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Synthesis, reactivity and applications of 1-fluoroalkyl carboxylates: novel synthetic substrates for esterases and lipases

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Abstract—A series of 1-fluoroalkyl carboxylate derivatives was synthesised by reacting a carboxylic acid and a ketone or aldehyde with (diethylamino)sulfur trifluoride (DAST). The reactivity of these compounds towards the nucleophiles benzylamine and water was investigated. The hydrolysis of the 1-fluoroalkyl carboxylates by an esterase was observed, along with the concomitant release of the fluoride ion, demonstrating the potential for a new esterase assay platform. Other applications may include a detectable in situ inhibitor synthesis protocol.

1. Introduction

1-Fluoroalkyl carboxylate derivatives are a class of esters for which there is only a modest amount of literature information, both with regard to their synthesis and their stability/reactivity characteristics. An interesting attribute of these 1-fluoroalkyl carboxylates is that upon hydrolysis of the ester, they release a fluoride ion. The liberation of this easily detectable leaving group could then be utilised in a number of chemical and biological applications. We have investigated a one step synthesis of a variety of 1-fluoroalkyl carboxylate derivatives using the fluorinating agent (diethylamino)sulfur trifluoride (DAST), their reactivity towards nucleophiles and their application as novel substrates for carboxylic acid esterases and lipases.

Our initial interest in 1-fluoroalkyl carboxylates stemmed from the thought that the release of the fluoride ion resulting from the reaction with a nucleophile could be an effective way to monitor the progress of a coupling reaction between two partners of suitable reactivity (Fig. 1). In addition to altering nucleophiles, the coupling reaction may be tunable by varying the nature of the 'leaving group' moiety of the 1-fluoroalkyl carboxylate. It is envisioned that with a suitable nucleophile and 1-fluoroalkyl carboxylate, the coupling reaction would not occur unless the two components were brought together in close proximity, such as in the active site of an enzyme. Thus, one might imagine an easily detectable in situ inhibitor synthesis for a particular target using a library of nucleophiles and 1-fluoroalkyl carboxylates. Other groups have shown that potent ligands to particular targets can be self-assembled in situ from weakly binding fragments,[1–4] allowing for the screening of smaller, fragment libraries rather than larger, more complicated screening libraries. However, many of these techniques employ reversible chemical reactions, and the detection of these coupling events is not necessarily trivial, often involving laborious HPLC and mass spectroscopy techniques.

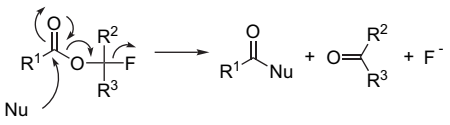

Figure 1. Reaction of a 1-fluoroalkyl carboxylate with a nucleophile (Nu).

A wide assortment of techniques exist to measure the fluoride ion including a fluoride ion-selective electrode as well as a number of chemical 'sensor' compounds that selectively bind the fluoride ion to produce a change in fluorescence or colour. The initial leaving group formed from the reaction of a 1-fluoroalkyl carboxylate with a nucleophile is the highly unstable α-fluoro alkoxide, which immediately decomposes to produce a ketone or aldehyde and the fluoride ion.[5] The release of the fluoride ion from a similar system has been observed with the hydrolysis of 5-fluoro glycosides by glycosidases.[6] As the glycosidic linkage is hydrolysed in this reaction, a reactive fluorohydrin is generated at carbon 5 of the sugar (open-chain form), which rapidly eliminates the fluoride ion. The decomposition of 1-fluoroalkyl carboxylates has been observed[7,8] and utilised, for example, in the conversion of enol acetates to ketones[9] or α-fluoroketones.[10]

Keywords: Fluoroalkyl carboxylate; Enzyme catalysis; Esterase; Assay; DAST.
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Another application of 1-fluoroalkyl carboxylates lies in a novel assay platform for carboxylic acid esterase or lipase activity. Using a 1-fluoroalkyl carboxylate as a synthetic substrate, the progress of the enzyme reaction could be monitored through the release of the fluoride ion. We have found that the 1-fluoroalkyl carboxylates are easily synthesised in one step from the acid precursors, and the properties of the 'leaving group' moiety can be tailored for a specific esterase with respect to size, hydrophobicity and functional groups. We have shown that the 1-fluoroalkyl carboxylates described in this paper are hydrolysed by an esterase, resulting in the release of the fluoride ion (vide infra).

2. Results and discussion

2.1. Synthesis

There are several ways to synthesise 1-fluoroalkyl carboxylates, however, many are specific to the particular type of product (e.g., difluoromethyl esters), require more than one synthetic step, or produce the 1-fluoroalkyl carboxylate as a minor by-product.[5,9,11–16] The synthesis of the 1-fluoroalkyl carboxylates reported herein was accomplished using the fluorinating agent (diethylamino)sulfur trifluoride (DAST), based on a paper which reported the synthesis of compound **9**.[17] The 1-fluoroalkyl carboxylates were synthesised in moderate to good yields by reacting the appropriate acid and ketone or aldehyde with DAST, using dichloromethane (DCM) to solubilise the starting materials if necessary (Fig. 2). The presence of fluorine in the products was confirmed by characteristic couplings in both the ^{1}H and ^{13}C NMR spectra, in addition to ^{19}F NMR spectra.

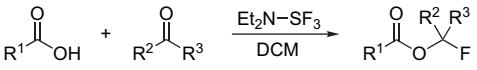


Figure 2. General scheme for the synthesis of 1-fluoroalkyl carboxylates.

The precise reaction mechanism for the formation of the 1-fluoroalkyl carboxylates remains to be elucidated. Contrary to one report,[17] no reaction was observed between benzoyl fluoride and acetone (with or without DAST), or between 1,1-difluorocyclohexane and benzoic acid. Thus one may postulate that the intermediate formed from the initial attack of the carboxylic acid with DAST reacts with the ketone or aldehyde, or perhaps with the α-fluoro alcohol generated from the reaction of the ketone or aldehyde with trace amounts of HF in the reaction mixture (Fig. 3).

We determined that the reaction to give compound **8** was very insensitive to changes in reaction conditions. The use of dry DCM (distilled over CaH_2) or 'wet' DCM from a reagent bottle made no difference to the isolated yield. Reacting DAST and water in DCM to produce HF prior to adding cyclopentanone, benzoic acid and additional DAST had very little effect on the yield. Reaction times of 20 min and 24 h showed no difference to the yield or purity of the product, nor did reactions conducted at 0 °C, or with a slow addition of DAST (over 1 h), or with a large excess of DAST (8 equiv).

Not all desired 1-fluoroalkyl carboxylates could be synthesised, and some were too unstable to be isolated. Reactions with 1,1-dichloroacetone or hexachloroacetone and benzoic acid did not produce any desired products. The 1-fluoroalkyl carboxylate formed from the reaction of acetaldehyde and benzoic acid was isolated, but was unstable; its ^{1}H NMR spectrum showed evidence of decomposition into benzoic acid and acetaldehyde after a short period of time. Similarly, the reaction product formed from butyric acid and acetone was isolated, but decomposed upon standing overnight at room temperature. Reactions with benzoic acid and either 2-cyclopenten-1-one, 2-cyclohexen-1-one, *trans*-4-phenyl-3-buten-2-one, or 2-furaldehyde appeared to produce the desired 1-fluoroalkyl carboxylate products by TLC, however, no product was isolated from purification attempts of the crude reaction mixtures by either silica gel or neutral alumina column chromatography.

2.2. Reactivity

The progress of the reactions between a series of 1-fluoroalkyl carboxylates and either benzylamine or water was monitored by quantifying the amount of product formed over time by the HPLC analysis of reaction mixtures. The presence of the fluoride ion in the reaction mixtures was confirmed by using the compound 1-[9,10-dioxo-1-(3-phenyl-thioureido)-9,10-dihydro-anthracen-2-yl]-3-phenyl-thiourea,[18] a selective fluoride ion sensor; an increase in absorbance at 561 nm characteristic of its complexation with the fluoride ion was observed. In addition, the ketone or aldehyde reaction products were often observed in the HPLC analysis of the reaction mixtures. The amide products *N*-benzylpropionamide and *N*-benzylphenylacetamide from the reaction of benzylamine with compounds **1** and **4**, respectively, were isolated and purified by silica gel chromatography for production of the HPLC standard curves; the ^{1}H NMR spectra agreed with published data.[19]

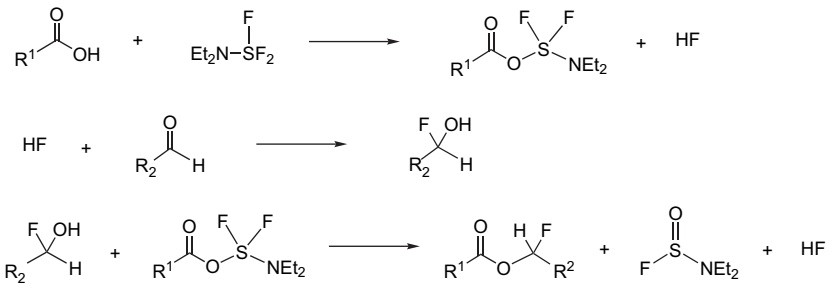


Figure 3. Possible reaction mechanism for the formation of 1-fluoroalkyl carboxylates.

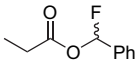
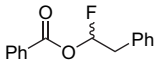
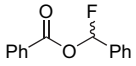
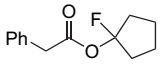
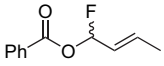
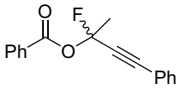
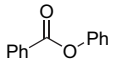
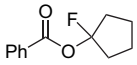
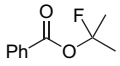
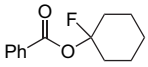
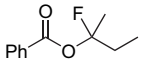
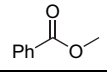
The initial rates for the reactions of various 1-fluoroalkyl carboxylates with benzylamine or water to form the corresponding amides or carboxylic acids are presented in Table 1. As reference points, the reactions with phenyl benzoate (**7**) and methyl benzoate (**12**) were also monitored; note that no reaction was observed with methyl benzoate under the conditions employed. The alkyl 1-fluoroalkyl carboxylates (**1** and **4**) were more susceptible towards nucleophilic attack than were their aryl counterparts (**3** and **8**) presumably due to the more bulky and conjugated aryl carbonyl group hindering nucleophilic attack. A good comparison can be made between the alkyl compound **4** and the aryl compound **8** having the same fluorocyclopentyl moiety; in the reaction with benzylamine, compound **4** reacted 25-fold faster than compound **8**.

All reactions were significantly faster with benzylamine compared with water. As a consequence, 20 equiv of water were used compared with 3 equiv of benzylamine in order to ensure a reaction rate fast enough to be reasonably monitored. Unfortunately, the reactions of the most unreactive compounds (**8**–**12**) with water were still too slow to be measured accurately. An overall reactivity range of 300-fold was observed for the reaction of benzylamine with the 1-fluoroalkyl carboxylates used in this study. This reactivity range could conceivably be expanded upon by further experimentation with other candidate molecules (different nucleophiles and fluoroalkyl 'leaving groups'), allowing for the fine tuning of the coupling reaction to suit a particular application.

2.3. Hydrolysis by esterase

The release of the fluoride ion when hydrolysed may allow the 1-fluoroalkyl carboxylates to be used as a novel assay platform for a variety of esterases and lipases. The background hydrolysis rate with water is sufficiently slow as not to compete and interfere with the enzymatic hydrolysis. A selection of the 1-fluoroalkyl carboxylates (**4**, **8**, **9** and **11**)

Table 1. Initial reaction rates

Compound		Benzylamine nucleophile		Water nucleophile	
		Initial rate[a] ($\times10^{-2}$ mM/min)	Relative Rate[c]	Initial rate[b] ($\times10^{-3}$ mM/min)	Relative rate[c]
1		18.4	39.0	3.0	9.9
2		6.8	14.4	1.5	5.0
3		6.0	12.7	1.8	5.9
4		3.6	7.7	n.d.[d]	
5		3.1	6.5	0.99	3.3
6		2.0	4.3	0.38	1.3
7		0.47	1.0	0.30	1.0
8		0.14	0.29	N/A[e]	
9		0.08	0.17	N/A[e]	
10		0.07	0.15	N/A[e]	
11		0.06	0.13	N/A[e]	
12		No product detected		No product detected	

[a] [Compound] was 97 mM in CH_3CN, 3 equiv of benzylamine, 50 °C.
[b] [Compound] was 94 mM in CH_3CN, 20 equiv of water, 2 equiv Et_3N, 50 °C.
[c] Relative to phenyl benzoate (**7**) as 1.0.
[d] Not determined.
[e] Reaction was too slow to be measured accurately.

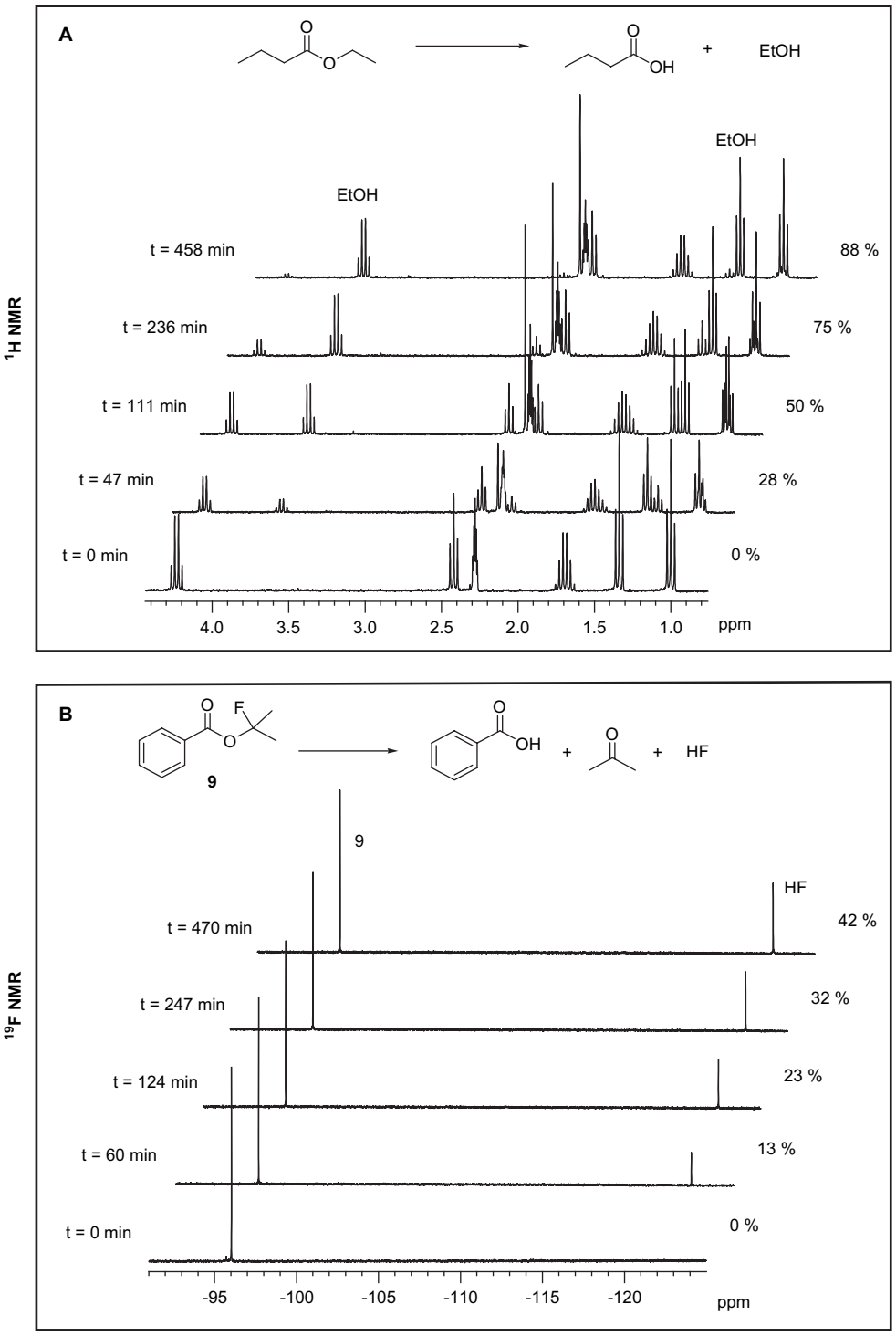


Figure 4. NMR spectra showing the hydrolysis of ethyl butyrate (A, ^{1}H NMR) and compound **9** (B, ^{19}F NMR) by an esterase from porcine liver. Reaction time is given on the left and % conversion on the right. Reaction conditions: [substrate]=7.4 mM; buffer=7.6 mM sodium phosphate in D_2O, pD=8.0, 24% acetone; 2 units of enzyme, room temperature. ^{19}F spectra are ^{1}H-decoupled.

were found to be degraded by an esterase from porcine liver (EC 3.1.1.1, Sigma E-3019). The remaining compounds were not tested. The hydrolysis catalysed by the esterase resulted in the release of the fluoride ion as evidenced by its characteristic ^{19}F NMR peak at −122.4 ppm; tetrabutylammonium fluoride gives a signal at −122.4 ppm (relative to CCl_3F). No measurable hydrolysis occurred in the absence of enzyme over a 24 h period. The poor aqueous solubility of the 1-fluoroalkyl carboxylates prevented complete characterisation of all of the esterase-catalysed hydrolysis reactions; however, ^{1}H and ^{19}F NMR experiments performed on 'cloudy' mixtures in D_2O buffer containing up to 30% deuterated acetone confirmed the activity of this esterase on all of the 1-fluoroalkyl carboxylates investigated. It is conceivable that water soluble 1-fluoroalkyl carboxylates could be synthesised to be used in an assay platform.

Compound **9** was soluble in reasonable amounts in aqueous solutions containing about 24% acetone, and its rate of hydrolysis by the porcine liver esterase was compared to that of ethyl butyrate, a standard commonly used to quantify the enzyme activity. Under the conditions used the turnover of compound **9** by the esterase was approximately half as fast as for ethyl butyrate. Figure 4 shows the NMR spectra for the hydrolysis of ethyl butyrate (^{1}H) and compound **9** (^{19}F) by the esterase over time. Enzyme and substrate specificity was demonstrated by the fact that no fluoride ion release was observed after 24 h using an esterase from *Mucor miehei* with compound **9** under the same conditions used for the porcine liver esterase, while ethyl butyrate was readily hydrolysed by the same enzyme.

3. Conclusion

The reaction of DAST with carboxylic acids and ketones or aldehydes provides a fast, one step method to produce a range of 1-fluoroalkyl carboxylates. The reactivity of the 1-fluoroalkyl carboxylates towards nucleophiles can be adjusted by the choice of fluoroalkyl 'leaving group', and the release of the fluoride ion provides a way to monitor the reaction. 1-Fluoroalkyl carboxylates may find application as easily prepared synthetic substrates for the assay of carboxylic acid esterase or lipase activity, and as alternative screening fragments to those used currently in click chemistry and dynamic combinatorial chemistry.

4. Experimental

4.1. HPLC analysis of reactions

Aliquots of the reaction mixtures were diluted with CH_3CN (2–20-fold), which were then injected (5 μL) into the HPLC. The column used was a Phenomenex Luna 3u C18(2) 100A, 50×3.00 mm, 3 μm particle size. A linear gradient over 6 min from 20% CH_3CN in water to 100% CH_3CN was used. All solvents also contained 0.1% formic acid. The area under the corresponding product peak was measured and the concentration of product was calculated from a standard curve. Reaction rates were calculated based on the initial linear portion of the concentration versus time graphs.

4.2. General methods

All reagents were obtained from commercial suppliers and were used without further purification. Column chromatography was performed with silica gel (230–400 mesh). TLC was performed on Merck pre-coated 60 F_{254} silica plates. CH_2Cl_2 was distilled over CaH_2. The abbreviation 'PE' refers to petroleum ether (bp 40–60 °C). ^{1}H and ^{13}C NMR spectra are referenced to TMS. ^{19}F NMR spectra are referenced to CCl_3F.

4.3. General procedure

(Diethylamino)sulfur trifluoride (DAST) (2 equiv) was added dropwise to a solution of the acid (1 equiv), and the ketone or aldehyde (3 equiv) in dichloromethane (DCM) (only enough to ensure a homogeneous solution) as the flask was cooled in an ice bath (note: pre-cooling of the reaction mixture often resulted in the starting materials precipitating). Where applicable, the ketone or aldehyde was used as the solvent of the reaction, with no DCM added. The reaction mixture was allowed to warm to ambient temperature upon completion of the DAST addition, and was stirred for 2–4 h. The reaction mixture was then diluted with DCM and poured into a mixture of saturated $NaHCO_3$(aq) and ice. The organic layer was washed once more with $NaHCO_3$(aq), and the combined aqueous layers were extracted with DCM (1×). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude material was purified by column chromatography (conditions given for each compound below).

4.3.1. Fluoro(phenyl)methyl propionate, 1. Purified using PE/toluene 3:1; very pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.45 (2H, m, Ar), 7.44–7.39 (3H, m, Ar), 7.21 (1H, d, J_{CF} 55.2 Hz, C*H*F), 2.47 (2H, q, J 7.5 Hz, CH_2), 1.20 (3H, t, J 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.45 (C═O), 134.74 (d, J_{CF} 23.0 Hz, *C*–CHF), 130.12 (d, J_{CF} 1.8 Hz, CH), 128.58 (CH), 126.61 (d, J_{CF} 5.5 Hz, CH), 101.41 (d, J_{CF} 220.6 Hz, CHF), 27.49 (CH_2), 8.62 (CH_3).

4.3.2. 1-Fluoro-2-phenylethyl benzoate, 2. Purified using PE/Et_2O 20:1; pale yellow oil; ^{1}H NMR (300 MHz, CD_3CN) δ 8.03 (2H, ddd, J 8.4, 1.3, 1.3 Hz, Ar_{ortho}), 7.67 (1H, tt, J 7.5, 1.3 Hz, Ar_{para}), 7.52 (2H, ddd, J 8.4, 7.5, 1.3 Hz, Ar_{meta}), 7.40–7.23 (5H, m, Ar), 6.70 (1H, dt, J_{HF} 55.8, J_{HH} 5.0 Hz, C*H*F), 3.29 (2H, dd, J_{HF} 17.2, J_{HH} 5.0 Hz, CH_2); ^{13}C NMR (75 MHz, CD_3CN) δ 165.19 (C═O), 135.02 (CH), 134.93 (d, J_{CF} 5.5 Hz, C), 130.90, 130.63, 129.74 (3CH), 129.74 (C), 129.43, 128.08 (2CH), 104.49 (d, J_{CF} 223.4 Hz, CHF), 40.16 (d, J_{CF} 23.0 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −127.49 (ddd, J 55.8, 17.2, 16.3 Hz); IR (neat) 3064, 3033, 1736, 1260, 998 cm^{-1}.

4.3.3. Fluoro(phenyl)methyl benzoate, 3. Purified using PE/toluene 2:1; very pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (2H, dd, J 8.4, 1.6 Hz, Ar_{ortho}), 7.64–7.54 (3H, m, Ar), 7.50–7.43 (5H, m, Ar), 7.45 (1H, d, J_{HF} 55.2 Hz, C*H*F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.53 (C═O), 134.81 (d, J_{CF} 23.0 Hz, *C*–CHF), 133.94 (CH), 130.20 (d, J_{CF} 1.8 Hz, CH), 130.16 (CH), 128.97 (C), 128.67, 128.57 (2CH), 126.15 (d, J_{CF} 5.5 Hz, CH), 102.02 (d, J_{CF} 222.4 Hz, *C*HF); ^{19}F NMR (282 MHz, $CDCl_3$) δ −122.30 (d, J 55.2 Hz); IR (neat) 3067, 3039, 1737, 1257, 983, 708 cm^{-1}.

4.3.4. 1-Fluorocyclopentyl 2-phenylacetate, 4. Purified using PE/toluene 1:1→1:2; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (5H, m, Ar), 3.62 (2H, s, CH_2), 2.40–2.20 (2H, m), 2.10–1.90 (2H, m), 1.80–1.60 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.01 (C═O), 133.39 (C), 129.20, 128.55, 127.14 (3CH), 123.31 (d, J_{CF} 235.3 Hz, CF), 41.62 (Ar–*C*H_2), 36.82 (d, J_{CF} 24.8 Hz, CH_2), 22.92 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.74 (m); IR (neat) 3064, 3031, 2966, 2880, 1757, 1340, 1126, 978, 771, 690 cm^{-1}.

4.3.5. (*E*)-1-Fluorobut-2-enyl benzoate, 5. Purified using PE/toluene 2:1; very pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (2H, ddd, *J* 8.4, 1.4, 1.4 Hz, Ar_{ortho}), 7.59 (1H, tt, *J* 7.3, 1.4 Hz, Ar_{para}), 7.45 (2H, ddd, *J* 8.4, 7.3, 1.4 Hz, Ar_{meta}), 6.83 (1H, m, J_{HF} 55.0 Hz, OC*H*F), 6.14 (1H, dddq, *J* 15.7, 6.7, 3.9, 0.9 Hz, C*H*CH_3), 5.77 (1H, dddq, *J* 15.7, 7.8, 6.2, 1.7 Hz, CHF–C*H*=), 1.81 (3H, dddd, *J* 6.7, 4.5, 1.7, 0.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.39 (C=O), 134.26 (d, J_{CF} 10.3 Hz, =CH), 133.72, 130.01 (2CH), 128.93 (C), 128.47 (CH), 124.52 (d, J_{CF} 24.1 Hz, =CH), 102.38 (d, J_{CF} 216.1 Hz, CH), 17.54 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −121.36 (m); IR (neat) 3064, 2974, 2921, 1736, 1678, 1247, 958, 708 cm^{-1}.

4.3.6. 2-Fluoro-4-phenylbut-3-yn-2-yl benzoate, 6. Purified using PE/toluene 2:1; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (2H, dd, *J* 8.4, 1.4 Hz, Ar), 7.59 (1H, tt, *J* 7.5, 1.4 Hz, Ar), 7.51–7.42 (4H, m, Ar), 7.36–7.26 (3H, m, Ar), 2.13 (3H, d, J_{HF} 17.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.78 (C=O), 133.57, 132.06, 129.98, 129.45, 129.36, 128.46, 128.28, 120.94, 103.96 (d, J_{CF} 217.8 Hz, *C*F), 86.72 (d, J_{CF} 7.4 Hz, ≡*C*–Ph), 83.39 (d, J_{CF} 39.5 Hz, *C*≡C–Ph), 28.08 (d, J_{CF} 27.6 Hz, CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −89.59 (q, *J* 17.8 Hz); IR (neat) 3064, 3006, 2253, 2227, 1739, 1264, 898, 711 cm^{-1}; HRMS (ESI): M+Na$^+$, found 291.0795. $C_{17}H_{13}O_2FNa$ requires 291.0797.

4.3.7. 1-Fluorocyclopentyl benzoate, 8. Purified using PE/toluene 1.3:1; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (2H, ddd, *J* 8.5, 1.4, 1.4 Hz, Ar_{ortho}), 7.56 (1H, tt, *J* 7.4, 1.4 Hz, Ar_{para}), 7.43 (2H, ddd, *J* 8.5, 7.4, 1.4 Hz, Ar_{meta}), 2.54–2.35 (2H, m), 2.28–2.10 (2H, m), 1.86–1.70 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.98 (C=O), 133.30 (CH), 129.97 (C), 129.80, 128.36 (2CH), 123.56 (d, J_{CF} 236.2 Hz, CF), 37.04 (d, J_{CF} 25.7 Hz, CH_2), 23.10 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −99.36 (m); IR (neat) 3064, 2973, 2946, 2877, 1732, 1275, 1173, 1100, 715 cm^{-1}.

4.3.8. 2-Fluoropropan-2-yl benzoate, 9.[17] Purified using PE/toluene 6:5; very pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (2H, ddd, *J* 8.5, 1.4, 1.4 Hz, Ar_{ortho}), 7.56 (1H, tt, *J* 7.4, 1.4 Hz, Ar_{para}), 7.43 (2H, ddd, *J* 8.4, 7.4, 1.4 Hz, Ar_{meta}), 1.87 (6H, d, J_{HF} 19.2 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.64 (d, J_{CF} 3.7 Hz, C=O), 133.16 (CH), 130.29 (C), 129.65, 128.29 (2CH), 115.57 (d, J_{CF} 221.5 Hz, CF), 25.37 (d, J_{CF} 26.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.76 (sep, *J* 19.2 Hz); IR (neat) 3065, 3000, 2948, 1736, 1278, 1154, 1089, 870, 706 cm^{-1}.

4.3.9. 1-Fluorocyclohexyl benzoate, 10. Purified using PE/toluene 1.3:1; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (2H, ddd, *J* 8.5, 1.4, 1.4 Hz, Ar_{ortho}), 7.56 (1H, tt, *J* 7.4, 1.4 Hz, Ar_{para}), 7.43 (2H, ddd, *J* 8.5, 7.4, 1.4 Hz, Ar_{meta}), 2.35–2.06 (4H, m), 1.80–1.40 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.58 (C=O), 133.15 (CH), 130.45 (C), 129.69, 128.32 (2CH), 115.83 (d, J_{CF} 232.6 Hz, CF), 34.17 (d, J_{CF} 23.0 Hz, CH_2), 24.59 (CH_2), 22.87 (d, J_{CF} 4.6 Hz, CH_2); IR (neat) 3063, 2940, 2866, 1734, 1238, 1064, 933, 706 cm^{-1}; HRMS (ESI): M+Na$^+$, found 245.0954. $C_{13}H_{15}O_2FNa$ requires 245.0954.

4.3.10. 2-Fluorobutan-2-yl benzoate, 11. Purified using PE/toluene 2:1; pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (2H, ddd, *J* 8.4, 1.3, 1.3 Hz, Ar_{ortho}), 7.56 (1H, tt, *J* 7.5, 1.3 Hz, Ar_{para}), 7.43 (2H, ddd, *J* 8.4, 7.5, 1.3 Hz, Ar_{meta}), 2.19 (2H, dq, J_{HH} 7.5, J_{HF} 2.9 Hz, CH_2), 1.86 (3H, d, J_{HF}=19.3 Hz, CF–CH_3), 1.03 (3H, t, *J* 7.5 Hz, CH_2–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.60 (d, J_{CF} 3.7 Hz, C=O), 133.17 (CH), 130.29 (C), 129.66, 128.34 (2CH), 117.28 (d, J_{CF} 225.2 Hz, CF), 31.98 (d, J_{CF} 24.8 Hz), 23.02 (d, J_{CF} 25.7 Hz), 7.22 (d, J_{CF} 4.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −104.77 (m); IR (neat) 3064, 2981, 2946, 2887, 1735, 1268, 1090, 888, 706 cm^{-1}.

Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **1–6** and **8–11** are available as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.02.059.

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