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Review

Unique solvent effects on selective electrochemical fluorination of organic compounds

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Abstract

Recent studies on solvent effects on electrochemical partial fluorination are reviewed. At first, the historical background and some problems of electrochemical fluorination in organic solvents like acetonitrile (MeCN) are briefly mentioned. Ethereal solvents like dimethoxyethane (DME) and a mixture of DME and MeCN were found to improve both the yield and current efficiency for electrochemical fluorination since these solvent systems effectively suppress anode passivation and overoxidation of fluorinated products once formed during the electrolysis. It was also found that DME stabilizes radical cationic intermediates of 4-arylthio-1,3-dioxolan-2-ones and 3-phenylthiophthalide leading to α-fluorination while dichloromethane (CH_2Cl_2) destabilizes them leading to fluorodesulfurization. On the other hand, imidazolium ionic liquids and liquid fluoride salts like $Et_4NF{\cdot}4HF$ and $Et_3N{\cdot}5HF$ exhibited similar effects to CH_2Cl_2. Selective fluorination of hardly oxidizable phthalide was also achieved using a combination of two kinds of ionic liquids (imidazolium triflate and liquid fluoride salts).

Keywords: Anodic fluorination; Solvent effect; Partial fluorination; Ionic liquid; Product selectivity

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1. Introduction

Selective fluorination of organic compounds is indispensable in various fields like material science, medicinal chemistry, and theoretical chemistry [1–3]. Among fluorination methods, selective electrochemical fluorination is one of the most ideal methods since fluorine atoms can be introduced to organic compounds in one step under mild conditions using relatively simple equipment to avoid hazardous or toxic reagents which are usually necessary in chemical fluorination [4–7].

In sharp contrast to well-established anodic perfluorination which is carried out in anhydrous HF without any solvents [8], anodic partial fluorination (selective anodic fluorination), has been performed mainly in organic solvents containing supporting fluoride salts like $Et_3N{\cdot}3HF$, $Et_4NF{\cdot}n$HF, and pyridine polyhydrogenfluoride salts (Py·*n*HF) [8,9].

Anodic partial fluorination of organic substrates has been usually accomplished in acetonitrile (MeCN). However, MeCN electrolytic solutions very often cause severe passivation of the

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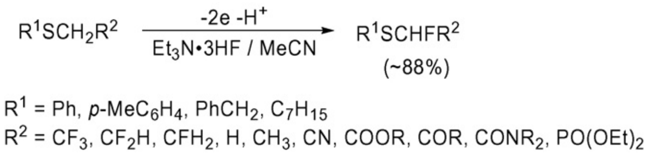
anode (formation of polymeric film on the anode, which suppresses anodic current) [8]. Moreover, the desired fluorinated products were not always obtained in good yields due to a side acetoamidation reaction. In order to avoid these problems, other solvents like sulfolane and dichloromethane have been used [10,11]. Furthermore, most of the supporting fluoride salts used for the selective anodic fluorination are ionic liquid; therefore, they can be used for the fluorination even without any electrolytic solvents. In fact, there have been several reports on selective fluorination in liquid fluoride salts [12–15]. It is interesting to know how liquid fluoride salts affect the anodic fluorination. However, no paper has been reported on solvent effects of liquid fluoride salts besides our papers [14,15].

2. Solvent effects on anodic fluorination

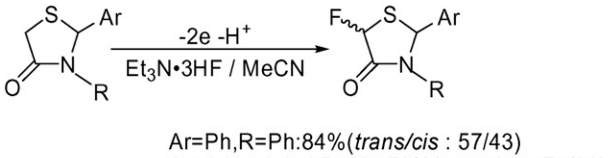
2.1. Solvent effect on the efficiency of selective anodic fluorination

The anodic fluorination efficiency is very often significantly affected by the kind of solvents and supporting fluoride salts. Therefore, the choice of a combination of a solvent and supporting fluoride salt is of much importance. The use of organic solvents and $Et_3N{\cdot}3HF$ as a supporting fluoride salt sometimes causes anodic passivation, which results in low efficiency for the anodic fluorination. In order to avoid the anode passivation, pulse electrolysis and indirect electrolysis using mediators are often employed [7,16–18].

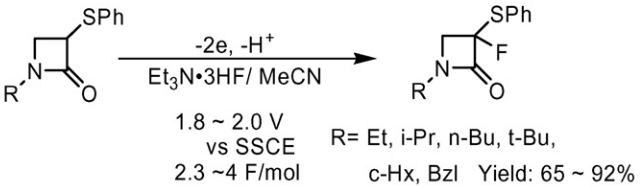
As shown in Schemes 1 and 2, due to the anode passivation, pulse electrolysis is necessary for the anodic fluorination of sulfides having various α-substituents and thiazolidinones [16,19]. On the other hand, anodic fluorination of β-lactams having an α-phenylthio group and a flavone derivative as shown in Schemes 3 and 4 proceeds quite well even without pulse electrolysis because passivation does not take place [20,21].



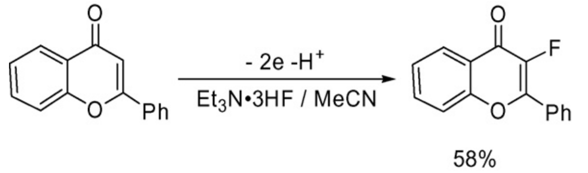
Scheme 1.



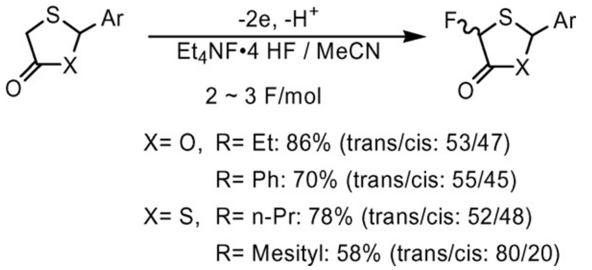
Scheme 2.



Scheme 3.



Scheme 4.

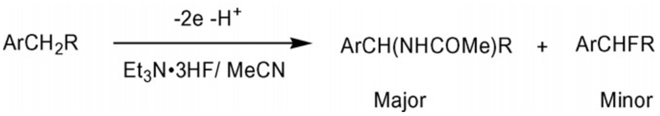


Scheme 5.

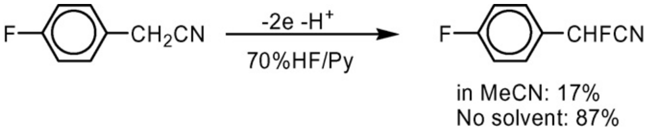
In the cases of 1,3-oxathiolanones and 1,3-dithiolanones, even pulse electrolysis does not suppress the passivation to result in low yields or no formation of the desired fluorinated products. However, when oxidatively stable $Et_4NF{\cdot}4HF$ is employed, both products yield and current efficiency for the fluorination markedly increase even in an MeCN electrolytic solution (Scheme 5) [22,23].

On the other hand, as exemplified by the anodic benzylic fluorination (Scheme 6), acetoamidation side reaction often takes place preferentially when MeCN is used as an electrolytic solvent [10,24,25]. In order to avoid the anodic acetoamidation, anodic fluorination in ionic liquid fluoride salts without any solvents is an alternative method. For example, as shown in Scheme 7, solvent-free anodic fluorination in a mixture of 70% HF and 30% pyridine (Olah's reagent) is also quite effective for suppression of the anodic passivation [26].

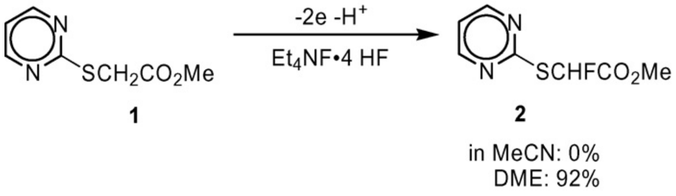
On the other hand, we recently found that ethereal solvents like 1,2-dimethoxyethane (DME) were much more suitable than MeCN for the anodic fluorination of various heterocyclic sulfides as shown in Schemes 8 and 9 [27–29]. The use of MeCN results in extremely low yields or no formation of fluorinated products, while the use of DME markedly increases the yields.



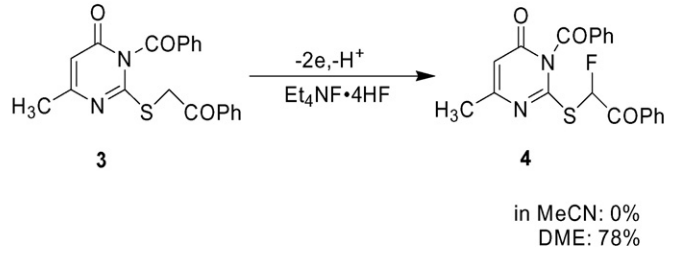
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

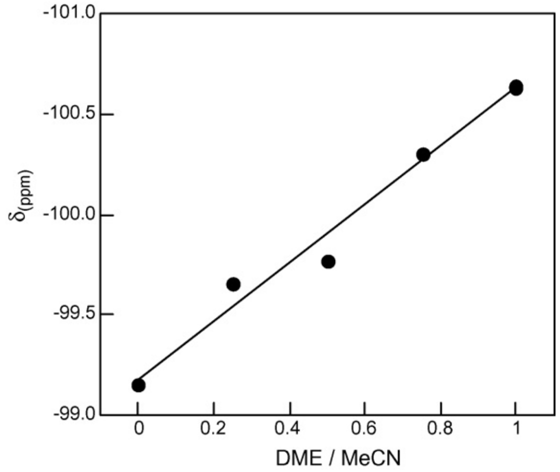


Fig. 2. Dependence of the chemical shift of fluoride ions observed in ^{19}F NMR on the ratio of DME to MeCN.

To clarify the real role of DME in the anodic fluorination process, we examined the anodic fluorination of ethyl α-(2-pyrimidylthio)acetate (**1**) and 1-benzoyl-5-methyl-2-methylthio-4-pyrimidinone (**3**) as the model compound in a mixed solvent of DME and MeCN at various ratios containing $Et_4NF{\cdot}4HF$. As shown in Fig. 1, monofluorinated product **4** was not formed in MeCN at all; however, the yield of **4** increased markedly when DME was added to the MeCN containing $Et_4NF{\cdot}4HF$. Namely, with an increase in the ratio of DME to MeCN, the yield increased continuously, and good yield was obtained when DME was used solely. A quite similar trend was observed in the case of anodic fluorination of **1**.

Such a marked solvent effect of DME can be explained as follows. Anode passivation was efficiently suppressed by the addition of DME to MeCN. In addition, the fluoride ion nucleophilicity should be enhanced by DME since DME may strongly solvate the cations of the fluoride salts to make the anions more reactive. In support of this, it is known that DME has a much higher donor number (23.9) than MeCN (14.1). In fact, the signal due to $Et_4NF{\cdot}4HF$ in the ^{19}F NMR spectrum shifted almost linearly to a higher magnetic field with an increase in the ratio of DME to MeCN (Fig. 2), and it was found that the fluorine signal in DME appeared at about 1 ppm higher magnetic field than that in MeCN. Namely, the fluoride ion nucleophilicity should be enhanced almost linearly with an increase in the ratio of DME to MeCN, which was consistent with the results in Fig. 1.

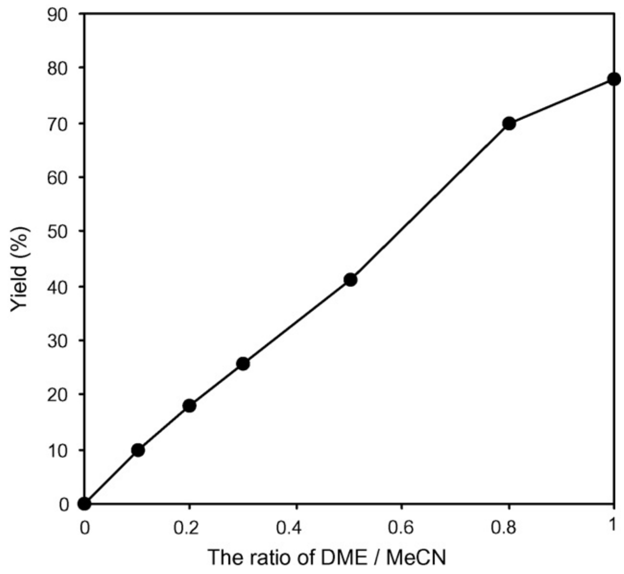


Fig. 1. Dependence of the yield of **4** on the ratio of DME/MeCN.

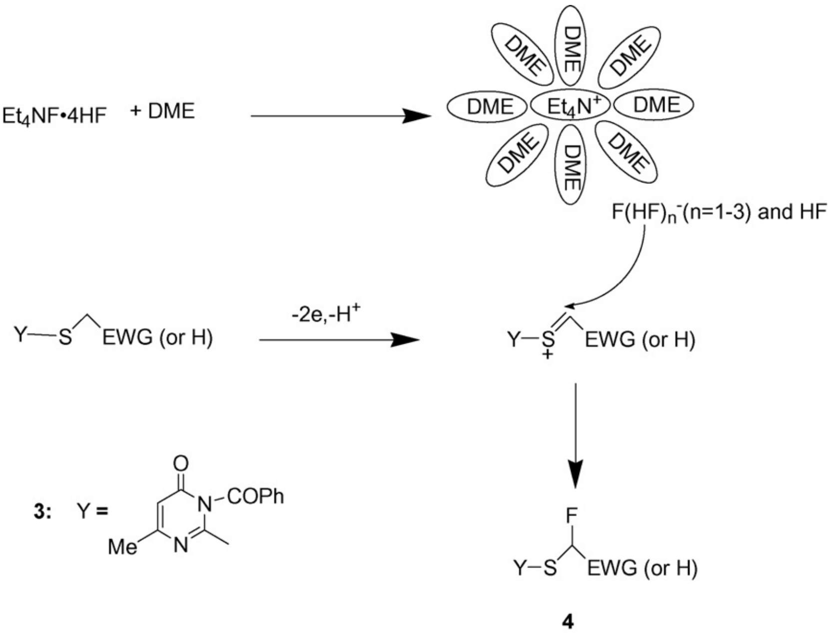
Consequently, a reactive fluoride ion released by DME easily attacks the anodically generated cationic intermediate as shown in Scheme 10. In a solution such as DME, $Et_4NF{\cdot}4HF$ may dissociate to Et_4N^+, $F(HF)n^-$ ($n = 1$–3), and HF [30–33]. Moreover, it was also found that DME was oxidized simultaneously during the electrolysis of substrates, which can suppress overoxidation of both the substrates and products, particularly at a later stage of the electrolysis [27].

2.2. Solvent effects on fluorinated product selectivity

As mentioned above, DME or a mixture of DME and MeCN as the electrolytic solution is highly efficient for the selective anodic fluorination. Recently, we found that DME has also a unique solvent effect on fluorinated product selectivity.

As shown in Scheme 11 ($Et_4NF{\cdot}4HF$ was used. $F(HF)n^-$ is the solvated ion of F^- and is now written as F^-), anodic fluorination of 4-arylthio-1,3-dioxolane-2ones **5** in CH_2Cl_2 containing a fluoride supporting electrolyte provided the fluorodesulfurization product **6** preferentially while anodic fluorination in DME resulted in α-fluorination without desulfurization to provide **7**, selectively [33,34].

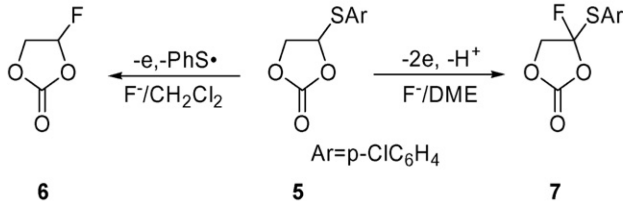
In order to clarify the solvent effect, we investigated anodic fluorination of **5** in a mixed solvent of DME and CH_2Cl_2 containing $Et_4NF{\cdot}4HF$. As shown in Fig. 3, the product ratio of **6** to **7** increased with an increase in the ratio of CH_2Cl_2 to DME. Notably, addition of only 25% CH_2Cl_2 to DME caused a



Scheme 10.

dramatic change in the product ratio, and **6** was mainly formed in ca. 60% yield.

This interesting phenomenon can be explained as follows. The fluorination can be rationalized by postulating a radical intermediate **A** as shown in Scheme 12. CH_2Cl_2 has poor ability to solvate carbocations; therefore, **A** seems to be unstable in CH_2Cl_2. Then, cleavage of a carbon–sulfur bond followed by fluorination mainly takes place prior to α-fluorination of **A**. On the other hand, DME is known to strongly coordinate cations. Therefore, DME should stabilize the intermediate **A** and DME also enhances the fluoride ion nucleophilicity. Then, the deprotonation of **A** with fluoride ions takes place prior to desulfurization followed by further oxidation to generate cation **B** and this cation reacts with a fluoride ion to provide the α-fluorinated product **7**. This is the first example of a solvent effect on fluorinated product selectivity.



Scheme 11.

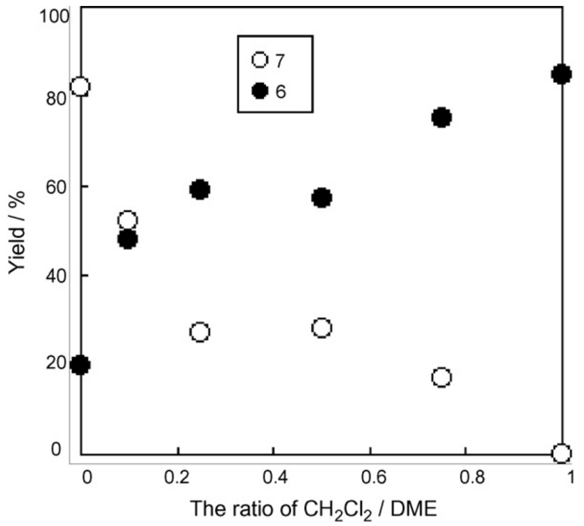
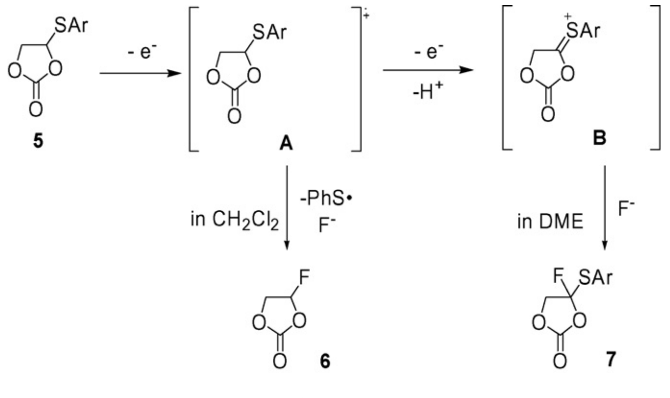
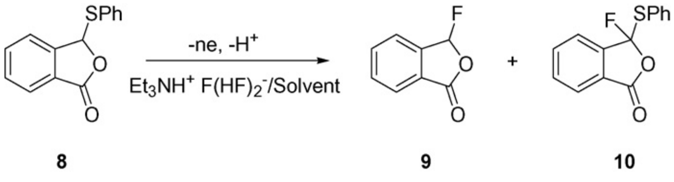


Fig. 3. Dependence of yield of **6** and **7** on the ratio of CH_2Cl_2 to DME.

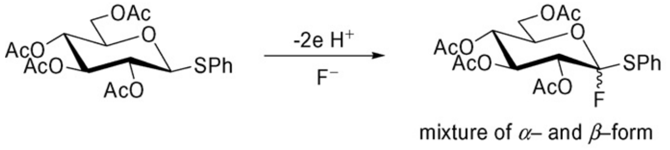


Scheme 12.



	9	10
in MeCN:	44%	0%
CH_2Cl_2:	66	0
THF:	6	22
DME:	9	72

Scheme 13.



in DME(32%), THF(67%),
MeCN(57%), CH_2Cl_2(58%)

Scheme 14.

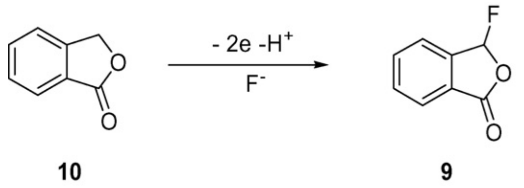
Similar solvent effect was observed in the anodic fluorination of 3-phenylthiophthalide **8** as shown in Scheme 13 [35].

However, in sharp contrast, anodic fluorination of 1-phenylthio-β-D-glucopyrnoside resulted in α-fluorination without desulfurization exclusively regardless of solvents as shown in Scheme 14 [36].

2.3. *Unique effects of ionic liquid fluoride salts on anodic fluorination*

Most of the supporting fluoride salts commonly used for selective anodic fluorination are room-temperature molten salts, namely, ionic liquids [12,14]. They are generally non-viscous and highly conductive even at a low temperature. Therefore, such liquid fluoride salts are attractive media for solvent-free anodic fluorination. In fact, several reports on successful solvent-free anodic fluorination of organic compounds like arenas, furan, phenathroline, aldehydes, cyclic ketones, cyclic unsaturated esters, and phenols in $Et_3N{\cdot}3HF$, $Et_4NF{\cdot}nHF$ ($n = 4$, 5), and $Et_3N{\cdot}5HF$ have been reported by Meures, Momota, and Yoneda so far [15,26,37–43]. Ionic liquids consist of cations and anions; therefore, it is quite interesting to know that electrochemically generated cations are stabilized or destabilized in ionic liquids. However, effects of ionic liquids on organic electrochemical reactions have not been reported to date.

We found that imidazolium ionic liquid, fluoride salt ionic liquid, and dichloromethane show quite similar solvent effects on electrochemical fluorodesulfurization as shown in Scheme 15. In sharp contrast to Scheme 13 (in DME and THF), anodic desulfurization of 3-phenylthiophthalide takes place exclusively in ionic liquids such as [EMIM][OTf], [EMIM][BF_4], and $Et_4NF{\cdot}4HF$ [35,36].



in $Et_3N{\cdot}3HF$:17%; $Et_3N{\cdot}5HF$:16%
$Et_3N{\cdot}3HF$/[EMIM][OTf] : 78%
$Et_3N{\cdot}5HF$/[EMIM][OTf] : 90%
[EMIM][$H_{2.3}F_{3.3}$] : 30%

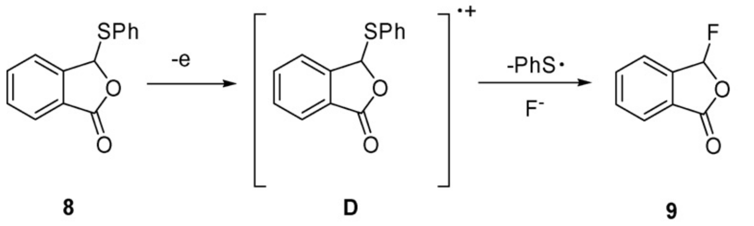
Scheme 16.

This suggests that these ionic liquids destabilize the radical cation intermediate **D** anodically generated from **8** similarly to CH_2Cl_2.

Moreover, we found that a combination of $Et_3N{\cdot}nHF$ ($n = 3$–5) and imidazolium ionic liquid [EMIM][OTf] was highly effective for anodic fluorination of hardly oxidizable phthalide (**10**) ($E_p^{ox} = 2.81$ V versus SCE). As shown in Scheme 16, even under solvent-free conditions (in liquid fluoride salts solely), the yield of the fluorinated product **9** was low. However, when ionic liquid, [EMIM][OTf], was used, the yield increased markedly [35]. Even easily oxidizable liquid salt, $Et_3N{\cdot}3HF$ was effective. Particularly, the combination of [EMIM][OTf] and anodically stable $Et_3N{\cdot}5HF$ is the best choice for the formation of the fluorinated product **9** in excellent yield. In such a double ionic liquid system, anion exchange would take place. Then, [EMIM][$H_{2.3}F_{3.3}$] [44] was tested for the anodic fluorination; however, the yield of **9** was much lower compared with that in the double ionic liquid system.

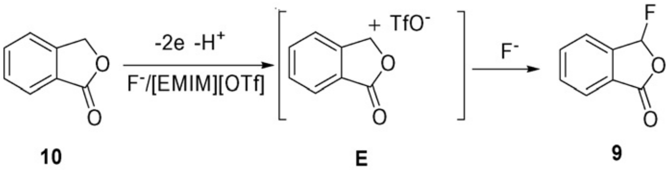
From these results, TfO^- should play an important role in this reaction. Namely, after generation of the cationic intermediate from phthalide, the cation should have TfO^- as the counter anion to form the activated cation **E**, which readily reacts with F^- to form the fluorinated phthalide in good yield (Scheme 17) [35].

Moreover, we successfully carried out for the first time selective anodic fluorination of cyclic and open-chain ethers, lactones, carbonates, and esters under solvent-free conditions (Schemes 18 and 19) [45]. Notably, a small amount of $Et_4NF{\cdot}5HF$ (only 2–3 equiv. of F^- to the substrate) is effective for their fluorination. In sharp contrast, the use of organic

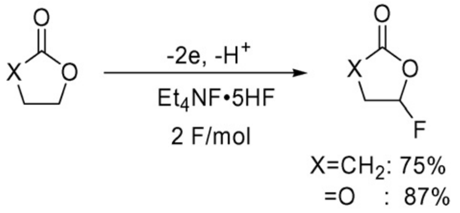


in $Et_3N{\cdot}3HF$/[EMIM][OTf]: 44%
$Et_3N{\cdot}5HF$/[EMIM][OTf]: 88
$Et_3N{\cdot}5HF$/[EMIM][BF_4]: 65
$Et_4NF{\cdot}4HF$: 99

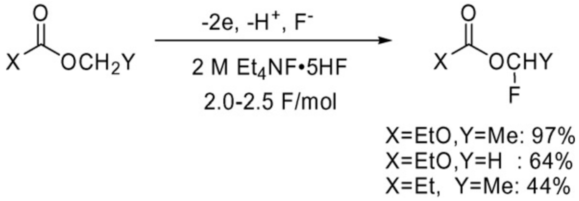
Scheme 15.



Scheme 17.



Scheme 18.



Scheme 19.

solvents or a large amount of $Et_4N{\cdot}5HF$ resulted in no formation or much lower yield of the desired fluorinated product. In these cases, a large amount of oxygen-containing substrates strongly stabilizes their anodically generated radical cations and also enhances the nucleophilicity of fluoride ions.

3. Conclusion

Highly efficient and selective fluorination of organic compounds is one of the most important subjects of modern organofluorine chemistry. We found quite unique solvent effects on anodic fluorination for the first time. Furthermore, we disclosed effects of ionic liquid fluoride salts on electrochemically generated cationic intermediates, and consequently we achieved efficient anodic fluorination of various oxygen-containing compounds.

Acknowledgements

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