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Polyfluoro- and perfluoroalkoxyenaminones in syntheses of nitrogen containing heterocycles

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ABSTRACT

2-Fluoroalkoxyenaminones were synthesized from α-fluoroalkoxyacetophenones and dimethylformamide dimethylacetal in almost quantitative yields. These compounds are promising aliphatic precursors for fluoroalkoxy containing heterocycles construction that was proved by reactions with hydrazine, hydroxylamine and amidines yielding corresponding pyrazoles, isoxazoles and pyrimidines.

1. Introduction

Among fluorine containing substituents polyfluoroalkoxy groups gain considerable interest of modern synthetic audience due to their high impact into biological and material science applicable properties of organic molecules. α-Fluorinated ethers of aromatic compounds since the first publication [1] in 1955 by Yagupolskii were extensively investigated and widely used, nevertheless, heterocycles bearing fluoroalkoxy groups remain rare [2,3].

Previously it was shown that synthesis of heterocyclic compounds from aliphatic fluoroalkoxy containing building blocks is promising and useful strategy [3]. We have reported the synthesis of α-bromo-α-fluoroalkoxyacetophenones and recognized their ability to undergo Hantzsch-type cyclization yielding thiazoles with fluoroalkoxy groups at the 5′-position.

In present paper we present our continuous investigation on the search of novel aliphatic fluoroalkoxy containing building blocks and their usage in heterocycles syntheses, that is focused on previously unknown enaminones modified by $-OR_F$ moieties [4].

Enaminones are chemical compounds containing an amino group linked through a C=C double bond to a carbonyl group. They are versatile readily available reagents and their chemistry has received considerable attention in recent years [5]. There are two electrophilic sites (C-1 and C-3) in the enaminone molecule [6], thus these substances can be considered as synthetic equivalents of β-dicarbonyl compounds in heterocycles syntheses. Preparation of β-enaminoketones bearing fluoroalkoxy groups provides promising possibility for synthesis of wide range of heterocycles with such groups.

2. Results and discussion

Ketones with methylene group condense readily with dimethylformamide dimethyl acetal (DMFDMA) to yield enaminones in refluxing toluene, DMF or by heating without solvent that are common reaction conditions [5].

We have tested all these conditions utilizing reaction of the readily available [3] α-tetrafluoroethoxyacetophenone **1a** and DMFDMA (Table 1). The best result was obtained, when reaction was carried out without any solvent (entry 3, Table 1). Efficiency and simplicity of reaction performance and isolation of product make this condition the most favorable. We applied this method to acetophenons with different fluoroalkoxy groups and prepared enaminones **2a–d** with similarly high yields (Scheme 1).

It is well known that enaminones readily react with hydrazine hydrate yielding corresponding pyrazoles [7]. Nevertheless, we detected no tetrafluoroethoxypyrazole formation reacting β-enaminoketone **2a** with hydrazine hydrate, and only signals of tetrafluoroethoxy group destruction were observed in ^{19}F NMR spectra of reaction mixture. The largest peak was the signal of the CHF_2-group as a doublet ($^2J_{FH}$ = 52.4 Hz) at −128.1 ppm, but the

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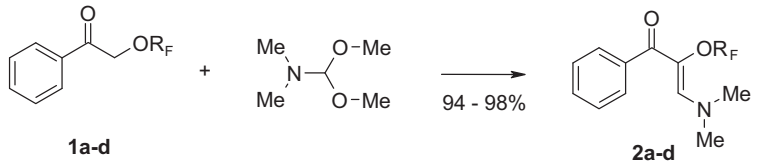


1a, **2a**: $R_F = CF_2CHF_2$; **1b**, **2b**: $R_F = CF_2CHClF$; **1c**, **2c**: $R_F = CF_3$; **1d**, **2d**: $R_F = C_2F_5$.

Scheme 1. Synthesis of fluoroalkoxyenaminones.

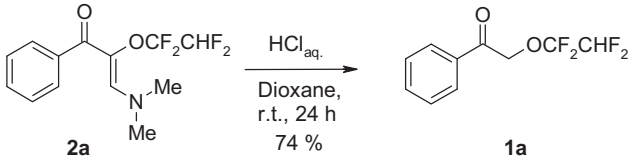
Table 1
Reaction conditions for synthesis of fluoroalkoxyenaminone **2a**.

Entry	Solvent	Temp (°C)	Reaction time (h)	Yield by NMR ^{19}F (%)
1	Toluene	90	8	~40
2	DMF	90	8	~60
3	–	90	8	100 (98)[a]

[a] Isolated yield.

signal of corresponding CF_2-moiety was absent. Probably, elimination of α-fluorine atoms occurred due to basic reaction conditions. The same result was obtained when hydrazine acetate in dioxane was used.

On the other hand, it is known that acidic media lead to destruction of C=C double bond of enaminones by retro-Mannich reaction [8], and we found out that treatment of β-enaminoketone **2a** with hydrochloric acid in dioxane at room temperature results in formation of acetophenone **1a** (Scheme 2).



Scheme 2. Retro-Mannich reaction of fluoroalkoxyenaminone **2a**.

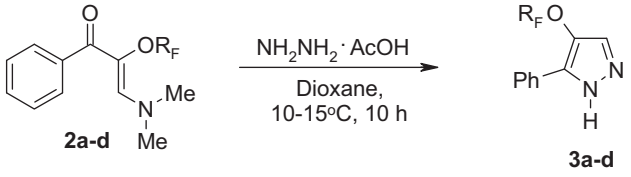
Thus, it became clear to us, that basic or strong acidic conditions prevent the formation of key compounds and we decided to use hydrazine salt with weak organic acid. Pyrazoles **2a** and **2b** were prepared in 85% and 78%, respectively, when hydrazine acetate and acetic acid were used (Method A) (Scheme 3). However, in cases of enaminones **2c** and **2d** elimination of α-fluorine atoms occurred under these conditions. The better results were obtained when acetic acid was replaced with trifluoroacetic acid (Method B). In this case all target pyrazoles, even **3c** and **3d**, were prepared in almost quantitative yields (Scheme 3).

As a rule, β-enaminoketones readily react with hydroxylamine to yield isoxazoles [8,9]. However, refluxing of enaminones **2a**–**b** in ethanol with hydroxylamine hydrochloride led to formation of oximes **4a**–**b**. It was found out that dehydratation of compounds **4a**–**b** in benzene in the presence of *p*-toluenesulphonic acid (PTSA) results in isoxazoles **5a**–**b** with high yields (Scheme 4).

Enaminones are also widely used for pyrimidines synthesis [7]. Taking into account abovementioned properties of fluoroalkoxyenaminones we used benzamidine salt with weak organic acid. Thus, 2,4-diphenylpyrimidine **6** was synthesized with high yield by reaction of compound **2a** with benzamidine acetate in dioxane under reflux (Scheme 5).

Heating of β-enaminoketones **2a**–**d** with formamidine acetate in the absence of any solvent results in desired fluoroalkoxypyrimidines **7a**–**d** in yields up to 88% (Scheme 6).

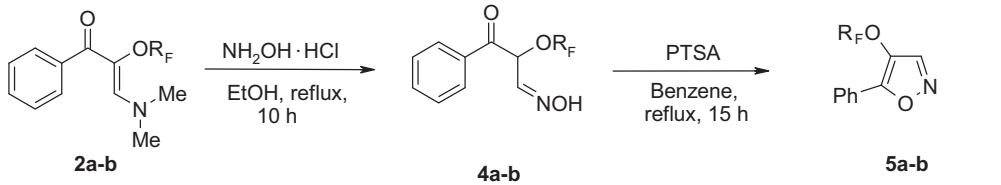
The corresponding fluoroalkoxyacetophenones were identified as byproducts in all cases. Their quantity varied from 10% for



Method A (10 eq. CH_3COOH): **3a**, **3b**; 78-85%.
Method B (10 eq. CF_3COOH): **3a**-**3d**; 92-98%.

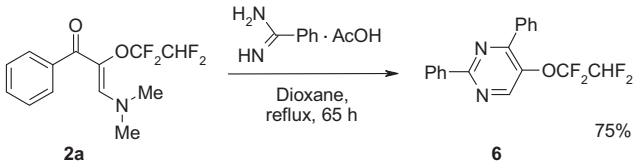
2a, **3a**: $R_F = CF_2CHF_2$; **2b**, **3b**: $R_F = CF_2CHClF$; **2c**, **3c**: $R_F = CF_3$; **2d**, **3d**: $R_F = C_2F_5$.

Scheme 3. Reaction of fluoroalkoxyenaminones with hydrazine acetate.

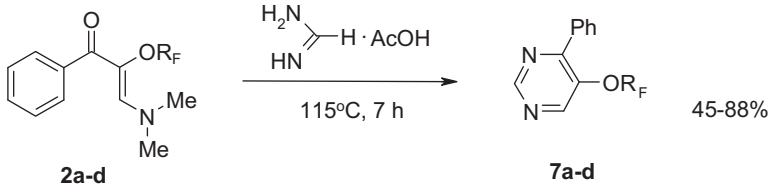


2a, **4a**, **5a**: $R_F = CF_2CHF_2$; **2b**, **4b**, **5b**: $R_F = CF_2CHClF$.

Scheme 4. Synthesis of isoxazoles with polyfluoroalkoxy groups.



Scheme 5. Reaction of fluoroalkoxyenaminone **2a** with benzamidine acetate.



2a, **7a**: $R_F = CF_2CHF_2$; **2b**, **7b**: $R_F = CF_2CHClF$; **2c**, **7c**: $R_F = CF_3$; **2d**, **7d**: $R_F = C_2F_5$.

Scheme 6. Reaction of fluoroalkoxyenaminones with formamidine acetate.

enaminones with polyfluoroalkoxy groups to 20% for perfluoroalkoxyenaminone derivatives, these byproducts were easily removed by column chromatography.

3. Conclusions

We developed a simple and practical method for the synthesis of enaminones with poly- and perfluoroalkoxy groups at the second position. It was demonstrated that these compounds are convenient and useful precursors for preparation of pyrazoles, isoxazoles and pyrimidines with such a group. This methodology might be promising to get other five- and six-membered nitrogen containing heterocycles.

4. Experimental

4.1. General

4.1.1. Materials

α-Fluoroalkoxyacetophenones were prepared according to literature procedures [3]. For α-fluoroalkoxyacetophenones syntheses see also [10]. Solvents were dried before use by standard methods. For column chromatography Merck Kieselgel silica gel 60 was used. Thin layer chromatography (TLC) was carried out on aluminum-backed plates coated with silica gel (Merck Kieselgel 60 F254).

4.1.2. Measurements

^{1}H NMR spectra were recorded on a Varian VRX-300 instrument (300 MHz). ^{13}C NMR (proton decoupled) spectra were recorded on a Bruker Avance DRX-500 instrument. The chemical shifts (δ) are given relative to external TMS. ^{19}F NMR spectra were recorded on a Varian Gemini-200 instrument (188 MHz). The chemical shifts (δ) are given relative to internal CCl_3F. Deuterated chloroform was the solvent in all cases. Mass spectra were recorded on a Hewlett-Packard HP GC/MS 5890/5972 (EI, 70 eV) or an Agilent 1100 LCMS SL instrument. Melting points were measured on a Stuart Scientific melting point apparatus SMP3.

4.2. Typical procedure for synthesis of enaminones (**2a**–**d**) without solvent

The mixture of the corresponding acetophenones **1a**–**d** (10 mmol) and DMFDMA (1.45 mL, 11 mmol) was heated at 90 °C for 7 h. Methanol, that formed in the reaction, and the excess of DMFDMA distilled off in vacuum (20 mbar), then in high vacuum (0.3 mbar) at 40–45 °C. The residue was dissolved in dichloromethane (50 mL), organic layer was washed with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent enaminones **2a**–**d** were obtained as reddish-brown low-melt solid.

4.2.1. 3-Dimethylamino-2-(1,1,2,2-tetrafluoroethoxy)-1-phenylpropenone (**2a**)

Yield 2.85 g (98%), mp 24–25 °C. ^{1}H NMR: δ 3.07 (s, 6H, $2CH_3$), 6.01 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 6.97 (bs, 1H, CH), 7.33–7.45 (m, 3H, arom. H), 7.55 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H). ^{13}C NMR: δ 43.3 (bs, $2CH_3$), 108.1 (tt, $^1J_{CF}$ = 251.4 Hz, $^2J_{CF}$ = 41.0 Hz, CHF_2), 116.9 (tt, $^1J_{CF}$ = 272.9 Hz, $^2J_{CF}$ = 27.5 Hz, CF_2), 121.7, 128.1, 128.2, 130.4, 139.5, 146.2, 189.1. ^{19}F NMR: δ −90.14 (s, 2F, CF_2), −137.22 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 291 $[M]^+$. Anal. calcd. for $C_{13}H_{13}F_4NO_2$: C, 53.61; H, 4.51; N, 4.81; found: C, 53.46; H, 4.35; N, 4.93.

4.2.2. 3-Dimethylamino-2-(2-chloro-1,1,2-trifluoroethoxy)-1-phenylpropenone (**2b**)

Yield 2.95 g (96%), mp 22–23 °C. ^{1}H NMR: δ 3.09 (s, 6H, $2CH_3$), 6.40 (d, $^2J_{HF}$ = 48.3 Hz, 1H, CHClF), 6.97 (bs, 1H, CH), 7.34–7.45 (m, 3H, arom. H), 7.55 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H). ^{13}C NMR: δ 43.8 (bs, $2CH_3$), 95.4 (dt, $^1J_{CF}$ = 251.5 Hz, $^2J_{CF}$ = 41.6 Hz, CHClF), 118.5 (td, $^1J_{CF}$ = 270.4 Hz, $^2J_{CF}$ = 25.3 Hz, CF_2), 122.1, 128.1, 128.3, 130.4, 139.5, 146.0, 189.2. ^{19}F NMR: δ −85.40 (d, $^2J_{FF}$ = 139.8 Hz, 1F, CF), −86.80 (d, $^2J_{FF}$ = 139.8 Hz, 1F, CF), −153.92 (d, $^2J_{FH}$ = 48.3 Hz, 1F, CHClF). GC–MS: m/z = 309 $[M\ (^{37}Cl)]^+$, 307 $[M\ (^{35}Cl)]^+$. Anal. calcd. for $C_{13}H_{13}ClF_3NO_2$: C, 50.74; H, 4.27; Cl, 11.52; N, 4.55; found: C, 50.60; H, 4.15; Cl, 11.51; N, 4.67.

4.2.3. 3-Dimethylamino-2-trifluoromethoxy-1-phenylpropenone (**2c**)

Yield 2.48 g (96%), mp 32–33 °C. ^{1}H NMR: δ 3.06 (s, 6H, $2CH_3$), 6.95 (bs, 1H, CH), 7.32–7.41 (m, 3H, arom. H), 7.55 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H). ^{13}C NMR: δ 42.0 (bs, $2CH_3$), 121.2 (q, $^1J_{CF}$ = 259.4 Hz, CF_3), 122.8, 128.1, 128.3, 130.5, 139.3, 145.4, 188.4. ^{19}F NMR: δ −59.32 (s, CF_3). GC–MS: m/z = 259 $[M]^+$. Anal. calcd. for $C_{12}H_{12}F_3NO_2$: C, 55.59; H, 4.68; N, 5.41; found: C, 55.46; H, 4.57; N, 5.50.

4.2.4. 3-Dimethylamino-2-pentafluoroethyloxy-1-phenylpropenone (**2d**)

Yield 2.9 g (94%), mp 27–28 °C. ^{1}H NMR: δ 3.07 (s, 6H, $2CH_3$), 7.11 (bs, 1H, CH), 7.34–7.45 (m, 3H, arom. H), 7.59 (d, $^3J_{HH}$ = 7.5 Hz,

2H, arom. H). ^{13}C NMR: δ 41.9 (bs, $2CH_3$), 114.6 (tq, $^1J_{CF}$ = 276.7 Hz, $^2J_{CF}$ = 41.0 Hz, CF_2), 116.8 (qt, $^1J_{CF}$ = 284.8 Hz, $^2J_{CF}$ = 44.6 Hz, CF_3), 120.8, 128.0, 128.3, 130.6, 139.1, 145.3, 188.6. ^{19}F NMR: δ −85.89 (s, 3F, CF_3), −88.71 (s, 2F, CF_2). GC–MS: m/z = 309 $[M]^+$. Anal. calcd. for $C_{13}H_{12}F_5NO_2$: C, 50.49; H, 3.92; N, 4.53; found: C, 50.41; H, 3.87; N, 4.68.

4.3. Acidic hydrolysis of enaminone **2a**

The mixture of enaminone **2a** (0.87 g, 3 mmol) and aqueous hydrochloric acid (2 mL) in dioxane (10 mL) was stirred at room temperature for 24 h. After removal of the solvent and hydrochloric acid in vacuum (20 mbar) the residue was quenched with water (30 mL). The product was extracted with dichloromethane (3× 50 mL). The organic layer was washed with saturated aqueous solution of sodium bicarbonate (3× 20 mL) and then with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent the product was obtained as a white solid. Yield 0.52 g (74%), mp 29–31 °C [3]. ^{1}H NMR: δ 5.18 (s, 2H, CH_2), 5.86 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 7.49 (t, $^3J_{HH}$ = 7.5, 2H, arom. H), 7.62 (t, 2H, $^3J_{HH}$ = 7.5, 1H, arom. H), 7.90 (d, $^3J_{HH}$ = 7.5, 2H, arom. H). ^{13}C NMR: δ 65.8 (t, $^3J_{CF}$ = 3.9 Hz, CH_2), 107.7 (tt, $^1J_{CF}$ = 251.5 Hz, $^2J_{CF}$ = 40.2 Hz, CHF_2), 117.4 (tt, $^1J_{CF}$ = 277.9 Hz, $^2J_{CF}$ = 21.4 Hz, CF_2), 127.9, 129.0, 134.0, 134.2, 190.0. ^{19}F NMR: δ −94.32 (s, 2F, CF_2), −138.63 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 236 $[M]^+$.

4.4. Typical procedures for pyrazoles (**3a**–**d**) syntheses

Method A. The mixture of the corresponding enaminones **2a**–**b** (3 mmol), hydrazine acetate (0.3 g, 3.3 mmol) and acetic acid (1.7 mL, 30 mmol) in 1,4-dioxane (5 mL) was stirred at 15 °C for 10 h. The solution was quenched with water (100 mL) and neutralized with sodium bicarbonate. The product was extracted with dichloromethane (3× 25 mL). Organic layer was washed with water (3× 15 mL) and dried with $MgSO_4$. After removal of the solvent the residue was purified by sublimation in vacuum (**3a**) or crystallization from hexane (**3b**).

Method B. The mixture of the corresponding enaminones **2a**–**d** (3 mmol), hydrazine acetate (0.3 g, 3.3 mmol) and trifluoroacetic acid (2.3 mL, 30 mmol) in 1,4-dioxane (5 mL) was stirred at 15 °C for 10 h. The solution was quenched with water (100 mL) and neutralized with sodium bicarbonate. The product was extracted with dichloromethane (3× 25 mL), organic layer was washed with water (3× 15 mL) and dried with $MgSO_4$. After removal of the solvent the product was purified by sublimation in vacuum (**3a**, **3c**, **3d**) or crystallization from hexane (**3b**).

4.4.1. 4-(1,1,2,2-Tetrafluoroethoxy)-5-phenyl-1H-pyrazole (**3a**)

Yield: method A – 0.66 g (85%), method B – 0.76 g (98%), white powder, mp 93–94 °C (after sublimation at 90–95 °C (0.3 mbar)). ^{1}H NMR: δ 5.93 (t, $^2J_{HF}$ = 52.4, 1H, CHF_2), 7.37–7.43 (m, 3H, arom. H), 7.59 (s, 1H, CH-pyrazole), 7.70 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H), 11.16 (bs, 1H, NH). ^{13}C NMR: δ 107.6 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 41.2 Hz, CHF_2), 116.5 (tt, $^1J_{CF}$ = 272.5 Hz, $^2J_{CF}$ = 28.7 Hz, CF_2), 126.7, 127.4, 128.7, 128.8, 128.9, 129.7, 138.3. ^{19}F NMR: δ −90.27 (s, 2F, CF_2), −137.04 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 260 $[M]^+$. Anal. calcd. for $C_{11}H_8F_4N_2O$: C, 50.77; H, 3.11; N, 10.77; found: C, 50.69; H, 3.26; N, 10.60.

4.4.2. 4-(2-Chloro-1,1,2-trifluoroethoxy)-5-phenyl-1H-pyrazole (**3b**)

Yield: method A – 0.65 g (78%), method B – 0.79 g (95%), white powder, mp 74–75 °C. ^{1}H NMR: δ 6.29 (d, $^2J_{HF}$ = 48.0 Hz, 1H, CHClF), 7.36–7.43 (m, 3H, arom. H), 7.60 (s, 1H, CH-pyrazole), 7.73 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H), 10.80 (bs, 1H, NH). ^{13}C NMR: δ 94.8 (dt, $^1J_{CF}$ = 251.8 Hz, $^2J_{CF}$ = 41.2 Hz, CHClF), 118.3 (td, $^1J_{CF}$ = 271.6 Hz, $^2J_{CF}$ = 26.0 Hz, CF_2), 126.8, 127.4, 128.7, 128.8, 128.9, 129.0, 130.0. ^{19}F NMR: δ −86.55 (s, 2F, CF_2), −154.24 (d, $^2J_{FH}$ = 48.0 Hz, 1F, CHClF). GC–MS: m/z = 278 $[M\ (^{37}Cl)]^+$, 276 $[M\ (^{35}Cl)]^+$. Anal. calcd. for $C_{11}H_8ClF_3N_2O$: C, 47.76; H, 2.92; Cl, 12.81; N, 10.13; found: C, 47.73; H, 2.92; Cl, 12.90; N, 10.14.

4.4.3. 4-Trifluoromethoxy-5-phenyl-1H-pyrazole (**3c**)

Yield: method B – 0.63 g (92%), white powder, mp 89–90 °C (after sublimation at 65–70 °C (0.5 mbar)). ^{1}H NMR: δ 7.39–7.45 (m, 3H, arom. H), 7.59 (s, 1H, CH-pyrazole), 7.71 (d, $^3J_{HH}$ = 7.5 Hz, 2 H, arom. H), 11.00 (bs, 1H, NH). ^{13}C NMR: δ 120.7 (q, $^1J_{CF}$ = 258.2 Hz, CF_3), 126.7, 127.1, 128.5, 128.8, 128.9, 130.6, 138.0. ^{19}F NMR: δ −60.9 (s, CF_3). GC–MS: m/z = 228 $[M]^+$. Anal. calcd. for $C_{10}H_7F_3N_2O$: C, 52.63; H, 3.10; N, 12.28; found: C, 52.71; H, 3.10; N, 12.24.

4.4.4. 4-Pentafluoroethoxy-5-phenyl-1H-pyrazole (**3d**)

Yield: method B – 0.78 g (94%), white powder, mp 93–94 °C (after sublimation at 80–85 °C (0.3 mbar)). ^{1}H NMR: δ 7.38–7.44 (m, 3H, arom.H), 7.60 (s, 1H, CH-pyrazole), 7.69 (d, $^3J_{HH}$ = 7.5 Hz, 2H, arom. H), 10.56 (bs, 1H, NH). ^{13}C NMR: δ 114.3 (tq, $^1J_{CF}$ = 274.4 Hz, $^2J_{CF}$ = 42.0 Hz, CF_2), 116.7 (qt, $^1J_{CF}$ = 284.4 Hz, $^2J_{CF}$ = 43.4 Hz, CF_3), 126.6, 127.4, 128.6, 128.8, 128.9, 129.2, 138.4. ^{19}F NMR: δ −86.31 (s, 3F, CF_3), −90.18 (s, 2F, CF_2). GC–MS: m/z = 278 $[M]^+$. $C_{11}H_7F_5N_2O$: C, 47.48; H, 2.54; N, 10.07; found: C, 47.61; H, 2.48; N, 9.98.

4.5. Typical procedure for isoxazoles (**5a**–**b**) synthesis

The mixture of the corresponding enaminones **2a**–**b** (5 mmol) and hydroxylamine hydrochloride (0.7 g, 10 mmol) in ethanol (20 mL) was refluxed for 10 h. After removal of the solvent in vacuum (20 mbar), the residue was dissolved in dichloromethane (75 mL). Organic layer was washed with water (3× 15 mL) and dried with $MgSO_4$. Dichloromethane was evaporated in vacuum. The residue (the corresponding oximes **4a**–**b**) was dissolved in benzene (60 mL), PTSA (0.86 g, 5 mmol) was added to the solution and the mixture was refluxed with Dean-Stark apparatus until no more water is distilled off (*c.a.* 15 h). The solvent was removed in vacuum (20 mbar) and the residue was dissolved in *t*-butylmethyl ether (150 mL). The organic layer was washed with saturated aqueous solution of sodium bicarbonate (3× 10 mL) and then with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent the product was purified by distillation in vacuum.

4.5.1. 3-Oxo-3-phenyl-2-(1,1,2,2-tetrafluoroethoxy)propionaldehyde oxime (**4a**)

Yield 1.4 g (100%), brown oil, that contains 90% of main product. ^{1}H NMR: δ 3.58 (bs, 1H, OH), 5.73 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 5.75 (s, 1H, CH), 5.93 (s, 1H, CH), 7.38–7.43 (m, 3H, arom. H), 7.65–7.70 (m, 2H, arom. H). ^{19}F NMR: δ −89.03 (d, $^2J_{FF}$ = 146.8 Hz, 1F, CF), −91.58 (d, $^2J_{FF}$ = 146.8 Hz, 1F, CF), −137.97 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). LC–MS: m/z = 280 $[M+H]^+$.

4.5.2. 3-Oxo-3-phenyl-2-(2-chloro-1,2,2-trifluoroethoxy)propionaldehyde oxime (**4b**)

Yield 1.48 g (100%), that contains 90% of main product. ^{1}H NMR: δ 3.54 (bs, 1H, OH), 5.74 (s, 1H, CH), 5.96 (s, 1H, CH), 6.04 (d, $^2J_{HF}$ = 48.0 Hz, 1H, CHClF), 7.40–7.45 (m, 3H, arom. H), 7.68–7.73 (m, 2H, arom. H). ^{19}F NMR: δ −85.17 to −87.89 (m, 2F, CF_2), −154.28 to −154.36 (m, 1F, CHClF). LC–MS: m/z = 298 $[M\ (^{37}Cl)+H]^+$, 296 $[M\ (^{35}Cl)+H]^+$.

4.5.3. 4-(1,1,2,2-Tetrafluoroethoxy)-5-phenylisoxazole (**5a**)

Yield 0.91 g (70%), yellowish oil, bp 73–75 °C (0.4 mbar). ^{1}H NMR: δ 5.97 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 7.48–7.50 (m, 3H, arom. H), 7.83–7.86 (m, 2H, arom. H), 8.56 (s, 1H, CH-isoxazole). ^{13}C NMR: δ 107.3 (tt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 40.6 Hz, CHF_2), 116.4

(tt, $^1J_{CF}$ = 275.3 Hz, $^2J_{CF}$ = 29.2 Hz, CF_2), 126.5, 127.5, 128.9, 129.6, 130.5, 149.1, 155.2. ^{19}F NMR: δ −91.13 (s, 2F, CF_2), −137.17 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 261 $[M]^+$. Anal. calcd. for $C_{11}H_7F_4NO_2$: C, 50.57; H, 2.71; N, 5.36; found: C, 50.69; H, 2.70; N, 5.20.

*4.5.4. 5-(2-Chloro-1,1,2-trifluoroethoxy)-4-phenylisoxazole (**5b**)*

Yield 1.14 g (82%), yellowish oil, bp 78–80 °C (0.4 mbar). ^{1}H NMR: δ 6.31 (d, $^2J_{HF}$ = 48.0 Hz, 1H, CHClF), 7.47–7.49 (m, 3H, arom. H), 7.85–7.87 (m, 2H, arom. H), 8.58 (s, 1H, CH-isoxazole). ^{13}C NMR: δ 94.4 (dt, $^1J_{CF}$ = 252.1 Hz, $^2J_{CF}$ = 40.5 Hz, CHClF), 118.2 (td, $^1J_{CF}$ = 274.3 Hz, $^2J_{CF}$ = 26.4 Hz, CF_2), 126.5, 127.6, 128.9, 129.9, 130.5, 149.0, 155.2. ^{19}F NMR: δ −87.20 (s, 2F, CF), −154.55 (d, $^2J_{FH}$ = 48.0 Hz, 1F, CHClF). GC–MS: m/z = 279 $[M\ (^{37}Cl)]^+$, 277 $[M\ (^{35}Cl)]^+$. Anal. calcd. for $C_{11}H_7ClF_3NO_2$: C, 47.59; H, 2.55; Cl, 12.77; N, 5.05; found: C, 47.68; H, 2.61; Cl, 12.72; N, 4.93.

*4.6. 5-(1,1,2,2-Tetrafluoroethoxy)-2,4-diphenylpyrimidine (**6**)*

The mixture of benzamidine (0.9 g, 7.5 mmol), enaminone **2a** (1.45 g, 5 mmol) and glacial acetic acid (0.43 mL, 7.5 mmol) in 1,4-dioxane (5 mL) was refluxed for 65 h. After cooling to room temperature the mixture was quenched with water (50 mL) and extracted with dichloromethane (3× 50 mL). The organic layer was washed with 5% sodium bicarbonate aqueous solution (15 mL) and then with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent in vacuum the residue was purified by silica gel column chromatography. Yield 1.3 g (75%), white solid, R_f = 0.3 (hexane/EtOAc = 50/1), mp 64–65 °C. ^{1}H NMR: δ 5.89 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 7.50–7.54 (m, 6H, arom. H), 8.05–8.08 (m, 2H, arom. H), 8.51–8.54 (m, 2H, arom. H), 8.80 (s, 1H, CH-pyrimidine). ^{13}C NMR: δ 107.4 (tt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 40.9 Hz, CHF_2), 116.6 (tt, $^1J_{CF}$ = 275.1 Hz, $^2J_{CF}$ = 29.3 Hz, CF_2), 128.4, 128.5, 128.7, 129.6, 130.8, 131.0, 134.5, 136.7, 140.2, 151.8, 158.4, 162.4. ^{19}F NMR: δ −89.28 (s, 2F, CF_2), −138.55 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 348 $[M]^+$. Anal. calcd. for $C_{18}H_{12}F_4N_2O$: C, 62.07; H, 3.48; N, 8.05; found: C, 62.25; H, 3.56; N, 8.13.

*4.7. Typical procedure for pyrimidines (**7a**–**d**) synthesis*

The mixture of the corresponding enaminones **2a**–**d** (5 mmol) and formamidine acetate (0.78 g, 7.5 mmol) was heated at 115 °C for 7 h. After cooling to room temperature the mixture was quenched with water (50 mL) and extracted with dichloromethane (3× 50 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (2× 20 mL) and then with water (3× 25 mL) and dried with $MgSO_4$. After removal of the solvent the residue was purified by silica gel column chromatography.

*4.7.1. 5-(1,1,2,2-Tetrafluoroethoxy)-4-phenylpyrimidine (**7a**)*

Yield 1.2 g (88%), yellowish oil, R_f = 0.2 (hexane/CH_2Cl_2 = 1/1). ^{1}H NMR: δ 5.87 (t, $^2J_{HF}$ = 52.4 Hz, 1H, CHF_2), 7.48–7.51 (m, 3H, arom. H), 7.92–7.95 (m, 2H, arom. H), 8.76 (s, 1H, 6′CH-pyrimidine), 9.17 (s, 1H, 2′CH-pyrimidine). ^{13}C NMR: δ 107.3 (tt, $^1J_{CF}$ = 252.6 Hz, $^2J_{CF}$ = 40.9 Hz, CHF_2), 116.5 (tt, $^1J_{CF}$ = 276.0 Hz, $^2J_{CF}$ = 29.4 Hz, CF_2), 128.5, 129.4, 130.9, 133.8, 141.8, 151.3, 156.4, 158.7. ^{19}F NMR: δ −87.84 (s, 2F, CF_2), −137.03 (d, $^2J_{FH}$ = 52.4 Hz, 2F, CHF_2). GC–MS: m/z = 272 $[M]^+$. Anal. calcd. for $C_{12}H_8F_4N_2O$: C, 52.94; H, 2.97; N, 10.29; found: C, 52.86; H, 3.06; N, 10.23.

*4.7.2. 5-(2-Chloro-1,1,2-trifluoroethoxy)-4-phenylpyrimidine (**7b**)*

Yield 1.2 g (85%), yellowish oil, R_f = 0.1 (hexane/CH_2Cl_2 = 1/1). ^{1}H NMR: δ 6.21 (d, $^2J_{HF}$ = 48.3 Hz, 1H, CHClF), 7.49–7.51 (m, 3H, arom. H), 7.92–7.95 (m, 2H, arom. H), 8.77 (s, 1H, 6′CH-pyrimidine), 9.17 (s, 1H, 2′CH-pyrimidine). ^{13}C NMR: δ 94.6 (dt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 40.7 Hz, CHClF), 118.4 (td, $^1J_{CF}$ = 275.1 Hz, $^2J_{CF}$ = 26.5 Hz, CF_2), 128.5, 129.5, 130.8, 133.8, 142.1, 151.3, 156.3, 158.7. ^{19}F NMR: δ −83.68 (s, 2F, CF_2), −154.01 (d, $^2J_{FH}$ = 48.0 Hz, 1F, CHClF). GC–MS: m/z = 290 $[M\ (^{37}Cl)]^+$, 288 $[M\ (^{35}Cl)]^+$. Anal. calcd. for $C_{12}H_8ClF_3N_2O$: C, 49.93; H, 2.80; Cl, 12.28; N, 9.71; found: C, 50.04; H, 2.85; Cl, 12.37; N, 9.59.

*4.7.3. 5-Trifluoromethoxy-4-phenylpyrimidine (**7c**)*

Yield 0.62 g (52%) yellowish oil, R_f = 0.1 (hexane/CH_2Cl_2 = 1/1). ^{1}H NMR: δ 7.49–7.53 (m, 3H, arom. H), 7.97–8.00 (m, 2H, arom. H), 8.74 (s, 1H, 6′CH-pyrimidine), 9.19 (s, 1H, 2′CH-pyrimidine). ^{13}C NMR: δ 120.3 (q, $^1J_{CF}$ = 259.6 Hz, CF_3), 128.7, 129.4, 131.1, 133.6, 142.0, 150.7, 156.7, 158.2. ^{19}F NMR: δ −59.78 (s, CF_3). GC–MS: m/z = 240 $[M]^+$. Anal. calcd. for $C_{11}H_7F_3N_2O$: C, 55.00; H, 2.94; N, 11.67; found: C, 55.12; H, 3.10; N, 11.61.

*4.7.4. 5-Pentafluoroethyloxy-4-phenylpyrimidine (**7d**)*

Yield 0.65 g (45%), yellowish oil, R_f = 0.1 (hexane/CH_2Cl_2 = 1/1). ^{1}H NMR: δ 7.45–7.53 (m, 3H, arom. H), 7.92–7.94 (m, 2H, arom. H), 8.75 (s, 1H, 6′CH-pyrimidine), 9.20 (s, 1H, 2′CH-pyrimidine). ^{13}C NMR: δ 114.3 (tq, $^1J_{CF}$ = 278.4 Hz, $^2J_{CF}$ = 42.8 Hz, CF_2), 116.4 (qt, $^1J_{CF}$ = 284.9 Hz, $^2J_{CF}$ = 42.9 Hz, CF_3), 128.5, 129.4, 131.0, 133.5, 141.4, 151.4, 156.9, 158.9. ^{19}F NMR: δ −86.23 (s, 3F, CF_3), −87.76 (s, 2F, CF_2). GC–MS: m/z = 290 $[M]^+$. Anal. calcd. for $C_{12}H_7F_5N_2O$: C, 49.66; H, 2.44; N, 9.66; found: C, 49.74; H, 2.45; N, 9.51.

References

[1] L.M. Yagupolskii, Dokl. Akad. Nauk SSSR 105 (1955) 100–103; Chem. Abstr. 50 (1955) 11270b.
[2] (a) F. Leroux, P. Jeschke, M. Schlosser, Chem. Rev. 105 (2005) 827–856; (b) F. Leroux, B. Manteau, J.-P. Vors, S. Pazenok, Beilstein J. Org. Chem. 4 (2008), http://dx.doi.org/10.3762/bjoc.4.13; (c) M.V. Vovk, O.M. Pinchuk, V.A. Sukach, A.O. Tolmachov, A.A. Gakh, in: A.A. Gakh, K.L. Kirk (Eds.), ACS Symposium Series, Vol. 1003 (Fluorinated Heterocycles), American Chemical Society, Washington, DC, 2009, pp. 307–345; (d) D. O'Hagan, J. Fluorine Chem. 131 (2010) 1008–1071.
[3] T.M. Sokolenko, Yu.A. Davydova, Yu.L. Yagupolskii, J. Fluorine Chem. 136 (2012) 20–25.
[4] General results of our investigation have been presented at 17th European Symposium on Fluorine Chemistry, Paris, July 21–25, 2013: (a) Yu. Davydova, T. Sokolenko, Yu. Yagupolskii, Book of Abstracts of 17th European Symposium on Fluorine Chemistry, Paris, July, 2013 (Paper P1.27); While preparing current paper, we became aware of a closely related work devoted to syntheses of OCF_3-containing enaminoketones and their transformation into trifluoromethoxy pyrazoles. See: (b) B.R. Langlois, Abstracts of Papers, 245th ACS National Meeting & Exposition, New Orleans, LA, United States, April 7–11, 2013 (Paper FLUO 8); (c) J. Barbion, B. Thierry, B. Langlois, O. Marrec, S. Pazenok, J.-P. Vors, EP Patent 2628722 (August 21, 2013).
[5] A.-Z.A. Elassar, A.A. El-Khair, Tetrahedron 59 (2003) 8463–8480.
[6] C.M. Kascheres, J. Braz. Chem. Soc. 14 (2003) 945–969.
[7] H. Bredereck, R. Sell, F. Effenberger, Chem. Ber. (1964) 3407–3417.
[8] R. Olivera, R. SanMartin, E. Dominguez, X. Solans, M.K. Urtiaga, M.I. Arriortua, J. Org. Chem. 65 (2000) 6398–6411.
[9] F.A. Rosa, P. Machado, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, J. Heterocycl. Chem. 45 (2008) 879–885.
[10] (a) C. Wakselman, J. Leroy, J. Fluorine Chem. 12 (1978) 101–109; (b) W.B. Farnham, W.J. Middleton, US Patent 4,628,094 (1986). Chem. Abstr. 105 (1986) 114600n; (c) A.A. Kolomeitsev, M. Vorobyev, H. Gillandt, Tetrahedron Lett. 49 (2008) 449–454; (d) R. Zriba, E. Magnier, J.-C. Blazejewski, Synlett 7 (2009) 1131–1135; (e) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B.R. Langlois, J. Fluorine Chem. 131 (2010) 200–207; (f) O. Marrec, T. Billard, J.-P. Vors, S. Pazenok, B.R. Langlois, Adv. Synth. Catal. 352 (2010) 2831–2837.