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Electroorganic Synthesis Using a Fluoride Ion Mediator under Ultrasonic Irradiation:[1] Synthesis of Oxindole and 3-Oxotetrahydroisoquinoline Derivatives

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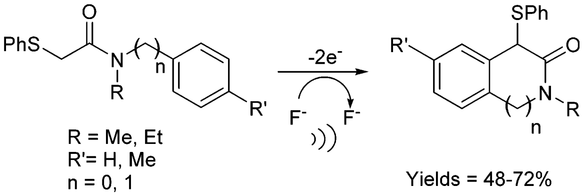
ABSTRACT



Anodic intramolecular cyclization of α-(phenylthio)acetamides using a fluoride ion mediator was realized. Under ultrasonic irradiation, cyclization was accelerated markedly to give desired cyclized products in moderate to good yields. The local heating effect of ultrasonic irradiation seems to be more advantageous than usual heating.

Electroorganic synthesis has developed remarkably because it offers unique selectivity and the high possibility of realizing specific reactions that cannot be accomplished by other chemical synthetic procedures.[2] One great advantage of the electrochemistry associated with mediators is that it carries out reactions under mild conditions and achieves high yields and selectivities.[3−6] To date, electroorganic synthetic efforts have specifically addressed carbon−carbon bond formation reactions; a wide variety of methods have been developed.[7,8] Recently, Motherwell et al. demonstrated that the cyclization reaction of *N*-phenyl- and *N*-benzyl-α-(phenylthio)acetamides proceeded with a fluoro-Pummerer-type mechanism using difluoroiodotoluene as an oxidizing reagent.[9] Nevertheless, those cyclization product yields were moderate. Difluoroiodotoluene is unstable. Moreover, preparation of the oxidant requires hazardous fluorine gas or costly XeF_2. On the other hand, we have shown that anodic generation of carbocations on the α-position to the sulfur atom occurs using a fluoride ion mediator. Methanol successfully trapped these intermediates to give α-methoxylated products (Scheme 1).[10] Presumably, the cation intermediates generated in these reactions can also be directly trapped with an aromatic ring. In addition, applying ultrasonic irradiation in electrochemical systems may cause various interesting and beneficial effects and can act as a probe of the reaction mechanism.[11−14] We

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[1] Electroorganic Synthesis Using a Fluoride Ion Mediator. 6.
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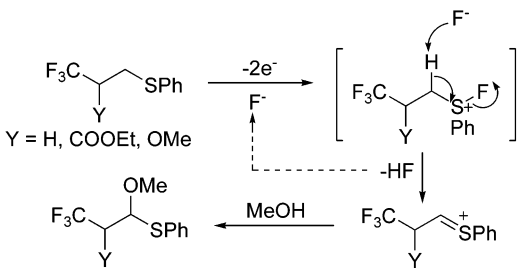
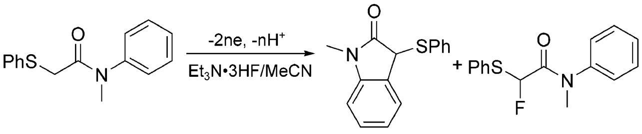
Scheme 1



were interested in proving how the ultrasonic irradiation might influence a fluoride ion mediated reaction.

With these facts in mind, the anodic cyclization of *N*-aryl- and *N*-benzyl-α-(phenylthio)acetamides **1** using a fluoride ion mediator was attempted using 1 mmol of α-(phenylthio)-*N*-methyl-*N*-phenylacetamide (**1a**) as a model substrate in 15 mL of acetonitrile containing $Et_3N{\cdot}3HF$ as both a supporting electrolyte and mediator in an undivided cell equipped with platinum plates (2 × 2 cm^2) as an anode and a cathode under various conditions, as shown in Table 1.

Table 1. Effect of Electrolytic Conditions on the Anodic Oxidation of **1a** Using a Fluoride Ion Mediator



1a **2a** **3a**

entry	mediator ($Et_3N{\cdot}3HF$) (mmol)	charge passed (F mol^{-1})	current density (mA cm^{-2})	yield (%)	
				2a	**3a**
1	0[a]	6	10	0	0
2	0.2	3	10	2	10
3	0.2	4	10	9	23
4	0.2	6	10	24	30
5	0.2	8	10	20	21
6	0.1	6	10	5	10
7	0.5	6	10	8	28
8	0.2	6	20	41	42
9	0.2	6	40	26	38

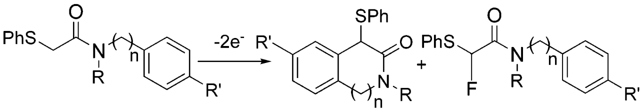
[a] 0.1 M Bu_4NBF_4 was used as a supporting electrolyte.

Although anodic oxidation did not proceed at all in the absence of fluoride ions (entry 1), fluoride ion mediated anodic oxidation proceeded to provide the desired product **2a** and fluorinated products **3a** regardless of electrolytic conditions.

First, we investigated the effect of a passed charge on the yield of **2a** (Table 1, entries 2−5). The yield of **2a** increased with the increase of the passed charge, and the best yield was obtained at 6 F mol^{-1} (entry 4). The yield decreased when more than 6 F mol^{-1} was passed. A considerable amount of substrate **1a** was recovered at less than 6 F mol^{-1} (entries 2 and 3), whereas the overoxidization of **2a** and **3a** occurred, thereby engendering lower yields at more than 6 F mol^{-1}(entry 5). Next, the charge was fixed at 6 F mol^{-1} and the amount of a fluoride ion mediator was varied (Table 1, entries 4, 6, and 7). As shown in entry 6, the low yields of **2a** and **3a** indicated that 0.1 mmol of $Et_3N{\cdot}3HF$ was not sufficient for the oxidation of **1a** because of its lower conductivity. The use of 0.5 mmol of $Et_3N{\cdot}3HF$ accelerated the further fluorination of **2a** and **3a** so that the yields of **2a** and **3a** were decreased (entry 7). Consequently, 0.2 mmol of $Et_3N{\cdot}3HF$ was found to be the most suitable concentration of the mediator. Furthermore, current density was obviously important for the oxidation of **1a**. In addition, Table 1 shows that the yields of products changed greatly depending on the current density (entries 4, 8, and 9). At 20 mA cm^{-2} of current density, the highest yields of **2a** (41%) and **3a** (42%) were obtained (entry 8).

Under these consequent optimum conditions (Table 1, entry 8), the anodic oxidation of other derivatives **1b−d** was carried out using fluoride ions as a mediator (Table 2). All reactions gave both corresponding cyclized products **2** and fluorinated products **3** in reasonable yields, which supported the proposed mechanism, as shown in Scheme 2. One-electron oxidation of starting amides **1a−d** generates radical cation **A**, which is trapped by a fluoride ion to give the corresponding radical **B**. Further oxidation of the radical **B** was followed by elimination of HF to afford intermediate **C**. At this stage, two pathways are possible as follows: an intramolecular Friedel−Crafts-type reaction gives desired cyclized products **2** (path 1), whereas **C** reacts with a fluoride ion to give α-fluorinated compounds **3**. In both cases, the fluoride ion works as a mediator for formation of the intermediate **C**.

Table 2. Anodic Oxidation of **1** Using a Fluoride Ion Mediator[a]



1 **2** **3**

entry	substrate no.	R	R′	*n*	E_p^{ox} [b] (V vs SCE)	yield (%) 2	yield (%) 3
1	**1a**	Me	H	0	1.59	41	42
2	**2a**	Et	H	0	1.59	14	32
3	**3a**	Me	H	1	1.57	13	31
4	**4a**	Me	Me	0	1.55	16	11

[a] Electrolytic conditions: 0.2 mmol of $Et_3N{\cdot}3HF$ and 1 mmol of substrate in 15 mL of MeCN, current density, 20 mA cm^{-2}; charge passed, 6 F mol^{-1}; *T*, 20 °C. [b] Substrate 3 mM in 0.1 M Bu_4NBF_4/MeCN; Pt disk anode (Φ = 1 mm); scan rate, 100 mV s^{-1}.

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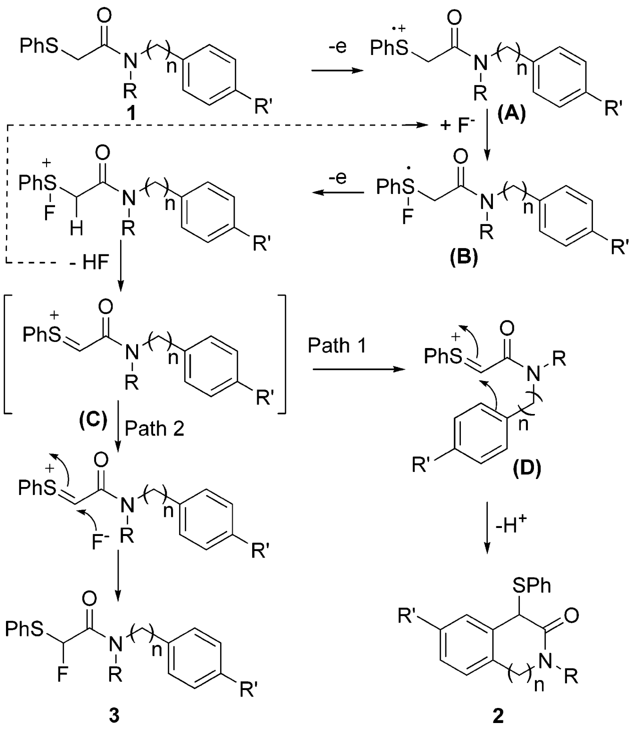
Scheme 2. Proposed Mechanism for the Anodic Oxidation of **1** in the Presence of Fluoride Ions



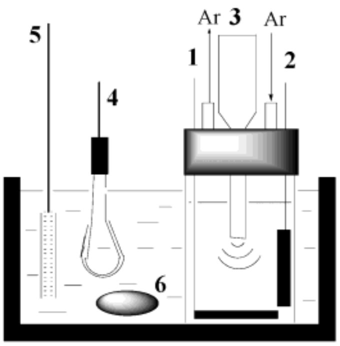


Figure 1. Apparatus for electrosynthesis under ultrasonic irradiation. Sonoelectrochemical system using a stepped horn: (1) working electrode (Pt 2 × 2 cm^2), (2) counter electrode (Pt 2 × 2 cm^2), (3) ultrasonic horn, (4) heater, (5) pipe-type cooler, (6) stirring bar.

However, the yields of the desired cyclized products **2** were not satisfactory under the above electrolytic conditions. Our experience in sonoelectrochemistry prompted us to apply ultrasonic irradiation to this anodic oxidative cyclization. Figure 1 shows the apparatus for electrolysis under ultrasonic irradiation. The working electrode is located on the bottom of the cell and an ultrasonic stepped horn is set vertically 1.5 cm apart from the work electrode.

The water bath temperature is maintained automatically at 20 °C using a heater and a pipe-type cooler to maintain the temperature inside cell under ultrasonic irradiation.

Electrooxidation under ultrasonic irradiation was attempted using **1c** as a model substrate. As shown in Figure 2, the yield of **2c** increased markedly with increased ultrasonic irradiation power. The yield achieved the maximum 68% yield at 43 W cm^{-2} of the ultrasonic power. On the other hand, the yield of fluorinated product **3c** decreased appreciably from 31% (non irradiation) to 15%. Encouraged by this good result, electrolysis of other derivatives **1a**,**b**,**d** was carried out under the same conditions. Table 3 lists the yields of cyclized products **2** and fluorinated products **3**. The desired cyclization was promoted markedly under ultrasonic irradiation to provide cyclized products **2** in much higher yields compared with the electrolysis under nonsonication (Table 2). The highest yield of **2a** reached 72% (Table 3, entry 1), whereas the corresponding fluorinated product **3a** was decreased radically to 12%, which indicates the strong effect of ultrasonic irradiation on product selectivity control.

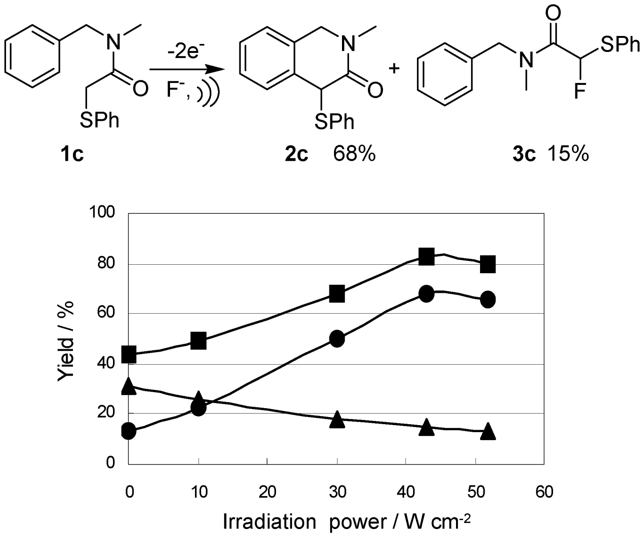


Figure 2. Effect of ultrasonic irradiation power on anodic cyclization using a fluoride ion mediator: ●, yield of **2c**; ▲, yield of **3c**; ■, total yield.

Table 3. Anodic Oxidation of **1** Using a Fluoride Ion Mediator under Ultrasonic Irradiation[a]

	substrate				yield (%)	
entry	no.	R	R′	*n*	**2**	**3**
1	**1a**	Me	H	0	72	12
2	**1b**	Et	H	0	58	9
3	**1c**	Me	H	1	68	15
4	**1d**	Me	Me	0	47	7

[a] Conditions: 0.2 mmol of $Et_3N{\cdot}3HF$ and 1 mmol of substrate **1** in 15 mL of MeCN; current density, 20 mA cm^{-2}; charge passed, 6 F mol^{-1}; *T*, 20 °C; ultrasonic irradiation power, 43 W cm^{-2}.

However, we wondered why the ultrasound irradiation affected the reaction pathways so drastically. Ultrasound exerts myriad effects upon electrochemical reactions.[14] Herein, it is important to understand which is the main effect of ultrasound on the electrolytic reactions. The following experiments were designed to disclose the effect. First, we investigated the effect of stirring speed using **1c** as a model substrate under electrolytic conditions similar to Table 3. Figure 3 shows that the yields of both **2c** and **3c** increase simultaneously. No change of selectivity was observed, which indicates that the acceleration of mass transport was not obviously allied with the selectivity. In the next experiment, the stirring speed was fixed at 1000 rpm. The temperature was varied from 20 to 70 °C. As shown in Figure 4, the yield of **2c** increased with an increase of temperature. In addition, the yield of **2c** became higher than that of **3c** at around 55 °C, indicating that high temperature is suitable for selective formation of **2c**. Because the intramolecular reaction pathway would involve smaller activation entropy, it would become more favorable than the intermolecular pathway as the reaction temperature increases. A similar temperature effect on anodic cyclization caused by C−O bond formation was reported by Moeller et al.[15] From results obtained under ultrasonication, the effect of ultrasound on the selectivity of **2c** seems to be attributable to its local heating action, which increases the temperature sufficiently for cyclization. On the other hand, such a high temperature is not available through usual heating because of the limited boiling points of organic solvents such as acetonitrile.

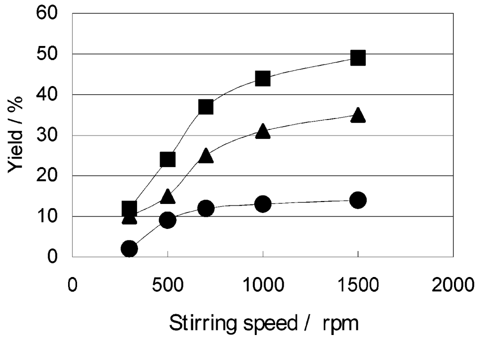


Figure 3. Effect of stirring speed on electrolysis of **1c**: ●, yield of **2c**; ▲, yield of **3c**; ■, total yield.

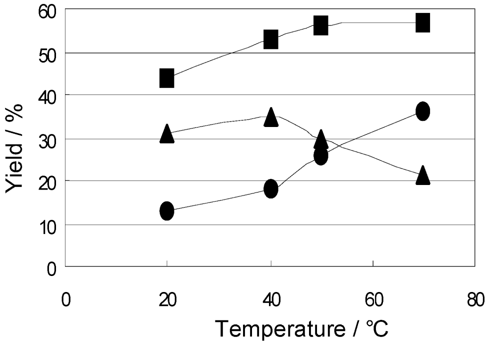


Figure 4. Effect of temperature on electrolysis of **1c**: ●, yield of **2c**; ▲, yield of **3c**; ■, total yield.

In conclusion, an intramolecular carbon−carbon bond formation was realized by anodic oxidation of sulfides using a fluoride ion mediator. Under ultrasonic irradiation, the cyclization is markedly accelerated to give the desired cyclic products in moderate to good yields. The local heating effect by ultrasonic irradiation seems to be more advantageous than usual heating. Further efforts to utilize this unique ultrasound-aided anodic cyclization synthetic method are in progress.

Supporting Information Available: A sample experiment for the electrochemical procedure and characterization data for electrochemical substrates and corresponding products are included along with copies of proton NMR spectra for **1b**, **2b**, and **3a**,**b**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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