



Electrochemically Generated Iodine Cations from a Glassy Carbon Electrode for Highly Selective Iodination of Anisole

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Abstract

The synthesis of aryl iodides from commercially available raw chemicals by simple, cheap and green strategies is of fundamental significance. Aryl iodides can undergo a series of homo-/cross-coupling reactions for the synthesis of important industrial chemicals and materials. Traditional methods require the electrophilic substitution on aromatic compounds by iodine or hypervalent iodine compounds, which suffers from the use of erosive halogens or hazardous oxidants. With the development of green chemistry in the field of electrochemical synthesis, anodic oxidation-derived I^+ cations have been used for substitution reactions. However, the selectivity of the iodination by these electrochemical methods remains unsatisfactory. We believed that the anolyte is contaminated by trace platinum species from the working electrode. Herein, we report the generation of active I^+ species from the anodic oxidation of I_2 in acetonitrile using a glassy carbon electrode. With the presence of H^+ , electrolyte prepared with a glassy carbon anode can react with anisole to selectively form 4-iodoanisole with a yield as high as 97%. On contrast, the electrolytes prepared from Pt and graphite anodes finished the reaction with yields of 16% and 60% for 4-iodoanisole, respectively. This electrochemical method also applies to the iodination of toluene, benzonitrile and bromobenzene, delivering the target *para*-iodination products with 92%, 84%, and 73% yields, respectively. Thus, an atom-efficient and highly selective aryl iodination method was developed without the use of excessive oxidants.

Keywords Iodination · Electrochemistry · Anodic oxidation · Aryl iodides · Selectivity

Introduction

Aryl iodides are a class of reactive precursors for the synthesis of complicated macromolecules or functional materials through C–C coupling [1]. Additionally, they can undergo a series of homo-/cross-coupling reactions catalyzed by transition metals [2, 3]. As important industrial raw chemicals, aryl iodides are capable of synthesizing organometallic reagents such as Grignard reagents and organolithium reagents [4]. In addition, they play vital roles in the synthesis of natural products, agricultural chemicals, pharmaceuticals and photoelectric materials [5]. Thus, the preparation

of aryl iodides from commercially available raw chemicals by simple, cheap and green strategies is of fundamental significance [6].

To date, a variety of aryl iodides are commercially available for laboratory and industrial applications. The preparation method of aryl iodides has also been significantly advanced in the past decades. The traditional protocol involved the electrophilic substitution on aromatic compounds by iodine [7]. However, the reaction proceeds under very harsh conditions because of the corrosivity of halogen [8]. Later, more favorable hypervalent iodine compounds, such as N-iodosuccinimide, were generated from the oxidation of simple iodide or iodine prior to the electrophilic substitution [9]. These novel iodination reagents are highly active but bear low-atom efficiency using equivalent oxidants [10]. With increasing concerns on the issues of green chemistry [11], the development of electrochemical generation of active hypervalent iodine reagents without the use of excessive oxidants has received overwhelming attention for aryl electrophilic substitution [12, 13].

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In the 1970s, Miller and coworkers [14, 15] reported the electrochemical oxidation of iodine into I^+ cation that can undergo aryl electrophilic substitution to synthesize aryl iodides. Nevertheless, the selectivity of the substitution site was not well controlled. On the basis of this strategy, Yoshida and coworkers [16] analyzed the $(CH_3CN)_2I^+$ species from the electrochemical oxidation of I_2 in CH_3CN solvent and increased the selectivity of the monoiodo compound from the reaction between I^+ and 1,3-dimethoxybenzene using a special micromixer system. Recently, Hilt and coworkers [17] also improved the selectivity of aryl electrophilic substitution with the electrochemically derived I^+ by introducing a trimethylsilyl directing group on the aryl ring. However, the selectivity of the iodination remains unsatisfactory, and the abovementioned techniques reduce the convenience of this electrochemistry-based green iodination strategy. Of particular note is that the anodic generations of active I^+ are all conducted with platinum electrodes in reported methods [18]. In our opinion, the leaching of platinum cations into the electrolyte is inevitable under anodic conditions. This phenomenon has recently been widely acknowledged in the electrocatalysis of water splitting but has not yet been considered in electrochemical organic synthesis [19]. The contamination of I^+ by platinum cations in the electrolyte will definitely make the subsequent electrophilic substitution uncontrolled because platinum cations can efficiently affect a variety of substitution and coupling reactions [20]. Herein, we report the generation of active I^+ species from the anodic oxidation of I_2 in acetonitrile using a glassy carbon electrode. We chose the iodination of anisole as the target reaction because the electron-donating methoxy group can increase the reactivity of the aryl ring, and the 4-iodoanisole product is an important platform chemical in both organic synthesis and material science. The electrophilic reagent (I^+) can first bond with the aromatic ring to form a π -complex, which will evolve into a σ -complex obeying the direct group effect. The σ -complex can later release a proton into the medium to accomplish the iodination.

With the presence of H^+ , electrolyte prepared with a glassy carbon anode can react with anisole to selectively form 4-iodoanisole with a yield as high as 97%. In contrast, the electrolytes prepared from Pt and graphite anodes finished the reaction with yields of 16% and 60% for 4-iodoanisole, respectively. The species in the electrolyte before and after the iodination were also examined in detail to understand the reason for the difference in selectivity. In addition, the synthesis of 4-iodoanisole from this electrochemistry-based method is meaningful in terms of convenience, greenness and mildness.

Results and Discussion

As shown in Fig. 1, I^+ cations were prepared from the electrochemical oxidation of I_2 (127 mg, 0.5 mmol) in an H-type cell divided by a 4G glass sand core separator. The cell was protected by an inert gas atmosphere. Acetonitrile (10 mL in each chamber) was used as the solvent with H_2SO_4 (2.0 mol/L) as the supporting electrolyte and proton source [16]. A Pt plate (10 mm \times 10 mm) was used as the cathode for the reduction of protons. Constant current electrolysis (20 mA) was carried out at 0 °C with magnetic stirring until 2.00 F/mol of electricity was consumed [21]. The depletion of I_2 was evaluated by the UV–Vis spectra of the solution, showing characteristic absorption of I_2 at 224 nm (Fig. 2). The I_2 can be completely oxidized within 2 h. On the basis of the depletion of electrons for the production of I^+ cation, the overall Faradaic efficiency of the reaction is calculated to be 67.0%. Platinum mesh, graphite rod or glassy carbon plate was selected as the anode to generate the anode chamber solution for subsequent organic reactions. After the electrolysis, the anode chamber solution was added to a solution of anisole (108 mg, 1.0 mmol) in 1, 2-dimethoxyethane (DME, 10 mL, cooled at 0 °C). After being stirred at 0 °C for 45 min, the reaction mixture was neutralized by an aqueous NaOH solution (3 N, 20 mL) and diluted with

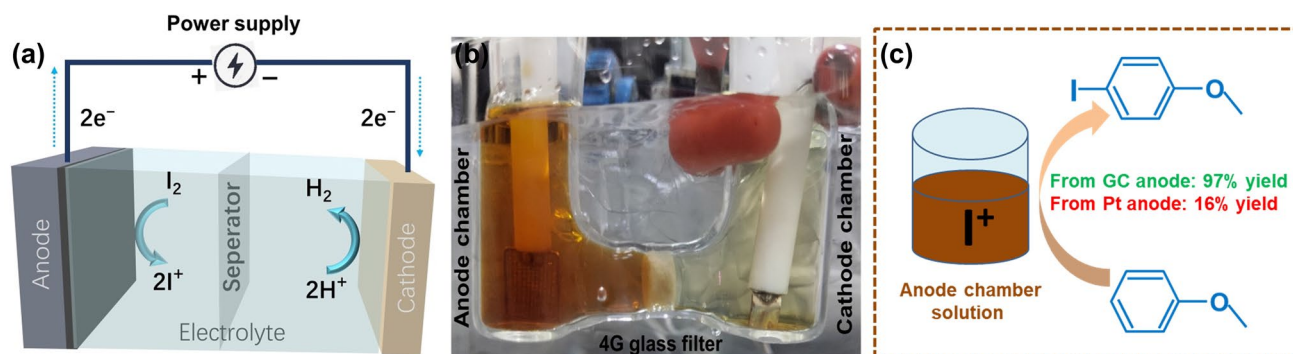


Fig. 1 Schematic diagram for a the electrochemical generation of I^+ using H_2SO_4 as the supporting electrolyte and b proton source in an H-type cell, and c the subsequent iodination of anisole for the formation of 4-iodoanisole

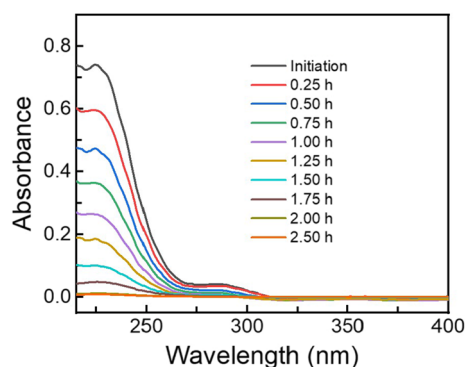


Fig. 2 UV-Vis absorption spectra of I_2 in constant current electrolysis (20 mA)

hexane (50 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (50 mL \times 2). The combined organic extracts were washed with brine and dried over Na_2SO_4 . After filtration, the solvent was removed under reduced pressure to obtain the 4-iodoanisole product.

The product was analyzed by nuclear magnetic resonance spectroscopy (NMR). As shown in Fig. 3, the product was a mixture of anisole and 4-iodoanisole when Pt mesh was used as the anode, with a very low yield of 16% for the latter component. When a graphite rod was used as the anode to prepare the I^+ cations, severe side reactions occurred with a yield of 60% for the target 4-iodoanisole and a yield of 38% for an unknown product. When the anode was changed to a glassy carbon electrode, the prepared anode chamber solution under the same conditions can efficiently and selectively convert anisole into 4-iodoanisole with a very high yield of 97%.

The contamination of the anode chamber solution was confirmed by inductively coupled plasma-mass spectrometry analysis. A trace amount of Pt ions ($\sim 1 \mu\text{g/mL}$) was detected in the anode chamber solution after the electrochemical oxidation using a Pt mesh anode, while no Pt was detected for the other two anodes [19]. To evaluate the effect of Pt contamination on the subsequent organic iodination reaction, K_2PtCl_4 was deliberately added to the solution obtained from the glassy carbon anode. The NMR results demonstrated

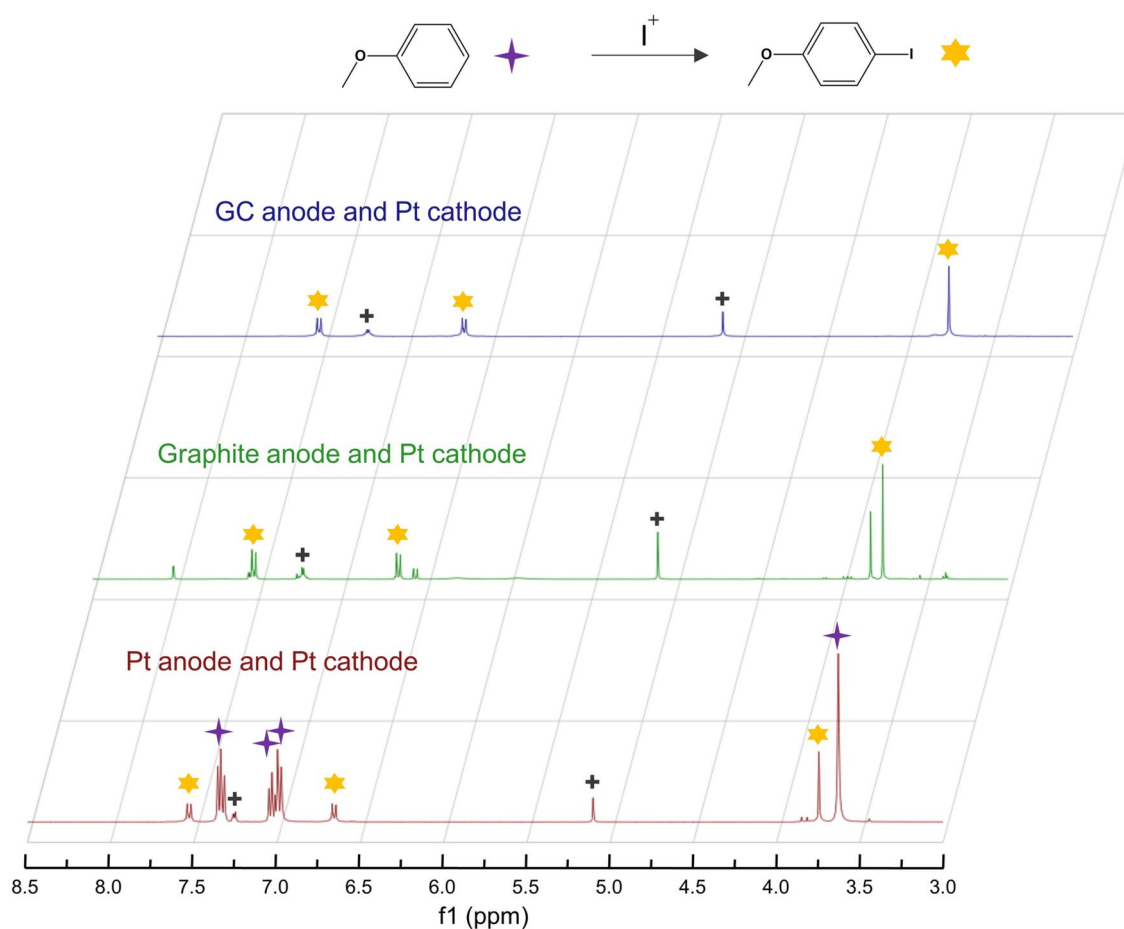


Fig. 3 ^1H NMR spectra (400 MHz, 298 K) of products from different anode chamber solutions obtained using a GC plate (top), graphite rod (middle) or Pt mesh (bottom) as the anode. Dihydroisobenzofuran was used as an internal standard (+)

that the iodination could not proceed efficiently, with only a very low yield of 4% for 4-iodoanisole (Fig. 4). In addition, an approximately 38% yield of unknown side product was obtained when the anode was graphite rod. Probably, the graphite rod can be oxidized into active and complicated materials to react with anisole [22]. To purposively generate more active oxidants from the graphite electrode, the time of electrochemical oxidation of I_2 was doubled. The subsequent iodination reaction using this anode chamber solution converted the anisole completely into the unknown side product (Fig. 5).

The scope of this electrochemical method was further demonstrated by the iodination between the anode chamber solution and substituted aryl compounds (Scheme 1). In addition to the high yield of 97% for 4-iodoanisole, the reactions with toluene, benzonitrile and bromobenzene delivered the target *para*-iodination products with 92%, 84%, and 73% yields, respectively. The methoxy and methyl groups on the aryl ring are electron-donating because of the *p*- π conjugation and σ - π hyperconjugation, respectively [23]. Thus, as shown in Scheme 1, the electrophilic substitution reaction

between anisole/toluene and the I^+ cation can proceed efficiently. The bromo and cyano groups on the aryl ring are electron-withdrawing because of the strong inductive effect. In these cases, the aryl ring is usually passivated for electrophilic substitution reactions [24]. However, the developed method still generated the relevant products of 4-iodobenzonitrile and 4-iodobromobenzene with satisfactory yields of 84% and 73%, respectively. To evaluate the effect of Pt contamination on the organic iodination reactions for the abovementioned aryl compounds, K_2PtCl_4 was deliberately added to the anode chamber solution for control experiments. The NMR results demonstrated that the iodination could not proceed efficiently, with only very low yields for the target products (Figs. S1–S3). These reactions prove the following two facts. First, our iodination method has good tolerance of the substitution groups on the aryl ring. Second, the Pt contamination has a significant effect on the selectivity of the electrochemical iodination protocol.

The cyclic voltammograms of 10 mmol/L I_2 in acetonitrile using GC or Pt as the working electrode were recorded to investigate the electrochemical generation of

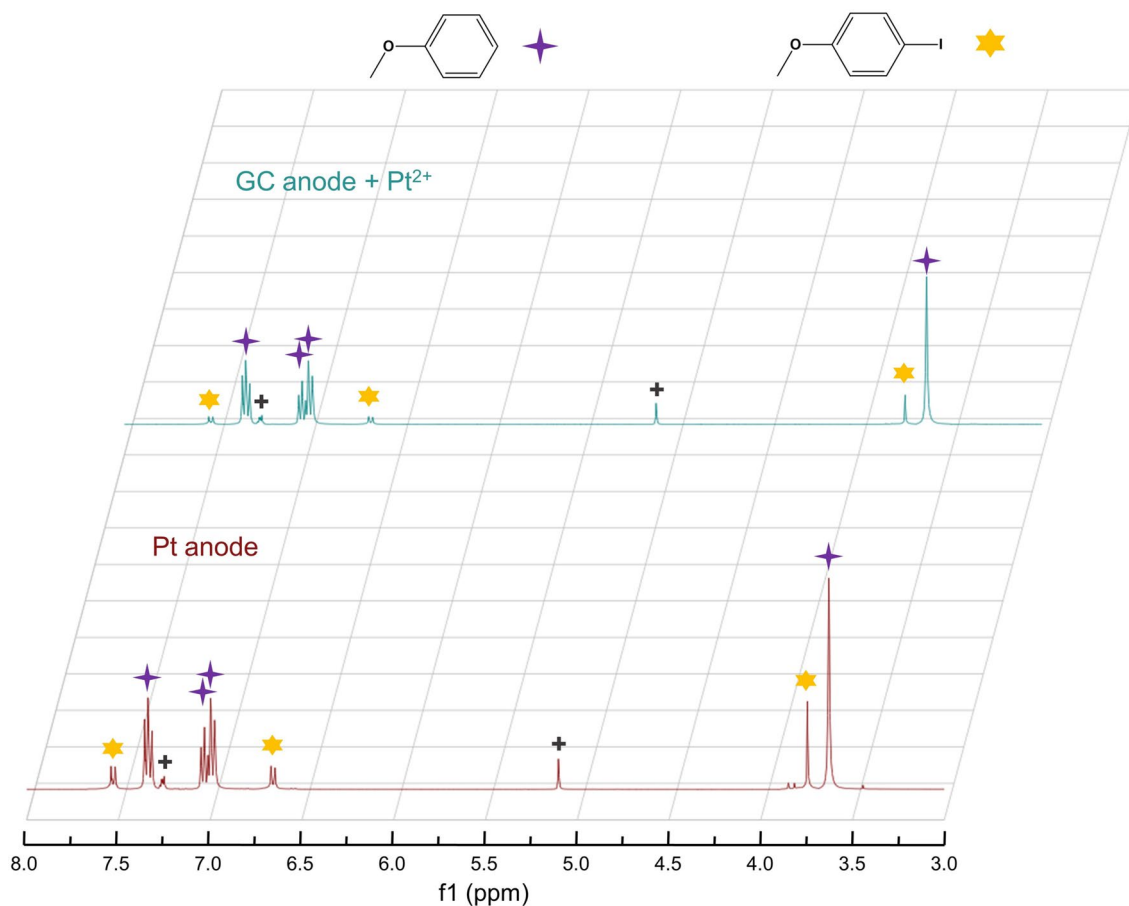


Fig. 4 1H NMR spectra (400 MHz, 298 K) of products from anode chamber solutions obtained using a GC plate with the addition of K_2PtCl_4 (top) or Pt mesh (bottom). Dihydroisobenzofuran was used as an internal standard (+)

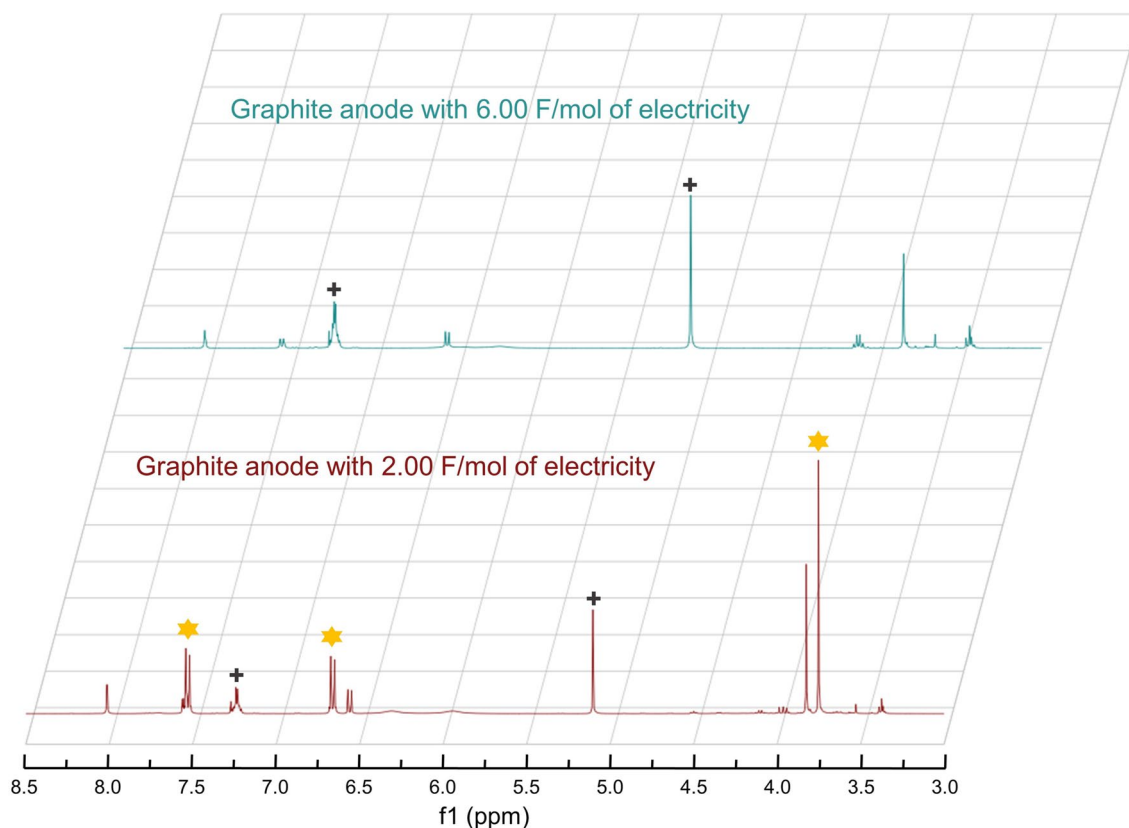
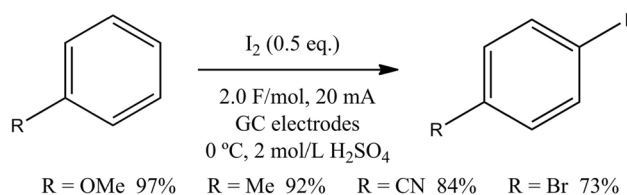


Fig. 5 ^1H NMR spectra of products from anode chamber solutions obtained using a graphite rod anode with 6.00 (top) and 2.00 (bottom) F/mol of electricity. Dihydroisobenzofuran was used as an internal standard (+)



Scheme 1 Representative iodination of aryl compounds with different substituent groups. Yields are determined from ^1H NMR analysis with dihydroisobenzofuran as an internal standard

I^+ cations (Fig. 6). As shown, the oxidation has a smaller overpotential on the Pt surface. Thus, the difference in the iodination reaction should not result from the efficiency of the generation the cations. We performed DFT calculations for the oxidizing property of the I^+ cation. According to these calculations, the I^+ cation can easily oxidize Pt^{2+} into Pt^{4+} , with a negative ΔH of -205.1 kJ/mol. However, the oxidizing property of the I^+ cation is insufficient to oxidize Pt^{4+} into Pt^{6+} (with a positive ΔH of 1109.7 kJ/mol). We used the solvent molecules to stabilize the ions

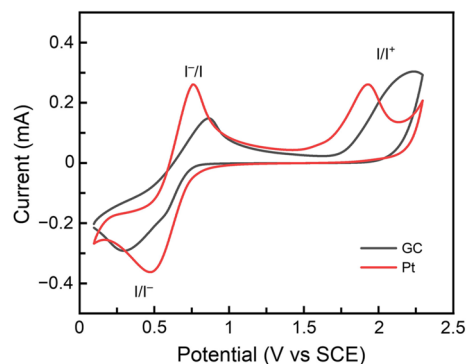


Fig. 6 Cyclic voltammograms of 10 mmol/L I_2 in acetonitrile using GC (black) or Pt (red) as the working electrode. Conditions: 0.1 mol/L Bu_4NPF_6 , Pt as the counter electrode, Ag/Ag^+ as the reference electrode, 100 mV/s scan rate

for more reliable calculations. These results show that Pt^{2+} generated from the self-oxidation of the Pt anode can have side reactions with I^+ cations to deteriorate the target iodination reaction.

$$\begin{aligned}
 &2(\text{MeCN} - \text{I})^+ + (4\text{MeCN} - \text{Pt})^{2+} \\
 &= (6\text{MeCN} - \text{Pt})^{4+} + \text{I}_2\Delta H \\
 &= -205.1 \text{ kJ/mol}
 \end{aligned}$$

$$\begin{aligned}
 &2(\text{MeCN} - \text{I})^+ + (6\text{MeCN} - \text{Pt})^{4+} \\
 &= (6\text{MeCN} - \text{Pt})^{6+} + 2\text{MeCN} + \text{I}_2\Delta H \\
 &= 1109.7 \text{ kJ/mol}
 \end{aligned}$$

Conclusions

In sum, the iodination of anisole by I^+ cations from the electrochemical oxidation of iodine is an effective way to produce important aryl iodides. The selectivity of the substitution site was not well controlled by transitional electrochemical oxidation using a Pt anode. The leaching of platinum cations into the electrolyte is inevitable under anodic conditions. The contamination of I^+ by platinum cations in the electrolyte makes the subsequent electrophilic substitution uncontrolled. In this work, the active I^+ species was generated from the anodic oxidation of I_2 in acetonitrile using a simple glassy carbon electrode. With the presence of H^+ , electrolyte prepared with a glassy carbon anode can react with anisole to selectively form 4-iodoanisole with a yield as high as 97%. In contrast, the electrolytes prepared from Pt and graphite anodes finished the reaction with yields of 16% and 60% for 4-iodoanisole, respectively. In addition, this iodination method applies to aryl compounds with different substitution groups at the *para*-position. Not only can anisole and toluene with electron-donating groups be converted into the *para*-iodination products with excellent yields, but also benzonitrile and bromobenzene with electron-withdrawing groups can be iodinated with good yields. This electrochemical protocol demonstrates the effectiveness in the green and simple synthesis of aryl iodides and the vital role of the nature of the anode material in sensitive organic synthesis.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12209-022-00337-8>.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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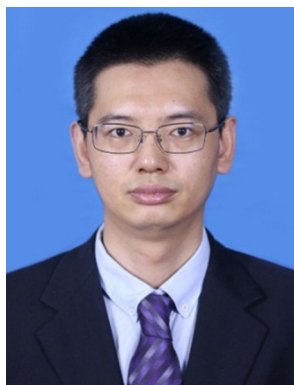
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