7.9 Hz, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.90 (d, *J* = 7.9 Hz, 1 H), 7.97 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 93.9 (s), 123.0 (q, *J* = 273.0 Hz), 124.5 (q, *J* = 3.8 Hz), 130.5 (s), 132.5 (q, *J* = 32.6 Hz), 134.3 (q, *J* = 3.8 Hz), 141.0 (s).

1-Iodo-3-nitrobenzene[18]
^{1}H NMR ($CDCl_3$): δ = 7.30 (t, *J* = 8.0 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 8.20 (dd, *J* = 8.0, 2.0 Hz, 1 H), 8.57 (t, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 93.5, 122.8, 130.8, 132.5, 143.5, 148.6.

Methyl 3-Iodobenzoate[19]
Mp 50–52 °C (Lit.[19] 54.5 °C).

^{1}H NMR ($CDCl_3$): δ = 3.92 (s, 3 H), 7.18 (t, *J* = 7.9 Hz, 1 H), 7.88 (d, *J* = 7.9 Hz, 1 H), 8.00 (d, *J* = 7.9 Hz, 1 H), 8.38 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 52.5, 93.9, 128.9, 130.2, 132.1, 138.6, 141.9, 165.7.

Pentafluoroiodobenzene[20]
^{13}C NMR ($CDCl_3$): δ = 66.1 (td, *J* = 28.2, 4.6 Hz), 134.3–140.1 (m), 138.8–144.5 (m), 144.6–149.9 (m).

MS: *m*/*z* (%) = 294 (M^+, 100), 275, 167, 148, 127, 117.

1-Iodo-3,5-dinitrobenzene[21]
Mp 100–101 °C (Lit.[21] 102–103 °C).

^{1}H NMR ($CDCl_3$): δ = 8.89 (d, *J* = 2.0 Hz, 2 H), 9.03 (t, *J* = 2.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 93.6, 118.6, 137.9, 148.7.

4-Iodo-2,6-dinitrotoluene[22]
Mp 87.5–90 °C (Lit.[22] 87.5–90 °C).

^{1}H NMR ($CDCl_3$): δ = 2.51 (s, 3 H), 8.28 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.9, 89.3, 126.9, 136.2, 152.0.

MS: *m*/*z* (%) = 308 (M^+), 291, 127, 89 (100), 77, 63, 50.

4-Chloro-3-iodo-5-nitrobenzoic Acid
Mp 188–189 °C

^{1}H NMR ($CDCl_3$): δ = 8.43 (d, *J* = 1.9 Hz, 1 H), 8.77 (d, *J* = 1.9 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 103.0, 125.2, 131.8, 132.9, 143.0, 148.2, 163.9.

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