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Recyclable Polymer-Supported Iodobenzene-Mediated Electrocatalytic Fluorination in Ionic Liquid

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Abstract: The electrochemical fluorination of organosulfur compounds in triethylamine/hydrofluoric acid (Et_3N-5HF) with polystyrene-supported iodobenzene (PSIB) and tetraethylammonium chloride (Et_4NCl) was performed successfully in an undivided cell under constant current conditions to afford the corresponding fluorinated compounds in moderate to good yields. Recycle use of the PSIB could be achieved due to its easy separation. Notably, the mediatory activity of the iodobenzene derivative was not appreciably changed even after 10 recycle uses.

Keywords: electrochemical fluorination; green chemistry; hypervalent iodoarenes; ionic liquids; mediators

The importance of selectively fluorinated compounds in medicinal chemistry has provided a strong incentive for the discovery of new fluorinating reagents which can operate in an efficient, safe and mild manner.[1] In consequence, the controlled introduction of one or more fluorine atoms into organic molecules continues to present a worthwhile challenge for modern synthetic methods.[1] We have developed a method for the electrochemical fluorination of organic compounds in organic solvents containing an ionic liquid hydrogen fluoride (HF) salt as a supporting electrolyte and fluorine source.[2] However, severe passivation of the anode (formation of a polymeric film on the anode, which suppresses anodic current) occurred often.[2] In order to suppress this anodic passivation, we have recently developed the electrochemical fluorination in neat ionic liquid HF salts without organic solvent.[3] This method is an environmental benign process because volatile organic solvents are not necessary. However, even in such an HF-based ionic liquid electrolytic system, anode passivation still takes place, depending on the substrates used.[4] One solution to the passivation problem is to employ indirect electrolysis using mediators.[5]

On the other hand, the synthetic use of hypervalent iodine species for organic synthesis has been studied widely.[6] For example, (diacetoxyiodo)benzene, iodosylbenzene, (dichloroiodo)benzene, [(hydroxy)-(tosyloxy)iodo]benzene, the most popular trivalent iodine reagents, are useful for organic synthesis as alternatives to toxic heavy-metal reagents.[7] Among them, hypervalent (difluoroiodo)benzene is an effective reagent for the direct fluorination of various organic compounds.[8] We have studied the synthetic use of (difluoroiodo)benzene and [(chloro)-(fluoro)iodo]benzene for indirect electrochemical fluorinations.[9] Previously, in our laboratory, simple hypervalent [(chloro)(fluoro)iodo]benzene derivatives were prepared by the electrochemical oxidation of Et_4NCl and *p*-substituted iodobenzene in Et_3N-3HF/CH_2Cl_2.[9c] The oxidizing power of hypervalent [(chloro)(fluoro)iodo]benzene was found to be much stronger than that of the corresponding (dichloroiodo)benzene. Recently, we reported that an ionic liquid-supported iodobenzene derivative worked well as a mediator for indirect anodic fluorination in HF-based ionic liquid and the mediator and ionic liquid were reusable for several runs.[10] In the case of such a homogeneous mediatory system, a small amount of the mediator was lost in the extraction process of products from the ionic liquid. Thus, a heterogeneous mediatory system for electrochemical fluorination is required to establish a better recyclable mediatory system.

Previously, Zupan and his co-workers synthesized polymer-supported (difluoroiodo)benzene by a chemi-

cal method, which was then utilized as a fluorinating reagent.[11] However, the preparation of such compounds requires costly XeF_2 in the presence of hazardous HF. Therefore, the application of polymer-supported iodobenzene for easy and safe electrochemical fluorination is well worth investigation. In this paper, we report on the electrochemical mediatory application of polystyrene-supported iodobenzene (PSIB) with Et_4NCl. The effect of the double mediator system using PSIB mediator on electrochemical fluorodesulfurization in Et_3N-5 HF and the reusability of the PSIB mediator by simple filtration were also investigated.

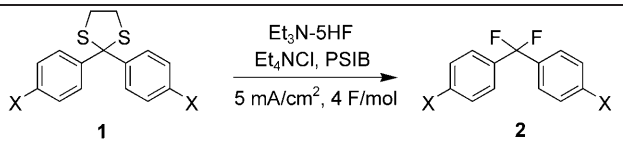
The polystyrene-supported iodobenzene was prepared by treatment of polystyrene with iodine and diiodine pentoxide in nitrobenzene/carbon tetrachloride in the presence of H_2SO_4 at 85 °C for 24 h.[12] The polymer was purified by reprecipitation into hexane and separated by filtration, then washed successively with acetonitrile, water, ethanol, and dried under reduced pressure to afford the polystyrene-supported iodobenzene (PSIB).

In a general indirect anodic reaction, a divided cell is used for the mediator system to prevent cathodic reduction of the oxidized species once generated at the anode. As the PSIB mediator is an insoluble polymer in ionic liquid, the reactive hypervalent iodine species generated by the indirect oxidation is not quenched at the cathode. Therefore, the PSIB mediatory electrolysis can be conducted in a simple undivided cell. First, the indirect anodic fluorodesulfurization of cyclic dithioacetals **1a** in the absence and presence of PSIB and/or Et_4NCl was carried out in Et_3N-5 HF in an undivided cell (Table 1). After the passage of 4 F/mol charge, the yield of the difluorinated product **2a** was low in the absence of either PSIB mediator or Et_4NCl. In the absence of Et_4NCl, an undesirable direct electrochemical oxidation occurs due to the site isolation between electrode and PSIB mediator (entry 2). On the other hand, the oxidizing power of electrogenerated Cl^+ was not enough to oxidize the **1a** in the absence of PSIB (entry 3).[9c] In sharp contrast, the use of both PSIB and Et_4NCl significantly enhanced the yield of **2a** (entry 4). The introduction of an electron-withdrawing group (EWG) at the *para*-position of the benzene ring effectively increased the electrophilicity of the benzylic cation intermediate, which resulted in good product yield (entries 5 and 6). Even in the cases of cyclic dithioacetals having electron-donating groups (EDG), the electrochemical fluorination proceeded efficiently by using the double mediatory system (entries 7 and 8). When the single mediatory system using iodobenzene for the electrocatalytic fluorination of **1d** and **1e** was employed, the yields of the corresponding compounds were decreased (**2d**: 45%, **2e**: 20%) because of their lower oxidation potentials compared to iodobenzene.[9a]

A representative mediatory system is illustrated in Scheme 1.[9c] Electrooxidation of Cl^- would give Cl^+, which reacts with iodobenzene moiety to form PhI^+Cl. This species then captures fluoride ion to give the hypervalent [(chloro)(fluoro)iodo]benzene moiety. The generated hypervalent iodine moiety seems to act as an oxidizing reagent to the substrate[9c]; consequently the starting PSIB is recovered. As reported previously,[9c] two equivalents of iodobenzene chlorofluoride and additional fluoride ions are required for the *gem*-difluorodesulfurization of dithioacetals. Moreover, this new system is heterogeneous. Therefore, 0.8 equiv. of PSIB was necessary for sufficient *gem*-fluorination.

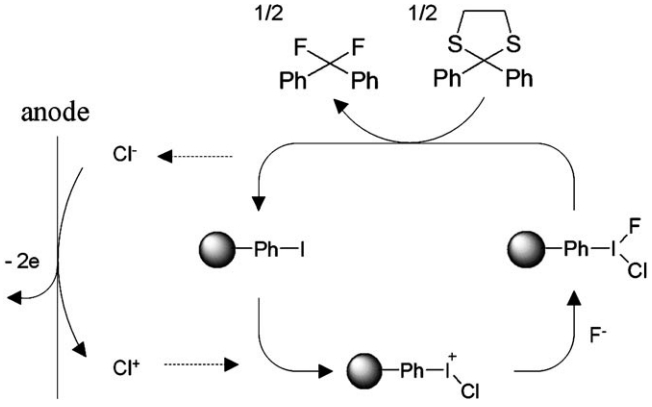
The reusability of the PSIB mediator system was investigated after simple filtration of an electrolytic solution. The recovered PSIB mediator was reused for subsequent runs, maintaining a good yield of **2a** through to the tenth run (86–79%).

Table 1. Indirect anodic fluorination of **1**.

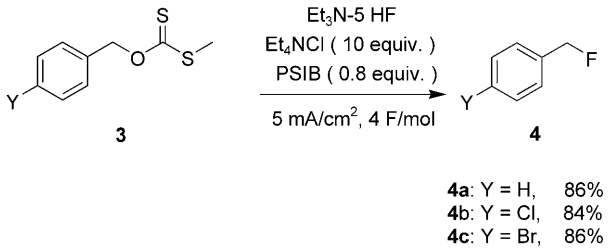


Entry	Substrate	X	E_p^{ox} [V *vs.* SCE]	Et_4NCl [equiv.]	PSIB [equiv.]	Product	Yield[a] [%]
1	**1a**	H	2.2	—	—	**2a**	42
2	**1a**	H	2.2	—	0.8	**2a**	40
3	**1a**	H	2.2	10	—	**2a**	51
4	**1a**	H	2.2	10	0.8.	**2a**	86 (79)[b]
5	**1b**	F	2.3	10	0.8	**2b**	84
6	**1c**	Cl	2.3	10	0.8	**2c**	86
7	**1d**	Me	2.0	10	0.8	**2d**	67
8	**1e**	OMe	1.9	10	0.8	**2e**	70

[a] Determined by ^{19}F NMR.
[b] Isolated yield.



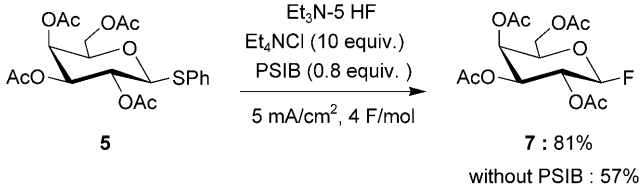
Scheme 1. Reaction pathway for the double mediatory anodic fluorination of **1**.



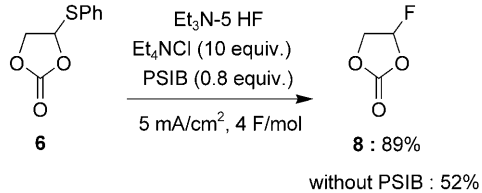
Scheme 2. Indirect anodic fluorination of **3**.

By the way, the replacement of a hydroxy group by a fluorine atom has often proved to be an effective strategy in the pharmaceutical industry for the preparation of biologically active molecules.[13] Thus, it is known that fluorination of xanthate esters easily derived from alcohols is well worth.[14] Next, the indirect anodic fluorination of xanthate esters was investigated in the double mediatory system. Scheme 2 shows the results of the indirect anodic fluorination of xanthate esters **3a**–**3c** in Et_3N-5 HF with PSIB mediator and Et_4NCl. The corresponding monofluorinated products were obtained in good to moderate yields as show in Scheme 2. In sharp contrast, in a conventional HF salt/CH_2Cl_2 solution, the anodic fluorination of xanthate ester **3b** (Y = Cl) in the absence and presence of triarylamine as an outer sphere mediator did not proceed efficiently (8% and 16% yields, respectively).

The indirect electrolysis by the double mediatory system was also applicable to the fluorodesulfurizaion of sugar derivative **5** and ethylene carbonate derivative **6** (Scheme 3 and Scheme 4). In 1991, Motherwell and co-workers reported the iodoarene-mediated electrochemical fluorodesulfurization of sugar derivatives having a phenylthio group.[15] Anomeric fluoroglycosides are not only useful biological probes in their own right but also serve as versatile chemical building blocks, especially for controlled glycosidation



Scheme 3. Indirect anodic fluorination of **5**.



Scheme 4. Indirect anodic fluorination of **6**.

reactions. On the other hand, fluorinated ethylene carbonates are promising organic electrolytic solvents or additives for rechargeable Li batteries since the introduction of fluorine atom(s) into ethylene carbonate is expected to increase its electrochemical stability and decrease its melting point.[16] Previously, we reported that the anodic fluorination of **5** and **6** in the absence of a mediator was carried out in an HF-based ionic liquid.[17] Unfortunately, the yields of the corresponding monofluorinated products were 66% and 51%, respectively. Moreover, the indirect electrolysis was not applicable to the fluorination of **5** and **6** in the presence of Et_4NCl without PSIB. However, even in these cases, the double mediator system worked sufficiently to afford the monofluorinated products in good yields (Scheme 3 and Scheme 4).

We have demonstrated that the double mediatory system using polystyrene-supported iodobenzene (PSIB) mediator is an effective system for the fluorodesulfurization of organosulfur compounds. The mediatory system enables the indirect electrochemical fluorination of substrates having a lower oxidation potential than iodoarene. The PSIB could be reused for the same electrochemical fluorination of cyclic dithioacetals, keeping good yields. Thus, the environmentally benign, indirect electrochemical fluorination was achieved using a reusable iodoarene mediator. Further synthetic studies using polymer-supported iodoarene are under way in this laboratory.

Experimental Section

General Procedure

Indirect anodic fluorinations of **1**, **3**, **5**, and **6** (0.05 mmol) were carried out in an undivided cell equipped with a platinum plate anode (1×1 cm^2) and a platinum cathode (1×1 cm^2) in Et_3N-5 HF (4.0 mL) in the presence of PSIB mediator (20 mg, 0.8 equiv.) and Et_4NCl (82 mg, 10 equiv.) at room temperature. A constant current (5.0 mA/cm^2) was passed until the starting material was mostly consumed (monitored by thin-layer chromatography). After electrolysis, PSIB was separated by filtration and washed with EtOAc. The filtrates were passed through a short column filled with silica gel using EtOAc as an eluent to remove HF salts. The yields of **2**, **4**, **7**, and **8** in eluent were estimated by ^{19}F NMR using monofluorobenzene as an internal standard. When the PSIB was reused, it was dried under a vacuum pump for 2 h at room temperature to remove volatile materials.

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