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Report

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Synthesis of Diverse Aryliodine(III) Reagents by Anodic Oxidation

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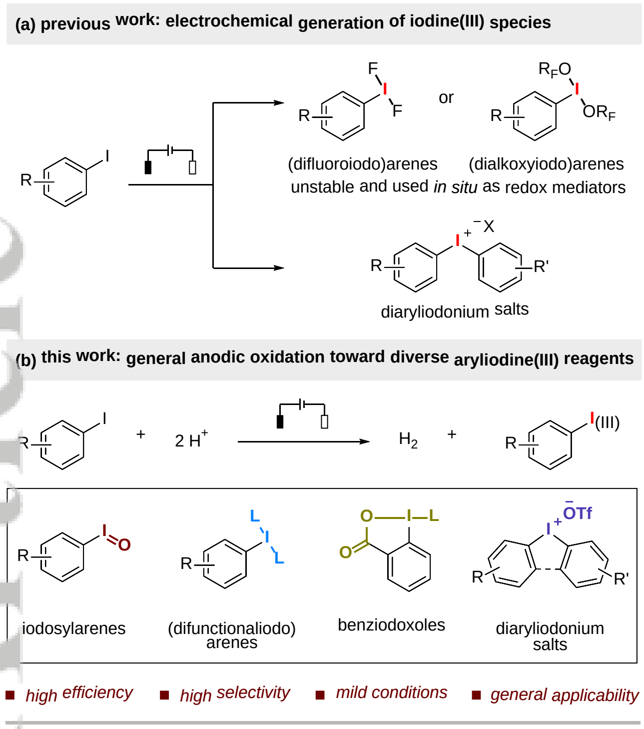
Summary of main observation and conclusion An anodic oxidation enabled synthesis of hypervalent iodine(III) reagents from aryl iodides is demonstrated. Under mild electrochemical conditions, a range of aryliodine(III) reagents including iodosylarenes, (difunctionaliodo)arenes, benziodoxoles and diaryliodonium salts can be efficiently synthesized and derivatized in good to excellent yields with high selectivity. As only electrons serve as the oxidation reagents, this method offers a more straightforward and sustainable manner avoiding the use of expensive or hazardous chemical oxidants.

Background and Originality Content

Hypervalent iodine reagents have taken a privileged position in modern organic synthesis due to their electrophilicity, valuable oxidizing properties and excellent leaving group ability, along with their nontoxic, environment-friendly nature.[1] These reagents, especially aryliodine(III) compounds, find tremendous applications in diverse chemical settings, including oxygenation and oxidative functionalization of various organic substrates,[2] functionalization of C−H bonds,[3] as group-transfer reagents in numerous bond-forming reactions,[4] and as carbon and heteroatom radical precursors or acceptors.[5] Therefore, development of facile, sustainable methods for the efficient preparation and derivatization of aryliodine(III) reagents is highly demanded.

Typically, synthesis of aryliodine(III) reagents from aryl iodide requires the use of stoichiometric amount or an excess of expensive or hazardous chemical oxidants, such as peroxides (*m*-chloroperbenzoic acid, hydrogen peroxide etc.), $NaBO_3$, $NaIO_4$, Oxone or Selectfluor, which makes the process cumbersome with a significant environmental footprint.[1a,1b,1i] Recently, utilization of O_2 as a terminal oxidant, Miyamoto, Uchiyama et al. and Powers et al. respectively developed an elegant aerobic oxidation of iodine(I) precursors producing hypervalent iodine reagents via aldehyde autoxidation intermediates without or with metal catalyst.[6] Since oxidation of aryl iodides is necessary for the generation of aryliodine(III) reagents, directly using electrons to perform oxidative transformation is undoubtably more straightforward. In fact, organic electrochemistry is known for a long time, offering an efficient and mild alternative to conventional chemical approaches for redox transformations.[7] As only electrons serve as reagents, it provides a cleaner manner avoiding the generation of chemical waste. Moreover, organic electrochemistry also allows for precise, external control of the electroorganic transformation by regulating the applied potential, which gives rise to inherently higher reaction selectivity, better functional group tolerance, milder reaction conditions, and safer processes.[8] With the development of equipment and technology in electrochemistry, the use of electricity in organic synthesis is currently experiencing a renaissance. A few studies have shown that anodic oxidation of aryl iodides provide an effective approach for the generation of unstable hypervalent iodine reagents ((difluoroiodo)arenes or (dialkoxyiodo)arenes), which are mainly used *in situ* as redox mediators for the further transformation of organic substrates.[9] For the electro-generation of stable aryliodine(III) reagents, the preliminary work is mainly focus on the electrochemical synthesis of diaryliodonium salts (Scheme 1a).[10] With the continued interest in electrosynthesis and hypervalent iodine chemistry, we questioned whether one simple and general anodic oxidation setting could be established for the direct synthesis of various types of hypervalent iodine(III) reagents. Herein we present a general electrochemical method for the synthesis of diverse aryliodine(III) reagents by anodic oxidation. Under mild conditions, a range of aryliodine(III) reagents including iodosylarenes, (difunctionaliodo)arenes, benziodoxoles and diaryliodonium salts can be efficiently synthesized and derivatized in good to excellent yields with high selectivity (Scheme 1b).

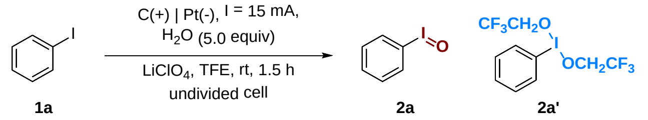
Scheme 1 Anodic oxidation of aryl iodides to aryliodine(III) reagents.



Results and Discussion

We initiated our investigation of anodic oxidation of aryl iodides for the generation of iodosylarenes, which are a broadly important class of hypervalent iodine(III) reagents to be used in many oxidation reactions.[1a,1b,1i] Normally, these iodosyl compounds are prepared by hydrolysis of (diacetoxyiodo)arenes or (dichloroiodo)arenes with aqueous NaOH. Therefore, we commenced our study of the anodic oxidation of iodobenzene **1a** in the presence of H_2O. After a careful examination of the anodic oxidation conditions, we found that the desired aryliodine(III) compound iodosylbenzene **2a** can be obtained in 80% yield under a constant current (j = 10 mA/cm^2) in 1.5 h by utilizing $LiClO_4$ as the electrolyte, 2,2,2-trifluoroethanol (TFE) as the solvent, in the presence of 5.0 equivalent H_2O (Table 1, entry 1). A lower yield was observed when ^{n}Bu$_4$NBF$_4$ replaced $LiClO_4$ as the electrolyte (entry 2). Either using platinum plate to replace the graphite anode or using graphite to replace the platinum plate cathode led to the decrease of reaction yields (entries 3 and 4). The solvent had a major influence on this anodic oxidation reaction. When the solvent was changed to CH_3CN, the yield of **2a** reduced sharply, while methanol was not suitable for this transformation at all (entries 5 and 6). When keeping electric quantity constant, both a decrease and an increase in current from the standardized value of 15 mA afforded slightly lower yields (entries 7 and 8). When the reaction was carried out in air without electricity, no oxidation product was obtained (entry 9). It is noteworthy that, in the absence of H_2O, unstable (difunctionaliodo)arenes **2a’** could be obtained in 91% NMR yield (entry 10).

Table 1 Effects of reaction parameters.

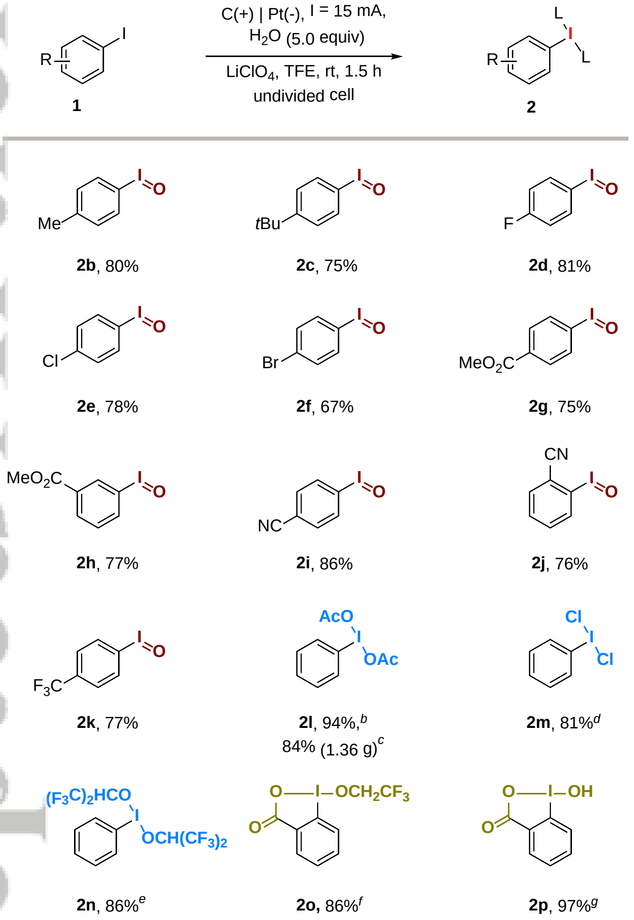


Entry	Variation from standard conditions	**2a** Yield^a /%
1	none	80
2	^{n}Bu$_4$NBF$_4$ instead of $LiClO_4$	57
3	Pt (+) | Pt (-) instead of C (+) | Pt (-)	66
4	C (+) | C (-) instead of C (+) | Pt (-)	12
5	CH_3CN instead of TFE	25
6	MeOH instead of TFE	trace
7	10 mA instead of 15 mA, 2.3 h	70
8	20 mA instead of 15 mA, 1.1 h	71
9	without current	n.d.
10^b	without H_2O	91 of **2a’**

Standard conditions: graphite anode, Pt plate cathode, constant current = 15 mA (j = 10 mA/cm^2), **1a** (0.2 mmol), H_2O (1.0 mmol), $LiClO_4$ (0.4 mmol), TFE (3.0 mL), room temperature, 1.5 h, undivided cell (2.1 F/mol). ^{a}Isolated yields. n.d. = not detected; ^{b}NMR yield of **2a’**, see Supporting Information for details.

With the optimized reaction conditions in hand for the preparation of iodosylarenes, we applied various aryl iodides to this electrochemical method (Table 2). Since iodosylarenes are widely used as effective oxidizing reagents in synthetic chemistry, substitution of the aromatic ring would offer a synthetic handle to tune both their oxidation potential and aggregation state.[11] We found that aryl iodides with substituents at the para, meta and ortho position of the aromatic ring all provided the desired products in good yields (**2b**-**2k**). Electron-withdrawing substituted groups on the aromatic ring were well tolerated under the electrochemical conditions, such as fluoro, chloro, bromo, ester, cyano and trifluoromethyl groups (**2d**-**2k**). Aryl iodides displaying alkyl substituents, such as methyl and *tert*-butyl group could also be introduced giving the corresponding oxidation product (**2b, 2c**). Moreover, simply replacing H_2O into AcOH, KCl, or changing the solvent into 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in the absence of H_2O, three classic (difunctionaliodo)arenes, $PhI(OAc)_2$,$PhICl_2$ and $PhI[OCH(CF_3)_2]_2$ (**2l**-**2n**) could be obtained in good to excellent yields with high selectivity, which are common hypervalent iodine(III) reagents in organic synthesis. It is worth mentioning that the gram scale synthesis of **2l** could also proceed smoothly in 84% yield. Unfortunately, electron-donating groups, such as methoxy, amino substituents, on the aromatic ring are not suitable in this process. Efforts to access dinuclear iodine(III) reagents from 2,2'-diiodo-1,1'-biaryl compounds under the current conditions are not successful. In addition, besides simple electron-transfer in oxidation reactions, the use of benziodoxoles as hetero- and carbon- atom transfer reagents offers a powerful method in numerous bond-forming reactions.[4b, 12] Under slightly modified electrochemical conditions, we found that 2-iodobenzoic acid could successfully convert into benziodoxole reagents in high yields, containing OCH_2CF_3 and OH groups (**2o**, **2p**). The electro-generation of these three types of aryliodine(III) species is proposed to proceed via a two electron anodic oxidation of iodoarene **1**. The reduction of protons represents the cathodic half-reaction, rendering H_2 as the by-product (see Scheme S1 in Supporting Information).

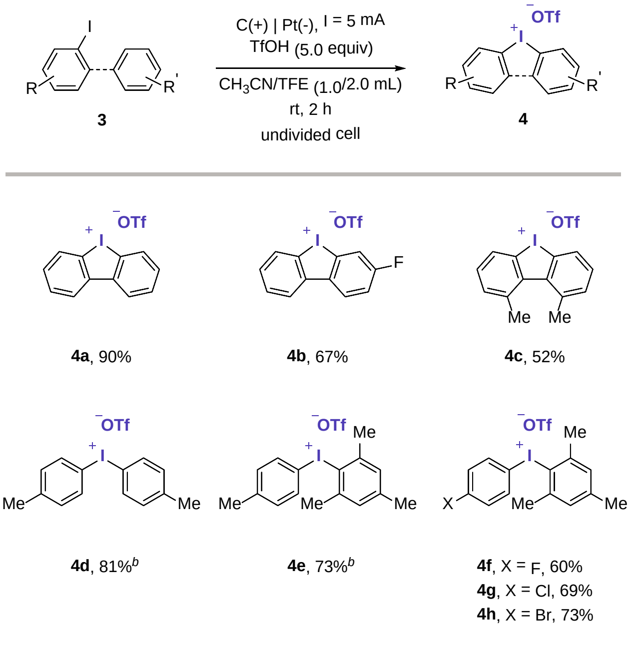
Table 2 Anodic oxidation for the synthesis of diverse aryliodine(III) reagents from aryl iodides[a].



[a]Standard conditions: graphite anode, Pt plate cathode, constant current = 15 mA (j = 10 mA/cm^2), **1** (0.2 mmol), H_2O (1.0 mmol), $LiClO_4$ (0.4 mmol), TFE (3.0 mL), room temperature, 1.5 h, undivided cell (2.1 F/mol), isolated yields. [b]**1a** (1.0 mmol), AcOH (5.0 mmol) instead of H_2O, $LiClO_4$ (0.2 mmol), TFE (6.0 mL), 7.5 h. [c]gram scale synthesis, see Supporting Information for details. [d]KCl (0.6 mmol) instead of water. [e]**1a** (0.6 mmol), without H_2O, nBu_4NBF_4 (0.6 mmol) instead of $LiClO_4$, HFIP (3.0 mL) instead of TFE, 3.0 h, NMR yield. [f]without H_2O. [g]CH_3CN (3.0 mL) instead of TFE.

We next explored the capability of this electrochemical setting for the anodic oxidative preparation of diaryliodonium salts. Diaryliodonium salts are usually air- and moisture-stable compounds, which are widely employed as exceptional aryl-group transfer reagents in cross-coupling reactions.[4a, 13] A few preliminary studies have shown that these compounds can be produced under electrochemical conditions.[10] After some further investigations, we found that utilizing trifluoromethanesulfonic acid (TfOH) as both the electrolyte and counteranion, CH_3CN and TFE as the mixed solvent, a variety of diaryliodonium salts could be obtained in good to excellent yields under 5 mA constant current in 2 h (Table 3). Both cyclic (**4a**-**4c**) and acyclic (**4d**-**4h**) iodonium salts could be produced smoothly by this electrosynthesis method. Halogen substituted groups F, Cl, and Br on the aromatic ring were well tolerated in the anodic oxidation (**4b**, **4f**-**4h**).

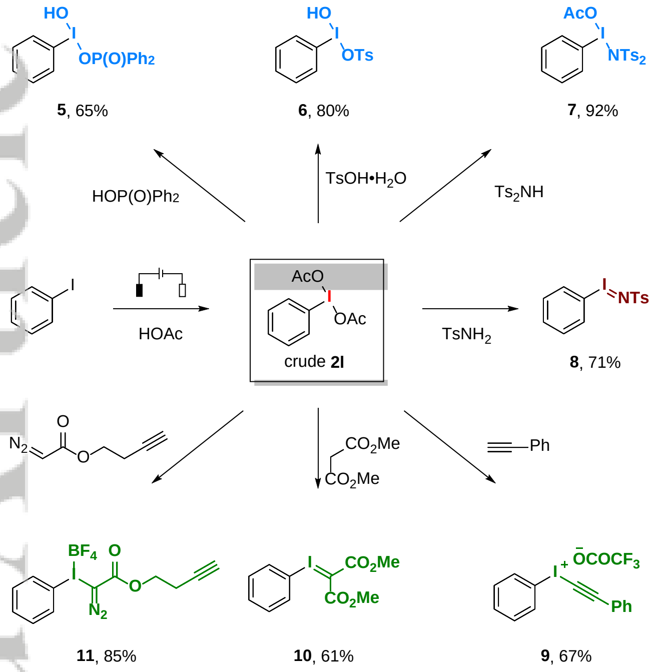
Table 3 Anodic oxidation for the synthesis of diaryliodonium salts[a].



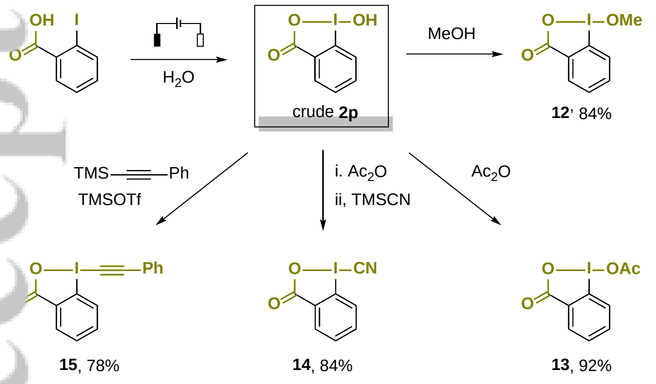
[a]Standard conditions: graphite anode, Pt plate cathode, constant current = 5 mA (j = 3.3 mA/cm^2), aryl iodide (0.2 mmol), arene (0.3 mmol, for intermolecular reaction), TfOH (1.0 mmol), CH_3CN (1.0 mL), TFE (2.0 mL), room temperature, 2 h, undivided cell (0.93 F/mol), isolated yields. [b]TFE (3.0mL), without CH_3CN.

Moreover, to demonstrate the efficacy of this electrochemical process for the anodic oxidation synthesis of diverse hypervalent iodine(III) reagents, we showed that simple iodobenzene can be efficiently transferred into phenyliodine diacetate (PIDA) under mild electrochemical conditions (Scheme 2). Further treatment with some common reagents led to the facile ligand exchange, derivatizing a variety of useful hypervalent iodine(III) reagents in good to excellent yields with high selectivity, including [hydroxy(phosphoryloxy)iodo] benzene (**5**),[14] Koser's reagent (**6**),[15] amidoiodane (**7**),[16] iodonium imide (**8**),[17] alkynyliodonium salt (**9**),[18] aryliodonium ylide (**10**),[19] and Weiss' reagent (**11**),[20] which all find numerous applications in various bond-forming reactions. Furthermore, a range of important benziodoxole reagents containing useful OMe (**12**), OAc (**13**), CN (**14**), and acetylene (**15**) groups could be obtained in good to high yields via the ligand exchange from crude hydroxy benziodoxolone **2p** (Scheme 3).

Scheme 2 Derivatization of PIDA in the anodic oxidation process.

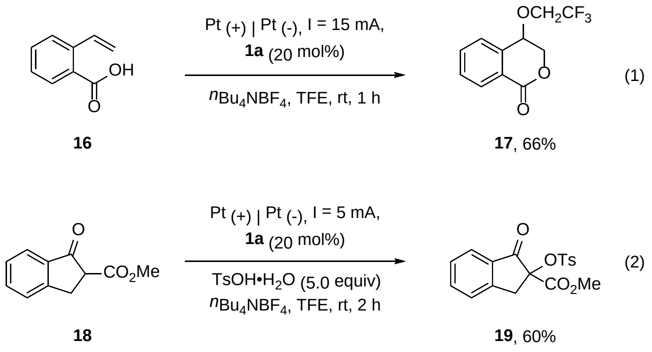


Scheme 3 Derivatization of hydroxy benziodoxolone in the anodic oxidation process.



Finally, as hypervalent iodine(III) reagents can be generated under electrochemical conditions, the development of anodic oxidation enabled aryl iodide catalyzed reactions have started to attract the attention of synthetic chemists more recently. Nevertheless, stoichiometric amount of aryl iodide is often needed in most of these *in situ* anodic oxidation reactions.[9a, 9b] Here we illustrate two oxidative transformations using 20 mol% iodobenzene **1a** as the catalyst precursor enabled by anodic oxidation (Scheme 4). The difunctionalization of alkene **16** and tosyloxylation of **18** proceed smoothly under mild aryl iodide catalyzed electrochemical conditions.

Scheme 4 Anodic oxidation enabled aryl iodide catalyzed reactions.



Conclusions

In summary, we have developed a general electrochemical method for the efficient and sustainable synthesis of diverse aryliodine(III) reagents by anodic oxidation. This process works for a variety of aryl iodide to generate a range of aryliodine(III) reagents including iodosylarenes, (difunctionaliodo)arenes, benziodoxoles and diaryliodonium salts in good to excellent yields with high selectivity under mild electrochemical conditions. All the aryliodine(III) products were easily produced with one simple anodic oxidation setting, and purified by simple filtering, washing, or extraction. We also demonstrate that simple aryl iodide can be used as catalyst precursor or catalytic mediator under anodic oxidation, which provides a more efficient and sustainable tactic for the rapid transformation of organic molecules.

Experimental

General Procedure for the electrosynthesis of iodosylbenzene (**2a**): To an ElectraSyn vial (5 mL) with a stir bar was added LiClO$_4$ (42.6 mg, 0.4 mmol, 2.0 equiv) and 2,2,2-trifluoroethanol (TFE, 3.0 mL). Iodobenzene (**1a**) (40.8 mg, 0.2 mmol, 1.0 equiv), H$_2$O (18.0 mg, 1.0 mmol, 5.0 equiv) were added to the above solution. The EletraSyn vial cap equipped with anode (graphite) and cathode (platinum) were inserted into the mixture. The reaction mixture was electrolyzed under a constant current of 15 mA for 1.5 h at room temperature. The EletraSyn vial cap was then removed and electrodes were rinsed with CH$_2$Cl$_2$. The solvent was removed *in vacuo* and residue was washed by H$_2$O (1.0 mL) and diethyl ether (1.0 mL), dried *in vacuo* to afford 35.2 mg of iodosylbenzene (**2a**) as yellow solid (80% yield).

Supporting Information

The supporting information for this article is available on the

WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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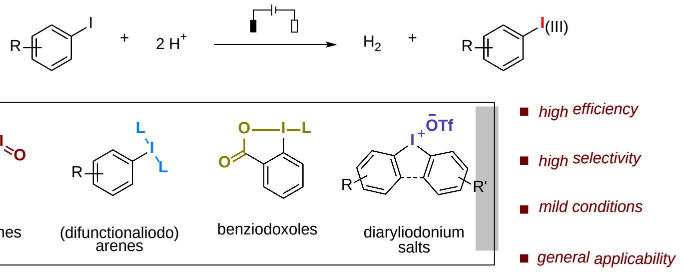
Synthesis of Diverse Aryliodine(III) Reagents by Anodic Oxidation



An anodic oxidation enabled efficient synthesis of hypervalent iodine(III) reagents from aryl iodides is demonstrated. Under mild electrochemical conditions, a range of aryliodine(III) reagents including iodosylarenes, (difunctionaliodo)arenes, benziodoxoles and diaryliodonium salts can be efficiently synthesized and derivatized in good to excellent yields with high selectivity. As only electrons serve as the oxidation reagents, this method offers a more straightforward and sustainable manner avoiding the use of expensive or hazardous chemical oxidants.

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