Alternative Strategies with Iodine: Fast Access to New Iodine(III) Compounds

Tobias Hokamp, Leonardo Mollari, Lewis C. Wilkins, Rebecca L. Melen and Thomas Wirth*

Abstract: *Non-iodinated arenes are easily and selectively converted into (diacetoxyiodo)arenes in a single step under mild conditions using iodine triacetates as reagents. The oxidative step is decoupled from the synthesis of hypervalent iodine(III) reagents which can now be prepared conveniently in a one-pot synthesis for subsequent reactions without prior purification. The chemistry of iodine triacetates was also expanded to heteroatom ligand exchanges to form novel inorganic hypervalent iodine compounds.*

Hypervalent iodine compounds have emerged as versatile and environmentally benign reagents for modern organic chemistry, where they have contributed to the realization of novel chemical transformations.[1] Due to their strongly electrophilic character in combination with the excellent leaving group ability of the phenyliodonio group, they can react with a broad range of nucleophiles. Their synthetic applications include oxidation,[2] halogenation,[3] carbon–carbon bond formation,[4] amination[5] and oxygenation.[6] (Diacetoxyiodo)arenes and similar polyvalent iodine carboxylates belong to arguably the most important class of hypervalent iodine compounds. The main route for their formation is the reaction of iodoarenes with oxidants such as Oxone®,[7] *m*-chloroperbenzoic acid,[8] peracetic acid,[9] sodium perborate[10] or Selectfluor®[11] in the presence of carboxylic acids to give the corresponding [bis(acyloxy)iodo]arenes. For this approach, iodoarenes must be prepared by iodinating arenes before being oxidized in a second step. Furthermore, excess and side-products of the oxidants must be removed in a purification step by washing or by recrystallization of the hypervalent iodine(III) products. Herein, we describe the development of a one-step synthesis of (diacetoxyiodo)arenes from non-iodinated arenes through reaction with iodine triacetate $I(OAc)_3$.[12] Furthermore, we demonstrate that the iodine(III) reaction products obtained in such processes can be used in subsequent reactions without further purification.

Most known hypervalent iodine(III) reagents have structures of type $ArIL_2$ **1** or Ar_2IL **2** with Ar being an aryl moiety and L a heteroatom (O, N, halogen) containing ligand (Figure 1). The iodine(III) compounds of type **1** have the overall trigonal bipyramidal geometry with the heteroatom ligands L in the axial position and the aryl moiety occupying the equatorial positions. Iodonium salts **2** show a similar geometry with a weakly bonded heteroatom containing ligand. One aryl moiety is located in the equatorial position and bound to the central iodine atom by a covalent bond while the remaining two substituents are located in the axial positions and, together with the iodine atom, form a linear 3-center 4-electron (3c-4e) bond, the hypervalent bond.[13] Recent computational results show an alternative assessment of the bonding situation in such compounds.[14] Conversely, the iodine(III) reagent IL_3 **3** with three heteroatom containing ligands on the iodine has been rarely investigated owing to their relative instability.[15] Only very few examples of iodine(III) tris(carboxylates), such as iodine triacetate **4**[16] and iodine tris(trifluoroacetate) **5**[17] have been reported (Figure 1), while iodotrichloride **6** is commercially available. Compounds **4** and **5** are best prepared by the oxidation of iodine with fuming nitric acid in the presence of an appropriate carboxylic acid and the corresponding carboxylic acid anhydride. Alternative oxidants such as oxone did not lead to the target reagents.[18] However, structural information of iodine(III) tris(carboxylates) remain scarce in the literature. Furthermore, the utilization of potential heteroatom-containing ligands towards ligand exchanges have been unexplored prior to this work.

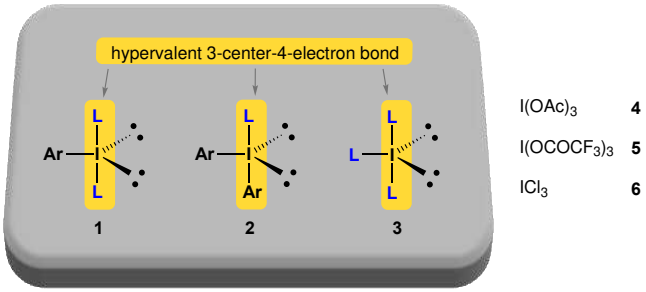

Figure 1. Different types of iodine(III) reagents **1** – **6**.

In the preparation of **4**, two different crystalline polymorphs were obtained depending on the crystallization temperature, one is in agreement with the structural information obtained by Birchall and co-workers.[19] Surprisingly, in the synthesis of **5**, crystals of a new compound **5a** were formed. Solid-state X-ray structure analysis of this compound revealed it to be dimeric in nature with the iodine atoms connected *via* a bridging trifluoroacetate ligand with a nitrosonium ion derived from nitric acid acting as the counterion (Figure 2).[20] Reaction of **4** with **5a** led to a ligand exchange of the trifluoroacetate and acetate ligands to give compound **7** $I(OCOCF_3)_2OAc$ with the more electron-withdrawing trifluoroacetates occupying the axial positions and the acetate being located in equatorial position. This was easily observed in the ^1H NMR spectra which showed a clear downfield shift of the acetate protons in **7** at δ = 2.42 ppm from that observed for the corresponding protons in **4** (δ = 2.19 ppm). This reactivity is explained by the molecular orbital description of the linear three-center-four-electron hypervalent bond in which the HOMO contains a node at the central iodine atom. This renders the hypervalent bond highly polarized resulting in the more electronegative ligands occupying the axial position.[13]

[*] T. Hokamp, L. Mollari, Dr. L. C. Wilkins, Dr. R. L. Melen, Prof. Dr. T. Wirth
School of Chemistry, Cardiff University
Main Building, Park Place, Cardiff CF10 3AT (UK)
E-mail: wirth@cf.ac.uk
Homepage: http://blogs.cardiff.ac.uk/wirth/

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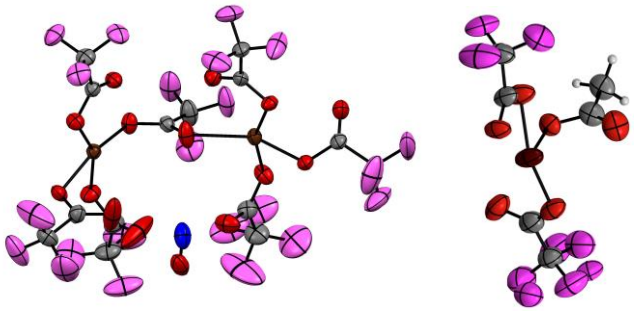


Figure 2. X-ray structures of iodine(III) reagents **5a** (left) and **7** (right). Thermal ellipsoids shown at 50% probability. I = brown, C = grey, O = red, N = blue, F = pink, H = white.

We subsequently investigated the behaviour of **4** towards Lewis acids and bases. In the presence of pyridine, the coordination compound **8** is obtained, while the addition of the frustrated Lewis pair (FLP),[21] $B(C_6F_5)_3$/2,6-lutidine led to further activation of **4** yielding **9**. Here the strong Lewis acid abstracts one acetate group giving the $[(C_6F_5)_3BOAc]^-$ anion with the $[(OAc)_2I]^+$ cation being stabilized by two lutidine Lewis bases which bind in the axial positions as revealed by solid-state structural analysis. Here, one acetate moiety remains in the covalent bond and one coordinates in a bidentate fashion to the iodine (Figure 3).[20] The iodine atom in iodine tris(trifluoroacetate) **5a** is too reactive to undergo similar ligand exchange with FLPs using the same conditions. In contrast to **4**, compound **5a** undergoes single and double ligand exchange with $B(C_6F_5)_3$ to form hypervalent iodine compounds C_6F_5-$I(OCOCF_3)_2$ **10** and $[(C_6F_5)_2I]$ $[OCOCF_3]$ **11** of type **1** and **2** that both crystallized from the reaction mixture and were structurally characterized (see supporting information).[20] Reaction products of **4** with ligands such as 2,2'-bipyridine, 1,10-phenanthroline, 2- or 4-dimethylaminopyridine and **4** with FLPs such as $B(C_6F_3)_3$/2,6-lutidine, $B(C_6F_5)_3$/2,4,6-collidine or $B(C_6F_5)_3$/tri-*tert*-butylphosphine could not be obtained.

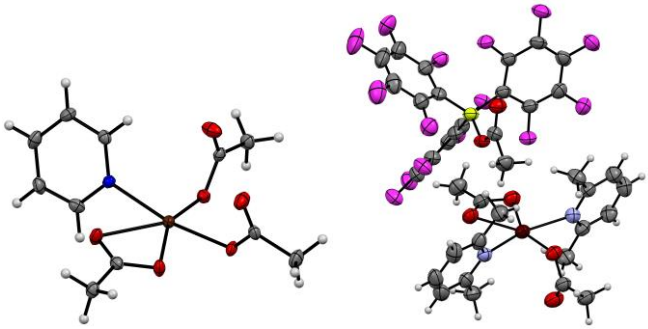
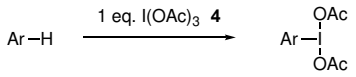


Figure 3. X-ray structures of iodine(III) reagents **8** (left) and **9** (right) derived from **4**. Thermal ellipsoids shown at 50% probability. I = brown, C = grey, O = red, N = blue, F = pink, H = white.

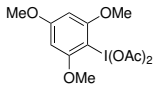
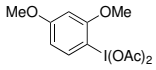
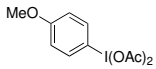
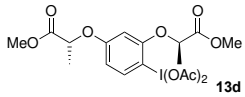
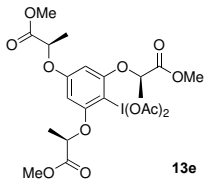
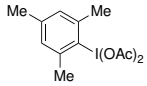
Reagents **4** and **5** were also shown to react as very powerful electrophiles in electrophilic aromatic substitutions. Due to its high electron density on the aromatic ring, we started our investigation by using 1,3,5-trimethoxybenzene **12a** as a test substrate. The reaction of **12a** with one equivalent of **4** led to quantitative formation of 2,4,6-trimethoxy(diacetoxyiodo)benzene (**13a**, 97%) in dichloromethane at room temperature after 1 hour (Table 1, entry 1), this structure was also confirmed by X-ray analysis.[20] Similar results were obtained with 1,3-dimethoxybenzene (**12b**), which reacted with **4** exclusively to yield 2,4-dimethoxy(diacetoxyiodo)benzene (**13b**, 95%, entry 2), with the selectivity being explained due to the steric hindrance between the two methoxy-groups. Several attempts to synthesise **13a** and **13b** *via* oxidation of 2-iodo-1,3,5-trimethoxybenzene and 1-iodo-2,4-dimethoxybenzene, with oxidants such as sodium perborate, Selectfluor®, *m*-chloroperbenzoic acid or Oxone® led to complete decomposition of starting material. The reaction of the arene precursors with $I(OAc)_3$ **4** seems to be currently the only route to the hypervalent compounds **13a** and **13b**. The reaction of $I(OAc)_3$ **4** with 2 equivalents of **12a** did not lead to the corresponding diaryliodonium derivative.

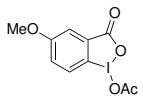
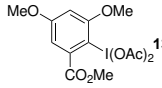
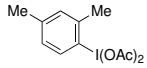
Less electron-rich aromatic systems are almost inert towards $I(OAc)_3$ **4** under these conditions. Anisole **12c** reacted very slowly to 4-methoxy(diacetoxyiodo)benzene **13c** (46% conversion after 8 h and 64% conversion after 27 h according to ^{1}H NMR analysis), while the use of acetic acid as solvent enhanced the reactivity of **4** dramatically and **13c** was obtained in very good yield after 20 h (87%, entry 3) without formation of the corresponding *ortho*-isomer. Chiral arenes can also be used in this process leading to **13d** and **13e** (87% and >99%, entries 4 and 5) and even reactions with less reactive arenes such as mesitylene **12f** may be performed at elevated temperatures of 60 ºC forming product **13f** in 76% yield (entry 6). Other substrates such as 3-methoxybenzoic acid **12g** or methyl 3,5-dimethoxybenzoate **12h** reacted smoothly to **13g** and **13h** (72% and 77% yield, respectively), however, reactivity limits are touched with *meta*-xylene **12i** leading to product **13i** in only 33% yield. Noteworthy is the incomplete reaction and the formation of 1-iodo-2,4-dimethylbenzene, which can either come from the thermal instability of **13i** or from the thermal instability of **4** as $I(OAc)_3$ may thermally decompose to IOAc,[13] which is itself known for its ability to iodinate aromatic compounds.[22] Other substrates such as 1-methylindole and azulene decomposed in presence of $I(OAc)_3$ **4**.

Table 1. Substrate scope for the one-step synthesis of (diacetoxyiodo)arenes using $I(OAc)_3$ **4**.

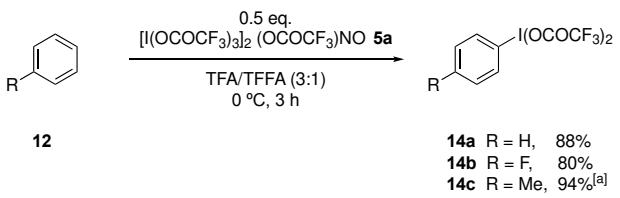


12 **13**

Entry	Product	Solvent	Time [h]	Temperature [ºC]	Yield [%]
1	 **13a**	CH_2Cl_2	1	20	97
2	 **13b**	CH_2Cl_2	1	20	95
3	 **13c**	AcOH	20	20	87
4	 **13d**	AcOH	5	20	87
5	 **13e**	AcOH	2	20	99
6	 **13f**	AcOH	20	60	76

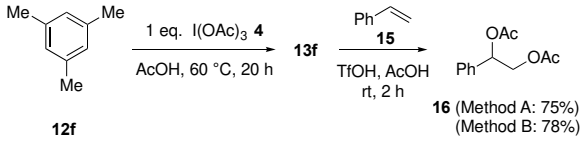
7	 **13g**	AcOH	4	60	72
8	 **13h**	AcOH	4	60	77
9	 **13i**	AcOH	41	60	33

Less reactive arenes can react with the more reactive iodine tris(trifluoroacetate) **5**/**5a**. As shown in Scheme 1, benzene, fluorobenzene or toluene produce the *para*-substituted [bis(trifluoroacetoxy)iodo]arenes **14** in high yields.[20,23]



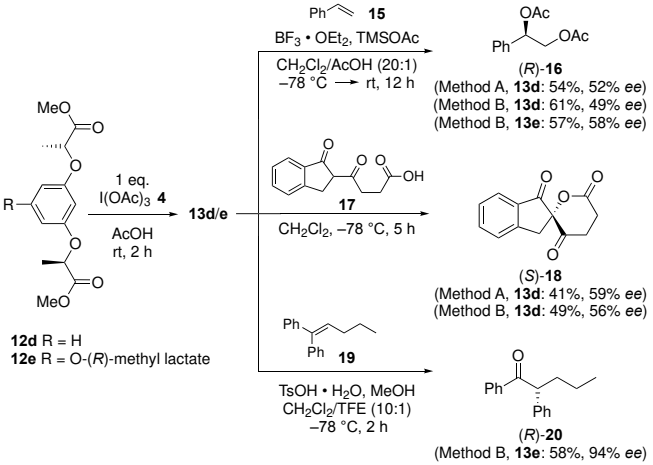
Scheme 1. Reaction of $[I(OCOCF_3)_3]_2(OCOCF_3)NO$ **5a** with electron-poor arenes. [a] Reaction in toluene performed at –40 ºC for 12 h.

Finally, the isolated [bis(acetoxy)iodo]arenes **13** were applied in the diacetoxylation of styrene **15** to **16**. As no side-product apart from acetic acid is formed during the atom-economic one-step synthesis of **13**, these reactions were carried out in a one-pot operation without purification of the iodine(III) reagent **13**. Firstly, styrene **15** was converted within 2 hours using purified **13f** and triflic acid to give **16** in good yield (75%, Scheme 2). Secondly, **13f** was prepared *in situ* from **12f** and $I(OAc)_3$ **4**. Subsequently, styrene **15** and triflic acid were added to the crude mixture to afford **16** after 2 hours in comparable yield (78%).



Scheme 2. Diacetoxylation of styrene **15** using purified **13f** (Method A) and *in situ* prepared **13f** (Method B).

These results encouraged us to tackle stereoselective reactions by using the chiral iodine(III) compound **13d** in a stereoselective diacetoxylation of **15** and in the stereoselective spirolactonization of **17** to **18** (Scheme 3). For both reactions, similar yields and selectivities were obtained with either pre-formed or *in situ* generated iodine(III) reagent **13d**. Due to the regioselective iodination, the iodine(III) moiety is not placed in between the two chiral substituents in **13d**. This can be overcome by treating **12e** with **4**. Diacetoxylation of styrene **15** with **13e** improved the enantiomeric excess of **16** to 58%, which is slightly less than in a previously described reaction (70% *ee*) with a similar hypervalent iodine reagent using the same conditions.[24] The lower enantiomeric excess presumably results from a higher electron density in **13e** through the third oxygen substituent. Also the rearrangement of **19** to **20** was performed using the reagent **13e** generated *in situ*. Compound **20** was obtained in 94% *ee*, identical to the previously reported reaction with a hypervalent iodine reagent with two methyl lactate substituents on either side of the iodine(III) moiety.[25] The one-step access to chiral hypervalent iodine(III) reagents without the need for purification will be of large benefit for their synthetic use.



Scheme 3. Stereoselective diacetoxylation, spirolactonization and rearrangement using isolated **13d**/**e** (Method A) and *in situ* prepared **13d**/**e** (Method B).

In conclusion, novel iodine(III) reagents of type IL_3 have been prepared through various readily accessible synthetic processes. The use of iodine triacylates allowed an alternative strategy for the rapid synthesis of (diacyloxyiodo)arenes from non-iodinated arenes. These hypervalent iodine(III) compounds can conveniently be used in subsequent reactions in a one-pot synthesis without prior purification.

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Keywords: aromatic substitution • hypervalent iodine • iodine • one-pot reactions • stereoselective synthesis

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[20] CCDC-1836715 (**4**), CCDC-1836708 (**5a**), CCDC-1836709 (**7**), CCDC-1836710 (**8**), CCDC-1836711 (**9**), CCDC-1837674 (**10**), CCDC-1836712 (**11**), CCDC-1836713 (**13a**), CCDC-1836714 (**14c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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