Electrolytic Partial Fluorination of Organic Compounds. 30.[1] Drastic Improvement of Anodic Monofluorination of 2-Substituted 1,3-Oxathiolan-5-ones Using the Novel Fluorine Source $Et_4NF·4HF$

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The highly regioselective anodic monofluorination of 2-substituted 1,3-oxathiolan-5-ones was successfully carried out using a novel supporting electrolyte, $Et_4NF·4HF$, while use of a conventional supporting electrolyte, $Et_3N·3HF$, resulted in no formation or extremely low yields of the fluorinated products.

Introduction

The displacement of hydrogen atoms of organic compounds by fluorine atoms sometimes significantly changes their physical, chemical, biological, and pharmacological properties.[2−5] Recently, electrochemical oxidative fluorination (anodic fluorination) has attracted much attention as an ideal method for direct fluorination since it can be performed in one step under safe and mild conditions.[5−10]

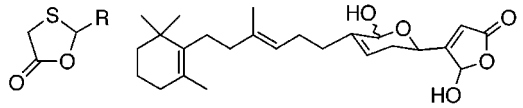
On the other hand, we recently found that 1,3-oxathiolan-5-one derivatives **1** which have a heterocyclic *O,S*-acetal ring system, possessed inhibitory activities toward human type-II (nonpancreatic) secretory phospholipase A_2 (PLA_2, EC 3.1.1.4)[11] (Table 1). These activities were comparable with the well-known PLA_2 inhibitor, manoalide.[12,13]

PLA_2 is an enzyme family which generates, for example, a precursors of eicosanoids, such as prostaglandins, or the platelet-activating factor.[14] Therefore, the PLA_2 isozyme family plays crucial roles in regulating diverse cellular responses, especially inflammation. At the present time, to elucidate how these isozymes are sharing the functions and to develop the biochemical, medical, and pharmacological applications, the synthesis and the development of these new compounds, which strongly and selectively inhibit or enhance one of the PLA_2 isozymes, are strongly desired.[15]

On the basis of these facts, we tried to incorporate fluorine atom into **1** in order to prepare more potent and more selective inhibitors by means of partial anodic fluorination.

Some examples of the partial anodic fluorination of heterocyclic compounds have been reported,[16−20] but the yields and selectivity of the products were generally low due to the low nucleophilicity of the fluoride ions and passivation of the anodes.[6] Therefore, it is important to find excellent supporting electrolytes, fluoride salts,

Table 1. Inhibitory Activity of Human Type-II Secretory Phospholipase A_2 by 2-Substituted 1,3-Oxathiolan-5-ones 1 and Manoalide



1 **manoalide**

substrate	R	IC_{50}/μg/mL
1a	Et	1.9
1b	*n*-Pr	0.9
1c	*i*-Pr	0.9
manoalide		0.14−0.34

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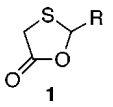
Table 2. Oxidation Peak Potentials (E_p^{ox}) of 2-Substituted 1,3-Oxathiolan-5-ones 1[a]



1

1	R	E_p^{ox}/V vs SSCE
1a	Et	2.34
1b	n-Pr	2.32
1c	i-Pr	2.44
1d	Ph	1.88
1e	*p*-CN-C_6H_4	2.17

[a] Pt electrodes; 0.1 M $NaClO_4$/MeCN; sweep rate, 100 mv s^{-1}.

which have high nucleophilicity, and do not cause passivation in order to achieve efficient partial anodic fluorination.

Results and Discussion

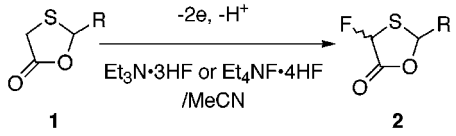
Oxidation Potentials of 2-Substituted 1,3-Oxathiolan-5-ones. The oxidation potentials (anodic peak potentials) of 2-substituted 1,3-oxathiolan-5-ones **1** were measured by cyclic voltammetry, using a divided cell with platinum electrodes in 0.1 M $NaClO_4$/anhydrous acetonitrile. These heterocycles exhibited irreversible anodic waves. The first peak potentials, E_p^{ox}, are summarized in Table 2.

These heterocyclic compounds were oxidized at 1.9−2.4 V vs a sodium saturated calomel electrode (SSCE). The compounds which have aryl substituents such as Ph (**1d**) or *p*-CN-C_6H_4 (**1e**) showed a lower E_p^{ox} than **1a**−**c** which have alkyl substituents.

Anodic Monofluorination of 2-Substituted 1,3-Oxathiolan-5-ones. In our previous studies on the partial anodic fluorination of heteroatom compounds including heterocycles, we found that Et_3N·3HF was a suitable supporting electrolyte and fluorine source for the selective anodic fluorination;[7−9,21−27] consequently, we initially used Et_3N·3HF. The anodic monofluorination of **1** was carried out at a platinum anode in an undivided cell. However, we obtained the fluorinated products **2** in negligible yields based on the ^{19}F NMR measurements in all cases, and no isolable product was formed, although the starting materials **1** were completely consumed. Severe passivation of the anode due to nonconductive film formation on the anode was observed during the electrolysis. To prevent the passivation to some extent, we used the pulse electrolysis technique[6] so that the anodic potential was maintained at the oxidizing potential for 90 s then at 0 V for 10 s, but the yields were not improved (Scheme 1 and Table 3).

The substrates **1** were almost stable in this electrolytic solution, but the products **2** were not sufficiently stable enough and gradually decomposed. It took a long time to complete the electrolytic reaction because of the passivation, and this lead to the decomposition of the products during the electrolysis.

Scheme 1



1 **2**

Table 3. Anodic Monofluorination of 2-Substituted 1,3-Oxathiolan-5-ones 1

1	supporting electrolyte	applied potential/ V[a]	electricity/ F mol^{-1}	product	yield/ %[b]	cis/ trans[b]
1a	Et_3N·3HF	2.3[c]	3.4	**2a**	0	
1a	Et_4NF·4HF	2.1	2.6		86	47:53
1b	Et_3N·3HF	2.2−2.3[c]	3.6	**2b**	5.4	*d*
1b	Et_4NF·4HF	2.1	2.2		67	45:55
1c	Et_3N·3HF	2.2[c]	2.2	**2c**	0	
1c	Et_4NF·4HF	2.1	2.4		78	43:57
1d	Et_3N·3HF	1.6[c]	4.0	**2d**	0	
1d	Et_4NF·4HF	2.0	2.3		70	45:55
1e	Et_3N·3HF	2.2[c]	3.4	**2e**	0	
1e	Et_4NF·4HF	2.0[c]	3.2		66	39:61

[a] Versus Ag/Ag^+ (0.01 M). [b] Determined by ^{19}F NMR spectra. [c] Pulse electrolysis was employed. [d] Not estimated due to the low yield of **2b**.

We recently reported the dehydrofluorination of difluorinated flavones by the free Et_3N in Et_3N·3HF during the anodic fluorination of flavones.[21] We had confirmed that this equilibratingly existing free Et_3N[28] was one of the reasons for the low yields, because the free Et_3N caused the passivation of the anode. Therefore, we tried to find another excellent supporting electrolyte/fluoride source which did not cause the passivation.

Eventually, we found that a novel type of fluoride supporting electrolyte, Et_4NF·4HF, drastically improved the reaction. This electrolyte is one of the recently developed new class as of fluoride supporting electrolytes represented by R_4NF·*m*HF (R = Me, Et, Pr; $m > 3.5$), and one of the authors (K.M.) has achieved the partial anodic fluorination of benzene, halobenzenes, and trifluoromethylbenzene using these fluoride salts without solvent.[29−31] These fluoride salts are nonviscous liquids and have a high electrolytic conductivity together with a high electrochemical stability.[29]

We then used Et_4NF·4HF as a fluoride supporting electrolyte and the anodic fluorination of **1** regioselectively proceeded in high yields with good current efficiencies. In these cases, no passivation took place except for **1e**. In the case of **1e**, a slight passivation was observed; therefore, the pulse electrolysis technique was used so that the anodic potential was maintained at the oxidizing potential for 45 s then at 0 V for 5 s. The electrolyzing time was also significantly reduced (from ca. 12 h to 2−4 h). Although one of us (K.M.) used this electrolyte without solvent for selective fluorination,[29−31] we obtained much better yields and current efficiencies by using the elec-

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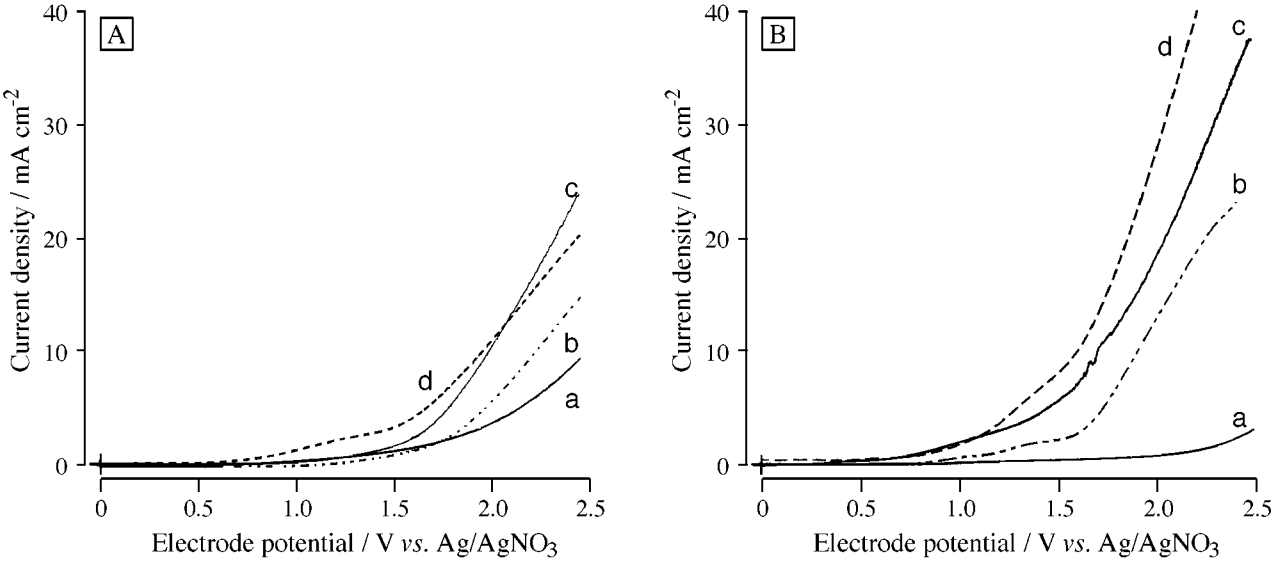
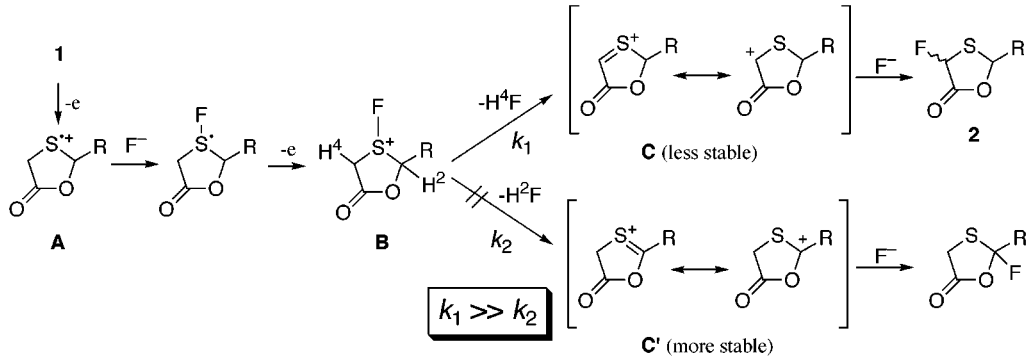


Figure 1. Linear sweep voltammogram of **1**: electrodes, Pt plates (2 × 3 cm^2); solvent, CH_3CN; sweep rate, 50 mV s^{-1}; electrolytic fluoride salt, (A) $Et_3N{\cdot}3HF$ (0.37 M), (B) $Et_4NF{\cdot}4HF$ (0.34 M); (a) without substrate; (b) with **1e** (0.1 M); (c) with **1d** (0.1 M); (d) with **1c** (0.1 M).

Scheme 2



trolyte diluted with acetonitrile (in a 0.34 M solution) compared with the use of the electrolyte without any solvents.

We next investigated the properties of these two electrolytic fluoride salts by measuring the linear sweep voltammograms using these two electrolytic fluoride salts with or without the substrate **1** (Figure 1).

While the conventional electrolytic system, $Et_3N{\cdot}3HF$/MeCN (Figure 1A, curve a) began to discharge around 1.5 V (2 V vs SSCE), presumably due to the free Et_3N[28] containing in $Et_3N{\cdot}3HF$, the new electrolytic solution, $Et_4NF{\cdot}4HF$/MeCN (Figure 1B, curve a) was highly stable against anodic oxidation up to ca. 2.5 V vs $Ag/AgNO_3$ (3 V vs SSCE). Current densities with substrates were also higher in the case of $Et_4NF{\cdot}4HF$ than that of $Et_3N{\cdot}3HF$. These observations explain the higher yields and current efficiencies when $Et_4NF{\cdot}4HF$ is used.

We proposed that the anodic fluorination of **1** proceeded through the electrochemical−chemical−electrochemical−chemical (ECEC) mechanism described in Scheme 2 as previously reported.[8,9,32] Fluoride ions play important roles in this reaction. Namely, fluoride ions are not only a fluorine source but also react with the first radical cation intermediate **A** at the sulfur atom and then promote the second oxidation to the fluorosulfonium cation intermediate **B**. From the viewpoint of the product **2**, the fluorination regioselectively took place at the 4-position. Especially, in the case of 2-aryl-substituted 1,3-oxathiolan-5-ones, **1d** and **1e**, benzylic fluorination was not observed at all, although in general anodic benzylic substitution easily takes place. Even though the cationic intermediate **C′** seemed to be thermodynamically more stable, fluorination proceeded through the less stable intermediates **C**. This selectivity can be explained in terms of the higher acidity and higher deprotonation ability of the H^4 proton compared to the H^2 in the intermediate **B**. The deprotonation ability of H^4 is more enhanced by the electron-withdrawing carbonyl group. After this kinetically controlled deprotonation of H,[4] the next fluorination selectively takes place at the 4-position via a Pummerer-type mechanism.[33−35] Another possibility is thermodynamically and stereochemically controlled fluoride ion attack to the less hindered C^4 carbon of intermediate **C**, even though intermediate **C′** seems to be much more stable cation because the C^2 cation

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conjugated with oxygen and sulfur atoms, and an alkyl or an aryl group. From these both effects, we concluded that such a remarkable regioselectivity in these anodic fluorination was achieved.

On the other hand, the cis/trans stereoselectivities for the fluorination was low and showed a slight excess of trans isomers.[36] This is presumably due to the steric hindrance with the substituent at the 2-position.

Conclusion

We have successfully carried out highly regioselective anodic monofluorination of 1,3-oxathiolan-5-ones using an Et_4N·4HF/MeCN electrolytic solution. This novel electrolytic system provided high current efficiency and did not cause severe passivation which has usually been observed during partial anodic fluorination of organic compounds. This successful electrolytic system using Et_4N·4HF has a large potential which can be applicable to other anodic fluorination including the difficult fluorination, previously resulting in low yields or low current efficiencies because of passivation or their high oxidation potentials.

Experimental Section

General. *Caution*: Et_3N·3HF and Et_4NF·4HF are toxic; if it comes in contact with skin, it causes a serious burn. Therefore, proper safety precautions should be taken at all times, and it is recommended that rubber gloves be used.

^1H NMR and ^{19}F NMR spectra were recorded at 270 and 254 MHz, respectively, in $CDCl_3$ as a solvent. The chemical shifts for ^{19}F are given in δ ppm downfield from external CF_3COOH. Preparative electrolysis experiments were carried out using a Potentiostat/Galvanostat HA-501, a Function Generator HB-104, and a Coulomb/Amperehour meter HF-201 (Hokuto Denko, Ltd., products) with a reference electrode (0.01 M $AgNO_3$, 0.1 M Et_4NBF_4 in CH_3CN/Ag wire) for potentiostat electrolysis.

Materials. The electrolytes, Et_3N·3HF and Et_4NF·4HF, were kind gifts of Morita Chemical Industries Co., Ltd. (Japan) and used for the electrolysis without further purification. Et_4NF·4HF was also prepared by mixing Et_4NF·2HF and anhydrous HF in a nitrogen atmosphere as described elsewhere.[37]

The starting materials, 1,3-oxathiolan-5-ones **1a**,**b**,**d**, were prepared from the condensation of thioglycolic acid with the corresponding aldehydes according to the known procedure.[38]

2-Isopropyl-1,3-oxathiolan-5-one (1c). Almost the same procedure[38] for the synthesis of **1a**,**b** was employed. To isobutyraldehyde (7.21 g, 0.1 mol) was added thioglycolic acid (9.21 g, 0.1 mol), and the resulting solution was stirred at room temperature for 24 h. The volatile materials were evaporated, and the residue was distilled in vacuo. The distillate was washed with 10% aqueous $NaHCO_3$ and redistilled in vacuo (75 °C/3 mmHg) to give 5.76 g (39%) of the product **1c**. ^1H NMR: δ 5.32 (d, J = 6.6 Hz, 1H), 3.69 (d, J_{AB} = 16.7 Hz, 1H), 3.61 (d, J_{AB} = 16.7 HZ, 1H), 2.12 (oct, J = 6.6 Hz, 1H), 1.06 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89. Found: C, 48.91; H, 6.78.

2-(4-Cyanophenyl)-1,3-oxathiolan-5-one (1e). Almost the same procedure for the synthesis of **1d**[38] was employed. To the solution of thioglycolic acid (4.61 g, 50 mmol) in benzene (70 mL) was added 4-cyanobenzaldehyde (13.1 g, 0.1 mol), and the resulting solution was refluxed overnight. The reaction mixture was washed with 10% aqueous $NaHCO_3$, and the volatile materials were evaporated. The residue was distilled in vacuo (110 °C/4 mmHg), and the distillate was recrystallized from a small amount of EtOAc and hexane: yield = 2.47 g (24%). ^1H NMR: δ 7.72 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 6.51 (s, 1H), 3.90 (d, J_{AB} = 16.5 Hz, 1H), 3.78 (d, J_{AB} = 16.5 Hz, 1H). Anal. Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82. Found: C, 58.55; H, 3.46; N, 6.60.

Electrolytic Procedures for Fluorination. Electrolysis Using Et_3N·3HF. Electrolysis was performed at a platinum anode and cathode (3 × 4 cm^2 each) in 0.37 M Et_3N·3HF/MeCN (50 mL) containing 5 mmol of **1** using a cylindrical one-compartment glass cell at ambient temperature under a nitrogen atmosphere until the starting material was completely consumed (checked by TLC or GC-MS). To avoid deposition of the polymerized products on the anode, pulse electrolysis [applied potential (90 s)/0 V (10 s), see Table 3] was performed.

Electrolysis Using Et_4NF·4HF. Electrolysis was carried out at a platinum anode and cathode (2 × 3 cm^2) in 0.34 M Et_4NF·4HF/MeCN (30 mL) containing 3 mmol of **1** using a cylindrical one-compartment cell made of PFA or PTFE[29] for protection from the corrosive HF salt at ambient temperature under a nitrogen atmosphere until the starting material was completely consumed (checked by TLC or GC-MS). In the case of **1e**, to avoid deposition of the polymerized products on the anode, pulse electrolysis [applied potential (45 s)/0 V (5 s), see Table 3] was performed.

Calculation of the Yields and the cis/trans Ratios Using ^{19}F NMR. The electrolytic mixture was evaporated in vacuo, and then a certain amount of monofluorobenzene as a internal standard material was added for the integration. The yields were calculated on the basis of the integral ratios between the monofluorobenzene and each stereoisomer of **2**.

Separation and Analysis of Products. The electrolytic mixture was diluted with ether and washed with two portions of H_2O. The organic phase was dried over anhydrous Na_2SO_4 and evaporated. The residual material was purified using bulb-to-bulb distillation (100−170 °C/4 mmHg) to give the fluorinated product **2**. Product **2** was almost decomposed under slightly basic and hydrous conditions or during column chromatography. We could not determine the isolated yields of **2** because **2** also began to decompose (seemed polymerizing) liberating hydrogen fluoride immediately after the bulb-to-bulb distillation at room temperature or even in freezer. Therefore, we had to dilute the distillate immediately with $CDCl_3$ to measure NMR spectra. In the diluted solution, product **2** was stable to some extent, finally decomposing at room temperature.

2-Ethyl-4-fluoro-1,3-oxathiolan-5-one (2a): ^1H NMR (cis and trans mixture) δ 6.20, 6.20 (2d, J = 5.4 and J = 8.4 Hz, 1H), 5.72, 5.49 (dd and dt, J = 11.6, 5.6 Hz and J = 5.81, 6.52 Hz, 2H), 2.2−1.8 (m, 2H), 1.08 (t, J = 7.43 Hz, 3H); ^{19}F NMR δ −65.51 (ddd, J = 53.8, 8.9, 3.1 Hz, trans isomer), −74.49 (dd, J = 55.8 Hz, J = 5.0 Hz, cis isomer); MS for both of the isomers *m/e* 150 (M^+), 121, 106, 93; GC-HRMS calcd for $C_5H_7FO_2S$ *m/e* 150.0151, found 150.0135 (faster) and 150.0165 (slower).

4-Fluoro-2-*n*-propyl-1,3-oxathiolan-5-one (2b): ^1H NMR (cis and trans mixture) δ 6.18 (d, J = 56.8 Hz, 1H), 5.75, 5.53 (dd and dt, J = 12.2, 5.6 Hz and J = 8.9, 6.8 Hz, 1H), 2.1 (m, 2H), 1.9 (m, 2H), 1.01, 0.99 (2t, J = 7.3 Hz, 3H); ^{19}F NMR δ −67.60 (dd, J = 56.5, 8.7 Hz, trans isomer), −74.80 (dd, J = 55.5, 5.3 Hz, cis isomer); MS *m/e* 164 (M^+), 102, 101, 100, 88, 86; GC-HRMS calcd for $C_6H_9FOS_2$ *m/e* 180.0078, found 180.0065.

2-Isopropyl-4-fluoro-1,3-oxathiolan-5-one (2c): ^1H NMR (cis and trans mixture) δ 6.21, 6.19 (2d, J = 57.4 and J = 56.1 Hz, 1H), 5.57, 5.33 (t and dd J = 6.44 Hz and J = 9.74, 6.77 Hz, 1H), 2.14 (m, 1H), 1.1 (m, 6H); ^{19}F NMR δ −67.44 (dd, J

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= 57.7, 9.9 Hz, trans isomer), −74.40 (dd, J = 55.8, 5.6 Hz, cis isomer); MS *m/e* for both of the isomers 164 (M^+), 121, 93, 73, 56; GC-HRMS calcd for $C_6H_9FOS_2$ *m/e* 180.0078, found 180.0065.

4-Fluoro-2-phenyl-1,3-oxathiolan-5-one (2d): ^{1}H NMR (cis and trans mixture) δ 7.41 (brs, 5H), 6.65, 6.48 (2d, J = 5.28 and J = 8.91 Hz, 1H), 6.32, 6.31 (2d J = 55.4 Hz and J = 56.4 Hz, 1H); ^{19}F NMR δ −67.05 (dd, J = 57.4, 9.0 Hz, trans isomer), −75.62 (dd, J = 55.8, 5.6 Hz, cis isomer); MS *m/e* for both of the isomers 198 (M^+), 154, 153, 121, 105, 77; GC-HRMS calcd for $C_9H_7FO_2S$ *m/e* 198.0151, found 198.0146 (faster), 198.0157 (slower).

2-(4-Cyanophenyl)-4-fluoro-1,3-oxathiolan-5-one (2e): ^{1}H NMR (cis and trans mixture) δ 7.76, 7.74 (2d, J = 8.6 Hz, 2H), 7.78, 7.74 (2d, J = 8.6 Hz, 2H), 6.72, 6.57 (2d, J = 5.6 and 7.9 Hz, 1H), 6.35, 6.34 (2d, J = 54.8 and 56.4 Hz, 1H); ^{19}F NMR δ −67.44 (dd, J = 57.7, 9.9 Hz, trans isomer), −74.40 (dd, J = 55.8, 5.6 Hz, cis isomer); MS for both of the isomers *m/e* 223 (M^+), 132, 130, 102; GC−HRMS calcd for $C_{10}H_6FNO_2S$ *m/e* 223.0103, found 223.0113 (faster), 223.0115 (slower).

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Supporting Information Available: ^{1}H and ^{19}F NMR spectra for **2a**−**e** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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