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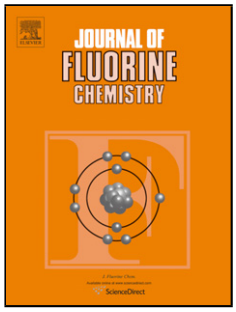

Title: Synthesis of Fluorinated Oxazoles by Oxidative Cyclization of Fluorinated Enamides

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PII: S0022-1139(16)30337-2
DOI: http://dx.doi.org/doi:10.1016/j.jfluchem.2016.09.014
Reference: FLUOR 8859

To appear in: *FLUOR*

Received date: 23-5-2016
Revised date: 20-9-2016
Accepted date: 22-9-2016

Please cite this article as: Oleg S.Shishlyk, Andrey V.Shcherbatiuk, Rustam T.Iminov, Anton V.Tverdokhlebov, Andrey A.Tolmachev, Pavel K.Mykhailiuk, Angelina V.Biitseva, Synthesis of Fluorinated Oxazoles by Oxidative Cyclization of Fluorinated Enamides, Journal of Fluorine Chemistry http://dx.doi.org/10.1016/j.jfluchem.2016.09.014

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Synthesis of Fluorinated Oxazoles by Oxidative Cyclization of Fluorinated Enamides

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Highlights

Fluorinated isoxazoles were obtained by oxidation of the corresponding enamides.
These fluorinated building blocks are useful for Drug discovery and Agrochemistry.
Di- and trifluoromethyl-containing compounds were obtained.

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Abstract: Novel approach to CF_3-/CHF_2-oxazoles was developed. The key reaction was oxidation of fluoroalkyl enamides with $PhI(RCO_2)_2$.

Keywords: Acylation, Fluoroalkyl, Hypervalent iodine, Oxazole, Ring closure

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1. Introduction

Oxazole core is widely presented within natural products and pharmaceuticals [1]. Therefore, the synthesis of oxazoles and their modifications play a role in the both – industry and academy [2]. At once introduction of fluoroalkyl groups to common heterocycles, including oxazoles, has become promising and widespread trend in modern medicinal chemistry and agrochemistry [3, 4]. For example, diacylglycerol acyltransferase (DGAT-1) inhibitors **1** and **2** (Figure 1) were discovered by *Hoffmann – La Roche* in 2011 [5]. Two years later, *Merck Laboratories* reported the compound **3** with similar activity and biological profile [6]. Compounds **1-3** are positioned as drug-candidates for obesity and type 2 diabetes treatment. This instance illustrates an increasing relevance of fluoroalkyl oxazoles for medicinal chemistry and high competition level in the field.

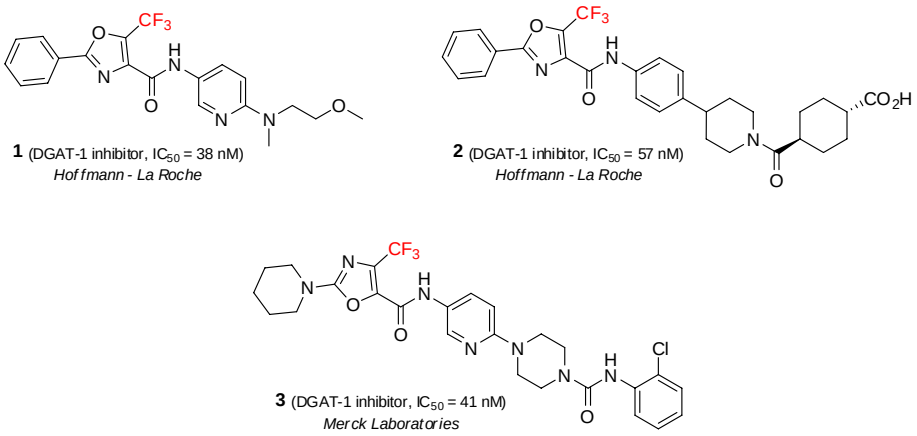

Figure 1. Known bioactive CF_3-oxazoles [5, 6].

Compounds **1**,**2** and **3** are derivatives of two isomeric CF_3-oxazolecarboxylic acids. While CF_3-oxazoles **5** are easily synthesized in good yields from diazo ester **4** and diverse nitriles [7], reaction between **4** and amides requires separation of mixture **6** and **7**, making this approach to the core **8** laborious (Scheme 1, a) [8]. Another way to 4-CF_3-oxazole-5-carboxylic acid core was based on reaction of ester **9** with ureas (Scheme 1, b) [6,9]. However, the method was strongly limited by preparation of 2-amino derivatives **10**, since with carboxamides the complex mixtures was formed.

So, 4-CF_3-oxazole-5-carboxylic acids are scarcely accessible, albeit the scaffold is relevant for medicinal chemistry. Hence elaboration of facile and general approach to the core is an actual task. Furthermore, an option to introduce other fluoroalkyl groups (for instance CF_2H) would be a great benefit of a method. Noteworthy, only a few 4-CHF_2-oxazoles were mentioned in the literature through fluorination of the corresponding aldehydes with R_2N-SF_3 [10]. In the course on our ongoing project on fluorinated azoles [11], herein we report on a novel general approach to 4-fluoroalkyl oxazole-5-carboxylic acids.

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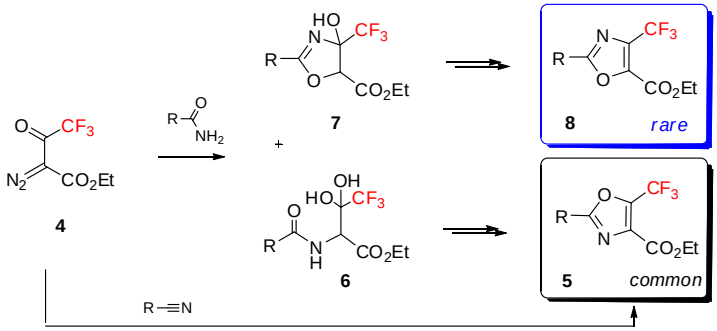
a)



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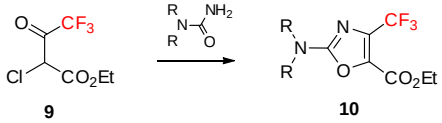

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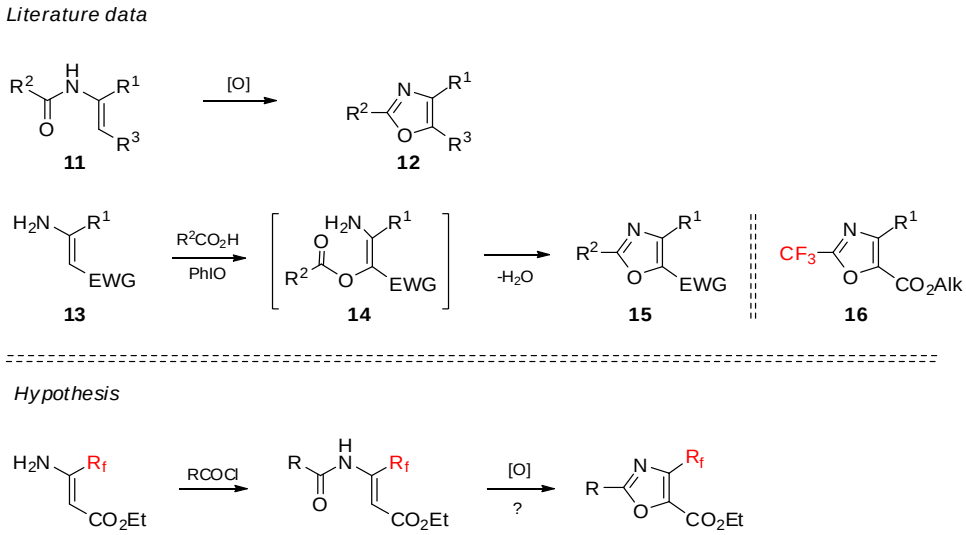
Scheme 1. Approaches to CF_3-oxazoles [6-9].

2. Results and Discussion

2.1. Hypothesis

Classical approaches to oxazoles, like Robinson-Gabriel and Fischer syntheses as well as the Cornforth protocol, were extensively exploited for almost a century; and their scope and limitation were well studied. Therefore, in the recent years significant attention has been paid to another approaches to oxazole ring formation. Among them oxidative cyclization of enamides **11** into oxazoles **12** (Scheme 2) has got an increasing interest [12,13]. Application of hypervalent iodine(III) reagents as the oxidants induced essential progress in this field [14], because these chemicals were cheap, available, non-toxic and environmental friendly [15]. As the result the similar transformation of enamines **13** into oxazoles **15** with or without isolation of the intermediates **14** was discovered [14].

It should be noted that a dozen of 2-CF_3 oxazoles **16** has already been prepared through the enamine oxidation approach [14b]. However, in this case the CF_3-group was introduced from the oxidant, $PhI(OCOCF_3)_2$, but not from the enamine moiety of the starting material. Hitherto nothing is reported on behaviour of fluoroalkyl substituted enamides **11** or enamines **13** in this reaction, despite the availability of the last ones from the corresponding acetoacetates [16]. Therefore, a possibility of the fluorinated enamines application for the oxazoles synthesis has been studied.



Scheme 2. Known [12–14] and proposed approaches to oxazoles.

2.2. Synthesis

Synthesis of CHF_2-derivatives was investigated first. Treating compound **17** with acid chlorides/pyridine smoothly gave N-acyl products **18**(**a-f**) (Scheme 3). Possible *C*-acylation was not observed in full agreement with the literature data [17]. Treatment of enamides **18a-f** with phenyliodonium diacetate ($PhI(CH_3CO_2)_2$ - PIDA) afforded the needed oxazoles **19**(**a-f**) in 50-80% yields. Finally, standard hydrolysis of the ester group with LiOH accomplished the target acids **20**(**a-f**). All syntheses were performed on a gram scale.

We next studied functionalized CHF_2-oxazoles. The chloromethyl- and 1-chloroethyl enamides **18g**/**18h** were obtained by acylation of **17g**/**17h**. However, in the presense of pyridine complex mixtures were formed. Therefore, the products were obtained by heating the reaction mixture in dioxane without a base. Oxidation of enamides **18g**/**18h** with PIDA gave the expected oxazoles **19g**/**19h** in good yields of 70-75%.

Unfortunately, all attempts to perform alkali hydrolysis of the ester group in **19g**/**19h** gave complex mixtures.

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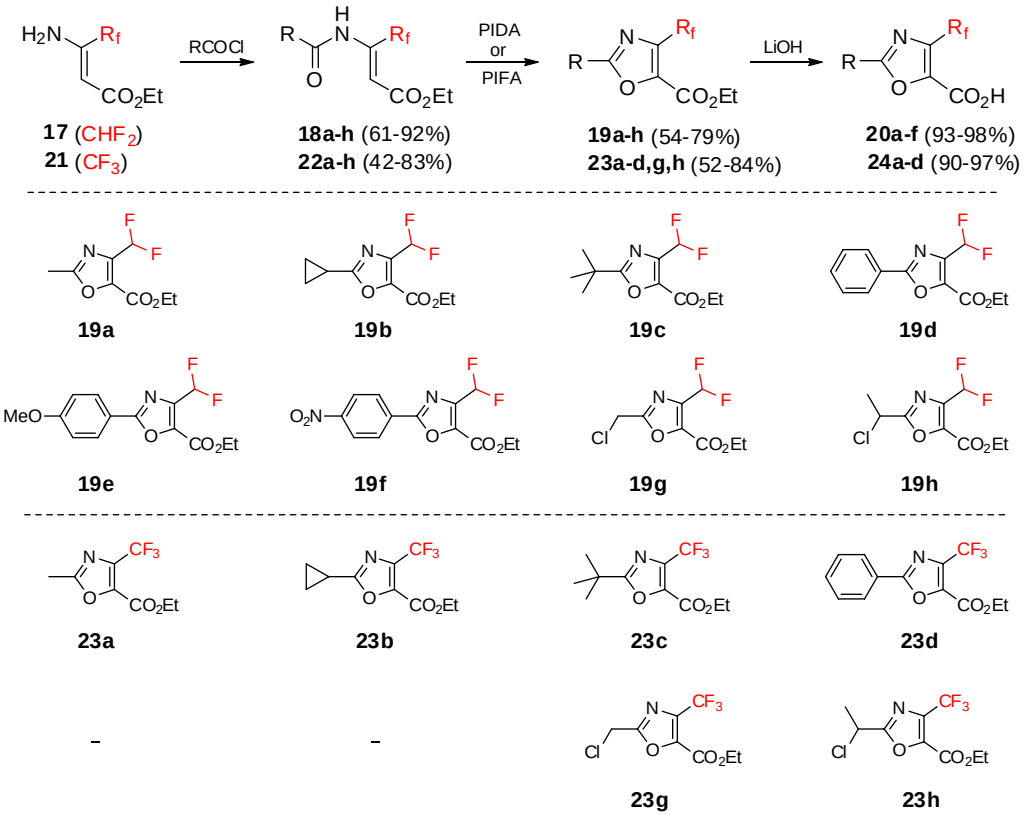
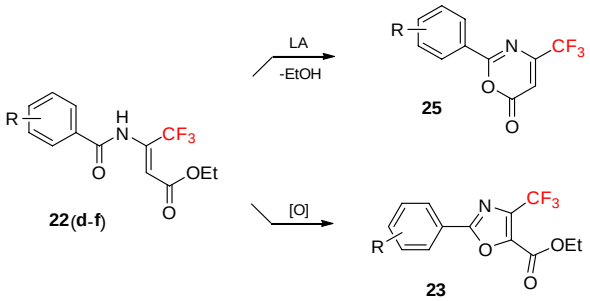


Scheme 3. Synthesis of fluorinated oxazoles.

Synthesis of CF_3-oxazoles was investigated next. Acylation of enamine **21** gave enamides **22a-h** in moderate yields. All attempts, however, to perform oxidative cyclization of **22a-h** with PIDA gave low conversion of the reaction and side products. The more active phenyliodonium *bis*-trifluoroacetate ($PhI(CF_3CO_2)_2$ - PIFA) was next challenged. It was easily generated *in situ* from PIDA and either trifluoroacetic acid [18] or its anhydride [19]. In fact, the reaction easily proceeded to give CF_3-oxazoles **23**(**a-c**,**g**,**h**) in 50-80 % yields. Nevertheless, aromatic enamides **22d-22f** still did not react. The use of even more potent oxidant - phenyliodonium di-triflate ($PhI(CF_3SO_2O)_2$ - PIDT) [20] - allowed to synthesize oxazole **23d** in 52% yield. The corresponding methoxy- and nitro-products **22e**/**22f** were observed in the reaction mixture, but not isolated due to a low conversion. In all cases formation of oxazines **25** (Scheme 4) was observed. During the synthesis of **23d** the both reactions occurred in parallel, while with enamides **22e/22f** formation of oxazines prevailed. It is worth mentioning that the formation of oxazines **25** upon treatment of enamides of **22** with oxalyl chloride was reported previously [17a].



Scheme 4. Oxidation of **22**(**d-f**) with $PhI(CF_3SO_2O)_2$ (PIDT).

Basic hydrolysis of the ester group in **23**(**a-d**) smoothly gave acids **24**(**a-d**). Hydrolysis of **23g**/**23h** failed, however. It should be also noted that the acid **24d** and the corresponding ester **23d** were reported previously [8, 21] through the diazo ester **4** route (Scheme 1), whereas the rest of the oxazoles prepared are new.

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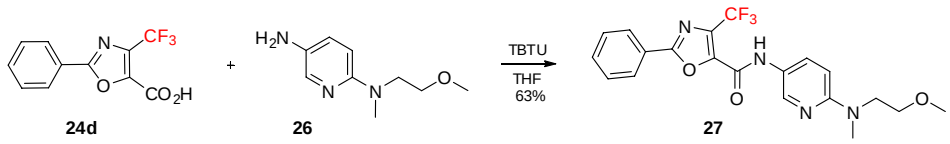
2.3. Practical Application

To demonstrate the practical utility of our approach, we synthesized compound **27** (Scheme 5) - the isomer of **1** (by Hoffmann – La Roche, Figure 1).



Scheme 5. Synthesis of compound **27** - the isomer of DGAT-1 inhibitor **1**.

3. Conclusions

The present research has resulted in simple and convenient novel approach to 4-CF_3 and 4-CHF_2-oxazole-5-carboxylic acids. The synthesis is based on the well known and readily available starting materials and comprises 3-steps sequence. The key transformation is the oxidative oxazole ring closure induced by common iodine (III) reagents, whereas two other steps are usual and routine. The both CF_2H and CF_3 series the proper methods have been elaborated providing the target acids in good yields and grams scales, except the case of 2-aryl-4-CF_3 derivatives. Availability of the obtained building blocks is believed to have high potential for pharmaceutical chemistry.

4. Experimental

4.1. General information

Enamines **17**, **21** [16] and amine **26** [5] were prepared as reported. Acid chlorides were either commercially available or prepared from the corresponding acids through standard procedures. Other reagents and solvents were commercially available. Melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) and Mercury Varian 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C and 376 MHz for ^{19}F) spectrometers in $CDCl_3$ or DMSO[D_6] solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si (for ^{1}H and ^{13}C) or $CFCl_3$ (for ^{19}F). Elemental analyses were performed at the Microanalytical Department of the Institute of Organic Chemistry, NAS, Kiev, Ukraine. The purity of all compounds prepared was checked with LC-MS on an Agilent 1100 instrument.

*4.2. Enamides **18a-f** and **22a-f**. General Procedure*

Acid chloride (66.7 mmol) was added in one portion to a solution of the corresponding enamine **17, 21** (60.6 mmol) in 1,2-dichloroethane (200 mL) at RT. Pyridine (8.6 mL, 106 mmol) was added thereto also in one portion, and the mixture was stirred at reflux temperature for 16 h. The solvent was evaporated in vacuo, and the residue was partitioned between water (200 mL) and ethyl acetate (200 mL). The organic layer was separated and washed sequentially with water (2 x 150 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), and dried ($MgSO_4$). Evaporation of the extract in vacuo afforded crude compounds **18a-f, 22a-f** as oils, which were used in the next step without purification. Analytical samples of the materials were purified by column chromatography on silica gel eluting with ethyl acetate – hexane (1:3, v/v) mixture.

*4.2.1. Ethyl 3-acetylamino-4,4-difluorobut-2-enoate (**18a**)*

Yellowish oil (11.4 g, 91 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.10 (s, 3 H, Me), 4.15 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 5.57 (s, 1 H, CH), 7.20 (t, $^2J_{H-F}$ = 54.2 Hz, 1 H, CHF_2), 10.67 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 24.2 (Me), 60.9 (CH_2CH_3), 96.9 (t, $^3J_{C-F}$ = 10.0 Hz, CH), 108.5 (t, $^1J_{C-F}$ = 242.0 Hz, CHF_2), 146.7 (t, $^2J_{C-F}$ = 23.5 Hz, C–CHF_2), 168.3, 168.4 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.84 (d, $^2J_{H-F}$ = 54.0 Hz, CHF_2) ppm.

MS: m/z = 208 $[M + H]^+$.

Anal. Calcd for $C_8H_{11}F_2NO_3$: C, 46.38; H, 5.35; N, 6.76. Found: C, 46.44; H, 5.30; N, 6.81.

*4.2.2. Ethyl 3-[(cyclopropylcarbonyl)amino]-4,4-difluorobut-2-enoate (**18b**)*

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Yellowish oil (13.8 g, 89 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89–0.94 (m, 2 H, CH_2), 1.04–1.08 (m, 2 H, CH_2), 1.31 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.57–1.63 (m, 1 H, CH), 4.23 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.64 (s, 1 H, CH), 7.27 (t, $^2J_{H–F}$ = 54.0 Hz, 1 H, CHF_2), 10.99 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.1 (2×CH_2), 14.0 (CH_2CH_3), 15.8 (CH), 60.9 (CH_2CH_3), 96.3 (t, $^3J_{C–F}$ = 9.5 Hz, CH), 108.5 (t, $^1J_{C–F}$ = 242.0 Hz, CHF_2), 146.9 (t, $^2J_{C–F}$ = 23.5 Hz, *C*–CHF_2), 168.6 (CO_2Et), 172.1 (CO) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.51 (d, $^2J_{H–F}$ = 54.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 234 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{13}F_2NO_3$: C, 51.50; H, 5.62; N, 6.01. Found: C, 51.41; H, 5.59; N, 5.89.

*4.2.3. Ethyl 3-[(2,2-dimethylpropanoyl)amino]-4,4-difluorobut-2-enoate (**18c**)*

Yellowish oil (11.1 g, 75 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (s, 9 H, $C(CH_3)_3$), 1.30 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.22 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.66 (s, 1 H, CH), 7.29 (t, $^2J_{H–F}$ = 54.2 Hz, 1 H, CHF_2), 11.07 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 27.2 ($C(CH_3)_3$), 40.0 ($C(CH_3)_3$), 60.9 (CH_2CH_3), 97.0 (t, $^3J_{C–F}$ = 9.5 Hz, CH), 108.7 (t, $^1J_{C–F}$ = 241.4 Hz, CHF_2), 147.3 (t, $^2J_{C–F}$ = 23.5 Hz, *C*–CHF_2), 168.7 (CO_2Et), 177.2 (CO) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.74 (d, $^2J_{H–F}$ = 54.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 250 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{17}F_2NO_3$: C, 53.01; H, 6.87; N, 5.62. Found: C, 52.93; H, 6.92; N, 5.69.

*4.2.4. Ethyl 3-benzoylamino-4,4-difluorobut-2-enoate (**18d**)*

White solid (13.5 g, 82 %) mp 65 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 4.30 (q, J = 6.8 Hz, 2 H, CH_2CH_3), 5.82 (s, 1 H, CH), 7.51 (t, $^2J_{H–F}$ = 53.7 Hz, 1 H, CHF_2), 7.53 (t, J = 7.8 Hz, 2 H, 2×H_{Ph}), 7.61 (t, J = 7.8 Hz, 1 H, H_{Ph}), 7.99 (d, J = 7.8 Hz, 2 H, 2×H_{Ph}), 11.83 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_2CH_3), 61.1 (CH_2CH_3), 97.7 (t, $^3J_{C–F}$ = 10.3 Hz, CH), 108.8 (t, $^1J_{C–F}$ = 242.1 Hz, CHF_2), 127.8 (2×CH_{Ph}), 129.0 (2×CH_{Ph}), 132.5 (C_{Ph}), 133.0 (CH_{Ph}), 147.3 (t, $^2J_{C–F}$ = 23.5 Hz, *C*–CHF_2), 164.7, 169.0 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.39 (d, $^2J_{H–F}$ = 54.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 270 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{13}F_2NO_3$: C, 57.99; H, 4.87; N, 5.20. Found: C, 58.04; H, 4.91; N, 5.18.

*4.2.5. Ethyl 4,4-difluoro-3-[(4-methoxybenzoyl)amino]but-2-enoate (**18e**)*

White solid (12.1 g, 67 %) mp 63#C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 3.89 (s, 3 H, OMe), 4.29 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.78 (s, 1 H, CH), 7.00 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 7.51 (t, $^2J_{H–F}$ = 54.2 Hz, 1 H, CHF_2), 7.96 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 11.76 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2 (CH_2CH_3), 55.5 (OMe), 61.0 (CH_2CH_3), 97.0 (t, $^3J_{C–F}$ = 9.5 Hz, CH), 108.8 (t, $^1J_{C–F}$ = 242.1 Hz, CHF_2), 114.2 (2×CH_{Ar}), 124.8 (C_{Ar}), 129.9 (2×CH_{Ar}), 147.6 (t, $^2J_{C–F}$ = 23.5 Hz, *C*–CHF_2), 163.4, 164.2, 169.1 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.31 (d, $^2J_{H–F}$ = 54.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 300 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{15}F_2NO_4$: C, 56.19; H, 5.05; N, 4.68. Found: C, 56.09; H, 4.97; N, 4.75.

*4.2.6. Ethyl 4,4-difluoro-3-[(4-nitrobenzoyl)amino]but-2-enoate (**18f**)*

Yellow solid (11.6 g, 61 %) mp 78 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 1.23 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.20 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.88 (s, 1 H, CH), 7.29 (t, $^2J_{H–F}$ = 54.1 Hz, 1 H, CHF_2), 8.13 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 8.41 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 11.34 (s, 1 H, NH) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 14.0 (CH_2CH_3), 61.0 (CH_2CH_3), 103.0 (t, $^3J_{C–F}$ = 9.0 Hz, CH), 109.8 (t, $^1J_{C–F}$ = 240.8 Hz, CHF_2), 124.2 (2×CH_{Ar}), 129.2 (2×CH_{Ar}), 138.0 (C_{Ar}), 144.2 (t, $^2J_{C–F}$ = 23.4 Hz, *C*–CHF_2), 150.0 (C–NO_2), 162.9, 166.8 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 121.22 (d, $^2J_{H–F}$ = 53.5 Hz, CHF_2) ppm.

MS: *m*/*z* = 315 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{12}F_2N_2O_5$: C, 49.69; H, 3.85; N, 8.91. Found: C, 49.78; H, 3.77; N, 9.02.

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*4.2.7. Ethyl 3-acetylamino-4,4,4-trifluorobut-2-enoate (**22a**)*

Yellowish oil (11.3 g, 83 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.13 (s, 3 H, Me), 4.19 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 5.77 (s, 1 H, CH), 10.17 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_2CH_3), 24.1 (Me), 61.3 (CH_2CH_3), 103.5 (q, $^3J_{C–F}$ = 5.9 Hz, CH), 119.7 (q, $^1J_{C–F}$ = 275.1 Hz, CF_3), 139.4 (q, $^2J_{C–F}$ = 35.9 Hz, C–CF_3), 166.6, 167.0 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 66.32 (s, CF_3) ppm.

MS: m/z = 226 $[M + H]^+$.

Anal. Calcd for $C_8H_{10}F_3NO_3$: C, 42.67; H, 4.48; N, 6.22. Found: C, 42.74; H, 4.39; N, 6.11.

*4.2.8. Ethyl 3-[(cyclopropylcarbonyl)amino]-4,4,4-trifluorobut-2-enoate (**22b**)*

Yellowish oil (11.7 g, 77 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.87–0.89 (br m, 2 H, CH_2), 1.05 (br s, 2 H, CH_2), 1.29 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.58–1.60 (br m, 1 H, CH), 4.22 (br q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.74 (s, 1 H, CH), 10.61 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 9.2 (2×CH_2), 14.1 (CH_2CH_3), 16.0 (CH), 61.5 (CH_2CH_3), 101.8 (q, $^3J_{C–F}$ = 6.0 Hz, CH), 119.8 (q, $^1J_{C–F}$ = 275.3 Hz, CF_3), 140.4 (q, $^2J_{C–F}$ = 35.9 Hz, C–CF_3), 167.7, 170.5 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 65.66 (s, CF_3) ppm.

MS: m/z = 252 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{12}F_3NO_3$: C, 47.81; H, 4.81; N, 5.58. Found: C, 47.93; H, 4.89; N, 5.65.

*4.2.9. Ethyl 3-[(2,2-dimethylpropanoyl)amino]-4,4,4-trifluorobut-2-enoate (**22c**)*

Yellowish oil (9.5 g, 59 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.27–1.30 (m, 12 H, $C(CH_3)_3$ + CH_2CH_3), 4.23 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.76 (s, 1 H, CH), 10.72 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.1 (CH_2CH_3), 27.3 ($C(CH_3)_3$), 40.3 ($C(CH_3)_3$), 61.5 (CH_2CH_3), 102.0 (q, $^3J_{C–F}$ = 6.0 Hz, CH), 119.9 (q, $^1J_{C–F}$ = 274.8 Hz, CF_3), 141.6 (q, $^2J_{C–F}$ = 35.4 Hz, C–CF_3), 167.9, 175.5 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 65.34 (s, CF_3) ppm.

MS: m/z = 268 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{16}F_3NO_3$: C, 49.44; H, 6.03; N, 5.24. Found: C, 49.54; H, 5.97; N, 5.29.

*4.2.10. Ethyl 3-benzoylamino-4,4,4-trifluorobut-2-enoate (**22d**)*

White solid (11.6 g, 58 %) mp 89 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.31 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.92 (s, 1 H, CH), 7.53 (t, J = 7.5 Hz, 2 H, 2×H_{Ph}), 7.61 (t, J = 7.5 Hz, 1 H, H_{Ph}), 8.01 (d, J = 7.5 Hz, 2 H, 2×H_{Ph}), 11.53 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_2CH_3), 61.6 (CH_2CH_3), 102.2 (q, $^3J_{C–F}$ = 5.9 Hz, CH), 119.8 (q, $^1J_{C–F}$ = 275.1 Hz, CF_3), 127.9 (2×CH_{Ph}), 129.0 (2×CH_{Ph}), 132.7 (C_{Ph}), 132.9 (CH_{Ph}), 141.5 (q, $^2J_{C–F}$ = 35.9 Hz, C–CF_3), 163.0, 168.1 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 64.96 (s, CF_3) ppm.

MS: m/z = 288 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.42; H, 4.17; N, 4.91.

*4.2.11. Ethyl 4,4,4-trifluoro-3-[(4-methoxybenzoyl)amino]but-2-enoate (**22e**)*

White solid (9.4 g, 49 %) mp 84 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 3.84 (s, 3 H, OMe), 4.25 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 5.83 (s, 1 H, CH), 6.96 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 7.93 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 11.45 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1 (CH_2CH_3), 55.5 (OMe), 61.5 (CH_2CH_3), 101.4 (q, $^3J_{C–F}$ = 6.6 Hz, CH), 114.2 (2×CH_{Ar}), 119.8 (q, $^1J_{C–F}$ = 275.1 Hz, CF_3), 125.0 (C_{Ar}), 130.0 (2×CH_{Ar}), 141.8 (q, $^2J_{C–F}$ = 35.9 Hz, C–CF_3), 162.5, 163.4, 168.3 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 64.84 (s, CF_3) ppm.

MS: m/z = 318 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}F_3NO_4$: C, 53.00; H, 4.45; N, 4.41. Found: C, 52.94; H, 4.41; N, 4.36.

*4.2.12. Ethyl 4,4,4-trifluoro-3-[(4-nitrobenzoyl)amino]but-2-enoate (**22f**)*

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Yellow solid (8.5 g, 42 %) mp 93 °C.

^{1}H NMR (DMSO[D_6], 400 MHz): δ = 1.33 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.28 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.94 (s, 1 H, CH), 8.13 (d, J = 8.5 Hz, 2 H, 2×H_{Ar}), 8.33 (d, J = 8.5 Hz, 2 H, 2×H_{Ar}), 11.70 (br s, 1 H, NH) ppm.

^{13}C NMR (DMSO[D_6], 100 MHz): δ = 14.0 (CH_2CH_3), 62.0 (CH_2CH_3), 103.4 (q, $^3J_{C-F}$ = 5.9 Hz, CH), 119.6 (q, $^1J_{C-F}$ = 275.1 Hz, CF_3), 124.2 (2×CH_{Ar}), 129.1 (2×CH_{Ar}), 138.1 (C_{Ar}), 140.9 (q, $^2J_{C-F}$ = 36.7 Hz, C–CF_3), 150.3 (C–NO_2), 161.0, 168.2 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 65.21 (s, CF_3) ppm.

MS: m/z = 333 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}F_3N_2O_5$: C, 47.00; H, 3.34; N, 8.43. Found: C, 47.08; H, 3.36; N, 8.40.

*4.3. Enamides **18g,h** and **22 g,h**. General Procedure*

Chloroacetyl or 2-chloropropionyl chloride (106 mmol) was added in one portion to a solution of the corresponding enamine **17, 21** (60.6 mmol) in anhydrous dioxane (100 mL) at RT, and the formed mixture was stirred at reflux temperature for 24 h. The solvent was evaporated in vacuo, and the residue was partitioned between water (150 mL) and ethyl acetate (150 mL). The organic layer was separated and washed sequentially with water (100 mL), saturated aqueous $NaHCO_3$ (2 x 100 mL), and brine (100 mL), and dried ($MgSO_4$). Evaporation of the extract in vacuo furnished crude compounds **18g,h, 22g,h** as oils, which were used in the next step without purification. Analytical samples of the materials were purified by column chromatography on silica gel eluting with ethyl acetate – hexane (1:3, v/v) mixture.

*4.3.1. Ethyl 3-[(chloroacetyl)amino]-4,4-difluorobut-2-enoate (**18g**)*

Yellowish oil (14.1 g, 92 %).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 4.09 (s, 2 H, CH_2Cl), 4.19 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 5.70 (s, 1 H, CH), 7.18 (t, $^2J_{H-F}$ = 54.1 Hz, 1 H, CHF_2), 11.52 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.5 (CH_2CH_3), 42.0 (CH_2Cl), 60.8 (CH_2CH_3), 99.1 (t, $^3J_{C-F}$ = 9.5 Hz, CH), 108.0 (t, $^1J_{C-F}$ = 241.8 Hz, CHF_2), 144.9 (t, $^2J_{C-F}$ = 23.4 Hz, C–CHF_2), 164.4, 167.4 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.90 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: m/z = 242 $[M + H]^+$.

Anal. Calcd for $C_8H_{10}ClF_2NO_3$: C, 39.77; H, 4.17; N, 5.80. Found: C, 39.88; H, 4.25; N, 5.76.

*4.3.2. Ethyl 3-[(2-chloropropanoyl)amino]-4,4-difluorobut-2-enoate (**18h**)*

Yellowish oil (14.2 g, 92 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.73 (d, J = 7.0 Hz, 3 H, $CH(CH_3)Cl$), 4.23 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.45 (q, J = 7.0 Hz, 1 H, $CH(CH_3)Cl$), 5.74 (s, 1 H, CH), 7.22 (t, $^2J_{H-F}$ = 54.2 Hz, 1 H, CHF_2), 11.53 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 21.9 ($CH(CH_3)Cl$), 54.9 ($CH(CH_3)Cl$), 61.1 (CH_2CH_3), 99.4 (t, $^3J_{C-F}$ = 9.5 Hz, CH), 108.4 (t, $^1J_{C-F}$ = 242.1 Hz, CHF_2), 145.6 (t, $^2J_{C-F}$ = 24.2 Hz, C–CHF_2), 167.9, 168.2 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 122.91 and – 122.46 (2×d, $^2J_{H-F}$ = 53.5 Hz and $^2J_{H-F}$ = 54.0 Hz, CHF_2) ppm.

MS: m/z = 256 $[M + H]^+$.

Anal. Calcd for $C_9H_{12}ClF_2NO_3$: C, 42.28; H, 4.73; N, 5.48. Found: C, 42.14; H, 4.79; N, 5.39.

*4.3.3. Ethyl 3-[(chloroacetyl)amino]-4,4,4-trifluorobut-2-enoate (**22g**)*

Yellowish oil (12.2 g, 78 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 4.18 (s, 2 H, CH_2Cl), 4.30 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 5.95 (s, 1 H, CH), 11.19 (br s, 1 H, NH) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 42.7 (CH_2Cl), 61.7 (CH_2CH_3), 105.0 (q, $^3J_{C-F}$ = 5.9 Hz, CH), 119.6 (q, $^1J_{C-F}$ = 275.1 Hz, CF_3), 139.0 (q, $^2J_{C-F}$ = 35.9 Hz, C–CF_3), 162.9, 168.8 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 65.65 (s, CF_3) ppm.

MS: m/z = 260 $[M + H]^+$.

Anal. Calcd for $C_8H_9ClF_3NO_3$: C, 37.01; H, 3.49; N, 5.40. Found: C, 37.10; H, 3.46; N, 5.37.

*4.3.4. Ethyl 3-[(2-chloropropanoyl)amino]-4,4,4-trifluorobut-2-enoate (**22h**)*

Yellowish oil (12.1 g, 73 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.77 (d, J = 6.8 Hz, 3 H,

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CH(C*H*$_3$)Cl), 4.28 (q, *J* = 7.3 Hz, 2 H, C*H*$_2$CH$_3$), 4.49 (q, *J* = 6.8 Hz, 1 H, C*H*(CH$_3$)Cl), 5.92 (s, 1 H, CH), 11.09 (br s, 1 H, NH) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 14.0 (CH$_2$*C*H$_3$), 22.0 (CH(*C*H$_3$)Cl), 55.1 (*C*H(CH$_3$)Cl), 61.6 (*C*H$_2$CH$_3$), 104.8 (q, $^3J_{C-F}$ = 5.9 Hz, CH), 119.6 (q, $^1J_{C-F}$ = 275.1 Hz, CF$_3$), 139.3 (q, $^2J_{C-F}$ = 35.9 Hz, *C*–CF$_3$), 166.4, 166.8 ppm.

^{19}F NMR (CDCl$_3$, 376 MHz,): δ = – 65.72 (s, CF$_3$) ppm.

MS: *m*/*z* = 274 [M + H]$^+$.

Anal. Calcd for $C_9H_{11}ClF_3NO_3$: C, 39.50; H, 4.05; N, 5.12. Found: C, 39.59; H, 3.99; N, 5.11.

*4.4. Ethyl 4-Difluoromethyloxazole-5-carboxylates **19a-h**. General Procedure*

PIDA (10.2 g, 56 mmol) was carefully added in small portions to a stirred and refluxed solution of appropriate enamide **18a-h** (40 mmol) and Et$_2$O-BF$_3$ complex (16.8 mL, 80 mmol) in 1,2-dichloroethane (200 mL). The addition took ~ 30 min. After it was completed the obtained mixture was stirred at reflux temperature overnight. Upon cooling the solvent was removed in vacuo and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The organic layer was separated and washed sequentially with water (200 mL), saturated aqueous NaHCO$_3$ (200 mL), and brine (200 mL), and dried (MgSO$_4$). The solvent was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column eluting with ethyl acetate – hexane (3:10, v/v) mixture to give compounds **19a-h** as oils some of which solidified upon standing.

*4.4.1. Ethyl 4-difluoromethyl-2-methyloxazole-5-carboxylate (**19a**)*

Yellowish oil (6.4 g, 79 %).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.35 (t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$), 2.53 (s, 3 H, Me), 4.37 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 7.04 (t, $^2J_{H-F}$ = 53.5 Hz, 1 H, CHF$_2$) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 14.1 (Me), 14.2 (Me), 62.3 (*C*H$_2$CH$_3$), 107.6 (t, $^1J_{C-F}$ = 235.5 Hz, CHF$_2$), 139.7 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF$_2$), 140.1 (t, $^3J_{C-F}$ = 8.1 Hz, *C*–CO$_2$Et), 156.8, 164.5 ppm.

^{19}F NMR (CDCl$_3$, 376 MHz,): δ = – 118.00 (d, $^2J_{H-F}$ = 53.5 Hz, CHF$_2$) ppm.

MS: *m*/*z* = 206 [M + H]$^+$.

Anal. Calcd for $C_8H_9F_2NO_3$: C, 46.83; H, 4.42; N, 6.83. Found: C, 46.91; H, 4.45; N, 6.80.

*4.4.2. Ethyl 2-cyclopropyl-4-(difluoromethyl)oxazole-5-carboxylate (**19b**)*

Yellowish oil (6.3 g, 68 %).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.13–1.22 (m, 4 H, 2×CH$_2$), 1.37 (t, *J* = 7.3 Hz, 3 H, CH$_2$C*H*$_3$), 2.10–2.17 (m, 1 H, CH), 4.38 (q, *J* = 7.3 Hz, 2 H, C*H*$_2$CH$_3$), 7.04 (t, $^2J_{H-F}$ = 53.5 Hz, 1 H, CHF$_2$) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 9.2 (CH), 9.7 (2×CH$_2$), 14.1 (CH$_2$*C*H$_3$), 62.1 (*C*H$_2$CH$_3$), 107.7 (t, $^1J_{C-F}$ = 236.2 Hz, CHF$_2$), 139.2 (t, $^3J_{C-F}$ = 8.1 Hz, *C*–CO$_2$Et), 140.0 (t, $^2J_{C-F}$ = 26.4 Hz, *C*–CHF$_2$), 156.8, 169.5 ppm.

^{19}F NMR (CDCl$_3$, 376 MHz,): δ = – 118.06 (d, $^2J_{H-F}$ = 53.0 Hz, CHF$_2$) ppm.

MS: *m*/*z* = 232 [M + H]$^+$.

Anal. Calcd for $C_{10}H_{11}F_2NO_3$: C, 51.95; H, 4.80; N, 6.06. Found: C, 52.04; H, 4.85; N, 5.99.

*4.4.3. Ethyl 2-(tert-butyl)-4-(difluoromethyl)oxazole-5-carboxylate (**19c**)*

Yellowish oil (6.2 g, 63 %).

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.39–1.44 (m, 12 H, CH$_2$C*H*$_3$ + C(C*H*$_3$)$_3$), 4.42 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 7.10 (t, $^2J_{H-F}$ = 53.5 Hz, 1 H, CHF$_2$) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 14.2 (CH$_2$*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$), 34.4 (*C*(CH$_3$)$_3$), 62.2 (*C*H$_2$CH$_3$), 107.9 (t, $^1J_{C-F}$ = 236.2 Hz, CHF$_2$), 139.7 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF$_2$), 139.2 (t, $^3J_{C-F}$ = 8.1 Hz, *C*–CO$_2$Et), 157.1, 174.2 ppm.

^{19}F NMR (CDCl$_3$, 376 MHz,): δ = – 117.67 (d, $^2J_{H-F}$ = 53.5 Hz, CHF$_2$) ppm.

MS: *m*/*z* = 248 [M + H]$^+$.

Anal. Calcd for $C_{11}H_{15}F_2NO_3$: C, 53.44; H, 6.12; N, 5.67. Found: C, 53.49; H, 6.07; N, 5.70.

*4.4.4. Ethyl 4-difluoromethyl-2-phenyloxazole-5-carboxylate (**19d**)*

White solid (7.8 g, 73 %) mp 81 °C.

^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.47 (t, *J* = 7.0 Hz, 3 H, CH$_2$C*H*$_3$), 4.50 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 7.22 (t, $^2J_{H-F}$ = 53.2 Hz, 1 H, CHF$_2$), 7.50–7.60 (m, 3 H, 3×H$_{Ph}$), 8.20 (d, *J* = 7.0 Hz, 2 H, 2×H$_{Ph}$) ppm.

^{13}C NMR (CDCl$_3$, 100 MHz): δ = 14.2 (CH$_2$*C*H$_3$), 62.3 (*C*H$_2$CH$_3$), 107.9 (t, $^1J_{C-F}$ = 236.2 Hz, CHF$_2$),

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125.6 (C_{Ph}), 127.6 (2×CH_{Ph}), 129.0 (2×CH_{Ph}), 132.3 (CH_{Ph}), 139.8 (t, $^3J_{C-F}$ = 8.1 Hz, *C*–CO_2Et), 144.0 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF_2), 157.0, 163.7 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 118.01 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: *m*/*z* = 268 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}F_2NO_3$: C, 58.43; H, 4.15; N, 5.24. Found: C, 58.38; H, 4.11; N, 5.31.

*4.4.5. Ethyl 4-difluoromethyl-2-(4-methoxyphenyl)oxazole-5-carboxylate (**19e**)*

White solid (7.9 g, 67 %) mp 85 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 3.87 (s, 3 H, OMe), 4.46 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 6.98 (d, *J* = 9.0 Hz, 2 H, 2×H_{Ar}), 7.18 (t, $^2J_{H-F}$ = 53.2 Hz, 1 H, CHF_2), 8.10 (d, *J* = 9.0 Hz, 2 H, 2×H_{Ar}) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2 (CH_2CH_3), 55.4 (OMe), 62.2 (CH_2CH_3), 107.9 (t, $^1J_{C-F}$ = 235.5 Hz, CHF_2), 114.4 (2×CH_{Ar}), 118.1 (C_{Ar}), 129.5 (2×CH_{Ar}), 139.3 (t, $^3J_{C-F}$ = 8.1 Hz, *C*–CO_2Et), 141.0 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF_2), 157.1 (C–OMe), 162.8, 163.9 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 118.07 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: *m*/*z* = 298 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{13}F_2NO_4$: C, 56.57; H, 4.41; N, 4.71. Found: C, 56.64; H, 4.38; N, 4.66.

*4.4.6. Ethyl 4-difluoromethyl-2-(4-nitrophenyl)oxazole-5-carboxylate (**19f**)*

Yellow solid (7.0 g, 54 %) mp 89 °C.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.46 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 4.50 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 7.20 (t, $^2J_{H-F}$ = 53.2 Hz, 1 H, CHF_2), 8.37 (s, 4 H, 4×H_{Ar}) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 14.3 (CH_2CH_3), 62.9 (CH_2CH_3), 107.7 (t, $^1J_{C-F}$ = 236.9 Hz, CHF_2), 124.2 (2×CH_{Ar}), 128.6 (2×CH_{Ar}), 131.0 (C_{Ar}), 141.0 (t, $^3J_{C-F}$ = 7.5 Hz, *C*–CO_2Et), 141.3 (t, $^2J_{C-F}$ = 25.9 Hz, *C*–CHF_2), 150.0 (C–NO_2), 156.7, 161.4 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 118.04 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: *m*/*z* = 313 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{10}F_2N_2O_5$: C, 50.01; H, 3.23; N, 8.97. Found: C, 49.91; H, 3.16; N, 9.02.

*4.4.7. Ethyl 2-chloromethyl-4-(difluoromethyl)oxazole-5-carboxylate (**19g**)*

Yellowish oil (6.6 g, 69 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 4.37 (q, *J* = 7.3 Hz, 2 H, CH_2CH_3), 4.61 (s, 2 H, CH_2Cl), 7.03 (t, $^2J_{H-F}$ = 53.0 Hz, 1 H, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 35.0 (CH_2Cl), 62.7 (CH_2CH_3), 107.4 (t, $^1J_{C-F}$ = 236.2 Hz, CHF_2), 139.7 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF_2), 141.2 (t, $^3J_{C-F}$ = 7.3 Hz, *C*–CO_2Et), 156.3, 161.4 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 118.13 (d, $^2J_{H-F}$ = 53.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 240 $[M + H]^+$.

Anal. Calcd for $C_8H_8ClF_2NO_3$: C, 40.10; H, 3.37; N, 5.85. Found: C, 40.04; H, 3.41; N, 5.92.

*4.4.8. Ethyl 2-(1-chloroethyl)-4-(difluoromethyl)oxazole-5-carboxylate (**19h**)*

Yellowish oil (7.5 g, 74 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.88 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)Cl$), 4.36 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 5.08 (q, *J* = 7.0 Hz, 1 H, $CH(CH_3)Cl$), 7.03 (t, $^2J_{H-F}$ = 53.0 Hz, 1 H, CHF_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 22.0 ($CH(CH_3)Cl$), 47.4 ($CH(CH_3)Cl$), 62.6 (CH_2CH_3), 107.5 (t, $^1J_{C-F}$ = 236.2 Hz, CHF_2), 139.5 (t, $^2J_{C-F}$ = 25.7 Hz, *C*–CHF_2), 140.7 (t, $^3J_{C-F}$ = 7.3 Hz, *C*–CO_2Et), 156.4, 164.7 ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 118.14 and – 118.15 (2×d, $^2J_{H-F}$ = 53.5 Hz and $^2J_{H-F}$ = 53.0 Hz, CHF_2) ppm.

MS: *m*/*z* = 254 $[M + H]^+$.

Anal. Calcd for $C_9H_{10}ClF_2NO_3$: C, 42.62; H, 3.97; N, 5.52. Found: C, 42.69; H, 4.02; N, 5.55.

*4.5. Ethyl 4-Trifluoromethyloxazole-5-carboxylates **23a-c,g,h**. General Procedure*

PIFA (12.8 g, 56 mmol) was carefully added in small portions to a stirred and refluxed solution of appropriate enamide **22a-c,g,h** (40 mmol) and Et_2O-BF_3 complex (16.8 mL, 80 mmol) in 1,2-dichloroethane (200 mL). The addition took ~ 30 min. After it was completed the obtained mixture was stirred at reflux temperature overnight. Upon cooling the solvent was removed in vacuo and the residue was partitioned

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between water (300 mL) and ethyl acetate (200 mL). The organic layer was separated and washed sequentially with water (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column eluting with ethyl acetate – hexane (3:10, v/v) mixture to yield compounds **23a-c,g,h** as oils.

*4.5.1. Ethyl 2-methyl-4-(trifluoromethyl)oxazole-5-carboxylate (**23a**)*

Yellowish oil (7.5 g, 84 %).

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 2.57 (s, 3 H, Me), 4.35 (q, J = 7.1 Hz, 2 H, CH_2CH_3) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 13.6 (Me), 13.7 (Me), 62.1 (CH_2CH_3), 119.8 (q, $^1J_{C-F}$ = 268.8 Hz, CF_3), 134.3 (q, $^2J_{C-F}$ = 40.4 Hz, *C*–CF_3), 139.9 (q, $^3J_{C-F}$ = 3.0 Hz, *C*–CO_2Et), 155.3 (*C*–Me), 164.2 (CO_2Et) ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 61.65 (s, CF_3) ppm.

MS: m/z = 224 $[M + H]^+$.

Anal. Calcd for $C_8H_8F_3NO_3$: C, 43.06; H, 3.61; N, 6.28. Found: C, 43.12; H, 3.60; N, 6.24.

*4.5.2. Ethyl 2-cyclopropyl-4-(trifluoromethyl)oxazole-5-carboxylate (**23b**)*

Yellowish oil (6.6 g, 67 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15–1.25 (m, 4 H, 2×CH_2), 1.37 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 2.12–2.19 (m, 1 H, CH), 4.39 (q, J = 7.0 Hz, 2 H, CH_2CH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.0 (CH), 9.7 (2×CH_2), 13.9 (CH_2CH_3), 62.2 (CH_2CH_3), 119.7 (q, $^1J_{C-F}$ = 270.0 Hz, CF_3), 135.6 (q, $^2J_{C-F}$ = 41.0 Hz, *C*–CF_3), 139.3 (q, $^3J_{C-F}$ = 2.9 Hz, *C*–CO_2Et), 155.9, 168.4 (CO_2Et) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 62.51 (s, CF_3) ppm.

MS: m/z = 250 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.04; N, 5.62. Found: C, 48.12; H, 4.01; N, 5.55.

*4.5.3. Ethyl 2-(tert-butyl)-4-(trifluoromethyl)oxazole-5-carboxylate (**23c**)*

Yellowish oil (5.8 g, 55 %).

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 1.30 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.37 (s, 9 H, $C(CH_3)_3$), 4.37 (q, J = 7.0 Hz, 2 H, CH_2CH_3) ppm.

^{13}C NMR (DMSO[D_6], 100 MHz): δ = 14.2 (CH_2CH_3), 28.3 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 62.6 (CH_2CH_3), 120.3 (q, $^1J_{C-F}$ = 269.2 Hz, CF_3), 133.9 (q, $^2J_{C-F}$ = 38.9 Hz, *C*–CF_3), 140.3 (q, $^3J_{C-F}$ = 3.7 Hz, *C*–CO_2Et), 155.9 (*C*-*t*Bu), 173.2 (CO_2Et) ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 61.07 (s, CF_3) ppm.

MS: m/z = 266 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{14}F_3NO_3$: C, 49.81; H, 5.32; N, 5.28. Found: C, 49.90; H, 5.26; N, 5.26.

*4.5.4. Ethyl 2-chloromethyl-4-(trifluoromethyl)oxazole-5-carboxylate (**23g**)*

Yellowish oil (7.6 g, 74 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.40 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.62 (s, 2 H, CH_2Cl) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_2CH_3), 34.8 (CH_2Cl), 62.8 (CH_2CH_3), 119.3 (q, $^1J_{C-F}$ = 270.0 Hz, CF_3), 135.5 (q, $^2J_{C-F}$ = 41.8 Hz, *C*–CF_3), 141.5 (q, $^3J_{C-F}$ = 2.9 Hz, *C*–CO_2Et), 155.4 (*C*–CH_2Cl), 160.5 (CO_2Et) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 62.43 (s, CF_3) ppm.

MS: m/z = 258 $[M + H]^+$.

Anal. Calcd for $C_8H_7ClF_3NO_3$: C, 37.30; H, 2.74; N, 5.44. Found: C, 37.23; H, 2.76; N, 5.35.

*4.5.5. Ethyl 2-(1-chloroethyl)-4-(trifluoromethyl)oxazole-5-carboxylate (**23h**)*

Yellowish oil (7.4 g, 68 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.93 (d, J = 6.8 Hz, 3 H, $CH(CH_3)Cl$), 4.40 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 5.10 (q, J = 6.8 Hz, 1 H, $CH(CH_3)Cl$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8 (CH_2CH_3), 22.1 ($CH(CH_3)Cl$), 47.1 ($CH(CH_3)Cl$), 62.8 (CH_2CH_3), 119.4 (q, $^1J_{C-F}$ = 270.0 Hz, CF_3), 135.3 (q, $^2J_{C-F}$ = 41.1 Hz, *C*–CF_3), 140.9 (q, $^3J_{C-F}$ = 2.9 Hz, *C*–CO_2Et), 155.5 (*C*–$CH(CH_3)Cl$), 163.8 (CO_2Et) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 62.35 (s, CF_3) ppm.

MS: m/z = 272 $[M + H]^+$.

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Anal. Calcd for $C_9H_9ClF_3NO_3$: C, 39.80; H, 3.34; N, 5.16. Found: C, 39.89; H, 3.24; N, 5.07.

*4.6. Ethyl 2-Phenyl-4-(trifluoromethyl)oxazole-5-carboxylate (**23d**)*

PIDA (10.2 g, 56 mol) was carefully added in small portions to a stirred and refluxed solution of compound **22d** (11.5 g, 40 mmol) and $Me_3SiOSO_2CF_3$ (10.2 mL, 80 mol) in 1,2-dichloroethane (200 mL). The addition took ~ 30 min. After it was completed the obtained mixture was stirred at reflux temperature overnight. Upon cooling the solvent was removed in vacuo and the residue was partitioned between water (300 mL) and ethyl acetate (200 mL). The organic layer was separated and washed sequentially with water (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL), and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column eluting with ethyl acetate – hexane (1:5, v/v) mixture to give compound **23d** as white solid (5.9 g, 52 %) mp 90 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.46 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 4.49 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 7.52–7.61 (m, 3 H, 3×H_{Ph}), 8.18 (d, J = 7.0 Hz, 2 H, 2×H_{Ph}) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (CH_2CH_3), 62.5 (CH_2CH_3), 119.8 (q, $^1J_{C-F}$ = 268.5 Hz, CF_3), 123.8 (C_{Ph}), 127.5 (2×CH_{Ph}), 129.1 (2×CH_{Ph}), 132.4 (CH_{Ph}), 136.6 (q, $^2J_{C-F}$ = 41.1 Hz, *C*–CF_3), 139.9 (q, $^3J_{C-F}$ = 2.9 Hz, *C*–CO_2Et), 156.1 (*C*–Ph), 162.7 (CO_2Et) ppm.

^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 62.37 (s, CF_3) ppm.

MS: m/z = 286 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91. Found: C, 54.69; H, 3.49; N, 4.96.

*4.7. Oxazole-5-carboxylic acids **20a-f**, **24a-d**. General Procedure*

$LiOH·H_2O$ (2.0 g, 48 mmol) was added in one portion to a solution of the corresponding ester **19a-f**, **23a-d** (20 mmol) in THF – water (100 mL, 10:1 v/v), and the formed mixture was stirred at RT for 2 days. The solvent was removed in vacuo, and the residue was dissolved in water (100 mL). The water solution was washed with ethyl acetate (100 mL), then it was acidified with hydrochloric acid to pH 4 and extracted with ethyl acetate (2 x 50 mL). The extract was dried ($MgSO_4$) and evaporated in vacuo affording pure acids **20a-f**, **24a-d** as solids. Analytical samples were additionally recrystallized from a suitable solvent.

*4.7.1. 4-Difluoromethyl-2-methyloxazole-5-carboxylic acid (**20a**)*

White powder (3.4 g, 96 %); mp 178 °C.

^{1}H NMR (DMSO[D_6], 400 MHz): δ = 2.52 (s, 3 H, Me), 7.23 (t, $^2J_{H-F}$ = 53.0 Hz, 1 H, CHF_2), 14.37 (br s, 1 H, CO_2H) ppm.

^{13}C NMR (DMSO[D_6], 100 MHz): δ = 14.3 (Me), 108.7 (t, $^1J_{C-F}$ = 234.0 Hz, CHF_2), 138.6 (t, $^2J_{C-F}$ = 24.9 Hz, *C*–CHF_2), 141.4 (t, $^3J_{C-F}$ = 8.8 Hz, *C*–CO_2H), 158.2, 164.8 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 116.74 (d, $^2J_{H-F}$ = 53.0 Hz, CHF_2) ppm.

MS: m/z = 178 $[M + H]^+$.

Anal. Calcd for $C_6H_5F_2NO_3$: C, 40.69; H, 2.85; N, 7.91. Found: C, 40.76; H, 2.80; N, 7.84.

*4.7.2. 2-Cyclopropyl-4-(difluoromethyl)oxazole-5-carboxylic acid (**20b**)*

White powder (3.9 g, 97 %); mp 163 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 1.03–1.15 (m, 4 H, 2×CH_2), 2.19–2.24 (m, 1 H, CH), 7.18 (t, $^2J_{H-F}$ = 53.2 Hz, 1 H, CHF_2), 13.84 (br s, 1 H, CO_2H) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 8.6 (CH), 9.1 (2×CH_2), 108.2 (t, $^1J_{C-F}$ = 233.4 Hz, CHF_2), 138.3 (t, $^2J_{C-F}$ = 24.9 Hz, *C*–CHF_2), 140.3 (t, $^3J_{C-F}$ = 8.0 Hz, *C*–CO_2H), 157.7, 168.5 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 117.09 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: m/z = 204 $[M + H]^+$.

Anal. Calcd for $C_8H_7F_2NO_3$: C, 47.30; H, 3.47; N, 6.89. Found: C, 47.39; H, 3.51; N, 6.82.

*4.7.3. 2-(tert-Butyl)-4-(difluoromethyl)oxazole-5-carboxylic acid (**20c**)*

Yellowish oil (4.1 g, 95 %).

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 1.35 (s, 9 H, $C(CH_3)_3$), 7.23 (t, $^2J_{H-F}$ = 53.2 Hz, 1 H, CHF_2) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 27.9 ($C(CH_3)_3$), 34.0 ($C(CH_3)_3$), 108.3 (t, $^1J_{C-F}$ = 233.4 Hz, CHF_2), 137.8 (t, $^2J_{C-F}$ = 25.4 Hz, *C*–CHF_2), 140.9 (t, $^3J_{C-F}$ = 7.5 Hz, *C*–CO_2H), 157.9, 173.0 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 116.70 (d, $^2J_{H-F}$ = 53.5 Hz, CHF_2) ppm.

MS: m/z = 220 $[M + H]^+$.

Anal. Calcd for $C_9H_{11}F_2NO_3$: C, 49.32; H, 5.06; N, 6.39. Found: C, 49.41; H, 5.15; N, 6.37.

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*4.7.4. 4-Difluoromethyl-2-phenyloxazole-5-carboxylic acid (**20d**)*

White powder (4.7 g, 98 %); mp 175 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 7.35 (t, $^2J_{H–F}$ = 53.0 Hz, 1 H, CHF_2), 7.57–7.65 (m, 3 H, 3×H_{Ph}), 8.05 (d, J = 7.1 Hz, 2 H, 2×H_{Ph}), 14.43 (br s, 1 H, CO_2H) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 108.4 (t, $^1J_{C–F}$ = 233.9 Hz, CHF_2), 125.3 (C_{Ph}), 127.0 (2×CH_{Ph}), 129.5 (2×CH_{Ph}), 132.4 (CH_{Ph}), 139.3 (t, $^2J_{C–F}$ = 24.9 Hz, *C*–CHF_2), 141.2 (t, $^3J_{C–F}$ = 8.0 Hz, *C*–CO_2H), 157.9, 162.4 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 116.98 (d, $^2J_{H–F}$ = 53.0 Hz, CHF_2) ppm.

MS: m/z = 240 $[M + H]^+$.

Anal. Calcd for $C_{11}H_7F_2NO_3$: C, 55.24; H, 2.95; N, 5.86. Found: C, 55.26; H, 3.01; N, 5.90.

*4.7.5. 4-Difluoromethyl-2-(4-methoxyphenyl)oxazole-5-carboxylic acid (**20e**)*

White powder (5.0 g, 94 %); mp 158 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 3.83 (s, 3 H, OMe), 7.10 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 7.32 (t, $^2J_{H–F}$ = 52.7 Hz, 1 H, CHF_2), 7.97 (d, J = 8.8 Hz, 2 H, 2×H_{Ar}), 14.16 (br s, 1 H, CO_2H) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 55.6 (OMe), 108.4 (t, $^1J_{C–F}$ = 233.9 Hz, CHF_2), 114.9 (2×CH_{Ar}), 117.7 (C_{Ar}), 129.0 (2×CH_{Ar}), 139.3 (t, $^2J_{C–F}$ = 24.5 Hz, *C*–CHF_2), 140.6 (t, $^3J_{C–F}$ = 9.0 Hz, *C*–CO_2H), 158.0 (C–OMe), 162.5, 162.6 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 116.99 (d, $^2J_{H–F}$ = 53.5 Hz, CHF_2) ppm.

MS: m/z = 270 $[M + H]^+$.

Anal. Calcd for $C_{12}H_9F_2NO_4$: C, 53.54; H, 3.37; N, 5.20. Found: C, 53.49; H, 3.31; N, 5.23.

*4.7.6. 4-Difluoromethyl-2-(4-nitrophenyl) oxazole-5-carboxylic acid (**20f**)*

White powder (5.3 g, 93 %); mp 165 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 7.35 (t, $^2J_{H–F}$ = 53.0 Hz, 1 H, CHF_2), 8.27 (d, J = 8.5 Hz, 2 H, 2×H_{Ar}), 8.37 (d, J = 8.5 Hz, 2 H, 2×H_{Ar}) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 108.2 (t, $^1J_{C–F}$ = 234.4 Hz, CHF_2), 124.6 (2×CH_{Ar}), 128.4 (2×CH_{Ar}), 130.7 (C_{Ar}), 139.4 (t, $^2J_{C–F}$ = 24.9 Hz, *C*–CHF_2), 142.2 (t, $^3J_{C–F}$ = 8.5 Hz, *C*–CO_2H), 149.3 (C–NO_2), 157.7, 160.4 ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 117.05 (d, $^2J_{H–F}$ = 53.0 Hz, CHF_2) ppm.

MS: m/z = 285 $[M + H]^+$.

Anal. Calcd for $C_{11}H_6F_2N_2O_5$: C, 46.49; H, 2.13; N, 9.86. Found: C, 46.58; H, 2.21; N, 9.90.

*4.7.7. 2-Methyl-4-(trifluoromethyl)oxazole-5-carboxylic acid (**24a**)*

White powder (3.8 g, 97 %); mp 198 °C.

^{1}H NMR (DMSO[D_6], 500 MHz): δ = 2.54 (s, 3 H, Me) ppm.

^{13}C NMR (DMSO[D_6], 125 MHz): δ = 13.8 (Me), 120.0 (q, $^1J_{C–F}$ = 268.8 Hz, CF_3), 133.3 (q, $^2J_{C–F}$ = 39.4 Hz, *C*–CF_3), 141.2 (q, $^3J_{C–F}$ = 3.0 Hz, *C*–CO_2H), 156.8 (*C*–Me), 163.8 (CO_2H) ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 60.96 (s, CF_3) ppm.

MS: m/z = 196 $[M + H]^+$.

Anal. Calcd for $C_6H_4F_3NO_3$: C, 36.94; H, 2.07; N, 7.18. Found: C, 37.02; H, 2.11; N, 7.22.

*4.7.8. 2-Cyclopropyl-4-(trifluoromethyl)oxazole-5-carboxylic acid (**24b**)*

White powder (4.1 g, 93 %); mp 182 °C.

^{1}H NMR (DMSO[D_6], 400 MHz): δ = 1.04–1.18 (m, 4 H, 2×CH_2), 2.21–2.28 (br m, 1 H, CH) ppm.

^{13}C NMR (DMSO[D_6], 100 MHz): δ = 8.9 (CH), 9.7 (2×CH_2), 120.3 (q, $^1J_{C–F}$ = 268.5 Hz, CF_3), 133.9 (q, $^2J_{C–F}$ = 40.3 Hz, *C*–CF_3), 140.8 (q, $^3J_{C–F}$ = 2.9 Hz, *C*–CO_2H), 157.1, 168.2 (CO_2H) ppm.

^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 61.10 (s, CF_3) ppm.

MS: m/z = 222 $[M + H]^+$.

Anal. Calcd for $C_8H_6F_3NO_3$: C, 43.45; H, 2.73; N, 6.33. Found: C, 43.40; H, 2.80; N, 6.28.

*4.7.9. 2-(tert-Butyl)-4-(trifluoromethyl)oxazole-5-carboxylic acid (**24c**)*

White powder (4.2 g, 90 %); mp 107 °C.

^{1}H NMR (DMSO[D_6], 400 MHz): δ = 1.35 (s, 9 H, C(CH_3)$_3$) ppm.

^{13}C NMR (DMSO[D_6], 100 MHz): δ = 28.3 (C(CH_3)$_3$), 34.3 (C(CH_3)$_3$), 120.4 (q, $^1J_{C–F}$ = 267.8 Hz, CF_3), 133.3 (q, $^2J_{C–F}$ = 40.3 Hz, *C*–CF_3), 141.5 (q, $^3J_{C–F}$ = 2.9 Hz, *C*–CO_2H), 157.3 (*C*-*t*Bu), 172.7 (CO_2H) ppm.

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^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 60.82 (s, CF_3) ppm.
MS: m/z = 238 $[M + H]^+$.
Anal. Calcd for $C_9H_{10}F_3NO_3$: C, 45.58; H, 4.25; N, 5.91. Found: C, 45.66; H, 4.19; N, 5.87.

*4.7.10. 2-Phenyl-4-(trifluoromethyl)oxazole-5-carboxylic acid (**24d**)*

White powder (4.9 g, 95 %); mp 183 °C.
^{1}H NMR (DMSO[D_6], 500 MHz): δ = 7.56–7.65 (m, 3 H, 3×H_{Ph}), 8.02 (d, J = 7.8 Hz, 2 H, 2×H_{Ph}) ppm.
^{13}C NMR (DMSO[D_6], 125 MHz): δ = 120.0 (q, $^1J_{C–F}$ = 268.8 Hz, CF_3), 124.9 (C_{Ph}), 127.0 (2×CH_{Ph}), 129.5 (2×CH_{Ph}), 132.6 (CH_{Ph}), 134.5 (q, $^2J_{C–F}$ = 39.9 Hz, *C*–CF_3), 141.3 (q, $^3J_{C–F}$ = 2.9 Hz, *C*–CO_2H), 156.9 (*C*–Ph), 161.6 (CO_2H) ppm.
^{19}F NMR (DMSO[D_6], 376 MHz,): δ = – 61.07 (s, CF_3) ppm.
MS: m/z = 258 $[M + H]^+$.
Anal. Calcd for $C_{11}H_6F_3NO_3$: C, 51.37; H, 2.35; N, 5.45. Found: C, 51.29; H, 2.39; N, 5.48.

*4.8. 2-Phenyl-4-(trifluoromethyl)oxazole-5-[N-{6-[(2-methoxyethyl)-(methyl)amino]pyridin-3-yl}carboxamide] (**27**)*

TBTU (1.4 g, 4.3 mmol) was added in one portion to a stirred solution of the acid **24d** (1.0 g, 3.9 mmol), amine **26** (1 g, 5.5 mol) and DIPEA (1.5 mL, 8.6 mmol) in DMF (50 mL), and the mixture obtained was stirred at RT for 2 days. The solvent was removed in vacuo, and the residue was taken in ethyl acetate (50 mL), washed with water (2 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent furnished crude material, which was purified by chromatography on a silica gel column eluting with t-BuOMe – hexane (1:1, v/v) mixture to give compound **27** as solid (1.1 g, 63 %); mp 181 °C.
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.06 (s, 3 H, Me), 3.33 (s, 3 H, Me), 3.56 (t, J = 5.8 Hz, 2 H, CH_2), 3.71 (t, J = 5.8 Hz, 2 H, CH_2), 6.48 (d, J = 9.1 Hz, 1 H, $H_{β\text{-Py}}$), 7.49 (t, J = 7.7 Hz, 2 H, 2×H_{Ph}), 7.77 (t, J = 7.7 Hz, 1 H, H_{Ph}), 7.87 (dd, J = 9.1 Hz, J = 2.5 Hz, 1 H, $H_{γ\text{-Py}}$), 8.08 (d, J = 7.7 Hz, 2 H, 2×H_{Ph}), 8.20 (d, J = 2.5 Hz, 1 H, $H_{α\text{-Py}}$), 8.21 (s, 1 H, NH) ppm.
^{13}C NMR ($CDCl_3$, 125 MHz): δ = 37.0 (NMe), 49.5 (CH_2), 58.6 (OMe), 70.4 (CH_2), 105.0 ($CH_{β\text{-Py}}$), 119.6 (q, $^1J_{C–F}$ = 269.8 Hz, CF_3), 121.9, 124.7, 126,9 (2×CH_{Ph}), 128,7 (2×CH_{Ph}), 131.3 (CH), 132.0 (CH), 134.2 (q, $^2J_{C–F}$ = 41.4 Hz, *C*–CF_3), 140.6 ($CH_{α\text{-Py}}$), 141.9, 152.8, 156.2, 160.7 ppm.
^{19}F NMR ($CDCl_3$, 376 MHz,): δ = – 61.92 (s, CF_3) ppm.
MS: m/z = 421 $[M + H]^+$.
Anal. Calcd for $C_{20}H_{19}F_3N_4O_3$: C, 57.14; H, 4.56; N, 13.33. Found: C, 57.09; H, 4.55; N, 13.27.

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