Molecules **2003**, *8*, 45-52

molecules
ISSN 1420-3049
http://www.mdpi.org

Invited Lecture

Novel Easy Preparations of Some Aromatic Iodine(I, III, and V) Reagents, Widely Applied in Modern Organic Synthesis

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This lecture was presented at the International Symposium on Frontiers in Molecular Science 2002, July 15-18, Qingdao, China (lecture A018) and as a *review* at the Sixth Electronic Conference on Synthetic Organic Chemistry (ECSOC-6, http://www.mdpi.net/ecsoc-6/), September 1-30, 2002 (paper A011).

Abstract: We report our novel (or considerably improved) methods for the synthesis of aromatic iodides, (dichloroiodo)arenes, (diacetoxyiodo)arenes, [*bis*(trifluoroacetoxy)-iodo]arenes, iodylarenes and diaryliodonium salts, as well as some facile, *oxidative* anion metatheses in *crude* diaryliodonium or tetraalkylammonium halides and, for comparison, potassium halides. All our formerly published papers were discussed and explained in our review "Organic Iodine(I, III, and V) Chemistry: 10 Years of Development at the Medical University of Warsaw, Poland" (1990-2000) [1]. Our newest results are discussed below.

Keywords: Aromatic iodides, aromatic hypervalent iodine reagents, oxidative anion metatheses in ionic halides

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Introduction

Aromatic iodides, ArI, are generally ***more reactive***, though also more costly, than the respective bromides and chlorides. There are a considerable number of different methods, both direct and indirect, for their synthesis [2], and they are widely used in chemical laboratories and, to a lesser extent, in chemical industry. Moreover, ArI are able to form a large variety of aromatic *hypervalent iodine derivatives,* which found quickly increasing applications in modern organic synthesis [3].

In 1990 we decided that nearly all future research in our organic laboratory should be directed towards the title topics. We have placed special emphasis on the development of novel, easy and effective ***oxidative iodination procedures***, applicable for both *activated* and *deactivated* aromatics, ArH, and the resulting aryl/heteroaryl iodides, ArI, were often next applied in our subsequent novel (or improved) syntheses of the corresponding aromatic *hypervalent iodine derivatives*, mainly: (dichloroiodo)arenes, $ArICl_2$, (diacetoxyiodo)arenes, $ArI(OAc)_2$, [*bis*(trifluoroacetoxy)iodo]arenes, $ArI(OCOCF_3)_2$, iodylarenes, $ArIO_2$, and various diaryliodonium salts, $Ar_2I^+X^-$ or $Ar(Ar')I^+X^-$.

1. Syntheses of Aromatic Iodides

Since 1980 we have *indirectly* synthesized (in excellent yields) a number of heteroaromatic iodides from both symmetric and unsymmetric heteroaromatic mercurials, by applying the “classic” *iodo-demercuration* procedures. This topic is related in our newest review “Some Heteroaromatic Organomercurials, Their Syntheses and Reactions: A Review of Our Research (1980 – 2000)” ([4], pp 949-950); alternatively see [1] p 1333.

In the beginning, we oxidatively monoiodinated several *highly activated* arenes or heteroarenes using pure $Pb(OAc)_4$ as the oxidant in glacial AcOH at room temperature within 0.5 – 12 hours. With hot $Pb(OAc)_4$ solutions prepared *in situ* from commercial *minium*, Pb_3O_4, the iodination yields were often somewhat better than those obtained with the pure oxidant ([1], p 1333). Later, several *activated* aromatics were effectively mono-, di-, or even triiodinated at or near room temperature and within at most 15 minutes, with $PhI(OAc)_2$ in *anhydrous* $AcOH/Ac_2O$ mixtures acidified with catalytic quantities of conc. H_2SO_4 ([1], p 1343). In the both cases, some transient *iodine(I)* species, briefly denoted as $\mathbf{I^+}$, were the effective iodinating agents. In our next series of publications ([1], pp 1334-1345) we oxidatively iodinated/diiodinated a number of *activated* or *deactivated* aromatics (mostly arenes, ArH) with transient either *iodine(I)* species, $\mathbf{I^+}$, or *iodine(III)* species, $\mathbf{I^{3+}}$, always in *anhydrous* $AcOH/Ac_2O$/conc. H_2SO_4 mixtures. So far we have used the following ***oxidants*** for this purpose: CrO_3, $KMnO_4$, activated MnO_2, $NaIO_4$ or $NaIO_3$, a stable urea-H_2O_2 addition compound [1], sodium percarbonate [5], or sodium perborate [5]. In order to generate in the iodinating mixtures either $\mathbf{I^+}$ (appropriate to iodinate benzene, halobenzenes, and *activated* arenes) or more electrophilic $\mathbf{I^{3+}}$ transient species (appropriate to iodinate halobenzenes and *deactivated* arenes), we ***deliberately*** changed the proportions of the reactants and, consequently, the iodination *reaction mechanisms.* For example, when $\mathbf{CrO_3}$ was used as the oxidant, the following proportions of the reactants were used to generate either $\mathbf{I^+}$ or $\mathbf{I^{3+}}$ preponderant transient species in the *anhydrous* mixtures acidified with *varied quantities* of conc. H_2SO_4 (*a catalyst*):

$$3\ I_2 + 2\ Cr(VI) \rightarrow 6\ \mathbf{I^+} + 2\ Cr(III)$$

$$I_2 + 2\ Cr(VI) \rightarrow 2\ \mathbf{I^{3+}} + 2\ Cr(III)$$

Next, the following reactions took place in the iodinating mixtures:

$$\mathrm{ArH} + \mathbf{I^+} \xrightarrow[-\mathrm{H^+}]{} \mathbf{ArI} \quad \textit{(final products)}$$

$$\mathrm{ArH} + \mathbf{I^{3+}} \xrightarrow[-\mathrm{H^+}]{} \mathrm{ArI^{2+}} \xrightarrow[-2\mathrm{H^+}]{\mathrm{H_2SO_4}} \mathrm{ArISO_4}\ \textit{(aromatic iodine(III) intermediates)}$$

After pouring the final reaction mixtures into excess aq. Na_2SO_3 solutions, ArI were isolated in high yields:

$$\mathrm{ArISO_4}\ (\textit{not isolated}) + \mathrm{Na_2SO_3} + \mathrm{H_2O} \rightarrow \mathbf{ArI} + 2\ \mathrm{NaHSO_4}$$

Our novel *eco-friendly* method for the iodination of both activated and deactivated arenes, using a stable urea-H_2O_2 (**UHP**) addition compound as the oxidant, was earlier briefly explained in [1], p. 1345. Full details were disclosed at the International Symposium on Frontiers in Molecular Science 2002, July 14-18, Qingdao (China), and will be published elsewhere soon. Several examples of the oxidative iodination of some arylamines, accelerated with *multimode microwave irradiation*, using **UHP** as the oxidant, have just been published in [6].

2. Syntheses of (Dichloroiodo)arenes

Yellow crystalline (dichloroiodo)arenes, $ArICl_2$, known since 1885, have found growing importance in organic synthesis as potent, safe and fairly selective *chlorinating* and/or *oxidizing* agents. They may also be readily converted to other important hypervalent iodine reagents, viz. $ArIF_2$, $ArI(OAc)_2$, ArIO, $ArIO_2$, diaryliodonium salts, etc. [1, 3]. They are light- and heat-sensitive and often unstable to storage, hence they are usually used immediately after their preparation. Up to now the most common method for preparing $ArICl_2$ depends on passing the stream of Cl_2 through cold solutions of ArI in chlorinated solvents. To avoid the hazardous use of gaseous Cl_2 to prepare $ArICl_2$ from ArI, a large number of various either ***two-phase*** (CCl_4/conc. aq. HCl) or monophasic ***liquid-phase*** methods were reported; the full account of those methods (including the novel ones developed in our laboratory) is given in [1], Section 3. Cl_2 was generated there *in situ* from conc. hydrochloric acid, used either as a separate phase or as cosolvent, under the action of various oxidants: $2\ HCl + [O] \rightarrow Cl_2 + H_2O$; mostly, such procedures are easy and relatively safe. However, all former methods required the use of **iodoarenes**, ArI, as the starting substrates, which were then chlorinated at their iodine atoms to afford $ArICl_2$.

In 2001 we published two papers [7, 8], where we reported quite simple, two- or three-stage procedures for the ***one-pot*** conversions of various **arenes**, ArH, to the corresponding $ArICl_2$ obtained in high crude yields. The starting ArH were, at first, *oxidatively iodinated* with some *iodine(III)* transient species, $\mathbf{I^{3+}}$, to form the respective aromatic *iodine(III)* intermediates, $ArISO_4$ *(not isolated*; cf. Section 1 above). Next, by adding excess conc. hydrochloric acid to the final reaction mixtures, the soluble $ArISO_4$ were effectively metathesized into the *insoluble* $ArICl_2$ [7]. Alternatively [8], the starting more active ArH (benzene, halobenzenes, activated arenes) were, at first, *oxidatively iodinated* with some *iodine(I)* transient species, $\mathbf{I}^+$, to form the corresponding ArI *(not isolated).* Next, the second portion of CrO_3 was added, followed by excess conc. hydrochloric acid, which *oxidatively chlorinated* the ArI intermediates to form the final products, i.e. $ArICl_2$. So far, only $\mathbf{NaIO_4}$ and $\mathbf{NaIO_3}$ [7], or $\mathbf{CrO_3}$ [8] have been used by us as the oxidants – but it is possible to apply other oxidants for the same purpose [5]. Our novel *eco-friendly* method [7] for the effective preparation of crude $ArICl_2$ from the respective arenes and I_2 avoids the hazardous use of gaseous Cl_2 and chlorinated solvents, and the use of *costly* ArI. Strongly acidic wastes, after their neutralization and dilution, did *not* contain any toxic by-products. Thus, our novel method [7] would be particularly suitable for *large-scale preparations* of $ArICl_2$ from ***arenes.*** Of course, only those isomeric $RC_6H_4ICl_2$ may predominantly be obtained from the monosubstituted benzenes, RC_6H_5, which are formed in agreement with common orientation rules in the electrophilic substitutions of the used RC_6H_5 by the said electrophilic transient species, $\mathbf{I}^{3+}$ or $\mathbf{I}^+$.

3. Syntheses of (Diacetoxyiodo)arenes and [*Bis*(trifluoroacetoxy)iodo]arenes

(Diacetoxyiodo)arenes, $ArI(OAc)_2$, are potent, often fairly selective, *oxidizing* agents. They are also used for the facile syntheses of e.g. [*bis*(trifluoroacetoxy)iodo]arenes, [hydroxy(tosyloxy)-iodo]arenes (*selective oxidants*) and aromatic iodonium salts (*arylating reagents*), etc. [3]. $ArI(OAc)_2$ are crystalline compounds, which may be stored in the dark, preferably in a cooler. They were previously prepared from ArIO by the action of hot glacial AcOH, from $ArICl_2$ by the exchange of the chlorine atoms by acetoxy groups, and from ArI by their oxidation in *warm* AcOH by either $NaBO_3{\cdot}4H_2O$, or by peracetic acid, or electrolytically [1, p 1352]. In our laboratory, we primarily applied $\mathbf{CrO_3}$ as the oxidant in $AcOH/Ac_2O$/conc. H_2SO_4 mixtures to transform a number of ArI to $ArI(OAc)_2$ in 58 – 82% yields (for the purified compounds); this method is *unsuitable* for ArI bearing e.g. the OMe and NHAc groups, and is hardly applicable for iodotoluenes [1, p 1353]. For the preparation of pure $PhI(OAc)_2$ from PhI (in 79% yield) our method is *8 - 16 times faster* and ca. *5 times less expensive* than the method of McKillop and Kemp [9], who used $NaBO_3{\cdot}4H_2O$ as the oxidant in a large volume of warm glacial AcOH.

In 2001 we published an easy method for preparing $ArI(OAc)_2$ from ArI substituted with the Me and OMe groups – which nicely complements our former method (*vide supra*) [10]. PhI, halogeno-iodoarenes, iodotoluenes, and iodoanisoles were refluxed for 2 hours in $\mathbf{NaIO_4}/AcOH/Ac_2O/AcONa$ solutions to give finally the purified $ArI(OAc)_2$ in 44 - 77% yields; this novel method is *not applicable*, however, for ArI substituted with strong electron-withdrawing groups.

Recently, in our laboratory we have devised an easy and effective method for preparing $ArI(OCOCF_3)_2$ directly from ArI, using a **sodium percarbonate**/$(CF_3CO)_2O/CH_2Cl_2$ anhydrous system to afford high yields of the nearly pure products, $ArI(OCOCF_3)_2$ (98-99% purity by iodometry). After completing the reactions, the precipitated CF_3CO_2Na was filtered off, the filtrates were concentrated, the residues were triturated with hexane, washed with hexane on the filter, and quickly air-dried by the suction. For example, the nearly pure (98-99%) $Ph(OCOCF_3)_2$ was repeatedly prepared from PhI in 87% *crude* yield; details of this novel method have just been published in [11]. Similarly, we have just published in [12] our novel method for preparing the nearly pure (96-99%) $ArI(OAc)_2$

from ArI, using a **sodium percarbonate**/AcOH/Ac_2O/CH_2Cl_2 anhydrous system. As an example, the $PhI(OAc)_2$ thus prepared in 79% *crude* yield, was 99% pure (by iodometry).

4. Syntheses of Iodylarenes

Some iodylarenes, $ArIO_2$, are nowadays used as versatile *selective oxidants*. There are plenty of different methods for their preparation from ArI, $ArICl_2$, or ArIO [1, p 1355]. They are rather stable thermally, but their melting points are often accompanied by explosions, and their violent decomposition may be induced, e.g. by scraping them with a spatula or upon impact [3].

In 2001 we reported an easy, safe and effective method for preparing a number of various $ArIO_2$ from the corresponding ArI, using **$NaIO_4$** as the oxidant [10]. ArI were vigorously stirred and refluxed *for 8 – 16 hours* with aq. solutions of $NaIO_4$ to give the respective $ArIO_2$ in 58 – 91% crude yields. Iodometric titrations showed that the *crude* $ArIO_2$ thus obtained were 98 – 99% pure; after their recrystallization from boiling water we obtained analytically pure specimens. When ***sodium salts*** of 2-iodo- and 4-iodobenzoic acids (prepared *in situ*) were stirred and boiled with aq. $NaIO_4$ solutions, then this resulted in the formation and next isolation of "2-iodylbenzoic acid" (i.e. 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, **IBX**) or 4-iodylbenzoic acid in 71% or 88% *crude* yields, respectively; iodimetric titrations showed that they also were 98-99% pure. We tried, in vain, to accelerate these reactions with microwave irradiation. Finally, we have shortened the reaction times *to 3 – 6 hours*, by the use of a dilute aq. AcOH (30% by vol.) as the solvent of choice, instead of neat water, with preserving the same good yields and high purities (96-99%) of the *crude* final products, $ArIO_2$. 2-Iodobenzoic acid, after 4 hours of its boiling and stirring with a solution of $NaIO_4$ in 30% (by vol.) aq. AcOH, gave the nearly pure (98-99%) "2-iodosylbenzoic acid" (i.e. 1-hydroxy-1,2-benziodoxol-3(1*H*)-one) in 91-93% *crude* yields; these novel results will be published soon [5].

5. Syntheses of Diaryliodonium Salts

Solid symmetric and unsymmetric diaryliodonium salts, $Ar_2I^+X^-$ and $Ar(Ar')I^+X^-$, are widely used in organic synthesis as *arylating reagents* for various organic and inorganic nucleophiles, and some of them display biological activity and photochemical properties. They are mostly fairly stable towards heat, oxygen and humidity, but should preferably be stored in the dark. A large number of methods are available for their preparation [1, 3, 13], but many of them are rather costly and/or too complicated. We hope that our two novel methods related below are quite easy, cheap, and fairly effective.

In 1995 we reported [1, p 1358] a ***one-pot*** ("short-cut") synthesis of sparingly soluble diaryliodonium bromides and iodides (obtained in 20 - 89% *crude* yields) from various ArI oxidized firstly with *anhydrous* **CrO_3**/AcOH/Ac_2O/conc. H_2SO_4 mixtures, then coupled *in situ* with benzene and various activated arenes or heteroarenes [1, pp 1358-1360] and, finally, precipitated out with excess aq. KBr or KI solutions. In 2001 we published a similar, albeit more *eco-friendly* method, using *anhydrous* **$NaBO_3 \cdot H_2O$**/Ac_2O/conc. H_2SO_4 mixtures [13]. In our latter paper diaryliodonium bromides were obtained in 23 - 98% *crude* yields; no *toxic* residues are left after the reactions – in a strong contrast to our former method.

In 1999 we also improved considerably the old Willgerodt method (1897), which allows one to obtain various symmetric and unsymmetric diaryliodonium chlorides by reacting hot aqueous suspensions of *equal masses* of powdered $ArICl_2$ with powdered Ar_2Hg; sparingly soluble side-products, ArHgCl and ArIO, are hot-filtered off and discarded, whereas diaryliodonium bromides may be precipitated out from the filtrates with excess aq. KBr solutions; for more details see [1, p 1360] or [4, p 952].

6. Oxidative Anion Metatheses in Diaryliodonium Halides

For the *arylation* of organic and inorganic nucleophiles with diaryliodonium salts, the best yields are achieved by the use of diaryliodonium salts with substantially *non-nucleophilic* counterions, viz. tetrafluoroborates, tosylates, triflates, trifluoroacetates, etc. [3]. In our two earlier papers [1, pp 1362 – 1365] we reported numerous examples of ***oxidative anion metatheses*** in ***crude*** diaryliodonium bromides, iodides, and chlorides (see Section 5 above), which produced the corresponding ***pure*** diaryliodonium tetrafluoroborates, tosylates, trifluoroacetates, triflates as well as hydrogensulfates and nitrates, etc. in 54 – 86% yields. These new procedures are shorter and less expensive than many earlier methods. They are also applicable to some other *ionic* halides, e.g. tetraalkylammonium or potassium halides. The starting *crude* halides were suspended in boiling MeOH acidified with an excess of appropriate ***strong acid***, HX, and then excess 30% aq. H_2O_2 was added dropwise to oxidize the halide anions ($I^- > Br^- > Cl^-$; the fluorides do not react) to the respective *dihalogens*; 100% excess ***cyclohexene***, acting there as a “halogen scavenger”, was added there for the metatheses in diaryliodonium *bromides* and *chlorides*. For the diaryliodonium *iodides*, the diiodine evolved was simply *washed off* from the crude metathesized products with anhydrous Et_2O. When ***dry acetone*** was used as the solvent of choice for the oxidative anion metatheses in *crude* diaryliodonium bromides and chlorides, the addition of *cyclohexene* was not necessary – since the strongly acidified Me_2CO acts itself as a very efficient “halogen scavenger” [1, p 1363], due to the presence of its very quickly equilibrating and very reactive ***enol form***. The crude metathesized products were recrystallized from appropriate organic solvents to afford the *analytically pure* diaryliodonium salts in the yields given above.

Conclusions

This lecture shows our small group’s main interest in developing novel (or considerably improved) preparative procedures, which are suitable for easy, quick, cheap, and possibly *enviromentally benign* preparations of iodoarenes and some basic aromatic hypervalent iodine reagents: $ArICl_2$, $ArI(OAc)_2$, $ArI(OCOCF_3)_2$, $ArIO_2$, and diaryliodonium salts with substantially *non-nucleophilic* counterions (suitable for the arylation of organic and inorganic nucleophiles). Our earlier works (1990-2000) are related and discussed in our extensive *review* [1]; in this lecture our works published in 2001 [4, 7, 8, 10, 13] are also covered and referred to, as well as those published in 2002 [6, 11, 12].

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