Reactions of *N*-benzyl-pyridinium or -isoquinolinium ylides with ethyl 3-fluoro-3-(fluoroalkyl)acrylates to give fluoroalkyl-substituted indolizine and pyrrolo[2,1-*a*]isoquinoline derivatives

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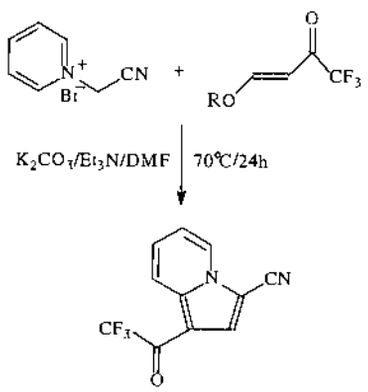
In the presence of base, *N*-benzylpyridinium and *N*-benzylisoquinolinium ylides generated *in situ* from the *N*-benzyl-pyridinium or -isoquinolinium bromides react with ethyl 3-fluoro-3-fluoroalkyl(except bromodifluoromethyl)acrylates to give one or two fluoroalkylated indolizine and pyrrolo[2,1-*a*]isoquinoline derivatives through 1,3-dipolar cycloaddition followed by an oxidative aromatization or 1,3-H-shift aromatization process. While ethyl 3-bromodifluoromethyl-3-fluoroacrylate reacts with 4-nitrobenzylpyridinium ylide, a trifluoromethylated indolizine derivative was obtained unexpectedly. It is more remarkable that the reaction of ethyl 3-bromodifluoromethyl-3-fluoroacrylate with *N*-benzylisoquinolinium ylide produces a fluorocarbonyl-substituted pyrrolo[2,1-*a*]isoquinoline derivative, which is fully characterized by spectroscopic methods and X-ray diffraction analysis, in addition to the 1,3-H-shift aromatization product.

Introduction

Indolizine is an important ring system in view of its similarity to indole. This heterocycle occurs commonly as a fully reduced form in natural products, such as the alkaloid δ-coniceine,[1] pharaoh ant trail pheromone[2] and slatramine,[3] *etc*. Numerous works on indolizines concerned with the search for drugs,[4] for dyestuffs[5] and for spectral sensitizers[6] have been reported previously. Owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology, and industrial application,[7] synthesis of fluorine-containing indolizines and pyrrolo[2,1-*a*]isoquinolines became of considerable interest to us.

Typical molecular constructions of indolizine have been well reviewed in the literature; among these, the 1,3-dipolar cycloaddition reaction of pyridinium *N*-ylide generated *in situ* from a pyridinium salt in the presence of base with an electron-deficient alkene was one versatile methodology.[8] For example, we have successfully prepared a series of 1-trifluoroacetyl-substituted indolizine derivatives through this method (Scheme 1).[9]



Scheme 1

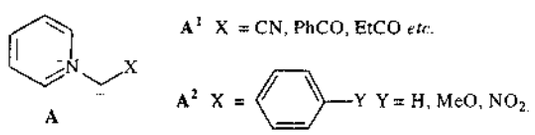


Fig. 1

However, the 1,3-dipolar cycloaddition involving fluorinated alkenes and pyridinium ylide was relatively undeveloped during the last decade.[10] In particular, previous works on the cycloaddition reactions of the pyridinium *N*-ylide **A** (Fig. 1) with electron-deficient alkenes were mostly concentrated on ylides $\mathbf{A^1}$ in which X was an electron-withdrawing group such as cyano, benzoyl, propanoyl *etc*.[11] The reaction of ylide $\mathbf{A^2}$ (in which X was phenyl or substituted phenyl) was reported in only one case.[12]

In continuation of our work on the fluorine-containing indolizines we recently studied the reactions of ylide $\mathbf{A^2}$ with fluorinated acrylate. It was found that ylides $\mathbf{A^2}$ reacted smoothly with ethyl 3-fluoro-3-(fluoroalkyl)acrylates[13] to give one or two fluoroalkylated indolizine derivatives through 1,3-dipolar cycloaddition followed by an oxidative aromatization or 1,3-H-shift aromatization process. Herein we report these results.

Results and discussion

Reactions of *N*-benzylpyridinium ylide with ethyl 3-fluoro-3-(fluoroalkyl)acrylates

First we tried this reaction following the literature method.[10b] Thus, 2,2-dihydropolyfluoroalkanoates were allowed as starting material to react with *N*-benzylpyridinium bromide in the presence of a mixed inorganic and organic base (K_2CO_3 and TEA) in DMF at 75 °C. However, it was found that the reaction progressed very slowly: it took 3 days to finish and gave a complicated mixture which was hard to separate. Alternatively, we

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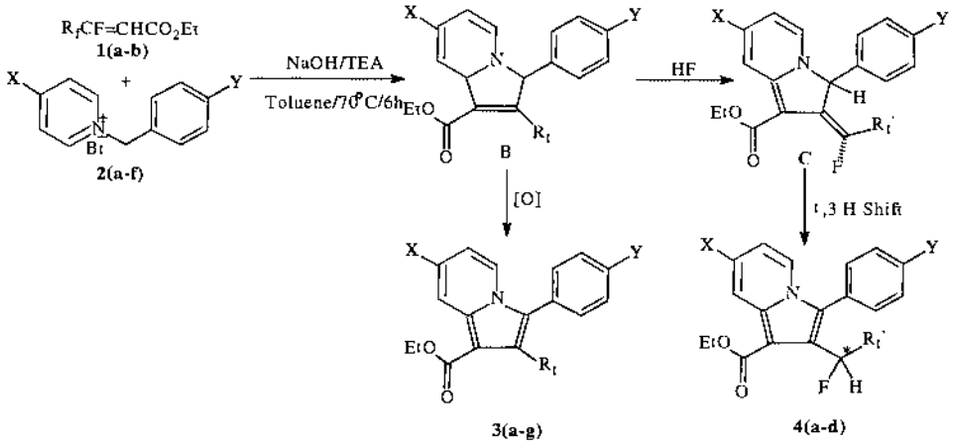


1a $R_f = ClC_3F_6$-
1b $R_f = ClCF_2$-
2a X = H Y = H
2b X = H Y = OMe
2c X = H Y = NO_2
2d X = COOEt Y = H
2e X = CH_3 Y = NO_2
2f X = COOEt Y = NO_2

3a $R_f = ClC_3F_6$- X = H Y = H
3b $R_f = ClC_3F_6$- X = H Y = OMe
3c $R_f = ClC_3F_6$- X = H Y = NO_2
3d $R_f = ClC_3F_6$- X = COOEt Y = H
3e $R_f = ClC_3F_6$- X = CH_3 Y = NO_2
3f $R_f = ClC_3F_6$- X = COOEt Y = NO_2
3g $R_f = ClCF_2$- X = H Y = NO_2

4a $R_f' = ClC_2F_4$- X = H Y = H
4b $R_f' = ClC_2F_4$- X = H Y = OMe
4c $R_f' = ClC_2F_4$- X = H Y = NO_2
4d $R_f' = ClC_2F_4$- X = COOEt Y = H

Scheme 2

used the ethyl 3-fluoro-3-(fluoroalkyl)acrylate ($R_f = ClC_3F_6$) **1a** as starting material to react with *N*-(4-nitrobenzyl)pyridinium bromide **2c** (as an example for illustration) in the presence of a stronger mixed base (NaOH and TEA), and the reaction was carried out in toluene at 75 °C, and we found that the reaction then proceeded smoothly.

In this reaction, NaOH, as a stronger inorganic base, could easily deprotonate the *N*-(4-nitrobenzyl)pyridinium bromide **2c** to form the ylide which was stabilized by the nitrophenyl group. Using the non-polar solvent toluene instead of DMF could make the concerted 1,3-dipolar cycloaddition more competitive.[14] After general work-up, the two products **3c** and **4c** were obtained (Scheme 2).

Compound **3c** was the main and normal product which could be easily determined.[10c] It was formed from oxidative aromatization of the intermediate **B** which was initially produced by [2+3]-dipolar cycloaddition of **1a** with *N*-(4-nitrobenzyl)pyridinium ylide followed by dehydrofluorination. The structure of another product, **4c**, was determined by its spectral data and elemental analysis. Its ^{19}F NMR spectrum had four peaks from −114.4 to −126.0 ppm, showing an AB system with geminal coupling constant $^2J_{FF}$ = 275.1 Hz, which corresponded to the coupling constant of the two fluorine nuclei on the carbon vicinal to the asymmetric carbon; another signal at −189.8 ppm could be assigned to the single fluorine nucleus at the asymmetric carbon. In addition to the aromatic ring and ethoxy group protons, the ^1H NMR spectrum of this compound also had another one-proton signal at δ 7.41, showing an obvious dd pattern ($^2J_{HF}$ = 43.6 Hz and $^3J_{HF}$ = 21.0 Hz) which was attributed to the proton at the asymmetric carbon, and the second *J*-value corresponds to the coupling constant between the proton and one of the two fluorine nuclei at the vicinal carbon atom; the other fluorine nucleus had a very small coupling constant with this proton. In its mass spectrum compound **4c** gave the molecular-ion peak *m*/*z* 476 as the base peak. Other analysis data all confirmed **4c** had the structure shown in Scheme 2. It was formed by dehydrofluorination of the intermediate **B**, followed by 1,3-H-shift aromatization in intermediate **C**. Similar treatment of the acrylate **1a** with bromide **2a**, **2b** and **2d** gave two fluoroalkylated indolizine derivatives (see Scheme 2).

We could not explain how, in the reactions of the acrylate **1a** with the bromide **2e** or **2f**, only the normal products **3e** and **3f**, formed from intermediate **B** by oxidative aromatization, were obtained in poor yield (5% and 33% respectively, Table 1 entries 5 and 6). For the reaction of the acrylate **1b** ($R_f = ClCF_2$) with bromide **2c**, only the normal product **3g** was formed in 28% yield (Table 1, entry 7), and in this case, it was also a puzzle that the initially formed cycloaddition product **B** did not dehydrochlorinate, but only oxidatively aromatize to the product **3g** (see Scheme 2).

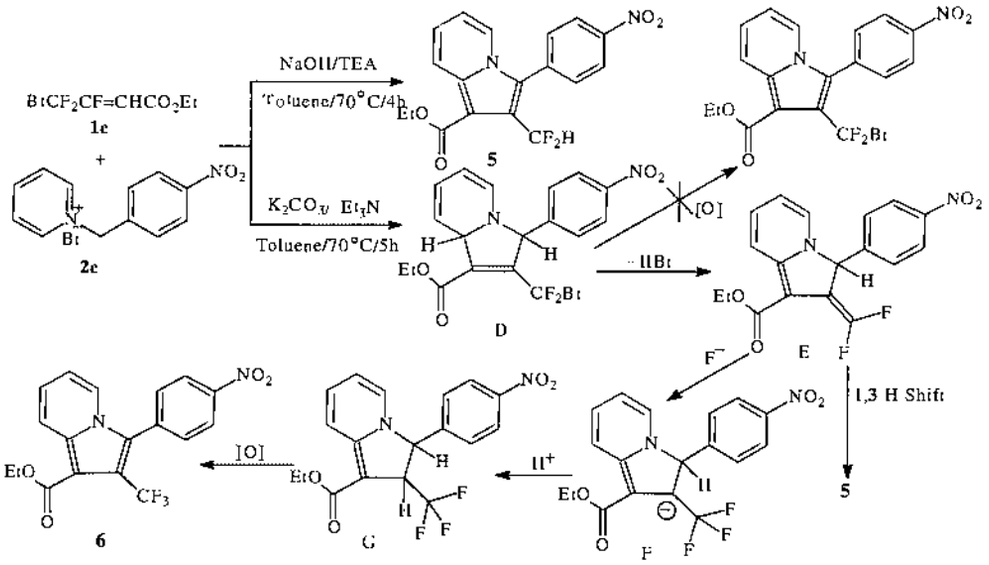
Table 1 Reaction of ethyl 3-fluoro-3-(fluoroalkyl)acrylates with *N*-benzyl-pyridinium and -isoquinolinium bromide (**2** and **7**)[a]

Entry	Acrylate	Pyridinium salt	Products and yield (%)	
1	**1a**	**2a**	**3a** (18)	**4a** (14)
2	**1a**	**2b**	**3b** (31)	**4b** (18)
3	**1a**	**2c**	**3c** (31)	**4c** (29)
4	**1a**	**2d**	**3d** (35)	**4d** (8)
5	**1a**	**2e**	**3e** (5)	
6	**1a**	**2f**	**3f** (33)	
7	**1b**	**2c**	**3g** (28)	
8	**1c**	**2c**		**5** (15)
9	**1c**	**2c**	**6** (25)[b]	**5** (20)[b]
10	**1a**	**7**	**8a** (42)[c]	
11	**1b**	**7**	**8b** (36)[c]	
12	**1c**	**7**	**9** (36)	**10** (10)

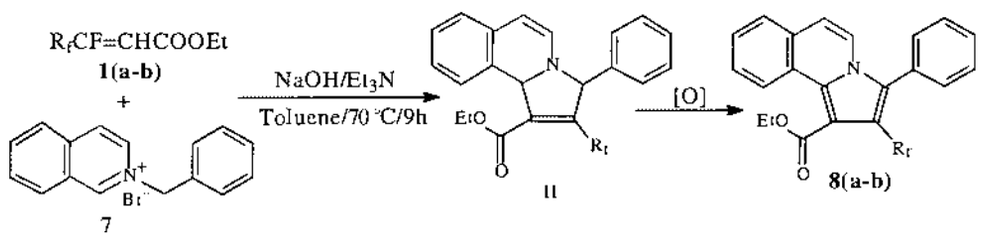
[a] The typical reaction conditions were described in the Experimental section using KOH as base and all yields were isolated yields. [b] Using K_2CO_3 as base. [c] Final yield including the product transformed from dihydrointermediate.

In contrast to the foregoing reaction results, when the acrylate **1c** ($R_f = BrCF_2$) was treated with *N*-(4-nitrobenzyl)-pyridinium bromide **2c** using NaOH as inorganic base, only the 1,3-H-shift product **5** was obtained in low yield (15%, Table 1, entry 8). Interestingly, when K_2CO_3 was used instead of NaOH, this reaction also occurred readily. Two products were isolated; one was 1,3-H-shift product **5**; however, the other product was not the normal bromodifluoromethyl-substituted indolizine formed by oxidative aromatization, but a trifluoromethylated indolizine **6**, which was fully characterized by ^{19}F NMR, MS and microanalysis (C, H, N and F). The formation of the two compounds might be as depicted in Scheme 3.

It is proposed that in this reaction, when the cycloaddition intermediate **D** was formed, elimination of hydrogen bromide



Scheme 3



Scheme 4

to intermediate **E** should prevail over oxidative aromatization to the bromodifluoromethyl-substituted product. The intermediate **E** in one way underwent 1,3-H-shift aromatization to the indolizine **5**; it could also be attacked by fluoride anion in another reaction route to give intermediate **E**, then successive protonation (to **G**) and oxidative aromatization gave the trifluoromethylated product **6**. However, the possibility of SET (single-electron transfer) reaction of the (bromodifluoromethyl)indolizine derivatives to produce these two compounds could not be ruled out.

Reactions of *N*-benzylisoquinolinium ylide with ethyl 3-fluoro-3-(fluoroalkyl)acrylates

The same reaction conditions were also successfully employed to the reaction of *N*-benzylisoquinolinium ylide with fluorinated acrylates **1a** and **1b**. Similar treatment of acrylates **1a** and **1b** with *N*-benzylisoquinolinium bromide **7** gave two products which were observed by TLC analysis after the reactions were complete. However, after general work-up, column chromatography gave only the respective high-polarity products, which were identified as fluoroalkyl-substituted pyrrolo[2,1-*a*]-isoquinolines **8a** and **8b**, respectively. The low-polarity products were transformed partly to **8a** and **8b** on the silica gel column. When exposed to atmosphere or treatment with chloranil (oxidative reagent) they were also readily transformed to the respective dehydrogenated compound **8a** and **8b**. It is reasonable to suppose that those low-polarity compounds should be the dihydrointermediate **H** instead of the 1,3-H-shift product (Scheme 4).

However, when the acrylate **1c** ($R_f = BrCF_2$) reacted with the *N*-benzylisoquinolinium bromide **7** under the same conditions, in addition to the obtained 1,3-H-shift product **9**, a 2-fluorocarbonyl-substituted product **10** was also unexpectedly formed under these strongly basic conditions. Similarly to this kind

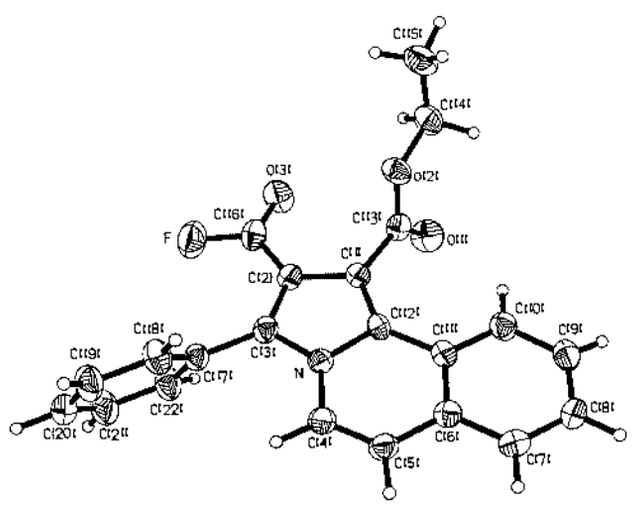
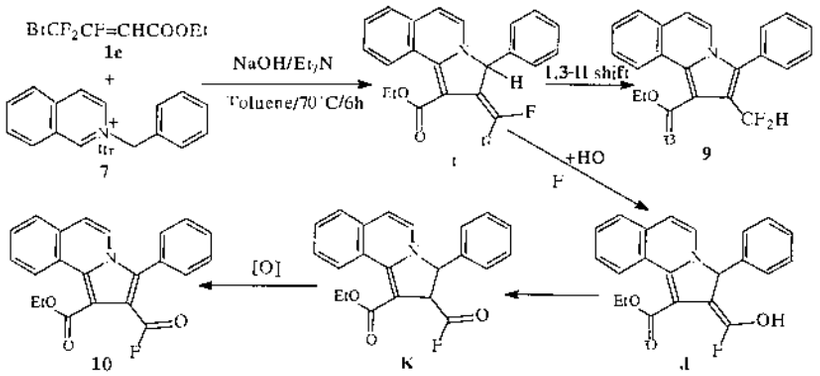


Fig. 2 Molecular structure of compound **10**, with crystallographic numbering scheme.

of compound reported before,[15] the acyl fluoride **10** was a stable solid to handle. Recrystallization from diethyl ether–hexane (1 : 10) afforded fine crystals for analysis. Its ^{19}F NMR spectrum revealed a very-low-field signal at 38.2 ppm which indicated the presence of a fluoroacyl group. The IR spectrum showed two strong carbonyl group absorptions, at 1780 cm^{-1} (COF) and 1713 cm^{-1} (COOEt), respectively.

This structure was further confirmed by a single-crystal diffraction study (Fig. 2). In molecule **10**, the planar pyrrolo[2,1-*a*]isoquinoline system is conjugated with the fluorocarbonyl group: the angle between the two planes is 3°, the C(2)–C(16) bond [1.435(4) Å] is significantly shorter than the standard $C(sp^2)$–$C(sp^2)$ single bond (1.49 Å),[16] while the C(16)–O(3)



Scheme 5

bond [1.226 (4) Å] is slightly longer than the standard carbon–oxygen double bond (1.20 Å).[16] On the other hand, the planes of the ethoxycarbonyl and phenyl substituents are inclined to the pyrrolo[1,2-*a*]isoquinoline plane by 75° and 70°, respectively, probably due to steric repulsion from the fluorocarbonyl group. This and C(1)–C(13) and C(3)–C(17) bond lengths [both 1.483(4) Å] indicate the absence of π–π conjugation between these substituents and the pyrrolo[2,1-*a*]isoquinoline system.

It was preferred that, notwithstanding the possibility of the SET pathway described before, in the reaction of **1c** with **7**, these two products **9** and **10** were formed through the process shown in Scheme 5.

Conclusions

The 1,3-dipolar cycloaddition reactions of *N*-benzylpyridinium ylide and *N*-benzylisoquinolinium ylide with ethyl 3-fluoro-3-(fluoroalkyl)acrylates were investigated. Thus 3-aryl-2-fluoroalkyl-substituted indolizine and pyrrolo[2,1-*a*]isoquinoline derivatives were obtained. In particular, in the case of ethyl 3-bromodifluoromethyl-3-fluoroacrylate, this reaction unexpectedly afforded a trifluoromethylated indolizine and a fluorocarbonyl-substituted pyrrolo[2,1-*a*]isoquinoline derivative, respectively. These reactions allow the preparation of products where the substituent at the 3 position of the produced heterocycle is not limited to an electron-withdrawing group.

Experimental

Instruments

All melting points were determined on a Melt-Temp apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 983G spectrophotometer (KBr disc). ^{1}H NMR and ^{19}F NMR spectra were recorded on Bruker AM-300 and Varian-360L spectrometers operating at 300 MHz and 56.4 MHz in $CDCl_3$ with TMS and TFA [$\delta(CFCl_3) = \delta(TFA) -76.8$, with high-field negative] as internal and external standard, respectively. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets. Coupling constants *J* are recorded in Hz. Low- and high-resolution mass spectra were obtained on an HP 5989a and a Finnigan MAT spectrometer, respectively. Elemental analyses were performed by this Institute.

General method

Solvents and reagents were obtained using standard procedures: benzene (Na metal), pyridine (CaH_2) and toluene (Na metal); all other reagents and solvents used as supplied. Flash column chromatography was performed using silica gel H, particle size 10–40 μ purchased from QingDao ocean chemical factory.

General procedure for preparation of *N*-benzylpyridinium bromide 2a–f and *N*-benzylisoquinolinium bromide 7[17]

A solution of the benzyl bromide (50 mmol) in benzene (30 cm^3) was added dropwise over 0.5 h to a stirred mixture of pyridine (50 mmol) or isoquinoline (50 mmol) in acetone (30 cm^3) at room temperature. After continual stirring at room temperature for 24 h (in some cases reflux was needed), the reaction mixture was filtered, and the solid was washed with diethyl ether and dried by vacuum. *N*-Benzylpyridinium bromides **2a**–**f** and *N*-benzylisoquinolinium bromide **7** were obtained nearly quantitatively.

General procedure for the reactions of *N*-benzylpyridinium ylide and *N*-benzylisoquinolinium ylide with ethyl 3-fluoro-3-(fluoroalkyl)acrylates

A mixture of an ethyl 3-fluoro-3-(fluoroalkyl)acrylate (1 mmol), *N*-benzylpyridinium bromide or *N*-benzylisoquinolinium bromide (1.2 mmol), triethylamine (0.28 cm^3, 2 mmol) and sodium hydroxide (120 mg, 3 mmol) in toluene (20 cm^3) was stirred at 70–80 °C for *ca.* 6 h to complete the conversion of the fluorine-containing substrates, after which the mixture was cooled, and acidified with 1 M HCl so that the final solution had pH 6–7. The organic layer was separated and the water layer was extracted with diethyl ether (3 × 20 cm^3); the combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under vacuum the residue obtained was separated by flash column chromatography using light petroleum–ethyl acetate mixtures as eluant to give the products.

Ethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-phenylindolizine-1-carboxylate 3a and ethyl 2-(3-chloro-1,2,2,3,3-pentafluoropropyl)-3-phenylindolizine-1-carboxylate 4a. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and *N*-benzylpyridinium bromide **2a** (300 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (35 : 1; R_f = 0.3–0.4) as eluant first afforded compound **4a** (64 mg, 0.14 mmol, 14%) as a white solid, mp 125.0–127.0 °C (Found: C, 55.58; H, 3.44; N, 3.21. $C_{20}H_{15}ClF_5NO_2$ requires C, 55.63; H, 3.50; N, 3.24%); ν_{max}(KBr)/cm^{-1} 1660, 1500, 1100–1200 and 800; δ_F (282.0 MHz; $CDCl_3$; $CFCl_3$) −68.8 (2 F, s, $ClCF_2$), −114.3, −125.4 (2 F, AB system, *J* 274.3, $ClCF_2CF_2$), −191.0 (1 F, m, $ClCF_2CF_2CFH$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.32 [1 H, d, *J* 9.0, C(5)-H], 7.68 [1 H, d, *J* 7.2, C(8)-H], 6.68–7.63 (8 H, m, ArH and CFH), 4.45 (2 H, q, *J* 7.4, OCH_2CH_3), 1.49 (3 H, t, *J* 7.4, OCH_2CH_3); *m*/*z* (EI) 431/433 (M$^+$, 100.00/35.5%), 403/405 (16.43/5.49), 386/388 (25.82/8.92), 359/361 (33.92/11.67). Then was furnished compound **3a** (35 : 1; R_f = 0.2–0.3) as a white solid (81 mg, 0.18 mmol, 18%), mp 102.0–104.5 °C (Found: C, 53.55; H, 3.17; N, 3.09. $C_{20}H_{14}ClF_6NO_2$ requires C, 53.41; H, 3.14; N, 3.11%); ν_{max}(KBr)/cm^{-1} 2910, 1700, 1500,

1430, 1100–1270 and 910; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −65.7 (2 F, s, $ClCF_2$), −95.2 (2 F, s, $ClCF_2CF_2CF_2$), −125.8 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.38 [1 H, d, *J* 9.1, C(5)-H], 6.60–7.70 (8 H, m, ArH), 4.38 (2 H, q, *J* 7.2, OCH_2CH_3), 1.41 (3 H, t, *J* 7.2, OCH_2CH_3); *m*/*z* (EI) 449/451 (M^+, 100.00/35.06%), 421/423 (5.81/1.98), 404/406 (29.09/9.59), 377/379 (25.01/8.14), 248 (84.58).

Ethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-(4-methoxyphenyl)indolizine-1-carboxylate 3b and ethyl 2-(3-chloro-1,2,2,3,3-pentafluoropropyl)-3-(4-methoxyphenyl)indolizine-1-carboxylate 4b. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and *N*-(4-methoxybenzyl)pyridinium bromide **2b** (336 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (10 : 1; R_f = 0.4–0.5) as eluant first afforded compound **4b** (82 mg, 0.18 mmol, 18%) as a white solid, mp 109.1–112.5 °C (Found: C, 54.60; H, 3.58; N, 2.87. $C_{21}H_{17}ClF_5NO_3$ requires C, 54.62; H, 3.71; N, 3.03%); ν_{max}(KBr)/cm^{-1} 2980, 1666, 1610, 1569, 1498, 1038–1324; δ_F (282.0 MHz; $CDCl_3$; $CFCl_3$) −68.6 (2 F, s, $ClCF_2$), −114.5, −125.3 (2 F, AB system, *J* 274.3, $ClCF_2CF_2$), −191.3 (1 F, m, $ClCF_2CF_2CFH$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.29 [1 H, d, *J* 9.0, C(5)-H], 7.66 [1 H, d, *J* 7.1, C(8)-H], 6.94–7.48 (7 H, m, ArH and CFH), 4.44 (2 H, q, *J* 7.3, OCH_2CH_3), 3.90 (3 H, s, OCH_3), 1.43 (3 H, t, *J* 7.3, OCH_2CH_3); *m*/*z* (EI) 461/463 (M^+, 100.00/38.79%), 433/435 (2.37/0.88), 416/418 (12.07/5.44), 389/391 (12.98/4.59), 278 (26.12). Then was furnished compound **3b** (10 : 1; R_f = 0.3–0.4) as a white solid (148 mg, 0.31 mmol, 31%), mp 81.0–83.5 °C (Found: C, 52.70; H, 3.19; N, 2.80. $C_{21}H_{16}ClF_6NO_3$ requires C, 52.67; H, 3.36; N, 2.92%); ν_{max}(KBr)/cm^{-1} 2999, 1705, 1610, 1555, 1505, 1058–1328 and 867; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −65.5 (2 F, s, $ClCF_2$), −96.4 (2 F, s, $ClCF_2CF_2CF_2$), −115.7 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.34 [1 H, d, *J* 9.0, C(5)-H], 7.51 [1 H, d, *J* 7.3, C(8)-H], 6.58–7.49 (6 H, m, ArH), 4.41(2 H, q, *J* 7.3, OCH_2CH_3), 3.91 (3 H, s, OCH_3), 1.41 (3 H, t, *J* 7.3, OCH_2CH_3); *m*/*z* (EI) 479/481 (M^+, 100.00/38.9%), 451/453 (4.06/1.42), 434/436 (13.55/5.47), 407/409 (11.87/3.97), 296 (14.48).

Ethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-(4-nitrophenyl)indolizine-1-carboxylate 3c and ethyl 2-(3-chloro-1,2,2,3,3-pentafluoropropyl)-3-(4-nitrophenyl)indolizine-1-carboxylate 4c. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and *N*-(4-nitrobenzyl)pyridinium bromide **2c** (354 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (7 : 1; R_f = 0.3–0.4) as eluent first afforded compound **4c** (138 mg, 0.29 mmol, 29%) as a yellow solid, mp 172.0–174.0 °C (Found: C, 50.53; H, 3.05; N, 5.83. $C_{20}H_{14}ClF_5N_2O_4$ requires C, 50.38; H, 2.95; N, 5.87%); ν_{max}(KBr)/cm^{-1} 1680, 1592, 1502, 1100–1280 and 771; δ_F (282.0 MHz; $CDCl_3$; $CFCl_3$) −68.8 (2 F, s, $ClCF_2$), −114.7, −125.4 (2 F, AB system, *J* 275.1, $ClCF_2CF_2$), −189.8 (1 F, m, $ClCF_2CF_2CFH$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.36–8.43 [3 H, m, C(5)-*H* and 2 × *o*-$NO_2C_6H_3H$], 7.64–7.69 [3 H, m, C(8)-H and 2 × *m*-$NO_2C_6H_3H$], 7.41 (1 H, dd, *J* 43.6 and 21.0, CFH), 6.78–7.25 (2 H, m, ArH), 4.50 (2 H, q, *J* 7.0, OCH_2CH_3), 1.49 (3 H, t, *J* 7.0, OCH_2CH_3); *m*/*z* (EI) 476/478 (M^+, 100.00/35.06%), 448/450 (14.67/5.16), 431/433 (24.37/8.14). Then was furnished compound **3c** (7 : 1; R_f = 0.2–0.3) as a yellow solid (153 mg, 0.31 mmol, 31%), mp 195.5–197.0 °C (Found: C, 48.57; H, 2.67; N, 5.52. $C_{20}H_{13}ClF_6N_2O_4$ requires C, 48.55; H, 2.65; N, 5.66%); ν_{max}(KBr)/cm^{-1} 1670, 1594, 1500, 1100–1257 and 759; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −66.0 (2 F, s, $ClCF_2$), −96.3 (2 F, s, $ClCF_2CF_2CF_2$), −115.8 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.42–8.45 [3 H, m, C(5)-H and 2 × *o*-$NO_2C_6H_3H$], 7.62 (2 H, d, *J* 9.0, 2 × *m*-$NO_2C_6H_3H$], 7.46 [1 H, d, *J* 6.8, C(8)-H], 6.80–7.25 (2 H, m, ArH), 4.40 (2 H, q, *J* 7.5, OCH_2CH_3), 1.46 (3 H, t, *J* 7.5, OCH_2CH_3); *m*/*z* (EI) 494/496 (M^+, 100.00/35.6%), 466/468 (23.04/8.30), 422/424 (47.93/16.73).

Diethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-phenylindolizine-1,7-dicarboxylate 3d and diethyl 2-(3-chloro-1,2,2,3,3-pentafluoropropyl)-3-phenylindolizine-1,7-dicarboxylate 4d. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and *N*-benzyl-4-(ethoxycarbonyl)pyridinium bromide **2d** (388 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (10 : 1; R_f = 0.5–0.6) as eluant first afforded compound **4d** (40 mg, 0.08 mmol, 8%) as a light yellow solid, mp 118.0–119.0 °C; ν_{max}(KBr)/cm^{-1} 2978, 1711, 1687, 1519, 1027–1315 and 764; δ_F (282.0 MHz; $CDCl_3$; $CFCl_3$) −68.7 (2 F, s, $ClCF_2$), −114.4, −125.2 (2 F, AB system, *J* 274.5, $ClCF_2CF_2$), −191.7 (1 F, m, $ClCF_2CF_2CFH$); δ_H (300 Hz; $CDCl_3$; Me_4Si) 9.08 [1 H, s, C(8)-H], 7.13–7.72 (7 H, m, ArH and CFH), 4.31–4.58 (4 H, m, 2 × OCH_2CH_3), 1.31–1.58 (6 H, m, 2 × OCH_2CH_3); *m*/*z* (EI) 503.091 79 (M^+. $C_{23}H_{19}ClF_5NO_4$ requires *M*, 503.092 28), 505 (39.92%), 475/477 (9.78/3.51), 458/460 (17.36/6.24), 431/433 (15.13/4.99). Then furnished compound **3d** (10 : 1; R_f = 0.4–0.5) as a light yellow solid (182 mg, 0.35 mmol, 35%), mp 70.0–73.0 °C (Found: C, 53.12; H, 3.50; N, 2.63. $C_{23}H_{18}ClF_6NO_4$ requires C, 52.94; H, 3.48; N, 2.68%); ν_{max}(KBr)/cm^{-1} 2924, 1714, 1521, 1184–1316 and 761; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −67.0 (2 F, s, $ClCF_2$), −97.4 (2 F, s, $ClCF_2CF_2CF_2$), −116.6 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 9.09 [1H, s, C(8)-H], 7.18–7.68 (7 H, m, ArH), 4.31–4.58 (4 H, m, 2 × OCH_2CH_3), 1.31–1.58 (6 H, m, 2 × OCH_2CH_3); *m*/*z* (EI) 521/523 (M^+, 100.00/38.00%), 476/478 (21.52/7.69), 448/450 (23.54/11.54), 310 (16.64).

Ethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-7-methyl-3-(4-nitrophenyl)indolizine-1-carboxylate 3e. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and 4-methyl-*N*-(4-nitrobenzyl)pyridinium bromide **2e** (370 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (10 : 1; R_f = 0.1–0.2) as eluant afforded compound **3e** (25 mg, 0.05 mmol, 5%) as a yellow solid, mp 166.0–168.0 °C (Found: C, 49.72; H, 3.10; N, 5.30. $C_{21}H_{15}ClF_6NO_4$ requires C, 49.57; H, 2.97; N, 5.51%); ν_{max}(KBr)/cm^{-1} 1679, 1600, 1515, 1057–1350 and 854; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −65.8 (2 F, s, $ClCF_2$), −96.1 (2 F, s, $ClCF_2CF_2CF_2$), −115.8 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.40 (2 H, d, *J* 8.9, 2 × *o*-$NO_2C_6H_3H$), 8.21 [1 H, s, C(8)-H)], 7.61 (2 H, d, *J* 8.9, 2 × *m*-$NO_2C_6H_3H$), 7.35 [1 H, d, *J* 7.1, C(5)-H], 6.61 [1 H, d, *J* 7.1, C(6)-H], 4.40 (2 H, q, *J* 7.3, OCH_2CH_3), 2.41 [3 H, s, C(7)-CH_3], 1.41 (3 H, t, *J* 7.3, OCH_2CH_3); *m*/*z* (EI) 508/510 (M^+, 100.00/38.9%), 480/482 (23.91/8.06), 463/465 (33.09/11.34), 436/438 (49.06/16.77).

Diethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-(4-nitrophenyl)indolizine-1,7-dicarboxylate 3f. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and 4-ethoxycarbonyl-*N*-(4-nitrobenzyl)pyridinium bromide **2f** (440 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (5 : 1; R_f = 0.4–0.5) as eluant afforded compound **3f** (187 mg, 0.33 mmol, 33%) as a yellow solid, mp 153.0–155.0 °C (Found: C, 48.72; H, 3.14; N, 4.83. $C_{23}H_{17}ClF_6N_2O_6$ requires C, 48.74; H, 3.02; N, 4.94%); ν_{max}(KBr)/cm^{-1} 2984, 1716, 1602, 1518 and 1027–1314; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −65.8 (2 F, s, $ClCF_2$), −96.8 (2 F, s, $ClCF_2CF_2CF_2$), −115.8 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 9.10 [1 H, s, C(8)-H], 8.43 (2 H, d, *J* 8.7, 2 × *o*-$NO_2C_6H_3H$), 7.62 (2 H, d, *J* 8.7, 2 × *m*-$NO_2C_6H_3H$), 7.46 [1 H, d, *J* 7.3, C(5)-H], 7.29 [1 H, d, *J* 7.3, C(6)-H], 4.40–4.47 (4 H, m, 2 × OCH_2CH_3), 1.41–1.47 (6 H, m, 2 × OCH_2CH_3); *m*/*z* (EI) 566/568 (M^+, 100.00/35.85%), 538/540 (19.32/6.58), 521/523 (35.85/12.86), 494/496 (53.41/18.82).

Ethyl 2-chlorodifluoromethyl-3-(4-nitrophenyl)indolizine-1-carboxylate 3g. Using the general procedure with ethyl 3-chlorodifluoromethyl-3-fluoroacrylate **1b** (203 mg, 1 mmol) and *N*-(4-nitrobenzyl)pyridinium bromide **2c** (354 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (5 : 1; R_f = 0.2–0.3) as eluant afforded compound **3g** (110 mg, 0.28 mmol, 28%) as a yellow solid, mp 214.3–217.5 °C (Found: C, 54.69; H, 3.40; N, 6.87. $C_{18}H_{17}ClF_2N_2O_4$ requires C, 54.77; H, 3.32; N, 7.10%); ν_{max}(KBr)/cm^{-1} 1676, 1602, 1515, 1049–1349 and 856; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −39.0 (s, $ClCF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.28–8.39 [3 H, m, 2 × *o*-$NO_2C_6H_3H$ and C(5)-H], 7.54–7.72 [3 H, m, 2 × *m*-$NO_2C_6H_3H$ and C(8)-H], 6.70–7.18 (2 H, m, ArH), 4.40 (2 H, q, *J* 7.0, OCH_2CH_3), 1.41 (3 H, t, *J* 7.0, OCH_2CH_3); *m*/*z* (EI) 394/396 (M^+, 100.00/35.20%), 366/368 (14.89/5.09), 349/351 (27.70/9.24), 322/324 (40.84/13.67), 360 (29.36).

Ethyl 2-difluoromethyl-3-(4-nitrophenyl)indolizine-1-carboxylate 5. Using the general procedure with ethyl 3-bromodifluoromethyl-3-fluoroacrylate **1c** (248 mg, 1 mmol) and *N*-(4-nitrobenzyl)pyridinium bromide **2c** (354 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (8 : 1; R_f = 0.2–0.3) as eluant afforded compound **5** (54 mg, 0.15 mmol, 15%) as a yellow solid, mp 145.0–147.2 °C (Found: C, 60.14; H, 4.07; N, 7.66. $C_{18}H_{14}F_2N_2O_4$ requires C, 60.00; H, 3.91; N, 7.77%); ν_{max}(KBr)/cm^{-1} 1679, 1600, 1514, 1019–1349 and 859; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −107.2 (d, *J* 55.3, HCF_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.20–8.57 [3 H, m, 2 × *o*-$NO_2C_6H_3H$ and C(5)-H], 6.74–7.97 (6 H, m, ArH and HCF_2), 4.45 (2 H, q, *J* 7.1, OCH_2CH_3), 1.46 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 360 (M^+, 100.00%), 332 (31.81), 315 (25.97), 288 (32.85), 269 (11.53), 241 (11.05).

Ethyl 2-trifluoromethyl-3-(4-nitrophenyl)indolizine-1-carboxylate 6. The same procedure described above for compound **5** but using K_2CO_3 as inorganic base instead of NaOH first afforded compound **5** (72 mg, 0.20 mmol, 20%) as a yellow solid with identical spectroscopic data to those reported above, then furnished compound **6** (8 : 1; R_f = 0.2–0.3) (95 mg, 0.25 mmol, 25%) as a yellow solid, mp 213.0–215.5 °C (Found: C, 57.20; H, 3.71; N, 7.62; F, 14.68. $C_{18}H_{13}F_3N_2O_4$ requires C, 57.15; H, 3.46; N, 7.40; F, 15.07%); ν_{max}(KBr)/cm^{-1} 1675, 1602, 1515, 1052–1350 and 852; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −52.1 (s, CF_3); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.36–8.43 [3 H, m, 2 × *o*-$NO_2C_6H_3H$ and C(5)-H], 7.62–7.65 [3 H, m, 2 × *m*-$NO_2C_6H_3H$ and C(8)-H], 6.78–7.20 (2 H, m, ArH), 4.45 (2 H, q, *J* 7.1, OCH_2CH_3), 1.46 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 378 (M^+, 100.00%), 350 (27.93), 333 (35.53), 306 (33.37), 287 (13.39), 259 (14.80), 240 (8.36), 69 (16.07).

Ethyl 2-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 8a. Using the general procedure with ethyl 3-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-3-fluoroacrylate **1a** (303 mg, 1 mmol) and *N*-benzylisoquinolinium bromide **7** (360 mg, 1.2 mmol) as reactant, the obtained residue, after exposure in air for one day followed by flash column chromatography using hexane–EtOAc (10 : 1; R_f = 0.5–0.6) as eluant, afforded compound **8a** (210 mg, 0.42 mmol, 42%) as a white solid, mp 143.0–145.5 °C (Found: C, 57.85; H, 3.49; N, 2.53. $C_{24}H_{16}ClF_6NO_2$ requires C, 57.67; H, 3.23; N, 2.80%); ν_{max}(KBr)/cm^{-1} 2986, 1711, 1526, 1026–1362 and 737; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −67.1 (2 F, s, $ClCF_2$), −98.8 (2 F, s, $ClCF_2CF_2CF_2$), −117.9 (2 F, s, $ClCF_2CF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.19 [1 H, d, *J* 8.0, C(5)-H], 7.22–7.72 (9 H, m, ArH), 6.80 [1 H, d, *J* 8.0, C(6)-H], 4.60 (2 H, q, *J* 7.1, OCH_2CH_3), 1.40 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 499/501 (M^+, 100.00/39.78%), 471/473 (8.59/2.84), 454/456 (38.81/14.09), 427/429 (32.68/13.39).

Ethyl 2-chlorodifluoromethyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 8b. Using the general procedure with ethyl 3-chlorodifluoromethyl-3-fluoroacrylate **1b** (303 mg, 1 mmol) and *N*-benzylisoquinolinium bromide **7** (360 mg, 1.2 mmol), the obtained residue, after exposure in air for one day followed by flash column chromatography using hexane–EtOAc (10 : 1; R_f = 0.5–0.6) as eluant, afforded compound **8b** (143 mg, 0.36 mmol, 36%) as a white solid, mp 122.0–124.5 °C (Found: C, 65.72; H, 4.05; N, 3.41. $C_{22}H_{16}ClF_2NO_2$ requires C, 66.09; H, 4.03; N, 3.50%); ν_{max}(KBr)/cm^{-1} 2967, 1710, 1527, 1041–1373 and 743; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −38.0 (2 F, s, $ClCF_2$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.49 [1 H, d, *J* 8.1, C(5)-H], 7.40–7.58 (9 H, m, ArH), 6.80 [1 H, d, *J* 8.1, C(6)-H], 4.54 (2 H, q, *J* 7.2, OCH_2CH_3), 1.48 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 399/401 (M^+, 95.35/34.26%), 316 ($M^+ - ClCF_2 + 1$, 100.00), 354/356 (27.48/10.47), 327/329 (25.10/8.89).

Ethyl 2-difluoromethyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 9 and ethyl 2-fluorocarbonyl-3-phenylpyrrolo[2,1-*a*]isoquinoline-1-carboxylate 10. Using the general procedure with ethyl 3-bromodifluoromethyl-3-fluoroacrylate **1c** (248 mg, 1 mmol) and *N*-benzylisoquinolinium bromide **7** (360 mg, 1.2 mmol) followed by flash column chromatography using hexane–EtOAc (18 : 1; R_f = 0.2–0.3) as eluant afforded compound **9** (131 mg, 0.36 mmol, 36%) as a white solid, mp 89.0–93.0 °C; ν_{max}(KBr)/cm^{-1} 2961, 1696, 1606, 1046–1367 and 787; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) −105.2 (d, *J* 54.6, HCF_2); δ_H (300 MHz; $CDCl_3$; Me_4Si) 9.05 [1 H, d, *J* 8.1, C(5)-H], 7.48–7.64 (9 H, m, ArH), 6.98 (1 H, t, *J* 54.6, HCF_2), 6.88 [1 H, d, *J* 8.1, C(6)-H], 4.55 (2 H, q, *J* 7.1, OCH_2CH_3), 1.50 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 365.12291 (M^+. $C_{22}H_{17}F_2NO_2$ requires *M*, 365.12273), 337 (19.24%), 320 (46.83), 293 (57.29). Then using hexane–EtOAc (10 : 1; R_f = 0.3–0.4) as eluant furnished compound **10** (36 mg, 0.10 mmol, 10%) as a white solid, mp 127.0–129.5 °C (Found: C, 73.20; H, 4.21; N, 3.77; F, 5.07. $C_{22}H_{16}FNO_3$ requires C, 73.12; H, 4.46; N, 3.88; F, 5.26%); ν_{max}(KBr)/cm^{-1} 2981, 1780, 1713, 1531, 1202 and 747; δ_F (56.4 MHz; $CDCl_3$; $CFCl_3$) 38.2 (s, COF); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.01 [1 H, d, *J* 7.6, C(5)-H], 7.46–7.61 (9 H, m, ArH), 6.87 [1 H, d, *J* 7.6, C(6)-H], 4.57 (2 H, q, *J* 7.1, OCH_2CH_3), 1.47 (3 H, t, *J* 7.1, OCH_2CH_3); *m*/*z* (EI) 361 (M^+, 100.00%), 333 (11.05).

Determination of the X-ray crystal structure †

A colourless crystal of 0.40 × 0.20 × 0.13 mm size was grown from hexane–diethyl ether. The experiment was carried out on a Bruker P4 four-circle diffractometer at room temperature, using graphite-monochromated Mo-Kα radiation (λ = 0.710 73 Å). Crystal data: $C_{22}H_{16}FNO_3$, M = 361.36, monoclinic, space group *C*2/*c* (No. 15), *a* = 20.375(4), *b* = 11.151(2), *c* = 16.522(4) Å, β = 103.55(1)°, *V* = 3649(1) Å^3 (by least-squares refinement on setting angles of 25 reflections with 5° < θ < 12.5°), *Z* = 8, D_c = 1.315 g cm^{-3}, μ = 0.09 mm^{-1}. 5026 Reflections (of which 4199 independent) with 2.06° < θ < 27.51° were measured in $\theta/2\theta$ scan mode and corrected for decay and absorption (by empirical method; R_{int} = 0.047). The structure was solved by the direct method and refined by least-squares against F_2 of all data, using the program SHELX-97,[18] to *R* = 0.065 [for 1565 observed reflections with $I > 2\sigma(I)$] and *wR*(*F*2) = 0.150 (for all data).

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