Iodine(III) Mediators in Electrochemical Batch and Flow Reactions

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Abstract
The anodic oxidation of aryl iodides is a powerful method for the synthesis of hypervalent iodine compounds, which have matured to frequently used reagents in organic synthesis. The electrochemical route eliminates the use of expensive or hazardous oxidants for their synthesis. Hypervalent iodine reagents generated at the anode are successfully used as either in-cell or ex-cell mediators for many valuable chemical transformations including fluorinations and oxidative cyclisations. The recent advances in the area of flow electrochemistry are providing additional benefits and allow new synthetic applications. Mechanistic insights and novel technologies enable the development of new concepts for sustainable chemistry.

Graphical Abstract

Keywords
Anodic oxidation, Electrochemistry, Flow synthesis, Hypervalent iodine, Redox mediator

Introduction
The use of hypervalent iodine reagents in organic synthesis is known for a long time. Their use has regained large interest in the past decades as these reagents are non-metallic, environmentally friendly and offer a broad range of reactivities while being, at the same time, mild and highly efficient reagents [1]. However, for their preparation strong oxidants are always necessary. Willgerodt, who prepared the first hypervalent iodine reagents, used elemental chlorine for the oxidation of iodoarenes for the direct generation of (dichloroiodo)arene derivatives [2]. Other commonly used oxidants include bromates, perborates, peracids or persulfates. Recently it has been established that the required peracids can also be generated in situ so that oxygen can be the terminal oxidant [3,4]. While the first electrochemical synthesis of iodine(III) compounds has been reported in 1925 [5], systematic investigations on the electrochemical generation of hypervalent iodine reagents date to the 1960s and 1970s [6], but only in the last decades this methodology was developed further and is now regarded as an established process [7,8,9]. Apart from being a process not generating any waste, the electrochemical oxidation of iodine derivatives also offers other advantages. The intrinsic sustainability of electrochemical methods provides a reliable alternative to conventional synthetic methods. The oxidation can be switched on or
off at will through the direct control of the electricity and allows not only efficient, but also high-yielding reactions to take place. Limitations applying to electrochemical methods are, of course, also in place here. The reaction occurs exclusively at the electrode surface and the choice of electrode material and its surface properties play important roles. Oxidation potentials of most iodoarenes are suitable for platinum or graphite working electrodes. To provide the necessary conductivity for the electrochemical oxidation, addition of electrolytes to the solution of iodoarenes in organic solvents is required. Most electrochemical oxidations lead to iodine(III) derivatives, there is only a singular example of an electrochemically generated iodine(V) species [10].

**Mechanistic Considerations**
The mechanism of these oxidations has been investigated. Early polarographic studies indicate that iodobenzene exhibits a clean and irreversible two electron wave which was not altered by the presence of benzene [11]. The iodoarene 1 must be pre-adsorbed on the electrode surface before the one electron oxidation to the radical cation 2 can proceed. This is the rate-limiting step as the subsequent reaction with another arene in the synthesis of diaryliodonium derivatives or the stabilisation through the addition of a nucleophilic ligand is a fast process, which is followed by the second one electron oxidation to the cation 4 as shown in Figure 1. If the nucleophilic ligand is an acetate, the stabilisation of the radical cation 2 as a transient iodine(II) intermediate 3 has been investigated in detail [12]. After the electrochemical generation of the iodine(III) species of type 5, three different processes are possible. (i) Depending on the nature of the iodine(III) reagent, it can be isolated and characterised which has been demonstrated on different occasions. (ii) A substrate can be added to the electrogenerated iodine(III) reagent and a reaction can be performed. Unstable and sensitive iodine(III) compounds 5 can be made and used in such a process without the need of isolation. (iii) The electrochemical generation of the iodine(III) species is performed in the presence of a substrate allowing an immediate reaction. Such a protocol would suffice with substoichiometric iodine compounds and is labelled as an electrocatalytic reaction. However, this process can only be applied for substrates which do not react themselves on the electrode surface under the electrochemical reaction conditions. In all cases, the cathodic half reaction is the reduction of protons rendering hydrogen as the sole by-product.

![Figure 1. Electrochemical oxidation of iodoarenes on the electrode surface.](image)

(i) Isolation of stable iodine(III) compound 5
(ii) Addition of a substrate reacting with 5
(iii) Generation of 5 in the presence of a substrate

**Recent Developments and Applications**
Electrochemical oxidation of iodoarenes in the presence of HF•amine mixtures has been widely investigated as the corresponding (difluoroiodo)arenes are very versatile fluorination reagents. It avoids the need of toxic anhydrous HF for their synthesis and did allow even their isolation. While the cyclisation of unsaturated amides 6 is compatible with an in situ
generation of the iodine(III) reagents [13], the difluorination of electron-rich alkenes such as 8 can be problematic and has to be separated from the synthesis of (difluoroiodo)arenes (Figure 2) [14]. Batch electrochemical procedures for the preparation of 7 and 9 have been established, but inherent safety concerns with scale-up can be addressed through flow electrochemical reactors as superior tools for electrochemical reactions [15,16,17,18,19]. In general, batch electrochemical methods have relatively small electrode areas, their need of supporting electrolytes and difficulties in scaling up can often be alleviated using electrochemical flow cells. Flow cells have high surface-to-volume ratios and enable exact control over temperature, flow rate, residence time and pressure. Their efficient mixing combined with enhanced mass and heat transfer and handling of small volumes leads to facile and safe scaling-up protocols. Additionally, electrolysis under flow conditions reduces the possibility of overoxidation as the reaction mixture is flown continuously out of the reactor in contrast to batch electrolysis. The reactions can be performed in a much shorter time, with similar yields and even through automated equipment avoiding interference with the experimenter. Electrocatalytic reactions using only catalytic amounts of iodine compounds have not yet been reported in a flow setup [20].

![Electrochemical synthesis of (difluoroiodo)arenes and their synthetic use.](image)

Electrolysis of iodoarenes in the presence of fluorinated alcohols allows the synthesis of unstable iodine(III) derivatives such as 5a and 5b (Figure 3). They cannot be isolated and have to be used immediately in subsequent reactions. Batch protocols for the synthesis of 5a in the cyclisation of 10 to 11 have been reported earlier [21], but only recently the transfer of this chemistry to flow systems was realised [22]. This now allows not only the direct oxidative functionalisation of substrates, but also the straightforward conversion of the unstable intermediates 5a/b into widely applied reagents 12 in high yields. An extension of the methodology towards chiral iodoarenes for stereoselective functionalisations was presented using spirolaconisations from 13 to 14 [23].
One main disadvantage in batch electrolysis, the addition of supporting electrolytes, has been overcome by flow reactors with short distances between the electrodes. Another interesting development is the synthesis of iodine derivatives serving at the same time as electrolytes. Compounds such as 15 and 16 have an ionic substituent and can be prepared in a short synthetic sequence. Compound 15 was used as the in situ prepared difluoroiodo derivative in electrocatalytic fluorinations yielding products such as 17 [20] as shown in Figure 4. Compound 16 has been pre-electrolysed to the corresponding iodine(III) derivative and then employed in cyclisations leading to benzoxazoles 18 [24,25]. The ionically tagged molecules 15 and 16 can be recovered easily after the reactions.

**Conclusions**

The electrochemical synthesis and use of hypervalent iodine(III) reagents in batch and flow system has seen increased interest in recent times. The clear advantage of an electrochemical oxidation over chemical oxidants is now being combined with electrocatalytic operations and with flow synthetic methodology towards environmentally benign and safe synthesis. As electrocatalytic reactions are still in their infancies and the substitution of reaction media such as fluorinated alcohols or HF•amine will be necessary to
further improve the ecological footprint of electrochemical reactions and their industrial applications.

Declaration of Interest
None.

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