

Advances in the direct iodination of aromatic compounds

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Methods for the direct iodination of aromatic compounds are reviewed.

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Aromatic iodo compounds play an important role in synthetic organic chemistry. In the past they have been used in many copper-catalysed and Grignard reactions in which new carbon–carbon bonds are formed. More recent developments in palladium-catalysed coupling reactions have enhanced their synthetic importance. Consequently there has been a resurgence of interest in the synthesis of aryl iodides. The topic was thoroughly reviewed in 1988¹ and it has been described in chapters in various textbooks² as well as forming part of more general reviews on organic halides.³ Methods for introducing iodine into an aromatic ring fall into two classes. Firstly there are the direct methods which involve the substitution of an aryl C–H by iodine and secondly there are the indirect methods which involve the displacement of another substituent such as a carboxyl or diazonium group by iodine. This review will concentrate on developments in the first class.

Iodine is a poorer electrophile than bromine or chlorine and aromatic iodinations using elemental iodine are only weakly catalysed by many of the typical Lewis acids that are used for other halogenations. Consequently novel methods have concentrated on generating more electrophilic iodine species. Whilst many of the modern methods give excellent yields with activated arenes such as phenols, phenyl ethers, amines and amides, they are less successful with deactivated arenes such as aryl acids and nitro compounds. In the case of activated arenes, there is often a regioselectivity for substitution *para* to the activating group. However, there have been some significant developments particularly using thallium salts which favour substitution at a position which is *ortho* to a chelating substituent.

Iodine and nitric acid

A standard procedure for the iodination of aromatic compounds involves reaction with iodine and concentrated nitric acid which acts as an oxidant.⁴ In a modification of this method the substrate, dissolved in glacial acetic acid, is treated⁵ with iodine followed by a mixture of nitric and sulfuric acids. If necessary the reaction mixture may be heated to 100 °C. The procedure may then be used for deactivated arenes such as nitrobenzene and benzoic acid. Mechanistic studies of the iodination of substituted benzenes using iodine and nitric acid in acetic acid, have shown⁶ that the iodinating species is protonated NO₂I. The reaction is catalysed by dinitrogen tetroxide and by acid. The slow step in the reaction is the attack of [HNO₂I]⁺ on the aromatic compound.

In a development of this procedure, iodination of activated arenes such as anisole, veratrole and acetanilide, has been achieved⁷ by bubbling dinitrogen tetroxide into a mixture of the substrate and iodine in solution in chloroform. Sulfuric acid was present as a catalyst. A disadvantage of these methods can be the formation of nitro compounds as impurities. Iodine in concentrated sulfuric acid or in 20% oleum can be used to iodinate⁸ a benzene ring containing one deactivating substituent (*e.g.* a carboxyl or a nitro group) at room temperature or with gentle heat. Dinitro compounds were formed under more vigorous conditions at 100–170 °C.

In the case of the reaction in oleum, the sulfur trioxide which was present acted as the oxidant to form the tri-iodine cation.

Iodine monochloride

The use of iodine monochloride for aromatic iodination has a long history.⁹ However, the rate of the reaction falls away as the liberated hydrogen chloride combines with the iodine monochloride to form the less reactive HICl₂. This has been overcome by using¹⁰ the stable iodine monochloride:pyridine complex. The pyridine which is released, combines with the hydrogen chloride. The products of the reaction between iodine monochloride and a phenol vary with the experimental conditions. In the absence of a solvent, the major product arises from a chlorination whereas in acetic acid or nitrobenzene, iodination occurs. The iodination of anisole and other reactive arenes with iodine monochloride, particularly at electron-rich and sterically hindered sites, has been shown to be accompanied by chlorination.¹¹

The kinetics of iodination of *p*-chloroaniline with an aqueous solution of iodine monochloride are in agreement with a reaction between the free amine and the ion H₂OI⁺.⁹ In a further mechanistic study of the reaction under anhydrous conditions, evidence has been presented¹² for the formation of a charge-transfer complex between the electron-rich arene and the iodine monochloride. This undergoes an electron-transfer reaction to form a radical cation ion-pair ArH⁺ICl⁻ which may collapse to give either iodination or chlorination.

Aromatic iodination with iodine monochloride can be enhanced by using¹³ a catalytic amount of ferrocenium tetrakis(3,5-bistrifluoromethyl)phenylborate and a mild Lewis acid such as zinc oxide. Exploration of other Lewis acids has led¹⁴ to an efficient system employing indium triflate as the catalyst in acetonitrile as the solvent. Chloramine-T and sodium iodide in the presence of acid represents a useful source of iodine monochloride for use in aromatic iodination.^{9,15}

A small scale method using iodine monofluoride has been described¹⁶ for the preparation of radiolabelled compounds. Potassium dichloroiodate (KICl₂) has been used¹⁷ to iodinate activated arenes such as vanillin in aqueous solution. Some π -excessive heteroaromatic compounds were also iodinated under these conditions.

Iodination using other oxidants

The use of hydrogen peroxide as an oxidant for the iodination of activated arenes with either iodine or potassium iodide has been used for many years.¹⁸ Several oxyanions including sodium molybdate¹⁹ will catalyse the oxidation of the iodide ion by hydrogen peroxide. Hydrogen peroxide or sodium perborate with sodium tungstate as the catalyst and potassium iodide as the source of iodine, have both been used²⁰ for the iodination of aromatic amides.

More recently the oxidative iodination of anisoles, phenols and anilines in high yield using hydrogen peroxide and potassium iodide in methanol in the presence of concentrated sulfuric acid has been described.²¹ However over-oxidation can occur with the formation of quinones and indeed a method which uses iodine and hydrogen peroxide has been developed²²

for the synthesis of polyalkyl-2-iodo-*p*-benzoquinones from alkylphenols. The further oxidation of a series of iodoarenes to the corresponding diacetoxyiodoarenes [$\text{ArI}(\text{OCOCH}_3)_2$] using sodium perborate in acetic acid at 40 °C has also been reported.²³

A mixture of peracetic acid and iodine in the presence of a sulfuric acid catalyst has provided²⁴ a system for the iodination of alkylbenzenes, anisoles and aromatic amides. The iodination of benzoic acid, albeit in poorer yield, was achieved under more vigorous conditions. Mechanistic studies suggested that the iodinating species was iodine acetate.

Oxone® ($\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) and ammonium iodide in methanol provides²⁵ a simple method for the oxidative iodination of aromatic compounds such as alkylbenzenes, anisoles and phenols. Tetrabutylammonium peroxydisulfate in acetonitrile is another oxidant that has been used²⁶ with iodine in the context of the iodination of activated arenes. However, potassium peroxodisulfate in acetic acid in the presence of strong acid can be used²⁷ as an oxidant to convert iodoarenes into diacetoxyiodoarenes.

The combinations of iodine and di-iodine pentoxide and of iodine and iodic acid have been used²⁸ to iodinate activated aromatic rings. The iodination of a series of *o*-hydroxyarylketones by the latter reagent, has been reported.²⁹ Mechanistic studies with the iodine:di-iodine pentoxide system have suggested³⁰ that the di-iodine pentoxide complexes with and polarises the iodine to make it more electrophilic. A mixture of potassium iodide and potassium iodate in the presence of acid provides a simple method of iodinating electron-rich aromatic compounds in good yields.³¹ However, some phenols underwent polyiodination.

Phenols have been regioselectively iodinated in good yield using sodium iodide and either *t*-butyl hypochlorite³² or sodium hypochlorite (bleach)³³ as the oxidant. The formation of polyiodinated products in these reactions was controlled by the amount of sodium iodide that was used. Phenyl iodine(III) bistrifluoroacetate has been used³⁴ in acetonitrile to oxidise iodine for the iodination of methoxyarylketones.

A number of systems using metal oxidants have been described. These include potassium permanganate and potassium iodide in acetonitrile³⁵ and ceric ammonium nitrate with iodine, also in acetonitrile.³⁶ When anhydrous chromium trioxide is used³⁷ with iodine in a mixture of acetic acid and acetic anhydride containing sulfuric acid, activated aromatic rings are easily iodinated. Deactivated arenes such as benzoic acid and nitrobenzene can be iodinated under more vigorous conditions. However, the procedure is unsatisfactory with some of the more easily oxidisable aromatic compounds such as naphthalene and fluorene.

Lead tetra-acetate in glacial acetic acid has been used³⁸ as an oxidant for the iodination of reactive arenes. The application of various other oxidants in 90% sulfuric acid has been examined.³⁹ A system based on iodine and sodium iodate in 90% concentrated sulfuric acid has been recommended for the iodination of deactivated arenes such as benzoic acid and nitrobenzene. Oxygen has also been used⁴⁰ as the oxidant in the presence of metal salts such sodium vanadate(V) as a catalyst in trifluoromethanesulfonic acid.

The use of metals that form insoluble iodides

Silver salts react with iodine to precipitate silver iodide and generate a reactive electrophilic iodine. Nitryl iodide (NO_2I) can be generated by the action of silver nitrite on iodine⁴¹ and this has been used to iodinate aromatic hydrocarbons although the reaction was accompanied by some nitration. However, when this reagent was used with steroidal alkenes,

the structures of the products were rationalised⁴² in terms of the formation of a nitro radical as the initial reactive species.

Silver trifluoroacetate and iodine in nitrobenzene yields a solution which behaves as iodinetrifluoroacetate and which has been used⁴³ to iodinate reactive aromatic compounds such as anisole and aniline and even, under vigorous conditions (heating to 150 °C), benzoic acid. This system has been developed⁴⁴ in various ways using silver acetate or silver sulfate in ethanol under mild conditions to give good yields of iodinated aromatic ethers, amines and amides.

Mercury, as in compounds such as mercury(II) oxide, can replace the silver. Although mercury salts are toxic, useful iodinations have been achieved⁴⁵ with the system HgO/I_2 in dichloromethane. The iodination of phenols with iodine and mercury(II) acetate has also been carried out as part of the synthesis of biphenylenediols.⁴⁶ In a study⁴⁷ of the use of different mercury salts it was found that the iodination of activated aromatic compounds proceeded more satisfactorily with mercury triflate than with the nitrate or the chloride. Mercury(II) oxide and tetrafluoroboric acid adsorbed on silica is a powerful reagent for aromatic mercuration.⁴⁸ After treatment of the arylmercury derivative with iodine, the corresponding aryl iodide is obtained. This can be used as a 'one:pot' reaction. The procedure works not only for activated aromatic compounds but also, albeit in poorer yield, with deactivated arenes such as benzoic acid and nitrobenzene.

The iodination of activated arenes using iodine and ferric nitrate supported on silica⁴⁹ or the ferric nitrate dinitrogen tetraoxide complex [$\text{Fe}(\text{NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4$] supported on charcoal, has been reported.⁵⁰ Silica-supported bismuth(III) nitrate has been described⁵¹ as a solid phase oxidant for iodine in the iodination of activated aromatic rings.

The iodination of reactive aromatic rings such as phenols and amines using copper(II) chloride and iodine has been examined.⁵² This procedure has been improved⁵³ by using a mixture of aluminium and copper(II) chlorides with iodine. An increased amount of *ortho* iodination of phenol has been observed⁵⁴ in the presence of copper(II) acetate, although anisole and aniline continued to give *para* substitution as the major product. Reactive aromatic compounds can be iodinated with iodine on alumina. Reaction takes place on the surface of the alumina with the formation of aluminium tri-iodide.⁵⁵

The use of thallium salts, which are toxic, nevertheless introduces another possibility. Many iodination reactions are *para* selective. However, the orientation of iodination using thallium(III) trifluoroacetate is dependent on the conditions and can be *ortho* selective.^{56,57} Thallium(III) trifluoroacetate (hazard) is an efficient reagent for electrophilic aromatic thallation. The resultant arylthallium di(trifluoroacetate) reacts⁵⁶ with aqueous potassium iodide to form the aryl iodide and thallium(I) iodide. The orientation of the iodination which is controlled by the position of thallation, is determined by the reaction conditions. *Ortho* substitution predominates under conditions of kinetic control where there is the possibility of chelation by the substituent to the thallium(III) trifluoroacetate. Thus benzoic acid and phenylacetic acid together with their methyl esters give *ortho* iodo-derivatives under mild conditions at room temperature. Under more vigorous conditions when thermodynamic control operates, *meta* substitution occurs. Thallium(I) acetate and iodine can also be used⁵⁷ to achieve the selective *ortho* iodination of compounds containing chelating groups including phenols. However, the prior preparation of the thallium salt of the phenol gave no particular advantage. The same result can be achieved by the iodination of *ortho*-lithiated derivatives.⁵⁸

Iodination with *N*-iodoamides

N-Iodoamides have provided a source of electrophilic and of radical iodine. *N,N*-Diiodo-5,5-dimethylhydantoin has been used⁵⁹ for the iodination of a series of methoxybenzenes and naphthalenes. Iodination with *N*-iodosuccinimide in acetonitrile has been reported.⁶⁰ The reaction conditions have been modified by the use of a catalytic amount of trifluoroacetic acid.⁶¹ In this case it was suggested that the iodinating species was iodine trifluoroacetate. Zirconium tetrachloride has been used⁶² as a Lewis acid in a selective *para* iodination of activated arenes such as aniline or phenol with *N*-iodosuccinimide. It has been suggested that this Lewis acid complexes with the carbonyl oxygen of the iodosuccinimide facilitating the heterolytic cleavage of the N–I bond and the formation of a reactive iodonium ion. *N*-Iodosaccharin in acetonitrile is another reagent which has been used⁶³ in this context. The regioselective iodination of activated aromatic compounds with a dimeric *N*-iodotoluene-*p*-sulfonamide, *N,N'*-diiodo-*N,N'*-1,2-ethanebis(*p*-toluenesulfonamide) in acetonitrile with trifluoroacetic acid as a catalyst, has been reported.⁶⁴

The Selectfluor® reagent derived from DABCO, 1-chloro-methyl-4-fluoro-1,4-diazabicyclo-2,2,2-octane bistetrafluoroborate, activates iodine in acetonitrile sufficiently for it to be used to iodinate aromatic ethers.⁶⁵ Bis(pyridine)iodonium tetrafluoroborate (IPy₂BF₄)⁶⁶ and bis(collidine)iodonium hexafluorophosphate⁶⁷ with and without acid catalysis, have also proved to be efficient methods for the iodination of aromatic compounds. The iodonium cations are stabilised by complexing with the pyridine rings. The iodination of tyrosine residues in peptides has been achieved with this reagent.⁶⁶

Iodination in the presence of base

The iodination of activated aromatic rings particularly phenols, has been achieved with iodine in the presence of base. An early method described the potentially hazardous iodination of phenols dissolved in ammonia with iodine.⁶⁸ The ammonia has been replaced by sodium hydroxide or calcium carbonate in the iodination of aromatic amines. However, the oxidation of a phenol by iodine in alkaline methanol can give rise to coupling products.⁶⁹ In the case of *p*-cresol the product was 2,6-diiodo-4-methylphenol. A base such as ethylenediamine has also been used⁷⁰ to act as a hydrogen iodide acceptor. More recently iodine in a pyridine/dioxan mixture has been used⁷¹ to iodinate activated aromatic rings.

In conclusion, there is a wide range of methods for the direct iodination of activated aromatic rings. Whilst the regioselectivity is commonly *para* to the activating substituent, some methods exist with *ortho* selectivity. Fewer methods exist for the substitution of deactivated arenes. In these cases indirect methods can sometimes be preferred.⁷² Thus *p*-iodobenzoic acid is prepared via the organomercury derivative whilst *p*-iodonitrobenzene is prepared via diazotisation and iodination of *p*-nitroaniline.

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