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# Highly efficient and selective electrochemical fluorination of organosulfur compounds in $Et_3N{\cdot}3HF$ ionic liquid under ultrasonication†

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**We found that ultrasonication is highly effective for increase of the yields, current efficiency, and selectivity in anodic fluorination in $Et_3N{\cdot}3HF$ ionic liquid.**

Although electrosynthesis has been established as a powerful tool in organic and polymer synthesis, it still is in the development stage to fulfill its potential as a "green" methodology.[1] Organic electrosynthesis has been very often carried out in aprotic organic solvents. However, most volatile organic compounds (VOC)s are flammable and not always safe from health and environmental perspectives. In the case of inorganic electrolysis, VOC-free electrolysis, such as electrorefining processes using molten salts, has been already commercialized. In sharp contrast, there has yet been no established VOC-free organic electrode process.

On the other hand, highly efficient methods for the preparation of organofluorine compounds are essential to produce novel types of pharmaceuticals, agrochemicals and functional materials.[2] Selective electrochemical fluorination has recently been shown to be a highly efficient new tool to synthesize various organic fluorine compounds.[3] The fluorination is usually conducted in aprotic solvents containing HF salt ionic liquids such as $Et_3N{\cdot}nHF$ ($n$ = 3–5) and $Et_4NF{\cdot}nHF$ ($n$ = 3–5) as both supporting salt and fluorine source. When organic solvents such as acetonitrile (MeCN) are used for anodic fluorination, anode passivation (the formation of a nonconducting polymer film on the anode surface that suppresses faradaic current) often takes place, which results in low efficiency.[4] Although we have solved such problems by using pulse electrolysis,[5,6] dimethoxyethane as a solvent,[7] new supporting fluoride salts,[8] and mediators,[9] other approaches are still necessary.

In recent years, ionic liquids have proved to be a new class of promising solvents because of their nonflammability, nonvolatility, thermal stability and good electroconductivity.[10] In spite of such advantages, there have been limited successful examples of organic electrosynthesis in ionic liquids because of their high viscosity resulting in extremely slow mass transport of substrates.[11] Ultrasonic effects on electrochemical processes have received much interest, since the product yield and selectivity are greatly affected by promotion of mass transport caused by a cavitational micro-jet stream.[12] To the best of our knowledge, there has been only one paper dealing with organic electrosynthesis under ultrasonication in ionic liquids[13] although sonochemistry and sonoluminescence of ionic liquids were reported by Suslick *et al.*[14] Compton and co-workers achieved a high current efficiency (89%) of cathodic reduction of *N*-methylphthalimide in ionic liquid under ultrasonication when only 5.5% of the theoretical amount of charge ($Q_t$) was passed. On the other hand, the current efficiency decreased to 66% without sonication.[13] However, when more charge (11% of $Q_t$) was passed, the current efficiency decreased to 66%. The yield was not mentioned in the completed electrolysis.

With these facts in mind, we investigated effects of ultrasonication on the VOC-free anodic fluorination of organosulfur compounds such as ethyl α-(phenylthio)acetate (**1**) and 2-phenyl-3-methyl-4-thiazolidinone (**4**) as model substrates in the ionic liquid hydrogen fluoride salt, $Et_3N{\cdot}3HF$[15] in this work.

At first, we carried out voltammetry of **1** in the ionic liquid $Et_3N{\cdot}3HF$ using a platinum plate electrode. Fig. 1 shows voltammograms of **1** in $Et_3N{\cdot}3HF$ ionic liquid under still conditions, mechanical stirring, and ultrasonication, respectively.

Even under mechanical stirring, the oxidation current did not increase significantly. However, it is noted that the limiting diffusion oxidation current of **1** increased markedly under ultrasonication compared with that under mechanical stirring. The viscosity of the ionic liquid fluoride salt is higher than that of ordinary organic solvents such as MeCN, therefore, the mass transport of substrate **1** to the anode surface from the bulk of the fluoride salt is much slower than that in organic solvents. The enhanced oxidation current is attributed to the marked promoted mass transport of **1**. Namely, ultrasonication to the ionic liquid $Et_3N{\cdot}3HF$ generates cavitation collapse, which leads to an acoustic stream[16] and micro-jet stream, and

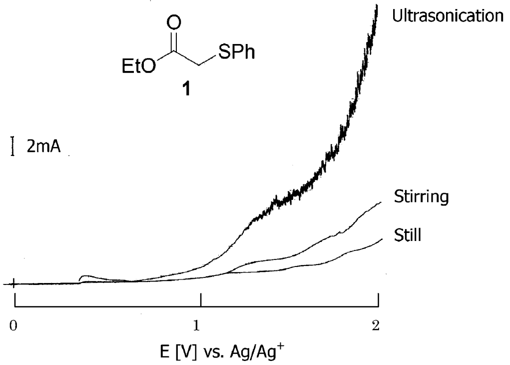

**Fig. 1** Voltammograms of **1** (10 mM) in $Et_3N{\cdot}3HF$ ionic liquid. Sweep rate was 1 mV $s^{-1}$. Pt plates (1 × 1 cm) were used as working electrode and counter electrode.

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promotes mass transport of **1** to the anode surface from the bulk of the ionic liquid. Many spikes observed in the oxidation wave under ultrasonication also clearly indicate that cavitation collapse takes place at the anode surface even in the ionic liquid. These results indicate that ionic liquid $Et_3N{\cdot}3HF$ behaves just like ordinary molecular solvents under ultrasonication.

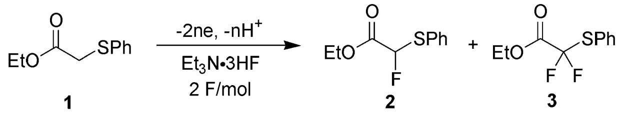
Next, constant current anodic oxidation of **1** was carried out at platinum electrodes in ionic liquid $Et_3N{\cdot}3HF$ in an undivided cell at ambient temperature. Anodic fluorination of **1** proceeded smoothly without anode passivation and α-monofluoro product **2** was mainly formed together with α,α-difluoro derivative **3** as a minor product at 2 F $mol^{-1}$ of charge passed.

As shown in Table 1, although the yield and selectivity of **2** were rather high at a low current density such as 2.5 mA $cm^{-2}$ even under mechanical stirring, a considerable amount of **3** was formed (run 1). The yield and selectivity were decreased with an increase of the current density under mechanical stirring (runs 3, 4 and 6). Particularly, the yield was drastically decreased and the selectivity was lost completely at a higher current density such as 25 mA $cm^{-2}$ (run 6). However, the yield was increased greatly, while the formation of **3** was suppressed completely or considerably by ultrasonication (runs 2, 5 and 7). This effect is remarkable particularly at a higher current density. Namely, the yield and selectivity of **2** were extremely low at a high current density such as 25 mA $cm^{-2}$ under mechanical stirring, while both the yield and selectivity increased markedly under ultrasonication (runs 6 and 7). Even at a much higher current density (50 mA $cm^{-2}$), good yield and selectivity were obtained under ultrasonication (run 8).

These interesting results can be explained as follows. Under mechanical stirring, the mass transport of **1** is insufficient compared with the electron transfer rate, particularly at a high current density. Therefore, the ionic liquid itself and monofluorinated product **2** once formed are oxidized simultaneously. Therefore, both the yield and selectivity of **2** were decreased. On the other hand, the ultrasonication greatly promotes the mass transport of **1**, thereby, substrate **1** was selectively oxidized to give monofluorinated product **2** in high yield and with high selectivity. This is a main reason for the high efficiency of the formation of **2** even at a high current density. In support of this, the anode potential under ultrasonication at high current density (25 mA $cm^{-2}$) was found to be of similar value to that under mechanical stirring condition at low current density (10 mA $cm^{-2}$). In addition, the local heating effect at the electrode caused by ultrasonication can not be always ruled out[17] although the temperature of the bath was carefully kept at 24 ± 2 °C.

Next, in order to obtain α,α-difluoro product **3**, we investigated the dependence of yields of **2** and **3** on charge passed in the anodic oxidation of **1** at 10 mA $cm^{-2}$. As shown in Fig. 2(a), the difluorination took place simultaneously at an early stage of the electrolysis under mechanical stirring. Even after a theoretical amount of charge (2 F $mol^{-1}$) was passed, the yield of difluroro product **3** was almost constant and did not increase at all. In sharp contrast, under ultrasonication, the yield of **2** increased to 85% with the amount of charge passed and after 2 F $mol^{-1}$, the yield decreased and the formation of product **3** started as shown in Fig. 2(b). With an increase of charge passed, the yield of **3** increased gradually to *ca.* 65% yield at 6 F $mol^{-1}$. This is notable because previously, we failed to induce anodic difluorination of **1** in $Et_3N{\cdot}3HF$–MeCN due to anodic instability and anode passivation.[5] So, we prepared **2** from **1** by anodic fluorination in $Et_3N{\cdot}3HF$–MeCN, and then subjected **2** to further anodic fluorination in $Et_3N{\cdot}3HF$–MeCN. After an extremely large amount of charge (20.7 F $mol^{-1}$) was passed, **3** was prepared in moderate yield (53%) as shown in Scheme 1. This is because of the anodic instability of the supporting electrolyte $Et_3N{\cdot}3HF$. It is interesting that anodic difluorination of **1** was

**Table 1** Anodic fluorination of ethyl α-(phenylthio)acetate **1** in $Et_3N{\cdot}3HF$ ionic liquid with or without ultrasonication



| Run | Ultrasonication | Current density/mA $cm^{-2}$ | Yield[a] (%) | | | Selectivity of **2** (%) |
|---|---|---|---|---|---|---|
| | | | **2** | **3** | Total | |
| 1 | No | 2.5 | 79 | 8 | 86 | 91 |
| 2 | Yes | 2.5 | 90 | 0 | 90 | 100 |
| 3 | No | 5.0 | 54 | 21 | 75 | 72 |
| 4 | No | 10 | 33 | 24 | 57 | 58 |
| 5 | Yes | 10 | 85 | 4 | 89 | 95 |
| 6 | No | 25 | 3 | 3 | 6 | 50 |
| 7 | Yes | 25 | 65 | 8 | 73 | 89 |
| 8 | Yes | 50 | 65 | 15 | 79 | 82 |

[a] Determined by $^{19}F$ NMR.

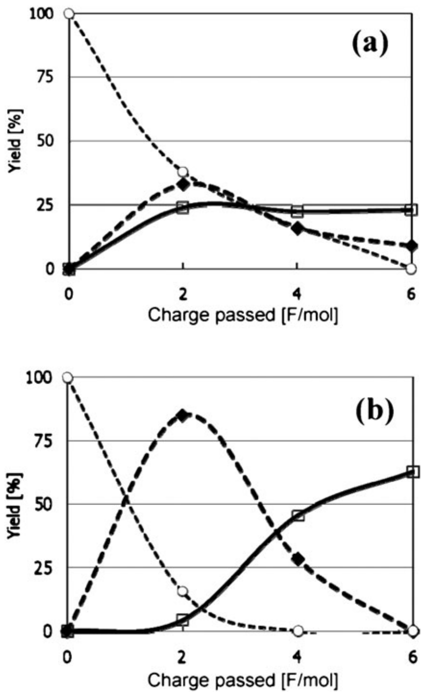
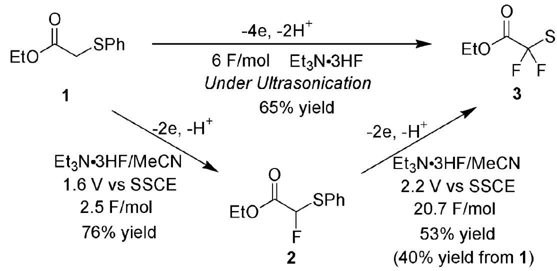
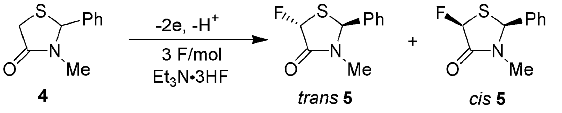


**Fig. 2** Dependence of yields of **2** and **3**, and amount of recovered **1** on charge passed: (◆) **2**, (□) **3**, (○) **1**. (a) Under mechanical stirring and (b) Under ultrasonication.



**Scheme 1**



Under mechanical stirring: 24% yield (*cis*/*trans* = 50/50)
Ultrasonication: 77% yield (*cis*/*trans* = 38/62)

**Scheme 2**

achieved in higher yield (65%) and with much higher current efficiency even in readily oxidizable ionic liquid $Et_3N{\cdot}3HF$ under ultrasonication.

Finally, we carried out VOC-free anodic fluorination of sulfur-containing heterocycles such as 4-thiazolidinone derivatives. Previously, we obtained an unsatisfactory yield (42%) of fluorinated product **5** (*cis* : *trans* = 35 : 65) by anodic fluorination of 2-phenyl-3-methyl-4-thiazolidinone (**4**) in $Et_3N{\cdot}3HF$–MeCN (4.5 F $mol^{-1}$).[6] In this case, we used pulse electrolysis in order to avoid passivation. In $Et_3N{\cdot}3HF$ ionic liquid, the anode passivation did not take place, however, the yield decreased significantly and the stereoselectivity was lost completely. Notably, we found that ultrasonication increased greatly not only the yield of anodic fluorination of **4** but also changed the stereoselectivity as shown in Scheme 2. The *trans*-fluorinated product was favorably formed under ultrasonication compared with anodic fluorination under mechanical stirring in the ionic liquid. The *trans* stereoselectivity can be explained in terms of desorption of the cationic intermediate from the anode surface by the micro-jet stream caused by ultrasonication.

In conclusion, we successfully carried out highly regioselective anodic mono- and difluorination of ethyl α-(phenylthio)acetate in $Et_3N{\cdot}3HF$ ionic liquid under ultrasonication. Efficient anodic fluorination of a 4-thiazolidinone derivative was also achieved similarly. We clarified that ultrasonication is highly effective for increase of the yield, current efficiency, and selectivity in anodic fluorination in HF salt ionic liquid.

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