

Electrolytic Partial Fluorination of Organic Compounds. 14.¹ The First Electrosynthesis of Hypervalent Iodobenzene Difluoride Derivatives and Its Application to Indirect Anodic *gem*-Difluorination

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Summary: The electrosynthesis of hypervalent iodobenzene difluorides was accomplished by anodic oxidation of *p*-nitro- and *p*-methoxyiodobenzenes with Et₃N·3HF in anhydrous acetonitrile, and *p*-methoxyiodobenzene difluoride was used as a mediator for indirect anodic *gem*-difluorination of dithioketals.

Much attention has been paid to hypervalent organoiodine compounds, in the form of both synthetic and mechanistic studies.² Hypervalent iodobenzene difluorides have been reported to be useful fluorinating reagents by Zupan³ and Motherwell.⁴ However, such compounds are unstable in general, and their preparation requires hazardous fluorine gas⁵⁻⁷ or costly XeF₂.³

The difluoromethylene functionality has attracted the interest of biological chemists since the difluoromethylene group is isopolar and isosteric with an ether oxygen.⁸ However, the preparation of difluoromethylene compounds also requires highly toxic reagents [MoF₆,⁹ SeF₄,¹⁰ SF₄,¹¹ (dimethylamino)sulfur trifluoride (DAST)¹²] and severe reaction conditions. Recently, oxidative fluorodesulfurization of dithioketals using *N*-halo compounds (NBS, NIS, or DBH) and pyridinium poly(hydrogen fluoride),¹³ Bu₄N·H₂F₃,¹⁴ or *p*-iodotoluene difluoride^{4b} has been shown to be an alternative synthetic approach. However, large amounts of oxidizing reagents are required by the former methods, and the preparation of *p*-iodotoluene difluoride for the latter method is not straightforward. Once the reagent is prepared, it is too unstable to be stored.

More than 30 years ago, Schmidt and Meinert reported the first electrosynthesis of iodobenzene difluoride from iodobenzene using silver fluoride as a supporting elec-

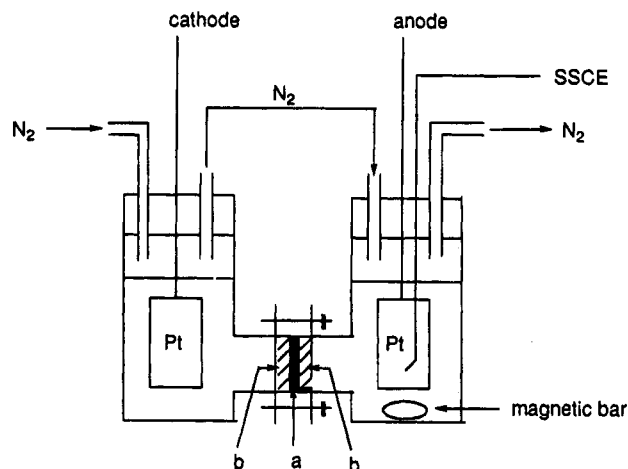


Figure 1. Electrolytic glass cell for anodic difluorination: (a) anion-exchange membrane, (b) gasket (silicone rubber).

trolyte and fluorine source.¹⁵ Later, Rozhkov found that this electrosynthesis could not be reproduced, since such a solution is nonconductive.¹⁶ In our continuing studies of the selective electrofluorination of organic molecules,¹⁷ we have found that the anodic fluorination of various types of tellurides gives hypervalent difluorinated tellurium compounds, efficiently.¹⁸

On this basis, we first attempted the electrosynthesis of hypervalent iodobenzene difluorides. We then tried to use these difluorides as mediators for indirect anodic *gem*-difluorination. To the best of our knowledge, no successful example of indirect anodic fluorination has been reported to date.

On the basis of our earlier report that Et₃N·3HF is suitable for anodic fluorination of organic compounds,^{17,18} anodic oxidation of iodobenzenes was carried out in the presence of Et₃N·3HF using a divided cell as shown in Figure 1. Simple iodobenzene (1a) gave mainly a dimer and the desired product was not formed. Similar anodic dimerization reaction of iodobenzene was reported by Miller and Hoffmann.¹⁹ In order to avoid such dimer-

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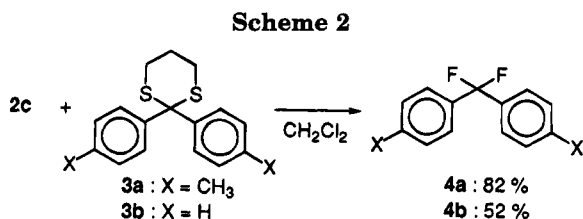
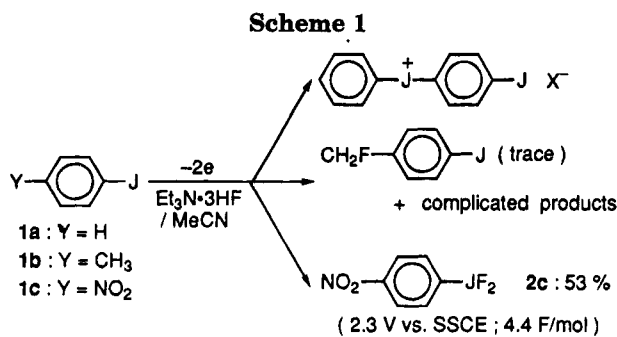
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ization, the *p*-position of the benzene ring was blocked with a methyl group. However, *p*-iodotoluene (**1b**) did not undergo the desired difluorination, either. In this case, benzylic fluorination took place to some extent, and many complicated products were formed. Finally, we found that *p*-iodonitrobenzene (**1c**) provided the desired hypervalent difluoride **2c** in a reasonable yield, as shown in Scheme 1.²⁰ The product **2c** was easily isolated from the electrolytic solution in pure form because it precipitated during the electrolysis. It was also found that this anodically prepared **2c** was effective for *gem*-difluorination of cyclic dithioketals as shown in Scheme 2. Although **2c** was found to be useful for *gem*-difluorination, oxidation of the starting iodide **1c** requires a high positive potential (2.3 V vs SCE) owing to the electron-withdrawing effect of the nitro group.

In order to decrease the oxidation potential of iodobenzene, the electron-donating *p*-methoxy group was substituted for the nitro group. In this case, anodic oxidation took place efficiently at a lower positive potential (1.9 V) to provide difluorinated product **2d**. Its formation was confirmed by mass spectrometry [m/e 287 (M^+), 268 ($M^+ - F$), 249 ($M^+ - 2F$)]; however, **2d** was difficult to isolate in pure form. The electrolytic solution containing **2d** was subsequently used for *gem*-difluorination of various dithioketals as shown in Scheme 3. As shown in Table 1, selective *gem*-difluorination smoothly proceeded to provide *gem*-difluoro compounds **4** in good yields.²¹ This reaction is an example of an ex-cell type anodic fluorination using **2d** as a mediator.

As reported by Motherwell and Wilkinson, at least 2 molar equiv of iodobenzene difluoride **2d** was required for efficient difluorination of these dithioketals.^{4b} In order to decrease the required amount of starting iodo-

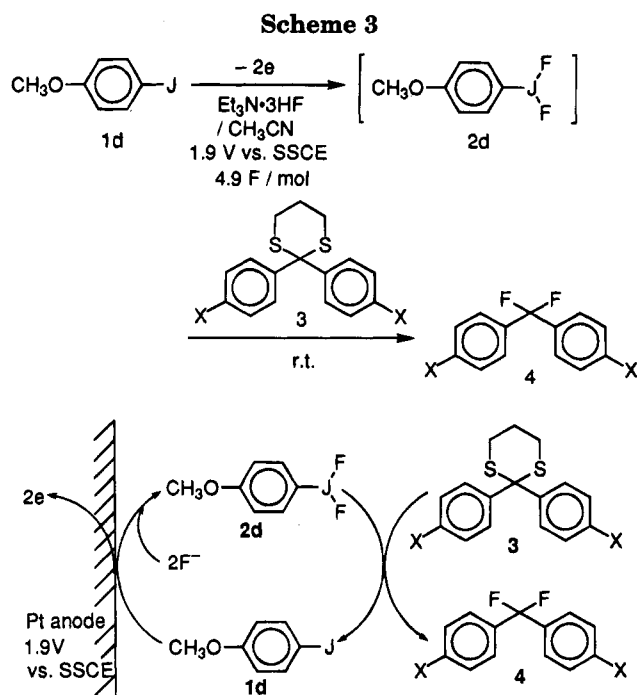


Figure 2. Utilization of *p*-methoxyiodobenzene difluoride (**2d**) as an in-cell mediator for *gem*-difluorination of dithioketals.

Table 1. Difluorination of Dithioketals by *p*-Methoxyiodobenzene Difluoride (**2d**)

run	3		yield (%)
	no.	X	
1	3a	CH ₃	4a (78)
2	3b	H	4b (69)
3	3c	Cl	4c (95)
4	3d	CH ₃ O	4d (78)

Table 2. Indirect Anodic *gem*-Difluorination of Dithioketals

run	1d		3		yield of 4 (%)
	equiv to 3	no.	X	charge passed (F/mol)	
1	0.2	3c	Cl	6.5	4c (87)
2	0.05	3c	Cl	4.5	4c (98)
3	0.2	3e	F	5.9	4e (96)

benzene **1d**, we attempted to use iodobenzene difluoride **2d** as an in-cell mediator for indirect anodic fluorination.

Our reasoning was as follows. Since dithioketals **3** have much higher oxidation potentials^{17e,23} than iodobenzene **1d**, **1d** can be anodically oxidized selectively at 1.9 V to form **2d**, which should immediately react with **3** to provide the corresponding *gem*-difluoro product **4**. The starting **1d** should be regenerated (Figure 2). That this mediatory system works nicely is revealed by Table 2.²⁴ The use of a catalytic amount of iodobenzene **1d** gave *gem*-difluoro products **4** in quantitative yield and with better current efficiency (run 2). In contrast, electrolysis of dithioketals **3** at 1.9 V in the absence of iodobenzene **1d** did not give any of the desired fluorinated product.

(20) The electrolysis was performed at a platinum anode and cathode ($3 \times 4 \text{ cm}^2$) in 0.67 M $\text{Et}_3\text{N}\cdot 3\text{HF}/\text{MeCN}$ (20 mL) containing 1.5 mmol of **1c** using a divided cell with an anion-exchange membrane (IE-DF34-5 TOSOH) under nitrogen atmosphere at ambient temperature. After the starting **1c** was completely consumed (TLC monitoring), the precipitating product was collected by filtration to give almost pure **2a**.⁶

(21) A typical procedure is as follows. After the electrolysis of **1d** (1.5 mmol) was performed in a manner similar to the case of **1c**, the electrolytic solution was mixed with a solution of 0.75 mmol of dithioacetal **3** in 10 mL of CH_2Cl_2 and the resulting mixture was stirred overnight under nitrogen atmosphere at room temperature. After evaporation of the solvent under reduced pressure, the residue was extracted with CH_2Cl_2 and the extracts were concentrated, and then the product **4** (**4a**,^{17e} **4b**,²² **4c**,^{4b} **4d**^{17e}) was isolated by column chromatography (silica gel, CH_2Cl_2 :hexane = 1:2).

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(23) Direct anodic oxidation of cyclic dithioacetals in the presence of $\text{Et}_3\text{N}\cdot 3\text{HF}$ does not provide the corresponding *gem*-difluoro products efficiently (less than 50% yield).^{17e}

(24) Anodic oxidation of **1d** (0.075 mmol) was carried out similarly at 1.9 V in 0.67 M $\text{Et}_3\text{N}\cdot 3\text{HF}/\text{MeCN}$ (20 mL) containing **3** (1.5 mmol). After **3** was completely consumed, the workup was done similarly and the product **4b** was isolated by column chromatography (silica gel, CH_2Cl_2 :hexane = 1:2).

Unlike chemical methods, this anodic *gem*-difluorination does not depend on oxidizing reagents or dangerous intermediates and can be carried out in normal glassware. Therefore, this method should be very promising for the development of biologically useful *gem*-difluoromethylene compounds.

In summary, we have successfully electrosynthesized hypervalent iodobenzene difluorides for the first time and

we have developed a novel and efficient mediatory system for anodic *gem*-difluorination of organic substrates.

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