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Unexpected Formation of Polysubstituted 1-Azabutadienes and 1,3-Dioxanes from the Reaction of 3-Fluoroalkyl-3-arylaminoacrylic Acid Esters with Formaldehyde

Fu-Lu Zhao and Jin-Tao Liu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

jtliu@mail.sioc.ac.cn

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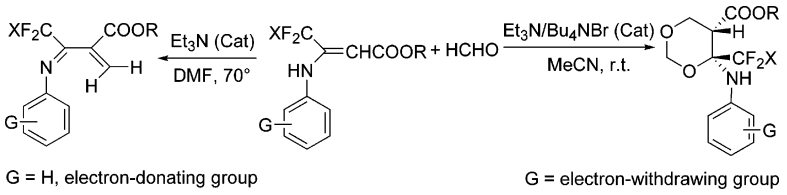

The reaction of 3-fluoroalkyl-3-arylaminoacrylic acid esters with formaldehyde was described. In the presence of a catalytic amount of triethylamine, the reaction took place readily in acetonitrile at 70 °C to give the corresponding 2-fluoroalkyl-1-azabutadienes in good yields. *cis*-Fluoroalkylated 1,3-dioxanes were obtained predominantly when the aryl ring contained an electron-withdrawing group and the reaction was carried out at room temperature under catalysis of triethylamine and tetrabutylammonium bromide. A possible mechanism was proposed.

Introduction

1,3-Dioxane is an important unit in both natural and synthetic organic compounds, and many compounds containing it showed interesting biological activities.[1−5] For example, 1,3-dioxane derivatives have been used for the treatment of dyslipidemia, atherosclerosis, and diabetes.[2] Accordingly, much attention has been paid to the synthesis of 1,3-dioxanes. The conventional method for the construction of 1,3-dioxanes is the condensation reaction of 1,3-diols with aldehydes or ketones.[3−6] Delmas et al.[7] synthesized 1,3-dioxanes by reaction of paraformaldehyde with alkenes or ketones bearing an α-methylene group. Recently, it was reported that β-butenols could also serve as precursors.[8] It is well-known that the introduction of a fluorine atom or fluoroalkyl groups in heterocyclic compounds may have a profound influence on their biological and physical properties.[9] To our knowledge, there has been only one report on fluorinated 1,3-dioxanes.[10] On the other hand, 1-azabutadienes are important synthetic intermediates and have been widely used in hetero-Diels−Alder (HAD) reactions.[11] Therefore, it is of great significance to develop synthetic methodologies for fluorine-containing 1,3-dioxanes and 1-azabutadienes. Herein we report a novel synthesis of fluoroalkylated 1,3-dioxanes and 1-azabutadienes by reaction of 3-fluoroalkyl-3-arylaminoacrylic acid esters with formaldehyde.

* Address correspondence to this author. Fax: 86-21-64166128.

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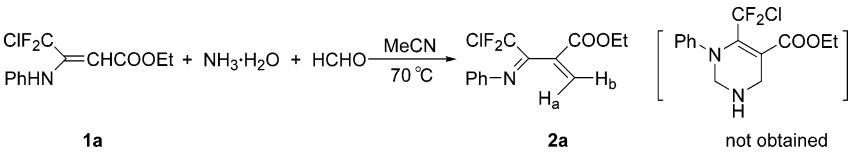
SCHEME 1



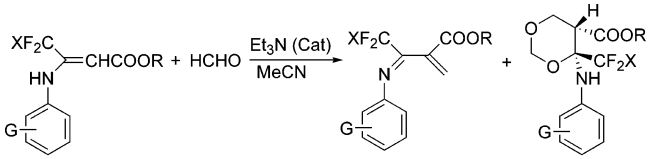
Results and Discussion

3-Fluoroalkyl-3-arylaminoacrylic acid esters (**1**), readily prepared from commercially available fluoroalkyl iodides, have been used as precursors in the synthesis of fluoroalkylated quinolin-4-ol[12] and indoles.[13] Recently, it was found in our laboratory that **1** reacted with a variety of primary aliphatic amines and formaldehyde in acetonitrile to give 6-fluoroalkyl-1,2,3,4-tetrahydropyrimidines in almost quantitative yields.[14] To examine the scope of that reaction, aqueous ammonia was employed as a primary amine to react with ethyl 3-chlorodifluoromethyl-3-phenylaminoacrylate (**1a**) and formaldehyde to prepare the corresponding chlorodifluoromethylated 1,2,3,4-tetrahydropyrimidines. It was surprising to find that a new compound was formed as a major product, instead of the desired chlorodifluoromethylated 1,2,3,4-tetrahydropyrimidine (Scheme 1). Elemental and spectral analysis showed that this compound was *N*-phenyl-2-chlorodifluoromethyl-3-ethoxycarbonyl-1-azabuta-diene (**2a**): in its ^{1}H NMR spectrum there were two singlet peaks for the two olefinic protons at 6.62 and 5.96 ppm, respectively, ^{1}H−^{13}C cosy spectra showed that the two protons were attached to the same carbon, and ^{1}H−^{1}H cosy spectra revealed no coupling between them. The DEPT 135° spectrum indicated that there were two CH_2 groups in **2a**.

The structure of **2a** indicates that the ammonia was not incorporated in the final product. Was compound **2a** formed directly from **1a** and formaldehyde? To obtain more mechanistic information about the reaction, **1a** was allowed to react with formalin in the absence of ammonia under similar conditions for 20 h, but no reaction occurred, suggesting that ammonia might serve as a catalyst in this reaction. Further investigations showed that other bases such as Et_3N, DABCO, Na_2CO_3, and quinine also catalyzed the reaction, and the former two gave the best results.

With Et_3N as catalyst, the reactions of various 3-fluoroalkyl 3-arylaminoacrylic acid esters with formaldehyde were examined. As shown in Table 1, the results were greatly influenced by the electronic nature of substituents on the aromatic ring in compound **1**. Esters containing electron-donating groups, such as methoxy and methyl, gave the corresponding azabutadiene as a major product (entries 2−6). In contrast a byproduct was obtained in addition to **2** when the aryl ring contained an electron-withdrawing group (entries 7−10). The structures of the byproduct were determined to be *cis*-4-fluoroalkyl-4-arylamino-5-ethoxycarbonyl-1,3-dioxanes (**3**) by spectral analysis and X-ray crystallography (Figure 1).

TABLE 1. The Reaction of 1 and Formaldehyde



entry[a]	**1** (X/R/G)	**2**/yield (%)[b]	**3**/yield (%)[b]
1	**1a** (Cl/Et/H)	**2a**/84	
2	**1b** (Cl/Me/H)	**2b**/74	
3	**1c** (CF_2CF_2Cl/Me/H)	**2c**/80	
4	**1d** (CF_2CF_3/Me/H)	**2d**/89	
5	**1e** (Cl/Me/4-MeO)	**2e**/78	
6	**1f** (Cl/Me/4-Me)	**2f**/73	
7	**1g** (Cl/Me/4-Cl)	**2g**/56	**3g**/17
8	**1h** (Cl/Me/4-Br)	**2h**/33	**3h**/27
9	**1i** (Cl/Me/3-COMe)	**2i**/45	**3i**/20
10	**1j** (Cl/Me/4-COOEt)	**2j**/4	**3j**/57

[a] Reaction conditions: **1** (0.5 mmol), 37% HCHO (4 mmol), and Et_3N (2.5 mg) in MeCN (5 mL), stirred at 70 °C for 1 h. [b] Isolated yields.

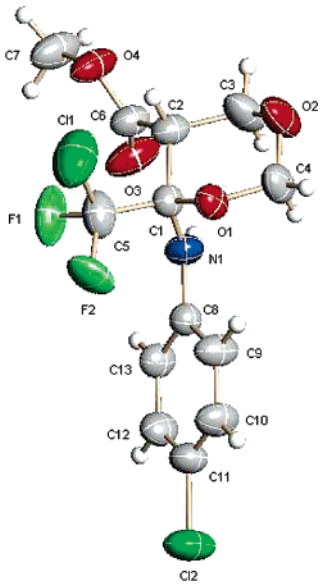


FIGURE 1. The X-ray crystallographic structure of **3g**.

Is there a possibility of preparing **3** as the major product? To make the reaction more useful and improve its selectivity, the scope of the reaction under various conditions was investigated. Solvents were first screened and it was found that the reaction proceeded smoothly in aprotic polar solvents such as DMF and DMSO, but favoring the formation of **2**. For example, reactions of **1g**, **1h**, and **1i** with formaldehyde in DMF under similar conditions gave **2g**, **2h**, and **2i** predominantly along with only a trace of compound **3** (Table 2). With ethereal solvents, such as THF and 1,4-dioxane, the reaction was very sluggish and complicated in alcohol. Then, the

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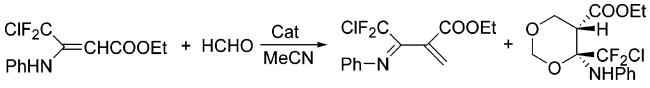
TABLE 2. The Reaction of 1 and Formaldehyde in DMF

Entry	1	2/yield (in MeCN)[a]	3/yield (in MeCN)[a]
1	**1g**	**2g**/75% (56%)	**3g**/trace (17%)
2	**1h**	**2h**/72% (33%)	**3h**/trace (27%)
3	**1i**	**2i**/72% (45%)	**3i**/trace (20%)
4	**1j**	**2j**/10% (4%)	**3j**/52 (57%)

[a] Isolated yields based on **1**.

TABLE 3. The Reaction of 1a and Formaldehyde under Different Conditions



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

entry	1a (mol/L)	37% HCHO (mol/L)	catalyst	time (h)	*T* (°C)	product distribution[a]
1	0.1	0.4	Et_3N	1	70	**2a**
2	0.2	0.8	Et_3N	1	70	**2a** (trace **3a**)
3	0.2	1.6	Et_3N	1	70	**2a**:**3a** = 4:1
4	0.4	3.2	Et_3N	1	70	**2a**:**3a** = 3:1
5	1.0	16.0	Et_3N	1	70	**2a**:**3a** = 3:1
6	1.0	16.0	Et_3N	1	rt	**2a**:**3a** = 3:1
7	1.0	16.0	Et_3N/Bu_4NBr	1	70	**2a**:**3a** = 1:0.7
8	1.0	16.0	Et_3N/Bu_4NBr	1	rt	**2a**:**3a** = 1:1

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

TABLE 4. Preparation of 3 from the Reaction of 1 with Formaldehyde

entry[a]	1 (X/R/G)	2/yield (%)[b]	3/yield (%)[b]
1	**1a** (Cl/Et/H)	**2a**/42	**3a**/45
2	**1g** (Cl/Me/4-Cl)	**2g**/16	**3g**/48
3	**1h** (Cl/Me/4-Br)	**2h**/7	**3h**/53
4	**1i** (Cl/Me/3-COMe)	**2i**/16	**3i**/50
5	**1j** (Cl/Me/4-COOEt)		**3j**/68
6	**1k** (F/Et/4-Cl)	trace	**3k**/63
7	**1*l*** (F/Et/4-Br)	trace	**3*l***/59
8	**1m** (F/Et/3-COMe)		**3m**/56
9	**1n** (F/Et/4-COOEt)		**3n**/64

[a] Reaction conditions: **1** (0.3 mmol), 37% HCHO (4.8 mmol, 0.38 mL), Et_3N (1.5 mg), and Bu_4NBr (0.03 mmol, 10 mg) in CH_3CN (0.3 mL), stirred at rt for 1 h. [b] Isolated yields.

reaction in acetonitrile under various conditions was examined (Table 3). The concentration of the reactants had a distinct influence. The addition of a catalytic amount of tetrabutylammonium bromide and running the reaction at low temperature were also favorable for the formation of **3**. Thus, with Et_3N/Bu_4NBr, **1a** reacted with excess formaldehyde in acetonitrile at room temperature for 1 h to give **2a** and **3a** in a mole ratio of 1:1 (entry 8).

By using optimized conditions, several fluoroalkylated 1,3-dioxanes were prepared as summarized in Table 4. As mentioned earlier, the reaction was strongly influenced by the substituents on the aromatic ring of **1**. Electron-deficient esters gave **3** as main products. Interestingly, only 1,3-dioxanes were obtained in the cases where CF_3 replaced CF_2Cl (entries 6−9). With esters **1c**−**f**, only **2c**−**f** were formed when reactions were carried out under similar conditions. Unfortunately, efforts to extend the scope of this reaction to non-fluorine-containing analogues, such as ethyl *β*-anilinocrotonate and 4-anilinopent-3-en-2-one, failed.

From the above results, a plausible mechanism is proposed as shown in Scheme 2. In the presence of triethylamine, nucleophilic attack of the α-carbon in compound **1** to formaldehyde gives anion **A**. Then there might be two competing routes. In route I, nucleophilic attack of **A** to another formaldehyde followed by trapping a proton from solution gives intermediate **B**. Intramolecular addition of the hydroxyl group in **B** to the carbon−nitrogen double bond via favored transition state **C** results in the formation of 1,3-dioxane **3** in the cis conformation. The transition state **C′** is disfavored due to the repulsion between the lone electron pairs of nitrogen and oxygen atoms. Therefore, no trans isomer of 1,3-dioxane is formed. In route II, **A** traps a proton from solution, followed by dehydration to give **2**. Electron-withdrawing groups are favorable for the stabilization of anion **A** and force the reaction to proceed via route I to form compound **3**. Tetrabutylammonium bromide is supposed to serve as a phase-transfer catalyst to make the reaction of **A** and formaldehyde in route I easier.

Conclusions

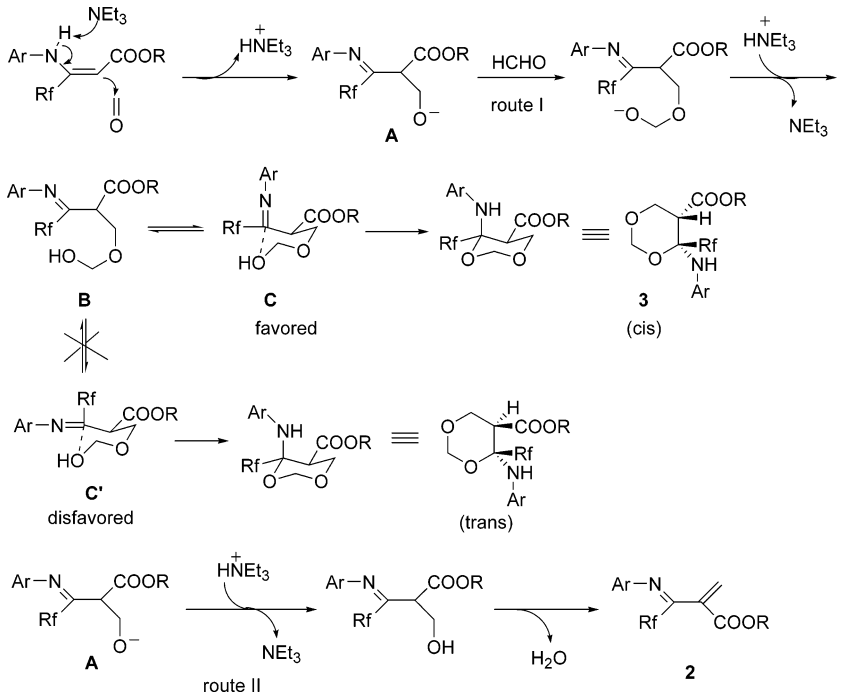
In summary, the reaction of 3-fluoroalkyl-3-arylaminoacrylic acid esters with formaldehyde was investigated and a novel method for the preparation of fluoroalkylated azabutadienes and 1,3-dioxanes was developed. The electronic nature of substituents on the aromatic ring in the starting material plays an important role in the reaction and electron-withdrawing substituents favored for the formation of 1,3-dioxanes. Further study on this reaction and the properties of these fluorine-containing compounds is in progress.

Experimental Section

Typical Procedure for the Preparation of 2. A mixture of **1** (0.5 mmol), 37% HCHO (4 mmol, 0.32 mL), and Et_3N (2.5 mg) in CH_3CN (5 mL) was stirred at 70 °C for 1 h (monitored by TLC or ^{19}F NMR). After completion of the reaction, ethyl ether (50 mL) was added to the reaction mixture and then washed three times with saturated NaCl solution and dried over anhydrous sodium sulfate. After the solvent was removed by rotary evaporation, the residue was chromatographed on silica gel eluting with petroleum/ethyl acetate to give **2** as yellow liquids.

2a: IR ν_{max} 3065, 2985, 1732, 1672, 1595, 1485, 1216, 1184, 1144, 1038, 932, 747, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2 H), 7.14 (m, 1 H), 6.86 (m, 2 H), 6.62 (s, 1 H), 5.96 (s, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 1.19 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.79 (s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 156.7 (t, $^2J_{C,F}$ = 28.9 Hz), 146.9, 133.7, 132.8, 128.7, 125.7, 123.0 (t, $^1J_{C,F}$ = 292.8 Hz, CF_2Cl), 119.6, 61.6, 13.7; EI-MS *m/z* (%) 287 (M^+, 8), 202 (75), 77 (100). Anal. Calcd for $C_{13}H_{12}ClF_2NO_2$: C, 54.27; H, 4.20; N, 4.87. Found: C, 54.29; H, 4.37; N, 4.98. **2b**: IR ν_{max} 3068, 2955, 1736, 1672, 1622, 1595, 1485, 1439, 1403, 1329, 1239, 1218, 1145, 1034, 921, 747, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2 H), 7.11 (m, 1 H), 6.82 (m, 2 H), 6.58 (s, 1 H), 5.96 (s, 1 H), 3.60 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.72 (s); EI-MS *m/z* (%) 273 (M^+, 9), 188 (100), 77 (95). Anal. Calcd for $C_{12}H_{10}ClF_2NO_2$: C, 52.67; H, 3.68; N, 5.12. Found: C, 52.60; H, 3.76; N, 5.31. **2c**: IR ν_{max} 3066, 2957, 1740, 1670, 1624, 1595, 1486, 1439, 1400, 1330, 1282, 1217, 1186, 1121, 1072, 978, 842, 745, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2 H), 7.07 (m, 1 H), 6.73 (m, 2 H), 6.48 (s, 1 H), 5.73 (s, 1 H), 3.60 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.16 (2 F), −111.73 (2 F), −119.22 (2 F); EI-MS *m/z* (%) 373 (M^+, 6), 188 (100), 77 (83).

SCHEME 2



Anal. Calcd for $C_{14}H_{10}ClF_6NO_2$: C, 45.00; H, 2.70; N, 3.75. Found: C, 45.37; H, 2.88; N, 3.75. **2d**: IR ν_{max} 3036, 2958, 1741, 1668, 1624, 1595, 1486, 1439, 1402, 1348, 1232, 1119, 1021, 918, 751, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 7.05 (m, 1 H), 6.72 (m, 2 H), 6.48 (s, 1 H), 5.74 (s, 1 H), 3.58 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.50 (3 F), −113.33 (2 F), −125.44 (2 F); EI-MS *m/z* (%) 357 (M^+, 6), 188 (52), 77 (100). Anal. Calcd for $C_{14}H_{10}F_7NO_2$: C, 47.07; H, 2.82; N, 3.92. Found: C, 47.21; H, 2.86; N, 4.13. **2e**: IR ν_{max} 3004, 2955, 2839, 1735, 1663, 1603, 1505, 1465, 1441, 1401, 1326, 1298, 1248, 1141, 1032, 918, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (m, 4 H), 6.65 (s, 1 H), 6.03 (s, 1 H), 3.77 (s, 3 H), 3.61 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.15 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 158.2, 154.7, 139.7, 134.0, 133.1, 123.3 (t, $^1J_{C,F}$ = 292.4 Hz, CF_2Cl), 122.3, 114.1, 55.3, 52.5; EI-MS *m/z* (%) 303 (M^+, 23), 218 (100). Anal. Calcd for $C_{13}H_{12}ClF_2NO_3$: C, 51.41; H, 3.98; N, 4.61. Found: C, 51.37; H, 3.95; N, 4.88. **2f**: IR ν_{max} 3030, 2955, 2869, 1736, 1670, 1620, 1576, 1504, 1439, 1402, 1327, 1239, 1219, 1143, 1033, 919, 828 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 8.4 Hz, 2 H), 6.67 (d, J = 8.4 Hz, 2 H), 6.52 (s, 1 H), 5.89 (s, 1 H), 3.54 (s, 3 H), 2.21 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.50 (s). EI-MS *m/z* (%) 287 (M^+, 22), 202 (100). Anal. Calcd for $C_{13}H_{12}ClF_2NO_2$: C, 54.27; H, 4.20; N, 4.87. Found: C, 54.60; H, 4.28; N, 5.16. **2g**: IR ν_{max} 2955, 1737, 1673, 1621, 1485, 1439, 1402, 1328, 1302, 1239, 1218, 1146, 1092, 1034, 920, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 2 H), 6.78 (d, J = 8.4 Hz, 2 H), 6.63 (s, 1 H), 5.98 (s, 1 H), 3.65 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.98 (s); EI-MS *m/z* (%) 309 (15), 307 (M^+, 17), 222 (100). Anal. Calcd for $C_{12}H_9Cl_2F_2NO_2$: C, 46.78; H, 2.94; N, 4.55. Found: C, 46.84; H, 3.00; N, 4.54. **2h**: IR ν_{max} 3001, 2955, 1737, 1674, 1621, 1482, 1439, 1398, 1328, 1301, 1216, 1146, 1071, 1034, 920, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2 H), 6.64 (d, J = 8.7 Hz, 2 H), 6.54 (s, 1 H), 5.90 (s, 1 H), 3.58 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.01 (s); EI-MS *m/z* (%) 353 (34), 351 (M^+, 27), 268 (94), 266 (100), 186 (54). Anal. Calcd for $C_{12}H_9BrClF_2NO_2$: C, 40.88; H, 2.57; N, 3.97. Found: C, 41.10; H, 2.61, N, 4.21. **2i**: IR ν_{max} 3005, 2956, 1736, 1688, 1620, 1580, 1479, 1435, 1359, 1270, 1145, 1035, 926, 856, 803, 770, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 1 H), 7.37 (m, 2 H), 6.98 (m, 1 H), 6.57 (s, 1 H), 5.96 (s, 1 H), 3.61 (s, 3 H), 2.51 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.41 (s); EI-MS *m/z* (%) 315 (M^+, 8), 230 (69), 43 (100). Anal. Calcd for $C_{14}H_{12}ClF_2NO_3$: C, 53.26; H, 3.83; N, 4.44. Found: C, 53.11; H, 3.98; N, 4.41. **2j**: IR ν_{max} 2984, 2957, 1717, 1678, 1603, 1501, 1440, 1368, 1277, 1171, 1101, 1035, 920, 874, 787 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2 H), 6.84 (d, J = 8.4 Hz, 2 H), 6.59 (s, 1 H), 5.96 (s, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 3.66 (s, 3 H), 1.37 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.23 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 162.8, 157.7 (t, $^2J_{C,F}$ = 29.6 Hz), 151.0, 134.5, 132.1, 130.5, 127.7, 122.7 (t, $^1J_{C,F}$ = 327.0 Hz, CF_2Cl), 118.9, 61.0, 52.6, 14.3; EI-MS *m/z* (%) 345 (M^+, 12), 260 (100); MALDI-HRMS calcd for $C_{15}H_{15}ClF_2NO_4$ [$(M + H)^+$] 346.0642, found 346.0652.

Typical Procedure for the Preparation of 3. A mixture of **1** (0.3 mmol), 37% HCHO (4.8 mmol, 0.38 mL), Et_3N (1.5 mg), and Bu_4NBr (0.03 mmol, 10 mg) in CH_3CN (0.3 mL) was stirred at room temperature for 1−2 h (monitored by TLC or ^{19}F NMR). After completion of the reaction, ethyl ether (50 mL) was added to the reaction mixture and then washed three times with saturated NaCl solution and dried over anhydrous sodium sulfate. After the solvent was removed by rotary evaporation, the residue was chromatographed on silica gel eluting with petroleum/ethyl acetate to give **3**.

3a: colorless liquid; IR ν_{max} 3363, 2889, 1718, 1604, 1537, 1500, 1377, 1305, 1203, 1164, 1120, 755, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 2 H), 6.98 (m, 2 H), 6.85 (m, 1 H), 6.18 (s, 1 H), 5.13 (d, J = 6.0 Hz, 1 H), 5.02 (d, J = 6.0 Hz, 1 H), 4.22 (m, 2 H), 4.09 (d, J = 8.1 Hz, 2 H), 3.51 (t, J = 8.1 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.22 (q_{AB}, J = 170.3 Hz); EI-MS *m/z* (%) 335 (M^+, 14), 250 (54), 106 (100), 55 (47). Anal. Calcd for $C_{14}H_{16}ClF_2NO_4$: C, 50.08; H, 4.80; N, 4.17. Found: C, 50.35; H, 4.84; N, 4.14. **3g**: Mp 112−113 °C; IR ν_{max} 3356, 3031, 2959, 2882, 1719, 1592, 1520, 1491, 1439, 1209, 1158, 1122, 1025, 998, 979, 952, 931, 826, 772, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.21 (s, br, 1 H), 5.09 (d, J = 6.0 Hz, 1 H), 5.03 (d, J = 6.0 Hz, 1 H), 4.11 (m, 2 H), 3.79 (s, 3 H), 3.54 (dd, J = 6.0 Hz, 9.6 Hz, 1 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.31 (q_{AB}, J = 169.5 Hz); EI-MS *m/z* (%) 357 (20), 355 (M^+, 31), 272 (33), 270 (100), 140 (99). Anal. Calcd for $C_{13}H_{13}Cl_2F_2NO_4$: C, 43.84; H, 3.68; N, 3.93. Found: C, 43.88; H, 3.65; N, 3.87. **3h**: mp 99−100 °C; IR ν_{max} 3354, 3029, 2958, 2881, 1720, 1588, 1520, 1488, 1438, 1325, 1208, 1158, 1129, 1116, 952, 931, 888, 824, 772 cm^{-1}; ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.28 (d, J = 9.0 Hz, 2 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.24 (s, br, 1 H), 5.07 (d, J = 6.3 Hz, 1 H), 5.03 (d, J = 6.3 Hz, 1 H), 4.11 (m, 2 H), 3.78 (s, 3 H), 3.54 (dd, J = 6.0 Hz, 9.9 Hz, 1 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.34 (q_{AB}, J = 170.0 Hz); EI-MS *m/z* (%) 399 (M^+, 10), 316 (41), 314 (43), 186 (58), 184 (61), 55 (100), 45 (66). Anal. Calcd for $C_{13}H_{13}BrClF_2NO_4$: C, 38.98; H, 3.27; N, 3.50. Found: C, 39.09; H, 3.35; N, 3.47. **3i**: mp 71−72 °C; IR ν_{max} 3364, 3011, 2957, 2885, 1723, 1687, 1604, 1592, 1538, 1486, 1439, 1358, 1209, 1162, 1122, 959, 878, 773, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.42 (m, 1 H), 7.22 (m, 2 H), 6.33 (br, s, 1 H), 5.05 (m, 2 H), 4.08 (m, 2 H), 3.76 (s, 3 H), 3.53 (m, 1 H), 2.54 (s, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.88 (q_{AB}, J = 168.9 Hz); EI-MS *m/z* (%) 363 (M^+, 8), 278 (43), 148 (100), 55 (70), 43 (70). Anal. Calcd for $C_{15}H_{16}ClF_2NO_5$: C, 49.53; H, 4.43; N, 3.85. Found: C, 49.74; H, 4.48; N, 3.80. **3j**: mp 84−85 °C; IR ν_{max} 3358, 2982, 2958, 2885, 1713, 1608, 1525, 1440, 1369, 1321, 1280, 1262, 1209, 1178, 1120, 1059, 1018, 960, 934, 852, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 2 H), 7.00 (d, J = 8.4 Hz, 2 H), 6.57 (s, br, 1 H), 5.03 (d, J = 6.0 Hz, 1 H), 4.98 (d, J = 6.0 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 4.09 (m, 2 H), 3.78 (s, 3 H), 3.54 (dd, J = 5.4 Hz, 10.8 Hz, 1 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.88 (q_{AB}, J = 170.4 Hz); EI-MS *m/z* (%) 393 (M^+, 9), 308 (62), 178 (100), 55 (48), 45 (37). Anal. Calcd for $C_{16}H_{18}ClF_2NO_6$: C, 48.80; H, 4.61; N, 3.56. Found: C, 48.86; H, 4.62; N, 3.41. **3k**: mp 124−126 °C; IR ν_{max} 3342, 2987, 2881, 1722, 1593, 1523, 1493, 1475, 1381, 1316, 1203, 1170, 1121, 1019, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 6.11 (s, 1 H), 5.09 (d, J = 6.0 Hz, 1 H), 4.98 (d, J = 6.0 Hz, 1 H), 4.23 (m, 2 H), 4.10 (d, J = 8.1 Hz, 2 H), 3.38 (t, J = 8.1 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.86 (s); EI-MS *m/z* (%) 355 (31), 353 (M^+, 90), 286 (32), 284 (96), 140 (90), 184 (72), 55 (100). Anal. Calcd for $C_{14}H_{15}ClF_3NO_4$: C, 47.54; H, 4.27; N, 3.96. Found: C, 47.82; H, 4.47; N, 3.84. ***3l***: mp 122−124 °C; IR ν_{max} 3342, 2986, 2880, 1722, 1589, 1522, 1490, 1380, 1315, 1203, 1182, 1171, 1121, 1025, 1018, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.13 (s, 1 H), 5.08 (d, J = 6.0 Hz, 1 H), 4.98 (d, J = 6.0 Hz, 1 H), 4.24 (m, 2 H), 4.10 (d, J = 8.1 Hz, 2 H), 3.37 (t, J = 8.1 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.90 (s); EI-MS *m/z* (%) 399 (36), 397 (M^+, 38), 330 (49), 328 (51), 186 (66), 184 (72), 55 (100). Anal. Calcd for $C_{14}H_{15}BrF_3NO_4$: C, 42.33; H, 3.80; N, 3.52. Found: C, 42.48; H, 4.04; N, 3.43. **3m**: colorless liquid; IR ν_{max} 3367, 2987, 2885, 1720, 1687, 1605, 1593, 1534, 1487, 1438, 1379, 1359, 1322, 1201, 1170, 1124, 1029, 997, 786 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.43 (m, 1 H), 7.29−7.22 (m, 2 H), 6.26 (s, 1 H), 5.08 (d, J = 6.0 Hz, 1 H), 4.99 (d, J = 6.0 Hz, 1 H), 4.31−4.15 (m, 2 H), 4.11 (d, J = 8.1 Hz, 2 H), 3.38 (t, J = 8.1 Hz, 1 H), 2.55 (s, 3 H), 1.30 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.90 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 170.4, 143.0, 138.0, 129.2, 123.3 (q, $^1J_{C,F}$ = 288.9 Hz, CF_3), 121.1, 120.4, 116.3, 86.9, 85.0 (q, $^2J_{C,F}$ = 32.0 Hz), 64.4, 62.3, 43.2, 26.6, 13.84; EI-MS *m/z* (%) 361 (M^+, 34), 292 (49), 148 (100); MALDI-HRMS calcd for $C_{16}H_{18}F_3NO_5Na$ [$(M + Na)^+$] 384.1029, found 384.1038. **3n**: colorless liquid; IR ν_{max} 3360, 2985, 2885, 1714, 1610, 1591, 1526, 1379, 1322, 1281, 1256, 1201, 1179, 1122, 1108, 1028, 853, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2 H), 7.01 (d, J = 8.7 Hz, 2 H), 6.50 (s, 1 H), 5.00 (s, 2 H), 4.37−4.09 (m, 6 H), 3.39 (dd, J = 9.9, 6.0 Hz, 1 H), 1.36 (t, J = 7.2 Hz, 3 H), 1.31 (t, J = 7.2 Hz, 3 H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.31 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.4, 146.9, 130.9, 123.3 (q, $^1J_{C,F}$ = 288.5 Hz, CF_3), 122.1, 115.7, 87.0, 84.8 (q, $^2J_{C,F}$ = 32.3 Hz), 64.4, 62.4, 60.4, 43.1, 14.4, 13.8; EI-MS *m/z* (%) 391 (M^+, 32), 346 (20), 322 (55), 178 (100); MALDI-HRMS calcd for $C_{17}H_{20}F_3NO_6Na$ [$(M + Na)^+$] 414.1135, found 414.1151.

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Supporting Information Available: DEPT and COSY spectra of **2a**; crystallographic information file for **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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