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Copper-Promoted Conjugate Addition of Carboxylic Acids to Ethenesulfonyl Fluoride (ESF) for Constructing Aliphatic Sulfonyl Fluorides

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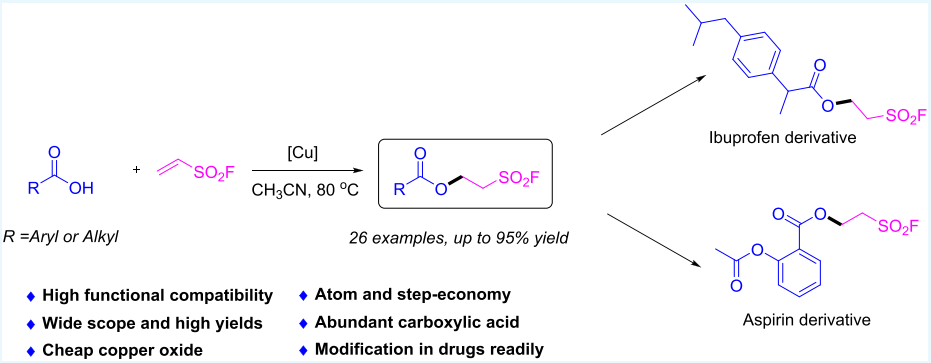

ABSTRACT: A CuO-promoted direct hydrocarboxylation of ethenesulfonyl fluoride (ESF) was developed using carboxylic acid as a nucleophile under mild conditions. A variety of molecules containing both ester group and aliphatic sulfonyl fluoride moiety exhibit great potential in medicinal chemistry and chemical biology. Furthermore, the modification of the known drugs Ibuprofen and Aspirin was also demonstrated.

INTRODUCTION

Since the seminal work reported by Sharpless group in 2014,[1] sulfur fluoride exchange (SuFEx), another representative exemplification of click chemistry,[2] has triggered immense interest among the community of researchers due to its extraordinary efficiency, unique reactivity, and absolute reliability for achieving the molecular diversity through a sulfur hub.[3] Furthermore, sulfonyl fluoride is one of the irreplaceable members of SuFEx chemistry family[4] and has been considerably applied to various productive fields based on its unique prominent features of stability−reactivity.[5]

Aliphatic sulfonyl fluorides, bearing the attractive sulfonyl fluoride motifs, have been considered as one of the most prominent covalent inhibitors or privileged drug warheads along with numerous other applications in the development of chemical biology and medicinal chemistry in recent decades.[6] Phenylmethanesulfonyl fluoride (PMSF), was found to act as a covalent enzyme inhibitor of serine proteases and also as a reactive probe in the routine preparation of cell lysates.[7] In addition, AM3506 and AM-374, effective inhibitors of fatty acid amide hydrolase (FAAH) and lipoprotein lipase inhibitor (L-28), were all functionalized with valuable aliphatic sulfonyl fluorides as core pharmacophores and showed excellent activity for treating the corresponding diseases.[8] In addition, molecules bearing sulfonyl fluoride moieties have been identified as inhibitors of esterase (Figure 1A).[7d7e] Moreover, substrates with sulfonyl fluoride moiety have also gained significant attention in polymer chemistry.[9] For instance, some well-known sulfonyl fluoride-containing monomers including "Nafion" and "Dow monomer" have been widely utilized to make sulfonic end-group fluorocarbon-based ion-exchange membrane via polymerization with various perfluoro alkenes and hydrolysis of sulfonyl fluoride functionality (Figure 1B).[10] Because of the great importance and omnipresent applications of sulfonyl fluorides, the development of reliable methods for the installation of sulfonyl fluoride moiety to the scaffolds of valuable industrial applications is highly desirable.

Additionally, ethenesulfonyl fluoride (ESF), an excellent Michael acceptor,[11] has been demonstrated as one of the most effective reagents for incorporating the sulfonyl fluoride group into the molecules via the classic Michael addition using carbon, nitrogen, sulfur, and oxygen nucleophiles (Scheme 1a).[1,12,13] On the other hand, carboxylic acids are among the

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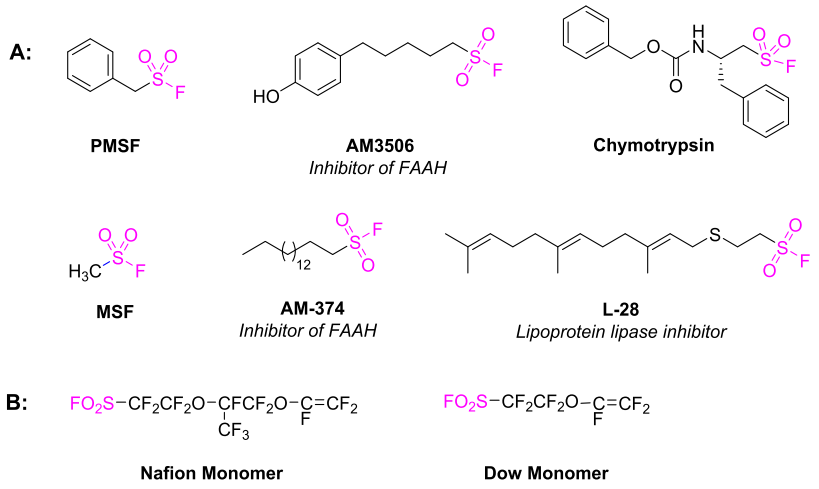
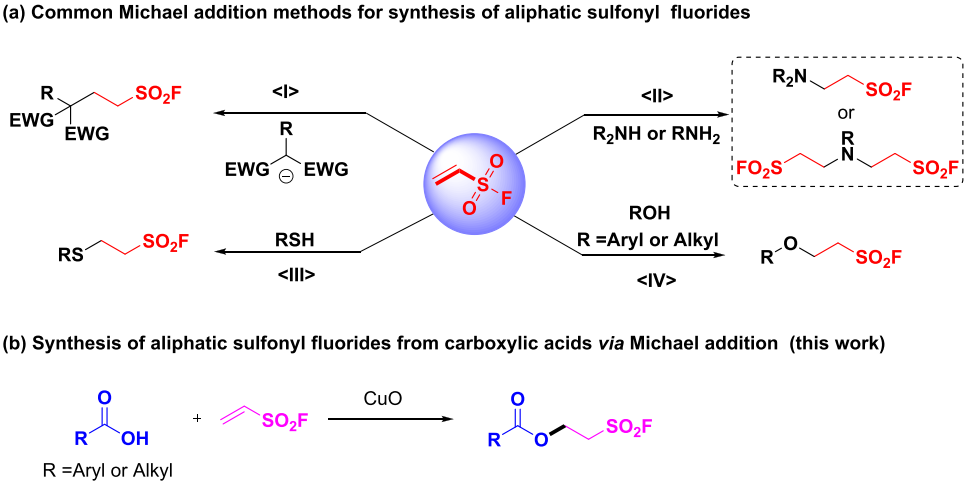


Figure 1. Representative enzyme inhibitors or covalent drugs (A) and perfluorofunctional polymers (B) containing aliphatic sulfonyl fluoride.

Scheme 1. Approaches to Aliphatic Sulfonyl Fluorides via Michael Addition of Various Nucleophiles



most common and available chemical compounds categories. Meanwhile, they are essential in organic chemistry and industry, among which various (hetero)-aromatic carboxylic acids are good structurally diverse, inexpensive, readily available, and bench-stable candidates for medicinal chemistry and agrochemistry.[14] Carboxylic acids occur widely in natural products and common chemicals, and the specific characteristics of this carboxylic acid functional group enable them to serve as central building blocks for the preparation of derivatives like carboxylate salts, anhydrides, esters, nitriles, and amides.[15] Also, the corresponding products find numerous applications for polymers, cosmetics, pharmaceuticals, agrochemicals, and other manufactured chemicals.[16] Notably, to the best of our knowledge, esters are commonly constructed through the coupling of alcohols with acids while the direct Michael addition of acids to electron-deficient alkenes for the synthesis of esters has been rarely reported due to their paucity of nucleophilic ability.[17] Therefore, nucleophilic activation of carboxylic acids has always been a challenging task in organic transformations.

The nucleophilic conjugate additions of oxygen-centered nucleophiles to conjugate acceptors are one of the most potent strategies for the C−O bond formation.[18] Inspired by the difunctionalization of terminal alkynes by Cu(III)−CF_3 complex in the combination of carboxylic acids,[19] and considering the significance of ester and aliphatic sulfonyl fluoride as the structurally irreplaceable scaffolds of the various molecules, we envision that the synthesis of this category of molecules bearing both these motifs will be very attractive in organic synthesis, chemical biology, drug discovery, and ionic membrane chemistry.[20] Herein, we reported the Michael addition of ESF using diverse carboxylic acids as the nucleophiles in the presence of CuO, affording a family of 2-fluorosulfonylethyl esters for further utilization (Scheme 1b).

RESULTS AND DISCUSSION

Originally, benzoic acid (**1a**) was selected as a model substrate to investigate the feasibility of synthesizing the desired 2-(fluorosulfonyl)ethyl benzoate (**2a**). When the reaction of benzoic acid (**1a**) with ESF was carried out in the presence of CuO using dry acetonitrile as a solvent under air, the desired product 2-(fluorosulfonyl)ethyl benzoate (**2a**) was obtained in 20% yield (Table 1, entry 1, see the Supporting Information for details). When the reaction was carried under an argon atmosphere, the yield of **2a** was improved to 74% (Table 1, entry 2). The use of dry solvent under an argon atmosphere (Table 1, entry 3, 89%) was found to be the best condition for the desired transformation. Besides, reducing the loading of CuO from 2.0 to 1.0 equiv afforded a similar yield of **2a**. However, the reaction was completely frustrated in the absence

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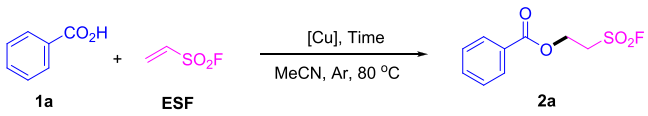
Table 1. Optimization of the Reaction Conditions[a]



1a ESF 2a

entry	[Cu] (*X* equiv)	ESF (*Y* equiv)	time (h)	yield (**2a**, %)[b]
1[c]	CuO (2.0)	2.0	20	20
2[d]	CuO (2.0)	2.0	20	74
3	CuO (2.0)	2.0	20	89
4	**CuO (1.0)**	**2.0**	**20**	**91**
5	/	2.0	20	trace
6	CuO (1.0)	4.0	20	73
7	CuO (1.0)	1.5	20	70
8[e]	CuO (1.0)	1.5	20	80
9[f]	CuO (1.0)	2.0	20	87
10	CuO (1.0)	2.0	5	N.D.
11	CuO (1.0)	2.0	48	89

[a]Reaction conditions: a mixture of benzoic acid (**1a**, 0.1 mmol), [Cu], ESF, and anhydrous MeCN (2 mL) reacted at 80 °C under argon atmosphere for the corresponding time. [b]The yields were determined by HPLC using **2a** as the external standard (t_R = 7.5 min, λ_{max} = 229.9 nm, water/acetonitrile = 50:50 (v/v)). [c]In the air. [d]Undried MeCN (2 mL). [e]Reacted at 70 °C. [f]Reacted at 90 °C.

of CuO (Table 1, entries 4 and 5). The loading of ESF was also assessed and 2.0 equiv of ESF turned out to be the most effective for the formation of 2-(fluorosulfonyl)ethyl benzoate (**2a**) (Table 1, entries 4, 6, and 7). It was worth noting that when the reactions were operated at an elevated temperature of 90 °C or a reduced temperature of 70 °C, the desired product was obtained in relatively lower yields, indicating that 80 °C was the most suitable reaction temperature (Table 1, entries 4, 8, and 9). Additionally, prolonging the reaction time to 48 h or decreasing the reaction time to 5 h diminished the yield of **2a** (Table 1, entries 10 and 11). Accordingly, the reaction condition of Table 1, entry 4 was chosen as the standard condition for further examination of substrate scope and functional group compatibility.

With the optimized reaction conditions in hand, we next evaluated the substrate scope and functional group tolerance of this oxa-Michael addition of ESF using various substituted carboxylic acids **1** as the reaction partners. As the results illustrated in Table 2, carboxylic acids functionalized with electron-withdrawing groups, such as the nitro group (**1b** and **1c**), halogen (**1d**–**1l**), the cyano group (**1m**), or electron-donating groups, such as the methoxyl group (**1n**), the methyl group (**1o**–**1r**) at *ortho*-, *meta*-, and *para*-positions of the aromatic rings tolerated this process smoothly to deliver the corresponding products **2b**–**2r** in moderate to excellent isolated yields (34–95%). Note that the aromatic carboxylic acids (**1g** and **1r**) bearing multisubstituted aromatic rings were also smoothly converted into the Michael addition products **2g** and **2r** in 63 and 60% yield, respectively. The acetal moiety in the piperic acid (**1s**) remained intact during the transformation and the targeted product **2s** was successfully isolated in 60% yield. Besides, the polycyclic molecule naphthyl (**1t**) turned out to be the suitable substrate as well under the standard conditions. In addition, the heterocyclic carboxylic acids furan (**1u**), benzofuran (**1v**), benzindole (**1w**), and benzothiophene (**1x**) can also be applied for this direct transformation with the additional 5 mol % ruthenium catalyst, which indicated the potential authentic value of this method for the synthesis of bioactive heterocycle-containing molecules. The heteroatoms (X = O, N, and S) in the heterocyclic carboxylic acids can coordinate with CuO easily to deactivate its reactivity in this transformation. In contrast, the metal complex $Ru(bpy)_3(PF_6)_2$ with a large steric hindrance can activate the carboxylic acid group more readily. Remarkably, the aliphatic carboxylic acids (**1y** and **1z**) were also compatible with this reaction system, albeit moderate yields of the anticipated products (**2y** and **2z**) were obtained. With regard to the cases of aliphatic carboxylic acids, the alkyl carboxylic acid group was relatively difficult to activate, while metal ruthenium was widely used to activate the carbon–hydrogen bonds,[21] can probably form metal complexes with benzoic acids in our reaction that served as key reaction intermediates. To demonstrate the practicality of this method, a gram-scale reaction of **1d** (1.00 g, 5 mmol) was also performed under identical conditions, affording **2d** in 76% yield (1.18 g).

Ibuprofen (**1aa**) and Aspirin (**1ab**, acetylsalicylic acid), both over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), are the most widely used analgesic–antipyretic and anti-inflammatory drugs in many countries.[22] Also, the carboxylic acid groups in these two molecules can also react with ESF smoothly to afford their corresponding aliphatic sulfonyl fluoride derivatives (Table 3, **2aa** and **2ab**) in good yields (54 and 68%, respectively).

On the basis of the previous studies,[23] a plausible reaction mechanism for the oxa-Michael addition of carboxylic acid **1** to electron-deficient alkene ESF with the promotion of CuO is postulated in Scheme 2. Initially, the treatment of carboxylic acid **1** with alkaline metal oxide CuO generated intermediate **A**, which can further coordinate with ESF to form a Cu complex **B**. The subsequent Michael addition of the thioxyl anion to ESF led to the formation of intermediate **C**, and in the presence of another molecule of carboxylic acid **1**, the intermediate **D** was successfully obtained. The regenerated copper–alkoxyl complex **A** was applied for the next catalytic cycle. Finally, the expected product **2** was achieved through isomerization of **D**. The deuterated experiment indicated that the proton of benzoic acid group ($-CO_2H$) was transferred to the α-carbon adjacent to sulfonyl fluoride group, which clearly revealed that the reactions of ESF and carboxylic acids proceeded through an oxa-Michael addition (see the Supporting Information for details).

In conclusion, we have developed a method for a direct transformation of carboxylic acids to a class of novel 2-(fluorosulfonyl)ethyl benzoate in the promotion of CuO. This protocol featured with broad substrate scope and sufficient structural diversity including the drugs Ibuprofen and Aspirin. Further studies on applications of these molecules in chemical biology and medicinal chemistry are underway in our laboratory.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an argon atmosphere unless otherwise specified. The NMR spectra were recorded in $CDCl_3$ on 500 MHz (for ^1H), 471 MHz (for ^{19}F), and 126 MHz (for ^{13}C) spectrometers. All chemical shifts were reported in ppm relative to TMS (^1H NMR, 0 ppm) as internal standards. The HPLC experiments were carried out on a Waters e2695 instrument (column: J&K, RP-C18, 5 μm, 4.6 × 150 mm^2), and the yields of the products were determined using the corresponding pure compounds as the external standards. The coupling constants were reported

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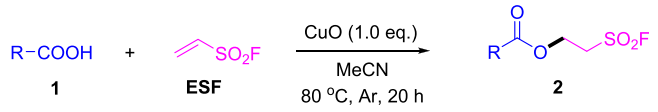
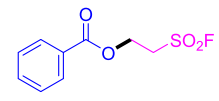
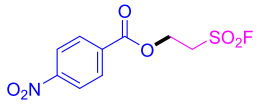
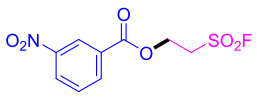
ACS Omega 2021, 6, 25972–25981

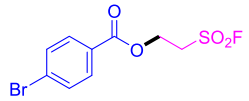
Table 2. Scope of the Addition of Carboxylic Acids to Ethenesulfonyl Fluoride (ESF)[ab]

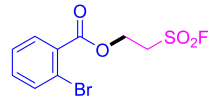


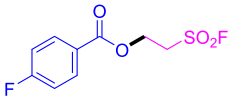

2a, 95%

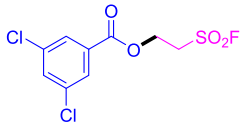

2b, 85%

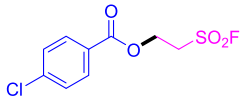

2c, 40%

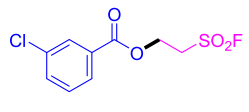

2d, 80% (76%)[c]

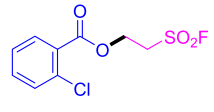

2e, 59%

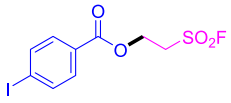

2f, 55%

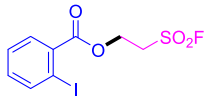

2g, 63%

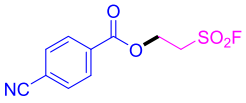

2h, 65%[d]

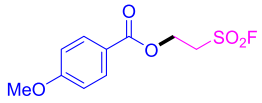

2i, 52 %

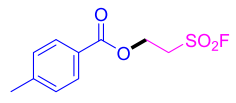

2j, 34 %

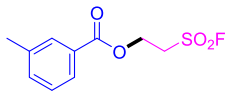

2k, 38%

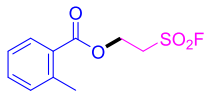

2l, 59 %

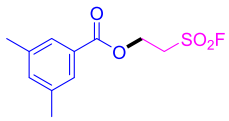

2m, 89%

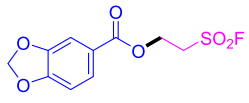

2n, 86%

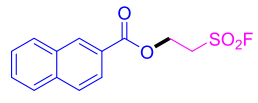

2o, 55%[d]

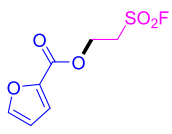

2p, 69%[d]

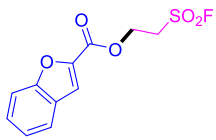

2q, 79%[d]

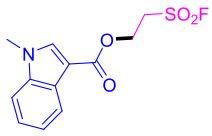

2r, 60%

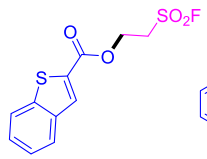

2s, 60%

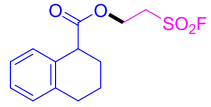

2t, 43%

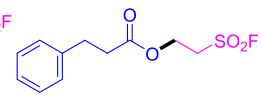

2u, 71%[d]


2v, 45%[d]


2w, 51%[d]


2x, 39%[d]


2y, 36%[d]


2z, 51%[d]

[a]Reaction condition: a mixture of carboxylic acid (**1**, 1.0 mmol), ESF (2.0 mmol), CuO (1.0 equiv), and MeCN (0.2 M, 5.0 mL) reacted at 80 °C under an argon atmosphere for 20 h. [b]Isolated yield. [c]The reaction was conducted on a 5 mmol scale (**1d**, 1.00 g). [d]Additional 5 mol % $Ru(bpy)_3(PF_6)_2$ was added.

in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Melting points were measured and uncorrected. The MS experiments were performed on a TOF-Q ESI or CI/EI instrument. Reagents used in the reactions were all purchased from commercial sources and used without further purification.

General Procedures for Synthesis of 2-(Fluorosulfonyl)ethyl benzoate with ESF and Carboxylic Acids. *Procedure A.* An oven-dried reaction tube (30 mL) was charged with (hetero) aromatic carboxylic acids or aliphatic carboxylic acids (**1**, 1.0 mmol), CuO (1.0 equiv, 80 mg), ESF (2.0 equiv, 2.0 mmol), and anhydrous acetonitrile (5 mL). The resulting mixture was stirred at 80 °C under an argon atmosphere for 18−22 h and monitored by TLC. The crude mixture was purified by column chromatography on a silica gel to give the desired product **2** and recycle the starting material **1**.

Procedure B. **2h**, **2o**−**2q**, **2u**−**2z**, and **2aa**−**2ab** were prepared according to the procedure to furnish better yields. An oven-dried reaction tube (30 mL) was charged with (hetero) aromatic carboxylic acids or aliphatic carboxylic acids (**1**, 1.0 mmol), CuO (1.0 equiv, 80 mg), $Ru(bpy)_3(PF_6)_2$ (5 mol %, 43 mg), ESF (2.0 equiv, 2.0 mmol), and anhydrous acetonitrile (5 mL). The resulting mixture was stirred at 80 °C under an argon atmosphere for 18−22 h and monitored by

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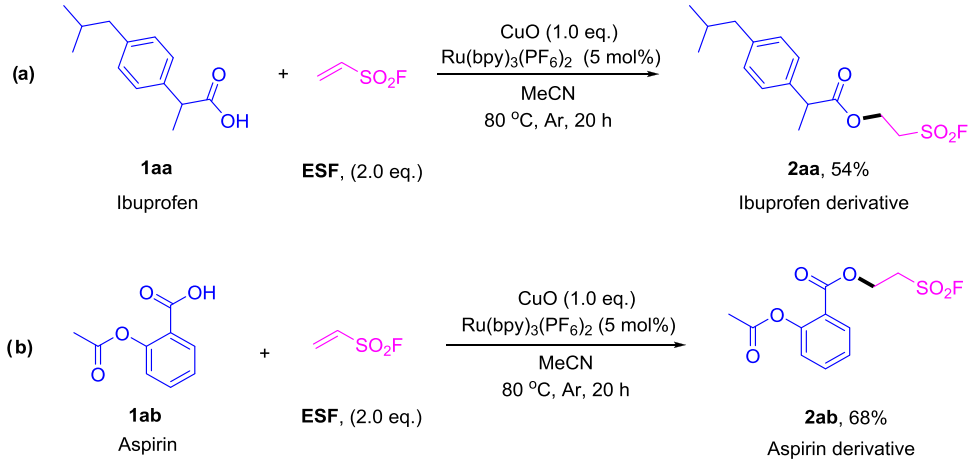
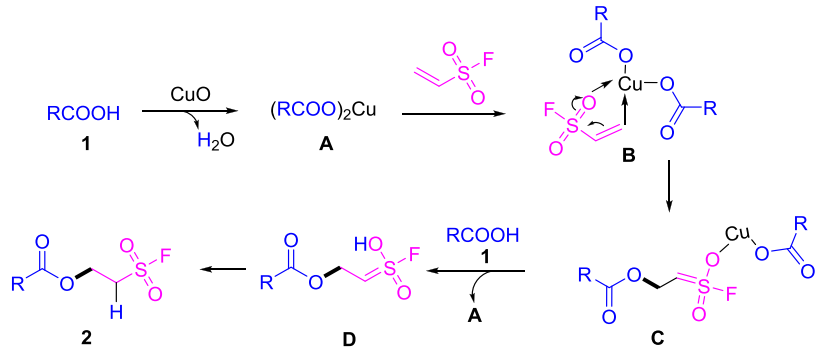
Table 3. Modifications of Ibuprofen and Aspirin



Scheme 2. Proposed Reaction Mechanism



TLC. The crude mixture was purified by column chromatography on silica gel to give the desired product **2** and recycle the starting material **1**.

*2-(Fluorosulfonyl)ethyl benzoate (**2a**).* Procedure A was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. White soild, mp 47−48 °C, 221 mg, 95% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.3 Hz, 2H), 7.62−7.59 (m, 1H), 7.48−7.45 (m, 2H), 4.81 (t, J = 5.3 Hz, 2H), 3.85 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 133.9, 130.0, 128.8, 57.5, 50.3 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_{10}FO_4S$ $[M + H]^+$: 233.0278, found 233.0276.

*2-(Fluorosulfonyl)ethyl 4-nitrobenzoate (**2b**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. White solid, mp 86−88 °C, 237 mg, 85% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32−8.31 (m, 2H), 8.24−8.22 (m, 2H), 4.87 (t, J = 5.1 Hz, 2H), 3.89 (q, J = 5.1 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.3 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1, 151.1, 134.2, 131.2, 123.9, 58.3, 50.1 (d, J = 19.0 Hz). ESI-MS HRMS calculated for $C_9H_9FNO_6S$ $[M + H]^+$: 278.0129, found 278.0129.

*2-(Fluorosulfonyl)ethyl 3-nitrobenzoate (**2c**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow solid, mp 71−72 °C, 111 mg, 40% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.45 (d, J = 8.2 Hz, 1H), 8.37 (d, J = 7.7 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 4.88 (t, J = 5.7 Hz, 2H), 3.91 (q, J = 5.2 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 148.5, 135.5, 130.6, 130.1, 128.2, 124.9, 58.2, 50.1 (d, J = 18.1 Hz). ESI-MS HRMS calculated for $C_9H_9FNO_6S$ $[M + H]^+$: 278.0129, found 278.0127.

*2-(Fluorosulfonyl)ethyl 4-bromobenzoate (**2d**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow solid, mp 82−83 °C, 248 mg, 80% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.80 (t, J = 5.3 Hz, 2H), 3.85 (q, J = 5.2 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 132.2, 131.5, 129.2, 127.8, 57.7, 50.3 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_9BrFO_4S$ $[M + H]^+$: 310.9383, found 310.9379.

*2-(Fluorosulfonyl)ethyl 2-bromobenzoate (**2e**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow oil, 185 mg, 59% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 7.1 Hz, 1H), 7.41−7.36 (m, 2H), 4.81 (t, J = 5.7 Hz, 2H), 3.87 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 134.8, 133.5, 131.9, 130.3, 127.5, 122.3, 57.9, 50.1(d, J = 17.2 Hz). ESI-MS HRMS calculated for $C_9H_9BrFO_4S$ $[M + H]^+$: 310.9383, found 310.9376.

*2-(Fluorosulfonyl)ethyl 4-fluorobenzoate (**2f**).* Procedure A was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. White solid, mp 82−83 °C, 138 mg, 55% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (q, J = 4.7 Hz, 2H), 7.14 (t, J = 8.6 Hz, 2H), 4.81 (t, J = 5.6 Hz, 2H), 3.85 (q, J = 5.2 Hz, 2H). ^{19}F NMR

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(471 MHz, $CDCl_3$) δ 59.1 (s, 1F), −104.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.4, 164.9, 132.6 (d, J = 10.0 Hz), 125.1, 116.0 (d, J = 21.8 Hz), 57.6, 50.3 (d, J = 17.3 Hz). ESI-MS HRMS calculated for $C_9H_9F_2O_4S$ $[M + H]^+$: 251.0184, found 251.0176.

*2-(Fluorosulfonyl)ethyl 3,5-dichlorobenzoate (**2g**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. White solid, mp 61−62 °C, 191 mg, 63% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 1.9 Hz, 2H), 7.59 (t, J = 2.0 Hz, 1H), 4.82 (t, J = 6.3 Hz, 2H), 3.85 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7, 135.8, 133.8, 131.7, 128.4, 58.2, 50.1 (d, J = 19.1 Hz). ESI-MS HRMS calculated for $C_9H_8Cl_2FO_4S$ $[M + H]^+$ 300.9499, found 300.9493.

*2-(Fluorosulfonyl)ethyl 4-chlorobenzoate (**2h**).* Procedure B was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow solid, mp 89−91 °C, 173 mg, 65% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 4.81 (t, J = 6.2 Hz, 2H), 3.85 (q, J = 5.2 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 140.5, 131.4, 129.2, 127.3, 57.7, 50.3 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_9ClFO_4S$ $[M + H]^+$ 266.9889, found 266.9882.

*2-(Fluorosulfonyl)ethyl 3-chlorobenzoate (**2i**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow oil, 137 mg, 52% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 4.78 (t, J = 5.7 Hz, 2H), 3.87 (q, J = 5.1 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 134.7, 133.7, 130.5, 130.0, 129.8, 127.9, 57.7, 50.0 (d, J = 17.3 Hz). ESI-MS HRMS calculated for $C_9H_9ClFO_4S$ $[M + H]^+$ 266.9889, found 266.9885.

*2-(Fluorosulfonyl)ethyl 2-chlorobenzoate (**2j**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Colorless oil, 91 mg, 34% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 1H), 7.48−7.47 (m, 2H), 7.36−7.33 (m, 1H), 4.82 (t, J = 5.8 Hz, 2H), 3.87 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 134.4, 133.5, 131.9, 131.5, 128.3, 126.9, 57.8, 50.1(d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_9ClFO_4S$ $[M + H]^+$ 266.9889, found 266.9883.

*2-(Fluorosulfonyl)ethyl 4-iodobenzoate (**2k**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. White solid, mp 76−77 °C, 134 mg, 38% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 4.80 (t, J = 5.5 Hz, 2H), 3.84 (q, J = 5.2 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1(s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 138.2, 131.3, 128.4, 102.0, 57.7, 50.3 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_9FIO_4S$ $[M + H]^+$ 358.9245, found 358.9239.

*2-(Fluorosulfonyl)ethyl 2-iodobenzoate (**2l**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Light yellow solid, mp 66−68 °C, 211 mg, 59% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.20 (td, J = 7.7 Hz, J = 1.3 Hz, 1H), 4.82 (t, J = 5.7 Hz, 2H), 3.88 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F), ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 141.9, 133.6, 133.1, 131.6, 128.3, 94.7, 58.0, 50.1(d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_9H_9FIO_4S$ $[M + H]^+$ 358.9245, found 358.9240.

*2-(Fluorosulfonyl)ethyl 4-cyanobenzoate (**2m**).* Procedure A was followed, with petroleum ether/ethyl acetate = 3:1 (v/v) as an eluent for column chromatography. White solid, mp 121−122 °C, 229 mg, 89% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 4.85 (t, J = 5.6 Hz, 2H), 3.87 (q, J = 5.1 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.3 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 132.6, 130.5, 117.9, 117.4, 58.2, 50.1 (d, J = 18.1 Hz). ESI-MS HRMS calculated for $C_{19}H_9FNO_4S$ $[M + H]^+$ 258.0231, found 258.0232.

*2-(Fluorosulfonyl)ethyl 4-methoxybenzoate (**2n**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. White solid, mp 50−51 °C, 226 mg, 86% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 4.77 (t, J = 5.2 Hz, 2H), 3.87 (s, 3H), 3.83 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 164.1, 132.1, 121.2, 114.0, 57.2, 55.6, 50.4 (d, J = 18.1 Hz). ESI-MS HRMS calculated for $C_{10}H_{12}FO_5S$ $[M + H]^+$ 263.0384, found 263.0382.

*2-(Fluorosulfonyl)ethyl 4-methylbenzoate (**2o**).* Procedure B was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. White solid, mp 58−60 °C, 135 mg, 55% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 4.78 (t, J = 5.7 Hz, 2H), 3.84 (q, J = 5.3 Hz, 2H), 2.42 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 144.8, 130.0, 129.5, 126.1, 57.3, 50.4 (d, J = 18.1 Hz), 29.8. ESI-MS HRMS calculated for $C_{10}H_{12}FO_4S$ $[M + H]^+$ 247.0435, found 247.0445.

*2-(Fluorosulfonyl)ethyl 3-methylbenzoate (**2p**).* Procedure B was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. Light yellow oil, 169 mg, 69% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.92−7.84 (m, 2H), 7.42−7.41 (m, 1H), 7.36−7.33 (m, 1H), 4.80 (t, J = 5.7 Hz, 2H), 3.85 (q, J = 5.3 Hz, 2H), 2.41(s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 138.6, 134.6, 130.4, 128.8, 128.6, 127.1, 57.4, 50.3(d, J = 17.3 Hz), 21.3. ESI-MS HRMS calculated for $C_{10}H_{12}FO_4S$ $[M + H]^+$ 247.0435, found 247.0444.

*2-(Fluorosulfonyl)ethyl 2-methylbenzoate (**2q**).* Procedure B was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. Light yellow oil, 194 mg, 79% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 1H), 7.46−7.43 (m, 1H), 7.28−7.26 (m, 2H), 4.78 (t, J = 5.8 Hz, 2H), 3.85 (q, J = 5.3 Hz, 2H), 2.62 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 141.2, 133.0, 132.0, 131.1, 127.9, 126.1, 57.2, 50.4 (d, J = 18.2 Hz), 22.4 (d, J = 116.2 Hz). ESI-MS HRMS calculated for $C_{10}H_{12}FO_4S$ $[M + H]^+$ 247.0435, found 247.0441.

*2-(Fluorosulfonyl)ethyl 3,5-dimethylbenzoate (**2r**).* Procedure A was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. White solid, mp 95−97 °C, 156 mg, 60% (isolated yield), ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.23 (s, 1H), 4.79 (t, J = 5.8 Hz, 2H), 3.84 (q, J = 5.3 Hz, 2H), 2.37 (s, 6H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 138.5, 135.6, 128.7, 127.7, 57.4, 50.3 (d, J =

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17.2 Hz), 21.3. ESI-MS HRMS calculated for $C_{11}H_{14}FO_4S$ $[M + H]^+$ 261.0591, found 264.0585.

*2-(Fluorosulfonyl)ethyl benzo[d][1,3]dioxole-5-carboxylate (**2s**).* Procedure A was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. White solid, mp 100−101 °C, 164 mg, 60% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.1 Hz, J = 1.3 Hz, 1H), 7.46 (d, J = 1.1 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.06 (s, 2H), 4.77 (t, J = 5.5 Hz, 2H), 3.83 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 152.5, 148.1, 126.1, 122.8, 109.7, 108.3, 102.1, 57.4, 50.4 (d, J = 17.3 Hz). ESI-MS HRMS calculated for $C_{10}H_{10}FO_6S$ $[M + H]^+$ 277.0177, found 277.0170.

*2-(Fluorosulfonyl)ethyl 2-naphthoate (**2t**).* Procedure A was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. Yellow solid, mp 73−75 °C, 124 mg, 43% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.06−8.04 (m, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.92−7.89 (m, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 4.88 (t, J = 5.5 Hz, 2H), 3.90 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 136.0, 132.6, 131.9, 129.6, 128.9, 128.6, 128.0, 127.1, 126.1, 125.1, 57.6, 50.4 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_{13}H_{12}FO_4S$ $[M + H]^+$: 283.0435, found 283.0439.

*2-(Fluorosulfonyl)ethyl furan-2-carboxylate (**2u**).* Procedure B was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Yellow oil, 157 mg, 71% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.27 (s, 1H), 6.56−6.55 (m, 1H), 4.79 (t, J = 5.9 Hz, 2H), 3.84 (q, J = 5.5 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 147.5, 143.4, 119.6, 112.3, 57.3, 50.2 (d, J = 18.2 Hz). ESI-MS (m/z) HRMS calculated for $C_7H_8FO_5S$: 223.0071, found 223.0071.

*2-(Fluorosulfonyl)ethyl 2,3-dihydrobenzofuran-2-carboxylate (**2v**).* Procedure B was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Yellow oil, 123 mg, 45% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.8 Hz, 1H), 7.61−7.59 (m, 2H), 7.49 (t, J = 7.9 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 4.86 (t, J = 5.8 Hz, 2H), 3.88 (q, J = 5.4 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.1 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 156.2, 144.1, 128.4, 126.8, 124.2, 123.3, 115.6, 112.6, 57.7, 50.1 (d, J = 18.1 Hz). ESI-MS (m/z) HRMS calculated for $C_{11}H_{10}FO_5S$: 273.0227, found 273.0276.

*2-(Fluorosulfonyl)ethyl 1-methyl-1H-indole-3-carboxylate (**2w**).* Procedure B was followed, with petroleum ether/ethyl acetate = 3:1 (v/v) as an eluent for column chromatography. Light yellow solid, mp 105−106 °C, 145 mg, 51% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16−8.14 (m, 1H), 7.82 (s, 1H), 7.38−7.31 (m, 3H), 4.81 (t, J = 5.6 Hz, 2H), 3.87−3.85 (m, 5H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8, 137.4, 136.1, 126.6, 123.2, 122.4, 121.5, 110.1, 105.5, 56.3, 50.7 (d, J = 17.3 Hz), 33.6. ESI-MS HRMS calculated for $C_{12}H_{13}FNO_4S$ $[M + H]^+$ 286.0544, found 286.0543.

*2-(Fluorosulfonyl)ethyl benzo[b]thiophene-2-carboxylate (**2x**).* Procedure B was followed, with petroleum ether/ethyl acetate = 3:1 (v/v) as an eluent for column chromatography. Brown oil, 113 mg, 39% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.91−7.87 (m, 2H), 7.51−7.48 (m, 1H), 7.45−7.42 (m, 1H), 4.84 (t, J = 5.8 Hz, 2H), 3.87 (q, J = 5.3 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.2 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1, 142.7, 138.7, 132.0, 131.8, 127.6, 126.0, 125.3, 122.9, 57.9, 50.2 (d, J = 18.2 Hz). ESI-MS HRMS calculated for $C_{11}H_{10}FO_4S_2$ $[M + H]^+$ 288.9999, found 288.9991.

*2-(Fluorosulfonyl)ethyl 1,2,3,4-tetrahydronaphthalene-1-carboxylate (**2y**).* Procedure B was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Yellow oil, 103 mg, 36% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19−7.13 (m, 4H), 4.58 (t, J = 5.7 Hz, 2H), 3.90 (t, J = 5.8 Hz, 1H), 3.70 (q, J = 5.3 Hz, 2H), 2.88−2.78 (m, 2H), 2.20−2.16 (m, 1H), 2.06−1.96 (m, 2H), 1.83−1.80 (m, 1H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 59.0 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 137.4, 132.4, 129.6 (d, J = 20.0 Hz), 127.3, 126.0, 57.3, 50.1 (d, J = 18.2 Hz), 44.5, 29.1, 26.4, 20.5. ESI-MS HRMS calculated for $C_{13}H_{16}FO_4S$ $[M + H]^+$ 287.0748, found 287.0770.

*2-(Fluorosulfonyl)ethyl 3-phenylpropanoate (**2z**).* Procedure B was followed, with petroleum ether/ethyl acetate = 5:1 (v/v) as an eluent for column chromatography. Yellow oil, 133 mg, 51% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.24−7.20 (m, 3H), 4.55 (t, J = 5.9 Hz, 2H), 3.65 (q, J = 5.4 Hz, 2H), 2.97 (t, J = 7.7 Hz, 2H), 2.71 (t, J = 7.8 Hz, 2H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.7 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 140.0, 128.7, 128.4, 126.6, 56.9, 50.1 (d, J = 17.2 Hz), 35.5, 30.8. ESI-MS (m/z) HRMS calculated for $C_{11}H_{14}FO_4S$: 261.0591, found 261.0607.

*2-(Fluorosulfonyl)ethyl 2-(4-isobutylphenyl)propanoate (**2aa**).* Procedure B was followed, with petroleum ether/ethyl acetate = 10:1 (v/v) as an eluent for column chromatography. Light yellow oil, 171 mg, 54% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.19 (m, 2H), 7.12−7.11 (m, 2H), 4.57−4.50 (m, 2H), 3.75 (q, J = 7.2 Hz, 1H), 3.68−3.63 (m, 2H), 2.46 (d, J = 7.2 Hz, 2H), 1.89−1.83 (m, 1H), 1.52 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 6.5 Hz, 6H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.8 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 141.1, 136.8, 129.6, 127.3, 57.2, 50.0 (d, J = 18.2 Hz), 45.0 (d, J = 22.7 Hz), 30.3, 22.5, 18.3. ESI-MS HRMS calculated for $C_{15}H_{22}FO_4S$ $[M + H]^+$ 317.1217, found 317.1223.

*2-(Fluorosulfonyl)ethyl 2-acetoxybenzoate (**2ab**).* Procedure B was followed, with petroleum ether/ethyl acetate = 3:1 (v/v) as an eluent for column chromatography. Light yellow oil, 197 mg, 68% (isolated yield), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 4.76 (t, J = 5.7 Hz, 2H), 3.82 (q, J = 5.2 Hz, 2H), 2.36 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ 58.9 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 163.6, 151.2, 134.8, 131.9, 126.3, 124.1, 121.9, 57.5, 50.2 (d, J = 17.2 Hz), 21.1. ESI-MS HRMS calculated for $C_{11}H_{12}FO_6S$ $[M + H]^+$ 291.0333, found 291.0268.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02804.

Reaction conditions screening, deuterated experiment, and characterization data of the products and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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ACS Omega 2021, 6, 25972−25981