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Journal of Fluorine Chemistry 111 (2001) 213–216

JOURNAL OF FLUORINE CHEMISTRY

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Synthesis of 2-[(*Z*)-1-hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones

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Received 29 March 2001; accepted 29 June 2001

Abstract

N,N′-dicyclohexylcarbodiimide induced condensation of 2,2-dihydropolyfluoroalkanoic acid and anthranilic acid or its derivatives followed by a dehydrating ring-closure reaction in the presence of Ac_2O gave 2-[(*Z*)-1-hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones in good to excellent yields.

Keywords: 2-[(*Z*)-1-Hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-one; 2,2-Dihydropolyfluoroalkanoic acid; Synthesis

1. Introduction

4H-3,1-Benzoxazin-4-ones have been known for more than a century [1] and show interesting pharmacological properties. For example, they are potent inactivators of chymotrypsin [2] as well as inhibitors of HSV-1 protease [3]. Since the phenyl derivative was first synthesized in 1883 [4], numerous 2-substituted-4H-3,1-benzoxazin-4-ones have been prepared. However, substituents at the C-2 position are usually the common alkyl, alkenyl or aryl groups. The synthesis of 2-polyfluoroalkyl or alkenyl substituted 4H-3,1-benzoxazin-4-ones has been comparatively less studied [5]. It is known that fluorine has profound and special effects on the biological activity of organic compounds [6], so it is our interest to develop efficient methods to synthesize fluorine-containing 4H-3,1-benzoxazin-4-ones and their derivatives. In this paper, we report a convenient synthesis of 2-[(*Z*)-1-hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones from 2,2-dihydropolyfluoroalkanoic acid.

2. Results and discussion

2,2-Dihydropolyfluoroalkanoic acids are versatile fluorine-containing building blocks developed in our laboratory. They are easily prepared from polyfluoroalkyl iodides as shown in Scheme 1 [7].

In the presence of *N,N′*-dicyclohexylcarbodiimide (DCC), 2,2-dihydropolyfluoroalkanoic acids condensed with anthranilic acid or its derivatives in CH_2Cl_2 at room temperature or under reflux to give the corresponding amides (**3**, major) as well as cyclic products (**4**, minor). The results are summarized in Table 1. Subsequently, treatment of the mixture with Ac_2O afforded 2-[(*Z*)-1-hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones in good to excellent yields (Scheme 2, Table 1).

Dicyclohexylurea formed in the reaction from DCC has very low solubility in CH_2Cl_2 and can be removed conveniently from the reaction mixture by filtration. This simplified the procedure for the separation of the desired product and raised the overall yield consequently.

The configuration of the carbon–carbon double bond in compound **4** was assigned to be the *Z*-form from the coupling constant between the olefinic hydrogen and fluorine atom ($J_{H-F} = 29.4$ Hz). No E-isomer was isolated in this reaction. The yields of **4** with short polyhaloalkyl tails were comparatively less than those of **4** with longer tails. The major by-product **5fh** was isolated and characterized to have the structure shown in Scheme 3, and was assumed to be formed by the reaction of **4** with acetic acid. Interestingly, this kind of by-product was not detected when R_F is C_5F_{11}, C_3F_6Cl or C_3F_7.

Boutevin et al. reported the synthesis of **4ag** in 1992 [5], but their method involved the use of $C_5F_{11}CH_2COCl$, which is difficult to handle, and the yield was low (43%). The above reactions provide a convenient and useful route to 2-[(*Z*)-polyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones with high yield and stereoselectivity, mild reaction conditions as well as easy availability of the starting material.

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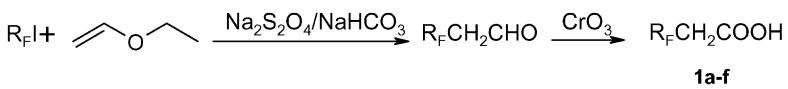
PII: S0022-1139(01)00456-0



R_F = **a**, C_5F_{11}; **b**, C_3F_6Cl; **c**, C_3F_7; **d**, CF_2Cl; **e**, CF_2Br; **f**, CF_3.

Scheme 1.

Table 1
Condensation of 2,2-dihydropolyfluoroalkanoic acids with anthranilic acids

Entry	1	2	Temperature	Time (h)	Product	
					4	Yields (%)[a]
1	**1a**	**2g**	RT	8.0	**4ag**	90.5
2	**1b**	**2g**	RT	7.0	**4bg**	92.0
3	**1c**	**2g**	RT	7.5	**4cg**	90.0
4	**1d**	**2g**	RT	7.0	**4dg**	75.0
5	**1e**	**2g**	RT	7.0	**4eg**	75.0
6	**1f**	**2g**	RT	7.0	**4fg**	75.0
7	**1a**	**2h**	RT	3.5	**4ah**	95.0
8	**1b**	**2h**	RT	3.0	**4bh**	93.5
9	**1c**	**2h**	RT	3.0	**4ch**	95.0
10	**1d**	**2h**	RT	3.0	**4dh**	78.5
11	**1e**	**2h**	RT	3.0	**4eh**	78.0
12	**1f**	**2h**	RT	3.0	**4fh**	78.0
13	**1a**	**2i**	Reflux	5.0	**4ai**	90.0
14	**1b**	**2i**	Reflux	5.0	**4bi**	88.5
15	**1c**	**2i**	Reflux	5.0	**4ci**	88.0
16	**1d**	**2i**	Reflux	4.0	**4di**	68.0
17	**1e**	**2i**	Reflux	4.0	**4ei**	65.0
18	**1a**	**2j**	Reflux	6.5	**4aj**	75.0
19	**1b**	**2j**	Reflux	6.5	**4bj**	76.0
20	**1c**	**2j**	Reflux	6.0	**4cj**	78.0

[a] Isolated yield of two steps.

3. Experimental

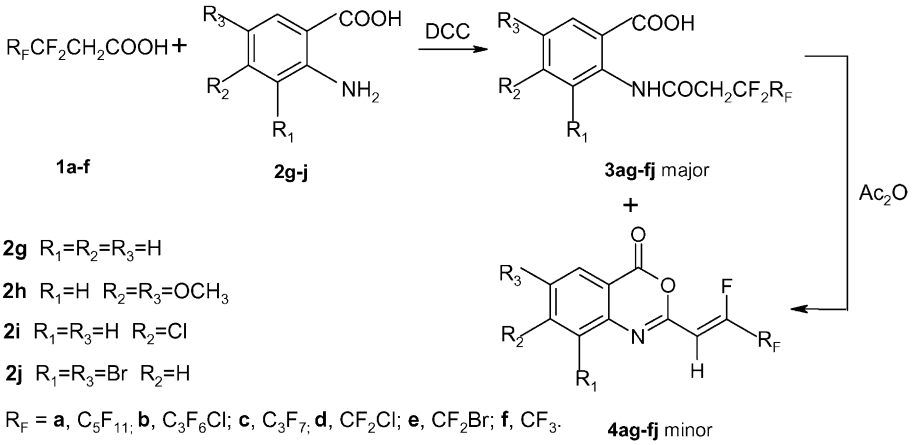
Melting points were uncorrected. IR spectra were taken on a Perkin-Elmer 983G IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer at 56.4 MHz using TFA as external standard. In ^{19}F NMR spectra, chemical shifts (in ppm) are regarded as positive for upfield shifts and the values are reported as δ_{CFCl_3} ($\delta_{CFCl_3} = \delta_{TFA} + 76.8$). Mass spectra were obtained on a Finnigan GC-MS 4021 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

3.1. Synthesis of 2-[(Z)-hydropolyfluoro-1-alkenyl]-4H-3,1-benzoxazin-4-ones

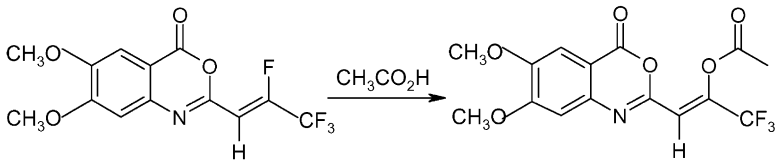
Typical procedure: A mixture of **1** (1.0 mmol) and DCC (1.1 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for a few minutes. A white suspension was formed. Then a solution of **2** (1.0 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the above suspension with stirring at room temperature. After addition, the resulting mixture was stirred at room temperature or under reflux till the reaction was complete (monitored by TLC). The reaction mixture was filtered with suction to give a clear yellow solution. After removal of the solvent, the pale yellow solid was dissolved in 10 ml Ac_2O and the mixture was stirred under reflux for 1.5–2.0 h. Excess Ac_2O was evaporated under vacuum and the oily residue thus obtained was subjected to column chromatography using light petroleum and EtOAc (20:1) as eluant to give compound **4** as white solids.

3.1.1. Compound *4ag*

Mp 103–104.5°C. ^{1}H NMR ($CDCl_3$) δ: 7.57–8.24 (4H, m, ArH), 6.31 (1H, d, J = 29.4 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.8 (3F, t, CF_3), 106.1 (1F, m, =CF), 114.5–122.5 (8F, m, $4CF_2$) ppm; IR ν_{max} (cm^{-1}): 1764 (C=O), 1230



Scheme 2.



4fh 5fh

Scheme 3.

(C–F), 1141 (C–O); MS *m/z* (%): 459 (M^+, 100.0), 146 (26.2); Anaysis: Found: C, 39.43; H, 1.43; N, 2.88%. $C_{15}H_5F_{12}NO_2$ requires: C, 39.24; H, 1.10; N, 3.05%.

3.1.2. Compound **4bg**

Mp 105–107°C. ^{1}H NMR ($CDCl_3$) δ: 7.55–8.22 (4H, m, ArH), 6.30 (1H, d, $J = 29.4$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, t, $ClCF_2$), 105.5 (1F, m, =CF), 116.6 (2F, m, CF_2), 120.1 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1765 (C=O), 1200 (C–F); MS *m/z* (%): 377 (34.3), 375 (M^+, 100.0), 146 (55.5); HRMS Found: 374.99088; $C_{13}H_5ClF_7NO_2$ requires: 374.98970.

3.1.3. Compound **4cg**

Mp 105–106°C. ^{1}H NMR ($CDCl_3$) δ: 7.57–8.24 (4H, m, ArH), 6.31 (1H, d, $J = 29.4$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.8 (3F, t, CF_3), 106.5 (1F, m, =CF), 118.6 (2F, m, CF_2), 126.3 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1776 (C=O), 1226 (C–F), 1124 (C–O); MS *m/z* (%): 359 (M^+, 100.0); 146 (29.9); Analysis: Found: C, 43.45; H, 1.45; N, 4.04%; $C_{13}H_5F_8NO_2$ requires: C, 43.47; H, 1.40; N, 3.90%.

3.1.4. Compound **4dg**

Mp 98–99°C. ^{1}H NMR ($CDCl_3$): δ: 7.56–8.24 (4H, m, ArH), 6.24 (1H, d, $J = 28.7$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$): δ: 60.1 (2F, d, $ClCF_2$), 106.8 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 1766 (C=O), 1275 (C–F), 1161 (C–O); MS *m/z* (%): 277 (37.1), 275 (M^+, 100.0), 146 (53.4); HRMS Found: 274.99969; $C_{11}H_5ClF_3NO_2$ requires: 274.99609.

3.1.5. Compound **4eg**

Mp 99–101°C. ^{1}H NMR ($CDCl_3$) δ: 7.56–8.23 (4H, m, ArH), 6.19 (1H, d, $J = 28.4$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 57.4 (2F, d, CF_2Br), 106.1 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 1766 (C=O), 1240 (C–F), 1152 (C–O); MS *m/z* (%): 321 (26.4), 319 (M^+, 26.8), 240 (100.0), 146 (17.0); Analysis: Found: C, 41.68; H, 1.72; N, 4.36; $C_{11}H_5BrF_3NO_2$ requires: C, 41.28; H, 1.57; N, 4.38%.

3.1.6. Compound **4fg**

Mp 97.0–98.5°C. ^{1}H NMR ($CDCl_3$) δ: 7.56–8.23 (4H, m, ArH), 6.27 (1H, d, $J_{HF} = 29.2$ Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 71.08 (3F, s. CF_3), 111.5 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 1758 (C=O), 1601 (C=N), 1258, 1211 (C–F), 1129 (C–O); MS *m/z* (%): 259 (M^+, 100.0), 240 (M^+–F, 5.9), 190 (M^+–CF_3, 36.4), 146 (M^+–CF_3CF=CH, 59.4); Analysis: Found: C, 50.83; H, 2.06; N, 5.17%; $C_{11}H_5NF_4O_2$ requires: C, 50.98; H, 1.94; N, 5.40%.

3.1.7. Compound **4ah**

Mp 138.5–140°C. ^{1}H NMR ($CDCl_3$) δ: 7.53 (1H, s, ArH), 7.04 (1H, s, ArH), 6.27 (1H, d, $J = 29.4$ Hz, =CH), 4.02 (3H, s, OCH_3), 4.00 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.3 (3F, t, CF_3), 107.1 (1F, m, =CF), 117.0 (2F, m, CF_2), 121.5 (4F, m, $2CF_2$), 124.8 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1751 (C=O), 1246 (C–F), 1132 (C–O); MS *m/z* (%): 519(M^+, 100.0); HRMS Found: 519.03446; $C_{17}H_9F_{12}NO_4$ requires: 519.03400.

3.1.8. Compound **4bh**

Mp 136–138°C. ^{1}H NMR ($CDCl_3$) δ: 7.53 (1H, s, ArH), 7.04 (1H, s, ArH), 6.26 (1H, d, $J = 29.5$ Hz, =CH), 4.01 (3H, s, OCH_3), 3.99 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.9 (2F, t, $ClCF_2$), 107.1 (1F, m, =CF), 116.8 (2F, m, CF_2), 120.1 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1753 (C=O), 1291 (C–F), 1175 (C–O); MS *m/z* (%): 437 (37.3), 435 (M^+, 100.0); HRMS Found: 435.01488; $C_{15}H_9ClF_7NO_4$ requires: 435.01083.

3.1.9. Compound **4ch**

Mp 133.5–135°C. ^{1}H NMR ($CDCl_3$) δ: 7.53 (1H, s, ArH), 7.04 (1H, s, ArH), 6.26 (1H, d, $J = 29.5$ Hz, =CH), 4.01 (3H, s, OCH_3), 4.00 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.3 (3F, t, CF_3), 107.3 (1F, m, =CF), 117.8 (2F, m, CF_2), 125.8 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1758 (C=O), 1248 (C–F), 1114 (C–O); MS *m/z* (%): 419(M^+, 100.0); Analysis: Found: C, 43.17; H, 2.55; N, 3.36%; $C_{15}H_9F_8NO_4$ requires: C, 42.97; H, 2.16; N, 3.34%.

3.1.10. Compound **4dh**

Mp 125–127°C. ^{1}H NMR ($CDCl_3$) δ: 7.51 (1H, s, ArH), 7.03 (1H, s, ArH), 6.19 (1H, d, $J = 28.9$ Hz, =CH), 4.01 (3H, s, OCH_3), 3.99 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 60.0 (2F, d, $ClCF_2$), 108.1 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}):1736 (C=O), 1274 (C–F), 1140 (C–F); MS *m/z* (%): 337 (34.1), 335 (M^+, 100.0), 300 (18.1), 250 (22.0); HRMS Found: 335.01842; $C_{13}H_9ClF_3NO_4$ requires: 335.01722.

3.1.11. Compound **4eh**

Mp 132–133°C. ^{1}H NMR ($CDCl_3$) δ: 7.50 (1H, s, ArH), 7.03 (1H, s, ArH), 6.19 (1H, d, $J = 28.8$ Hz, =CH), 4.01 (3H, s, OCH_3), 3.99 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 58.1 (2F, d, $BrCF_2$), 109.3 (1F, m, =CF) ppm; IR ν_{max}

(cm^{-1}): 1736 (C=O), 1272 (C–F), 1136 (C–O); MS *m/z* (%): 381 (44.3), 379 (M^+, 45.3), 300 (100.0); HRMS Found: 378.96643; $C_{13}H_9BrF_3NO_4$ requires: 378.96671.

3.1.12. Compound ***4fh***

Mp 127–128°C. ^{1}H NMR ($CDCl_3$) δ: 7.52 (1H, s, ArH), 7.03 (1H, s, ArH), 6.23 (1H, d, J = 29.3 Hz, =CH), 4.02 (3H, s, OCH_3), 4.00 (3H, s, OCH_3) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.8 (3F, s, CF_3), 113.2 (1F, m, =CF) ppm; IR ν_{max}(cm^{-1}): 1753 (C=O), 1604 (C=O), 1291, 1229 (C–F), 1131 (C–O); MS *m/z* (%): 319 (M^+, 100.0); 304(M^+–CH_3, 20.9); HRMS Found: 304.02159; $C_{13}H_9F_4NO_4$ requires: 304.02329.

3.1.13. Compound ***4ai***

Mp 120–121°C. ^{1}H NMR ($CDCl_3$) δ: 7.45–8.17 (3H, m, ArH), 6.26 (1H, d, J = 29.1 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 80.7 (3F, s, CF_3), 105.2 (1F, m, =CF), 118.1 (2F, m, CF_2), 122.4 (4F, m, $2CF_2$), 125.9 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1760 (C=O), 1253 (C–F), 1140 (C–O); MS *m/z* (%): 495 (34.2), 493 (M^+, 100.0), 180 (30.2); HRMS Found: 473.97743; $C_{15}H_4ClF_{12}NO_2$ requires: 473.97549.

3.1.14. Compound ***4bi***

Mp 121–123°C. ^{1}H NMR ($CDCl_3$) δ: 7.53 (3H, m, ArH), 6.42 (1H, d, J = 29.3 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, t, $ClCF_2$), 104.5 (1F, m, =CF), 116.8 (2F, m, CF_2), 120.3 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1754 (C=O), 1229 (C–F), 1145 (C–O); MS *m/z* (%): 409 (M^+, 5.5), 399 (80.4), 354 (100.0); HRMS Found: 408.94974, $C_{13}H_4Cl_2F_7NO_4$ requires: 408.95073.

3.1.15. Compound ***4ci***

Mp 119–120°C. ^{1}H NMR ($CDCl_3$) δ: 7.53–8.17 (3H, m, ArH), 6.30 (1H, d, J = 29.1 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 80.3 (3F, t, CF_3), 105.5 (1F, m, =CF), 119.0 (2F, m, CF_2), 126.5 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1770 (C=O), 1237 (C–F), 1126 (C–O); MS *m/z* (%): 395 (34.6), 393 (M^+, 100.0), 180 (34.7); HRMS Found: 373.98350; $C_{13}H_4ClF_8NO_2$ requires: 373.98188.

3.1.16. Compound ***4di***

Mp 118–119°C. ^{1}H NMR ($CDCl_3$) δ: 7.52–8.16 (3H, m, ArH), 6.22 (1H, d, J = 29.2 Hz, =CH) ppm. ^{19}F NMR ($CDCl_3$) δ: 60.3 (2F, d, CF_2Cl), 105.5 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}): 1755 (C=O), 1284 (C–F), 1147 (C–O); MS *m/z* (%): 313 (11.3), 311 (66.0), 309 (M^+, 100.0), 180 (45.6); HRMS Found: 308.95349; $C_{11}H_4Cl_2F_3NO_2$ requires: 308.94986.

3.1.17. Compound ***4ei***

Mp 118–119°C. ^{1}H NMR ($CDCl_3$) δ: 7.51–8.15 (3H, m, ArH), 6.22 (1H, d, J = 28.5 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 56.8 (2F, d, $ClCF_2$), 104.5 (1F, m, =CF) ppm; IR ν_{max} (cm^{-1}):1754 (C=O), 1214 (C–F), 1145 (C–O); MS *m/z* (%):357 (8.7), 355 (36.3), 353 (M^+, 41.3), 274 (100.0); Analysis: Found: C, 37.48; H, 1.42; N, 3.98%; $C_{11}H_4BrClF_3NO_2$ requires: C, 37.27; H, 1.14; N, 3.95%.

3.1.18. Compound ***4aj***

Mp 105–107°C. ^{1}H NMR ($CDCl_3$) δ: 8.33 (2H, dd, J = 2.1 Hz, ArH), 6.45 (1H, d, J = 28.9 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 80.3 (3F, t, CF_3), 103.8 (1F, m, =CF), 118.0 (2F, m, CF_2), 122.1 (4F, m, $2CF_2$), 125.6 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}):1770 (C=O), 1238 (C–F), 1138 (C–O); MS *m/z* (%): 619 (50.0), 617 (100.0), 615 (M^+, 53.2), 538 (9.7); HRMS Found: 614.83322; $C_{15}H_3Br_2F_{12}NO_2$ requires: 614.83388.

3.1.19. Compound ***4bj***

Mp 97–98°C. ^{1}H NMR ($CDCl_3$) δ: 8.40 (2H, dd, J = 2.1 Hz, ArH), 6.43 (1H, d, J = 28.9 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, t, $ClCF_2$), 103.0 (1F, m, =CF), 116.8 (2F, m, CF_2), 120.3 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1771 (C=O), 1297 (C–F), 1130 (C–O); MS *m/z* (%): 537 (3.3), 535 (19.7), 533 (54.2), 531 (M^+, 100.0); HRMS Found: 530.80947; $C_{13}H_3Br_2ClF_7NO_2$ requires: 530.81072.

3.1.20. Compound ***4cj***

Mp 101–102°C. ^{1}H NMR ($CDCl_3$) δ: 8.38 (2H, dd, J = 2.1 Hz, ArH), 6.50 (1H, d, J = 28.9 Hz, =CH) ppm; ^{19}F NMR ($CDCl_3$) δ: 79.5 (3F, t, CF_3),102.8 (1F, m, =CF), 118.3 (2F, m, CF_2), 126.0 (2F, m, CF_2) ppm; IR ν_{max} (cm^{-1}): 1772 (C=O), 1235 (C–F),1126 (C–O); MS *m/z* (%): 519 (9.4), 517 (19.3), 515 (M^+, 10.5), 241 (100.0); HRMS Found: 514.84026; $C_{13}H_3Br_2F_8NO_2$ requires: 514.84027.

3.1.21. Compound ***5fh***

Mp 135–137°C. ^{1}H NMR ($CDCl_3$) δ: 7.48 (1H, s, ArH), 6.97 (1H, s, ArH), 6.61 (1H, s, =CH), 3.99 (6H, s, $2OCH_3$), 2.47 (3H, s, $COCH_3$) ppm; ^{19}F NMR ($CDCl_3$) δ: 72.2 (3F, s, CF_3) ppm; IR ν_{max} (cm^{-1}): 1784, 1742 (C=O), 1596 (C=N), 1201 (C–F), 1149 (C–O); MS *m/z* (%): 359 (M^+, 2.6), 316 (M^+–CH_3CO, 100.0); Analysis: Found: C, 50.39; H, 3.89; N, 3.85%; $C_{15}H_{12}F_3NO_6$ requires: C, 50.15; H, 4.21; N, 3.90%.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 29772041 and 29902008) and Shanghai Municipal Scientific Committee (No. 00QA14030) for financial support.

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