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1,4-Additions of electron-rich heterocycles onto β-perfluoroalkyl enones

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Perfluoroalkyl Warfarin analogs
1,4-Addition

ABSTRACT

β-(Trifluoromethyl) enones, easily obtained in few steps from commercially available methyl hemiketal of trifluoroacetaldehyde, react with electron-rich O- and N-containing heterocycles (furans and benzofurans, pyrroles and indoles, hydroxycoumarins), through a 1,4 addition, to give heterocycles bearing a functionalized side-chain. β-(chlorodifluoromethyl)enones and β-(pentafluoroethyl)enones behave in the same way.

1. Introduction

Several years ago, we described the preparation, from commercially available methyl hemiketal of trifluoroacetaldehyde (fluoral), of stable and environmentally friendly hemiaminals of fluoral, especially the one derived from N-benzylpiperazine **1**. Under basic conditions, this hemiaminal constitutes as an efficient nucleophilic trifluoromethylating agent towards non-enolizable carbonylated substrates or disulfides and diselenides. Moreover, under fluoride activation, its O-silylated derivative **2** behaves in the same way [1–4] (Scheme 1). Analogs of reagents **1** and **2**, in which the CF_3 group was replaced by CF_2Cl or CF_3CF_2, were obtained in the same way from the corresponding aldehyde hydrates and reacted similarly.

Surprisingly, we observed that, in the presence of a catalytic amount of t-BuOK, the reaction of the **1** with enolizable ketones, such as acetophenone, did not deliver any α-(trifluoromethyl)-carbinol but a β-(trifluoromethyl)-β-piperazinoketone [5]. These compounds, which exhibit a limited stability, can be treated in acidic medium (TFA) to provide stable β-(trifluoromethyl) enones **3**. As it was suspected that, during this reaction, an iminium intermediate was trapped by the enolic form of the ketone, it appeared that **3** was more conveniently prepared in one pot from **2** after treatment with a Lewis acid (such as $BF_3{\cdot}Et_2O$) then with trifluoroacetic acid [5] (Scheme 2). It can be noticed that the occurrence of such an iminium intermediate has been amply demonstrated by trapping with various nucleophiles, such as alcohols, amines, azidosilanes, silyl hydrides, allyl silanes (which led to α-CF_3 homoallylamines), vinyl trifluoroborates (which led to α-CF_3 allylamines) or electron-rich aromatics [6,7].

Obviously, such β-(fluoroalkyl) enones look as very valuable building-blocks for the synthesis of numerous fluoroalkylated compounds and we already reported on their use in Diels–Alder reactions (which allowed us to produce fluoroalkylated norbornenes, acylcyclohexenes and acylcyclohexenones) [8] or Michael additions leading to (trifluoromethyl)cyclohexenones [9] and Δ^1-(trifluoromethyl)pyrrolines [10].

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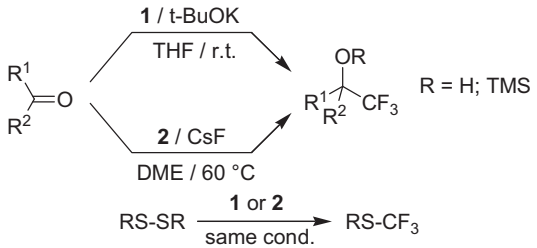
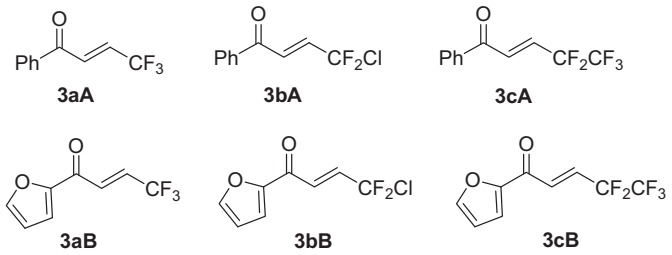


Scheme 1. Preparation and use of fluoral hemiaminals **1** and **2**.



Scheme 3. Substrates used in this study.

Now, we wish to present our results about the reaction of β-(fluoroalkyl)enones with electron-rich heterocycles.

2. Results and discussion

The reactivity with electron-rich heterocycles of the β-(fluoroalkyl) enones described in Scheme 3 have been studied.

Following our previous results from Diels–Alder reactions of these enones with cyclopentadiene, we thought that furan would react in the same way and provide bicyclic Diels–Alder adducts. However, no bicyclic adduct was obtained from **3aA**–**3cA**, even at 150 °C. When catalytic amounts of a Lewis acid were added to activate the reaction, the enone became more electrophilic and thus allowed furan to act as a nucleophile rather than a diene. Consequently, it underwent a 1,4-addition on **3aA** which delivered a β-(trifluoromethyl)-β-(2-furyl) ketone **4aA** (Scheme 4).

Catalysis of this 1,4-addition by several Lewis acids was also examined and it appeared that $Cu(OTf)_2$ and $In(OTf)_3$ were as efficient as $BF_3{\cdot}Et_2O$, whereas $Zn(OTf)_2$, $La(OTf)_3$ and $Yb(OTf)_3$ did not catalyzed the reaction (Scheme 5). The same alpha-regioselectivity was observed whatever the catalyst.

It can be also noticed that, when two equivalents of **3aA** and $TiCl_4$ were used, a double condensation of **3aA** with furan was observed (Scheme 6).

By analogy with a recent Jorgensen's work, dealing with the enantioselective addition of indole onto benzylidene methyl pyruvate, catalyzed by chiral $Cu(OTf)_2$/(S)-^{t}Bu-BOX [11], we examined the behavior of this Cu(II) complex and its indium congener, in the reaction of furan with **3aA**. Unfortunately, no condensation occurred in both cases, probably because Cu(II) or In(III), liganded in such a way, are not electrophilic enough to chelate the carbonyl moiety of **3aA**.

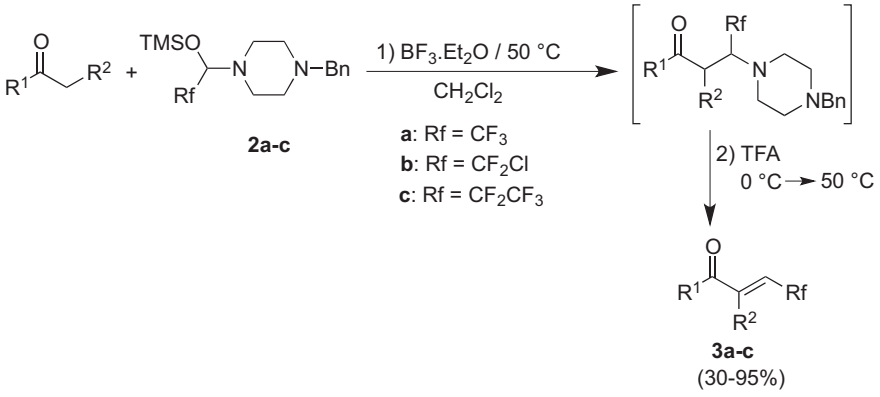
We then studied the $BF_3{\cdot}Et_2O$ catalyzed addition of **3aA**–**3cA** on other electron-rich heterocycles, namely benzofuran, N-methylpyrrole and N-benzylindole, under conditions similar to those used for furan (Fig. 1). As expected, N-containing heterocycles usually reacted faster and delivered better yields than furan at room temperature. As expected also, N-benzylindole reacted regioselectively at the 3-position. In contrast, benzofuran appeared less reactive than furan or N-containing substrates; consequently, heating up to 50 °C was necessary to get good yields.

Unprotected indole was also used as substrate against **3aA**. In this case, no adduct was obtained with $BF_3{\cdot}Et_2O$ as catalyst. It could be suspected that some intermolecular interactions could occur between the rather acidic hydrogen of the indole nucleus and the fluorine atoms of the adduct. Thus, elimination of HF cannot be ruled out, all the more so since such an elimination would be favored by a hard Lewis acid such as $BF_3{\cdot}Et_2O$. Nevertheless, a softer Lewis acid, such as $Cu(OTf)_2$, delivered the adduct but in a poor yield (Scheme 7).

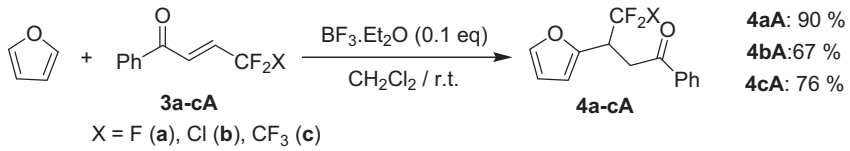
4-Hydroxycoumarin is also an electron-rich heterocycle which easily reacts with electrophiles under various conditions. For example, when opposed to benzylideneacetone, it provides Warfarin (Coumadin™) which is a well-known and potent anticoagulant [12]. This condensation has been achieved in an enantioselective way by Jorgensen, by using a chiral organocatalyst [13] (Scheme 8).

Because of the analogy of such a structure with those we obtained from **3aA**, we started studying the addition of 4-hydroxycoumarin with enones **3aA**–**3cA** and **3aB**–**3cB**, in order to get fluorinated analogs of Warfarin. As we were firstly interested in the racemic series, we did not use Jorgensen's conditions but, more simply, the reaction was carried out in basic medium (Scheme 9). As depicted in Fig. 2, good to excellent yields are generally obtained.

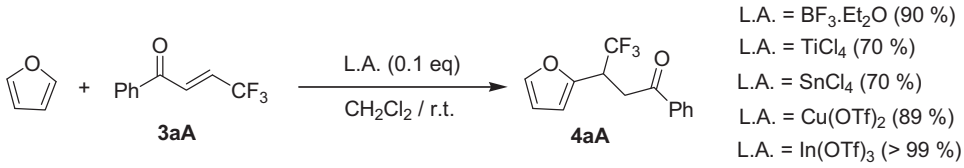
In conclusion, after several contributions from our laboratory and from others [14], this work demonstrates again that β-perfluoroalkylated enones are very powerful tools and very valuable building-blocks for the synthesis of various fluorinated products, and especially heterocyclic ones, which could find highly interesting applications in the design of bioactive molecules. There is no doubt that several other properties of these building-blocks have to be exploited. For our part, we are currently studying a stereoselective version of the condensations reported in this paper.



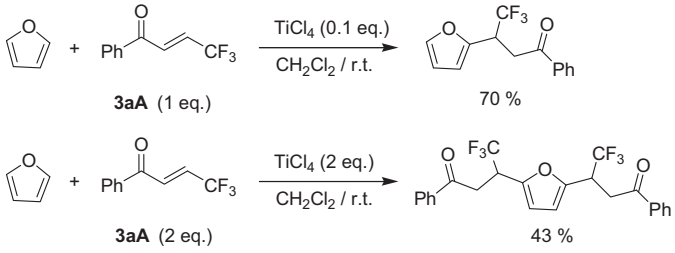
Scheme 2. Preparation of β-(fluoroalkyl) enones **3a**–**3c**.



Scheme 4. 1,4-Addition of furan onto **3aA**.



Scheme 5. 1,4-Addition of furan onto **3aA** with various Lewis acids.



Scheme 6. Double *vs.* single condensation of **3aA** with furan.

3. Experimental

Dichloromethane was dried over molecular sieves. Other reagents were used as purchased.

^{1}H, ^{13}C (CPD and DEPT 135) and ^{19}F NMR spectra were generally recorded in $CDCl_3$ at, respectively, 300, 75 and 282 MHz, otherwise specified. The signal's attribution of ^{1}H and ^{13}C NMR spectra may have required 2D NMR experiments (COSY, HSQC, HMBC, NOESY, and HOESY). Chemical shifts are given in ppm relative to TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F) as internal references. Coupling constants are given in Hertz. The following abbreviations have been used to describe NMR spectra: "s" singlet, "bs" broad singlet, "d" doublet, "bd" broad doublet, "t" triplet, "q" quadruplet, and "m" multiplet.

Flash chromatography was performed on silica gel 60 M (40–60 (m). Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

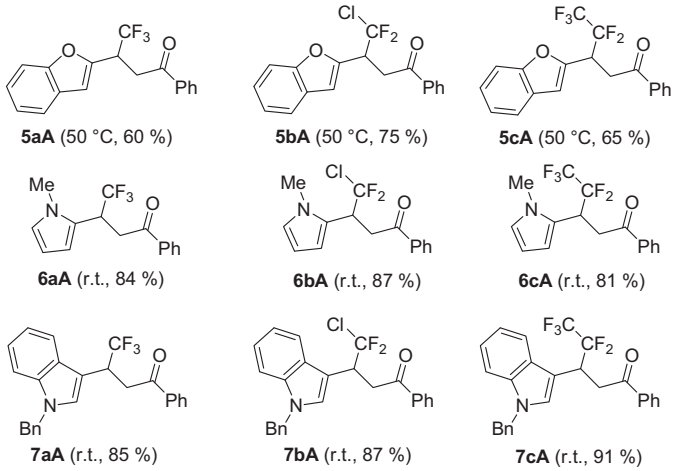


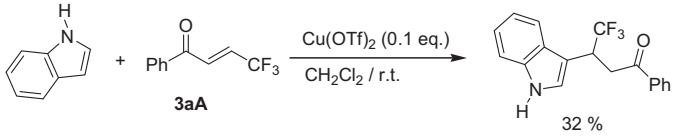
Fig. 1. Addition of benzofuran, N-methylpyrrole and N-benzylindole onto **3aA**–**3cA**.

3.1. General procedure for the Lewis acid-catalyzed addition of different heterocycles onto β-fluoroalkylated enones 3

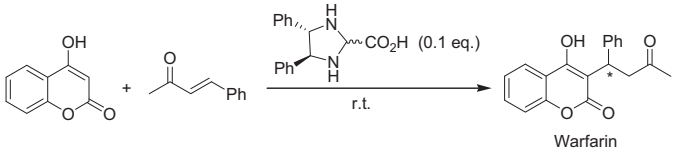
The Lewis acid (0.075 mmol, 0.1 eq.) was added to a solution of **3** (0.75 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL). After the reaction mixture has been stirred for 0.5 h at room temperature, the heteroaromatic compound (0.75 mmol, 1.0 equiv.) was added. The resulting solution was stirred at room temperature (or at 50 °C in the case of benzofuran) until no (or only traces) starting material was detected by ^{19}F NMR (ca. 16 h) then water was added. The reaction mixture was diluted with CH_2Cl_2 and treated with a 6% aqueous solution of $NaHCO_3$. After decantation, the aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed twice with a 6% aqueous solution of $NaHCO_3$, dried over Na_2SO_4 and evaporated under vacuum. The crude residue was purified by flash column chromatography on silica gel to afford the pure adduct.

3.2. 4,4,4-Trifluoro-3-(2-furyl)-1-phenylbutan-1-one (4aA)

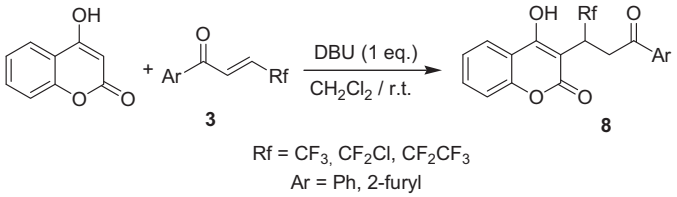
Orange oil. Yield: 90%. ^{1}H NMR: δ 7.96 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.34 (dd, J = 2 Hz, 1H), 6,34 (bd, J = 3 Hz, 1H), 6.32 (dd, J = 3, 2 Hz, 1H), 4.42 (ddq, J = 9, 9, 4 Hz, 1H), 3.77 (dd, J = 17, 9 Hz,



Scheme 7. Addition of **3aA** upon unprotected indole.



Scheme 8. Enantioselective synthesis of Warfarin (Coumalin™).



Scheme 9. Condensation of enones **3** with 4-hydroxycoumarin.

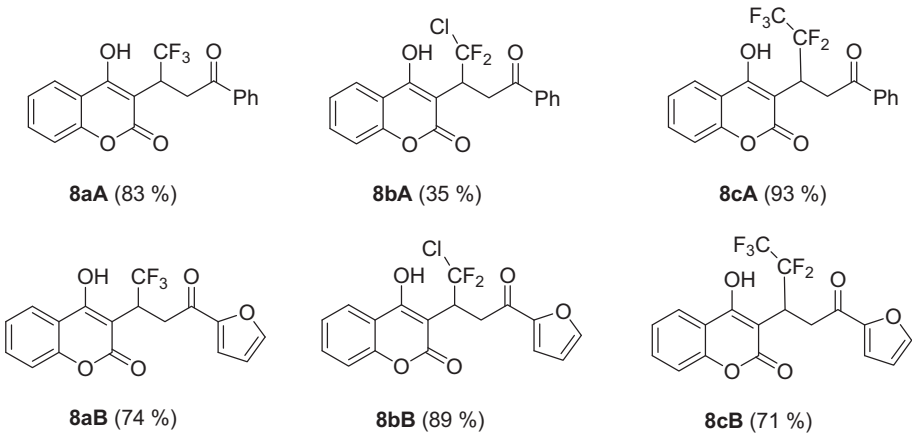


Fig. 2. Condensation of 4-hydroxycoumarin with various fluorinated enones **3**.

1H), 3.46 (dd, *J* = 17, 4 Hz, 1H). ^{13}C NMR: δ 194.9, 147.4, 142.4, 136.1, 133.5, 128.7, 128.0, 125.9 (q, $^{1}J_{C-F}$ = 278 Hz), 110.5, 109.3, 39.0 (q, $^{2}J_{C-F}$ = 29 Hz), 35.9. ^{19}F NMR: δ −70.8 (d, *J* = 9 Hz).

3.3. 4-Chloro-4,4-difluoro-3-(2-furyl)-1-phenylbutan-1-one (**4bA**)

Colorless oil. Yield: 67%. ^{1}H NMR: δ 8.00 (m 2H), 7.62 (m, 1H), 7.51 (m, 2H), 7.39 (dd, *J* = 2, 1 Hz, 1H), 6.38 (m, 2H), 4.58 (tdd, *J* = 10, 10, 3 Hz, 1H), 3.88 (dd, *J* = 18, 10 Hz, 1H), 3.58 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 195.5, 148.56 (dd, *J* = 4, 3 Hz), 143.1, 136.6, 134.1, 129.9 (t, *J* = 295 Hz), 129.2, 128.5, 111.1, 110.3, 45.8 (t, *J* = 25 Hz), 37.5 (t, *J* = 1.7 Hz). ^{19}F NMR: δ −54.7 (dd, *J* = 162, 10 Hz, 1F), −55.48 (dd, *J* = 162.0, 10 Hz, 1F).

3.4. 4,4,5,5-Pentafluoro-3-(2-furyl)-1-phenylpentan-1-one (**4cA**)

White solid. Mp: 87–89 °C. Yield: 76%. ^{1}H NMR: δ 7.87 (m, 2H), 7.49 (m, 1H), 7.38 (m, 2H), 7.26 (m, 1H), 6.23 (m, 2H), 4.38 (m, 1H), 3.71 (dd, *J* = 18, 10 Hz, 1H), 3.44 (dd, *J* = 18, 4 Hz, 1H). ^{13}C NMR: δ 195.4, 147.4 (dd, *J* = 7, 2 Hz), 143.3, 136.5, 134.1, 129.2, 128.5, 119.4 (qt, *J* = 285, 36 Hz), 113.95 (tq, *J* = 257, 36 Hz), 111, 110.4, 37.25 (dd, *J* = 24, 21 Hz), 35.8. ^{19}F NMR: δ −82.8 (s, 3F), −115.4 (dd, *J* = 269, 10 Hz, 1F), −120.3 (dd, *J* = 269, 21 Hz, 1F).

3.5. 2,5-bis-[2-(1,1,1-Trifluoro-4-oxo-4-phenylbutyl)]furan (mixture of diastereomers)

Orange oil. ^{1}H NMR: δ 7.88 (m, 4H), 7.57 (m, 2H), 7.45 (m, 4H), 6.30 (bs, 2H), 4.36 (qdd, 2H, *J* = 9, 9, 4 Hz), 3.70 (dd, 1H, *J* = 9, 18 Hz), 3.72 (dd, 1H, *J* = 9, 18 Hz), 3.39 (dd, 1H, *J* = 4, 18 Hz), 3.36 (dd, 1H, *J* = 4, 18 Hz). ^{13}C NMR: δ 194.5, 147.4, 135.8, 133.2, 128.4, 127.7, 125.2 (q, *J* = 280 Hz, CF_3), 110.1, 38.8 (q, *J* = 29 Hz), 38.8 (q, *J* = 31 Hz), 35.5, 35.3. ^{19}F NMR: δ −70.68 (d, *J* = 9 Hz), −70.72 (d, *J* = 9 Hz).

3.6. 4,4,4-Trifluoro-3-(2-benzofuryl)-1-phenylbutan-1-one (**5aA**)

Yield: 60%. ^{1}H NMR: δ 8.02 (m, 2H), 7.59 (m, 5H), 7.28 (m, 2H), 6.83 (s, 1H), 4.65 (qdd, *J* = 9, 10, 4 Hz, 1H), 3.97 (dd, *J* = 18, 10 Hz, 1H), 3.63 (dd, *J* = 18, 4 Hz, 1H). ^{13}C NMR: δ 195.1, 155.3, 150.8 (q, *J* = 2 Hz), 136.4, 134.2, 129.2, 128.6, 128.4, 126.2 (q, *J* = 280 Hz), 125.0, 123.4, 121.6, 111.8, 107.1, 40.0 (q, *J* = 29 Hz), 36.4 (q, *J* = 1 Hz). ^{19}F NMR: δ −69.9 (d, *J* = 9 Hz).

3.7. 4-Chloro-4,4-difluoro-3-(2-benzofuryl)-1-phenylbutan-1-one (**5bA**)

White solid. Mp: 49–55 °C. Yield: 75%. ^{1}H NMR: δ 7.83 (m, 2H), 7.41 (m, 2H), 7.31 (m, 3H), 7.09 (m, 2H), 6.66 (s, 1H), 4.57 (tdd, *J* = 10, 10, 3 Hz, 1H), 3.84 (dd, *J* = 18, 10 Hz, 1H), 3.51 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 195.2, 155.3, 151.4 (t, *J* = 3 Hz), 136.5, 134.2, 129.8 (t, *J* = 296 Hz), 129.2, 128.6, 128.4, 125.0, 123.5, 121.6, 111.8, 107.5, 46.5 (t, *J* = 25 Hz), 37.5. ^{19}F NMR: δ −54.18 (ddd, *J* = 163, 10, 3 Hz), −54.89 (ddd, *J* = 163, 10, 3 Hz).

3.8. 4,4,5,5-Pentafluoro-3-(2-benzofuryl)-1-phenylpentan-1-one (**5cA**)

White solid. Mp: 46–63 °C. Yield: 65%. ^{1}H NMR: δ 7.82 (m, 2H), 7.40 (m, 2H), 7.30 (m, 3H), 7.10 (m, 2H), 6.64 (s, 1H), 4.53 (dddd, *J* = 21, 10, 10, 3 Hz, 1H), 3.80 (dd, *J* = 18, 10 Hz, 1H), 3.51 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 195.1, 155.5, 150.34 (d, *J* = 7, 2 Hz), 136.4, 134.2, 129.2, 128.6, 128.3, 125.1, 123. 5, 121.6, 119.5 (qt, *J* = 286, 36 Hz), 114.0 (tq, *J* = 259, 37 Hz), 111.8, 107.6, 37.8 (dd, *J* = 24, 21 Hz), 35.8. ^{19}F NMR: δ −82.6 (s, 3F), −115.1 (dd, *J* = 270, 10 Hz, 1F), −119.3 (dd, *J* = 270, 21 Hz, 1F).

3.9. 4,4,4-Trifluoro-3-(N-methyl-2-pyrrolyl)-1-phenylbutan-1-one (**6aA**)

Yield: 84%. ^{1}H NMR: δ 7.97 (m, 2H), 7.62 (m, 1H), 7.49 (m, 2H), 6.62 (m, 1H), 6.16 (m, 1H), 6.09 (m, 1H), 4.36 (qdd, *J* = 9, 10, 3 Hz, 1H), 3.78 (dd, *J* = 18, 10 Hz, 4H), 3.55 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 196.0, 136.7, 134.0, 129.1, 128.5, 127.0 (q, *J* = 279 Hz), 126.4 (q, *J* = 2 Hz), 123.4, 107.9, 107.5, 39.3 (q, *J* = 2 Hz), 36.6 (q, *J* = 29 Hz), 34.4. ^{19}F NMR: δ −71.1 (d, *J* = 9 Hz).

3.10. 4-Chloro-4,4-difluoro-3-(N-methyl-2-pyrrolyl)-1-phenylbutan-1-one (**6bA**)

Yellow solid. Mp: 59–63 °C. Yield: 87%. ^{1}H NMR: δ 7.82 (m, 2H), 7.45 (m, 1H), 7.33 (m, 2H), 6.47 (m, 1H), 6.04 (m, 1H), 5.95 (m, 1H), 4.33 (dddd, *J* = 11, 12, 10, 3 Hz, 1H), 3.69 (dd, *J* = 18, 10 Hz, 1H), 3.66 (s, 3H), 3.47 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 196.1, 136.7, 134.0, 131.1 (t, *J* = 295 Hz), 129.2, 128.5, 127.2 (t, *J* = 2 Hz), 123.4, 108.2, 107.5, 43.22 (t, *J* = 25 Hz), 40.6, 34.5. ^{19}F NMR: δ −55.1 (ddd, *J* = 161, 11, 2 Hz, 1F), −55.9 (ddd, *J* = 161, 12, 3 Hz, 1F).

3.11. 4,4,5,5-Pentafluoro-3-(N-methyl-2-pyrrolyl)-1-phenylpentan-1-one (**6cA**)

White solid. Mp: 87–89 °C. Yield: 81 ^{1}H NMR: δ 7.81 (m, 2H), 7.45 (m, 1H), 7.34 (m, 2H), 6.45 (m, 1H), 6.03 (m, 1H), 5.94 (m, 1H), 4.26 (m, 1H), 3.66 (dd, *J* = 18, 10 Hz, 1H), 3.65 (s, 3H), 3.45 (dd, *J* = 18, 3 Hz, 1H). ^{13}C NMR: δ 196.2, 136.7, 134.0, 129.1, 128.5, 125.9 (dd, *J* = 6, 1 Hz), 123.2, 119.7 (qt, *J* = 289, 38 Hz), 114.7 (tq, *J* = 260, 36 Hz), 108.6, 107.7, 39.2, 34.3 (dd, *J* = 23, 22 Hz), 34.2. ^{19}F NMR: δ

−82.5 (s, 3F), −116.2 (dd, J = 268, 12 Hz), −120.1 (dd, J = 268, 20 Hz).

3.12. 4,4,4-Trifluoro-3-(N-benzyl-3-indolyl)-1-phenylbutan-1-one (7aA)

Yield: 85%. ^{1}H NMR: δ 7.97 (m, 2H), 7.85 (m, 1H), 7.60 (m, 1H), 7.48 (m, 2H), 7.28 (m, 7H), 7.10 (m, 2H), 5.29 (s, 2H), 4.71 (m, 1H), 3.76 (m, 2H). ^{13}C NMR: δ 196.3, 137.5, 137.00, 136.96, 133.9, 129.2, 129.1, 128.5, 128.1, 128.0, 127.9 (q, J = 280 Hz), 127.8, 127.1, 122.7, 120.4, 120.0, 110.5, 109.3 (q, J = 2 Hz), 50.5, 38.9, 37.3 (q, J = 29 Hz). ^{19}F NMR: δ −70.4 (d, J = 10 Hz).

3.13. 4-Chloro-4,4-difluoro-3-(N-benzyl-3-indolyl)-1-phenylbutan-1-one (7bA)

White solid. Mp: 127–129 °C. Yield: 87%. ^{1}H NMR: δ 7.80 (m, 2H), 7.69 (m, 1H), 7.43 (m, 1H), 7.30 (m, 2H), 7.09 (m, 7H), 6.89 (m, 2H), 5.13 (s, 2H), 4.67 (dddd, J = 12, 11 8, 5 Hz, 1H), 3.65 (m, 2H). ^{13}C NMR: δ 196.3, 137. 6, 137.0, 136.9, 133.8, 132.0 (t, J = 304 Hz), 129.2, 129.1, 128.5, 128.2, 128.12, 128.06, 127.0, 122.7, 120.5, 120.1, 110.4, 110.3 (t, J = 3 Hz), 50.5, 44.0 (t, J = 24 Hz), 39.9. ^{19}F NMR: δ −54.3 (dd, J = 160, 11 Hz), −55.08 (dd, J = 160, 12 Hz).

3.14. 4,4,5,5-Pentafluoro-3-(N-benzyl-3-indolyl)-1-phenylpentan-1-one (7cA)

White solid. Mp: 105–113 °C. Yield: 91%. ^{1}H NMR: δ 7.94 (m, 2H), 7.78 (m, 1H), 7.59 (m, 1H), 7.45 (m, 2H), 7.25 (m, 7H), 7.01 (m, 2H), 5.31 (m, 2H), 4.74 (m, 1H), 3.78 (m, 2H). ^{19}F NMR: δ −81.85 (s, 3F), −114.28 (dd, J = 266, 10 Hz, 1F), −120.04 (dd, J = 266, 25 Hz, 1F).

3.15. General procedure for the base-catalyzed addition of 4-hydroxycoumarin onto β-fluoroalkylated enones 3

A solution of **3** (1.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 mL) was added to a suspension of 4-hydroxycoumarin (162 mg, 1.0 mmol, 1.0 equiv.) in dry CH_2Cl_2 (0.5 mL). Then, DBU (0.15 mL, 1.0 mmol, 1.0 equiv.) was added. The resulting solution was stirred at room temperature until no (or only traces) starting material was detected by ^{19}F NMR (16–20 h). The reaction mixture was diluted with CH_2Cl_2 and treated with a 2 N aqueous solution of HCl. After decantation, the aqueous phase was extracted with CH_2Cl_2, the combined organic phases were washed twice with a 2 N aqueous solution of HCl, dried over Na_2SO_4 and evaporated under vacuum. The crude residue was purified by recrystallisation from CH_2Cl_2/acetone/pentane to afford pure adduct **8**.

3.16. 3-[2-(1,1,1-Trifluoro-4-oxo-4-phenylbutyl)]-4-hydroxycoumarin (8aA)

Yield: 83%. ^{1}H NMR (DMSO d^6): δ 12.11 (bs, 1H), 8.06 (m, 1H), 7.97 (m, 2H), 7.64 (m, 2H), 7.52 (m, 2H), 7.38 (m, 2H), 4.81 (bs, 1H), 4.38 (dd, J = 18, 9 Hz, 1H), 3.66 (bd, J = 18, 1H). ^{13}C NMR (DMSO d^6): δ 196.8, 164.6 (bs), 161.2 (bs), 152.8, 136.4, 133.8, 133.2, 129.1, 128.3, 127.8 (d, J = 278 Hz), 124.4, 124.09, 116.7, 116.0, 98.3 (bs), 35.8 (bs), 35.0 (bs). ^{19}F NMR (DMSO d^6): δ −67.7 (d, J = 10 Hz).

3.17. 3-[2-(1-Chloro-1,1-difluoro-4-oxo-4-phenylbutyl)]-4-hydroxycoumarin (8bA)

Yellow solid. Mp: 123–127 °C. Yield: 35%. ^{1}H NMR (DMSO d^6): δ 12.12 (bs, 1H), 8.09 (m, 1H), 7.96 (m, 2H), 7.64 (m, 2H), 7.52 (m, 2H), 7.35 (m, 2H), 4.94 (bs, 1H), 4.46 (bs, 1H), 3.68 (bs, 1H). ^{13}C NMR (DMSO d^6): δ 196.8, 165.1 (bs), 161.2 (bs), 152.8, 136.5, 133.8, 133.2, 131.60 (t, J = 297 Hz), 129.1, 128.3, 124.4, 124.2 (bs), 116.7, 115.9, 99.0 (bs), 42.5 (bs), 35.8 (bs). ^{19}F NMR (DMSO d^6): δ −51.8 (bs).

3.18. 3-[3-(1,1,1,2,2-Pentafluoro-5-oxo-5-phenylpentyl)]-4-hydroxycoumarin (8cA)

Yellow solid. Mp: 83–90 °C. Yield: 93%. ^{1}H NMR: δ 9.40 (bs, 1H), 7.94 (m, 1H), 7.84 (m, 2H), 7.44 (m, 4H), 7.17 (m, 2H), 4.51 (bm, 1H), 4.33 (dt, J = 19, 10 Hz, 1H), 3.52 (dd, J = 19, 2 Hz, 1H). ^{13}C NMR: δ 199.9, 164.8, 162.8, 153.4, 135.8, 134.9, 133.3, 129.3, 129.0, 124.6, 124.5, 119.74 (qt, J = 277, 32 Hz), 117.0, 116.1, 115.6 (tq, J = 264, 37 Hz), 99.9, 36.0, 33.8 (dd, J = 24, 22 Hz). ^{19}F NMR: δ −83.9 (s, 3F), −111.3 (dd, J = 268, 16 Hz, 1F), −116.5 (dd, J = 268, 16 Hz, 1F).

3.19. 3-{2-[1,1,1-Trifluoro-4-oxo-4-(2-furyl)butyl]}-4-hydroxycoumarin (8aB)

Pale yellow solid. Mp: 145–146 °C. Yield: 74%. ^{1}H NMR (DMSO d^6): δ 12.10 (bs, 1H), 8.07 (m, 1H), 7.97 (m, 1H), 7.60 (m, 1H), 7.46 (m, 1H), 7.33 (m, 2H), 6.69 (m, 1H), 4.79 (bs, 1H), 4.13 (dd, J = 17, 9 Hz, 1H), 3.56 (bd, J = 17 Hz, 1H). ^{13}C NMR (DMSO d^6): δ 185.2, 164.5 (bs), 161.5 (bs), 152.6, 151.7, 148.3, 133.2, 127.59 (q, J = 281 Hz), 124.3, 124.1, 118.9, 116.7, 115.8, 112.9, 98.2 (bs), 35.35 (bs), 34.66 (bs). ^{19}F NMR (DMSO d^6): δ −67.83 (d, J = 10 Hz).

3.20. 3-{2-[1-Chloro-1,1-difluoro-4-oxo-4-(2-furyl)butyl]}-4-hydroxycoumarin (8bB)

Yellow solid. Mp: 141–142 °C. Yield: 89%. ^{1}H NMR (DMSO d^6): δ 11.84 (bs, 1H), 8.03 (m, 2H), 7.63 (m, 1H), 7.44 (m, 1H), 7.36 (m, 2H), 6.70 (m, 1H), 4.89 (bs, 1H), 4.19 (bs, 1H), 3.43 (bs, 1H). ^{13}C NMR (DMSO d^6): δ 185.2, 165.0 (bs), 161.0 (bs), 152.8 (bs), 151.8, 148.3, 133.2, 131.4 (t, J = 297 Hz), 124.3, 124.2 (bs), 119.0, 116.7, 115.9, 113.0, 98.9 (bs), 41.8 (bs), 35.4 (bs). ^{19}F NMR (DMSO d^6): δ −52.0 (bs).

3.21. 3-{3-[1,1,1,2,2-Pentafluoro-5-oxo-5-(2-furyl)pentyl]}-4-hydroxycoumarin (8cB)

Yellow solid. Mp: 60–65 °C. Yield: 71%. ^{1}H NMR (DMSO d^6): δ 12.1 (bs, 1H), 8.1 (m, 1H), 7.74 (m, 1H), 7.52 (m, 1H), 7.25 (m, 4H), 6.56 (m, 1H), 4.85 (m, 1H), 4.12 (dd, J = 18, 9 Hz, 1H), 3.32 (dd, J = 18, 4 Hz, 1H). ^{13}C NMR (DMSO d^6): δ 185.0, 164.5, 161.3, 152.9, 151.8, 147.5, 132.7, 124.2, 123.9, 119.3 (qt, J = 288, 39 Hz), 118.36, 117.1 (tq, J = 240, 38 Hz), 116.5, 115.5, 112.6, 98.0 (bs), 34.0 (bs), 32,6 (t, J = 23 Hz). ^{19}F NMR (DMSO d^6): δ −82.94 (s, 3F), −112.76 (dd, J = 267, 14 Hz, 1F), −116.73 (dd, J = 267, 19 Hz, 1F).

References

[1] T. Billard, S. Bruns, B.R. Langlois, Opt. Lett. 2 (2000) 2101–2103.
[2] T. Billard, B.R. Langlois, G. Blond, Tetrahedron Lett. 41 (2000) 8777–8780.
[3] T. Billard, B.R. Langlois, G. Blond, Eur. J. Org. Chem. (2001) 1467–1471.
[4] G. Blond, T. Billard, B.R. Langlois, Tetrahedron Lett. 42 (2001) 2473–2475.
[5] G. Blond, T. Billard, B.R. Langlois, J. Org. Chem. 66 (2001) 4826–4830.
[6] T. Billard, B.R. Langlois, J. Org. Chem. 67 (2002) 997–1000.
[7] T. Billard, S. Gille, A. Ferry, A. Barthélémy, C. Christophe, B.R. Langlois, J. Fluorine Chem. 126 (2005) 189–196.
[8] J. Leuger, G. Blond, R. Fröhlich, T. Billard, G. Haufe, B.R. Langlois, J. Org. Chem. 71 (2006) 2735–2739.
[9] C. Christophe, T. Billard, B.R. Langlois, Eur. J. Org. Chem. (2005) 3745–3748.
[10] O. Marrec, C. Christophe, T. Billard, B. Langlois, J.P. Vors, S. Pazenok, Adv. Synth. Catal. 352 (2010) 2825–2830.
[11] K.B. Jensen, J. Thorhauge, R.G. Hazell, K.A. Jorgensen, Angew. Chem. Int. Ed. 40 (2001) 160–163.
[12] S.C. Sweetman (Ed.), Martindale, the Complete Drug Reference, 36th ed., Pharmaceutical Press, London, 2009, p. 1425.
[13] N. Halland, T. Hansen, K.A. Jorgensen, Angew. Chem. Int. Ed. 42 (2003) 4955–4957.
[14] T. Billard, Chem. Eur. J. 12 (2006) 974–979 (Concept article).