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Synthesis and some transformations of all three isomers of α,α-difluoropyridinylacetonitrile

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ABSTRACT

An effective preparative approach to fluorinated pyridinylacetonitriles, based on electrophilic fluorination of pyridinylacetonitriles, was developed. Their synthetic potential for obtaining new fluorine-containing building blocks and heterocyclic systems was disclosed.

1. Introduction

Heterocycles bearing difluoromethylene moiety attract considerable interest for drug discovery due to its unique properties such as high lipophilicity [1, 2], and significant resistance to oxidative metabolism [3, 4]. The modification of pyridine derivatives with fluorine atoms is an elegant example of improving pharmacokinetic properties. For instance, 3-aminopyrazinone acetamide thrombin inhibitors **I, II** were discovered after metabolism-directed optimization by incorporation of difluoromethylpyridyl fragment [3, 4]. Moreover, recently it was shown that the modification of the antifungal drug itraconazole with pyridinyldifluoromethyl moiety gives the possibility to obtain the novel agent **III** with significantly improved pharmacokinetic parameters and solubility in water [5] (Figure 1).

Fluorinated pyridinylacetonitriles seem attractive and promising building blocks for the construction of many classes of organic compounds containing difluoromethylpyridinyl fragment. However, to the best of our knowledge, there are only few examples of such compounds having bulky substituents in the heterocycle nucleus [6], whereas unsubstituted fluorinated pyridinylacetonitriles are unknown so far. This is obviously due to the lack of synthetic approaches to this important type of compounds.

In the present work, we describe the synthesis of all possible isomers of α,α-difluoropyridinylacetonitriles and disclose their synthetic potential for the preparation of new building blocks with difluoromethylpyridinyl fragment.

2. Results and discussion

In recent years, a series of studies on the synthesis of difluoropyridinylacetic acid esters (convenient precursors of nitriles) have appeared, among which there are three main approaches: 1) deoxofluorination of pyridinylketoesters [4]; 2) cross-coupling of bromodifluoroacetic ester with pyridyl halides [4, 7]; 3) electrophilic *gem*-difluorination of pyridinylacetates with NF-reagents [3, 4, 8]. We elected to synthesize target difluoroacetonitriles by electrophilic fluorination of activated pyridinylacetonitriles with the commercially accessible and non-toxic N-fluorobenzenesulfonimide (NFSI). The latter was successfully used recently for the preparation of some difluoroalkylated pyridines [3, 8, 9].

It was found that the fluorination of nitriles **1a-c** with NFSI proceeds chemoselectively in the presence of *tert*-butyllithium (THF, –78°C) with complete conversion to give all isomers of α,α-difluoropyridinylacetonitriles **2a-c** (Scheme 1). The resulting nitriles **2a-c** were purified by distillation allowing the preparation of these novel building blocks in the analytically pure form with 52-76% yield.

Alternatively, difluoropyridinylacetonitriles **2a-c** can be obtained starting from fluorinated esters **4a-c**, which were synthesized by us also using electrophilic fluorination of esters **3a-c**. Thus, the esters **4a-c** were converted quantitatively into respective amides **5a-c**, the next dehydration of them with phosphorus pentoxide allowed to obtain difluoropyridinylacetonitriles **2a-c**, isolated with 55-69 % yields (Scheme 2).

The obtained difluorinated pyridinylacetonitriles **2a-c** are quite

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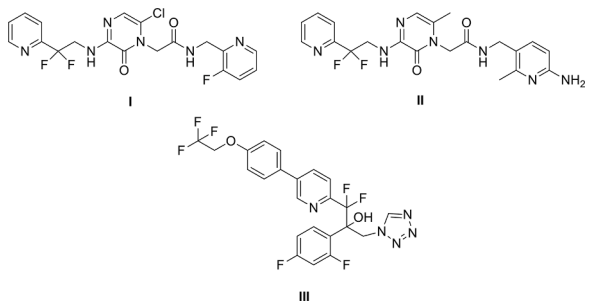


Fig. 1. xxx

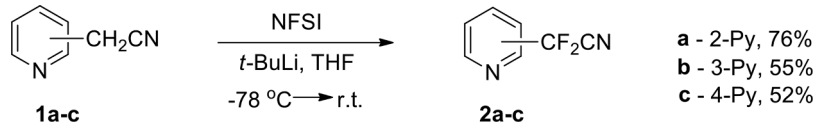
stable in inert atmosphere, although they rapidly hydrolyze in a humid media, even in the presence of trace amounts of base impurities. Electron withdrawing pyridinyldifluoromethylene group increases electrophilic character of nitriles and, as a result, markedly enhances their reactivity toward nucleophilic reagents, making them valuable building blocks for the synthesis of functionalized nitrogen containing compounds.

In the first stage of our effort to study α,α-difluoropyridinylacetonitriles we focused on their reduction. The reaction of nitriles **2a-c** with $BH_3{\cdot}Me_2S$ in THF leads to β,β-difluoropyridinylethylamines **6a-c** with preparative yields (Scheme 3).

The possibility of the pyridine ring reduction was demonstrated on the example of α-isomer of difluoropyridinylethylamine **6a** as an example (Scheme 4). Thus, after protection of amino function with Boc_2O, compound **7** was subjected to reduction on a rhodium catalyst to obtain fluorinated bifunctional aminopiperidine **8**, isolated in a pure form with a quantitative yield.

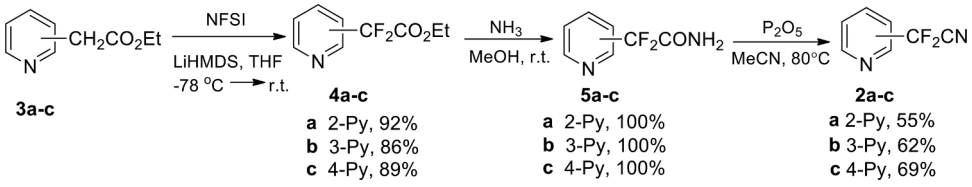
Fluorinated pyridinylacetates **4a-c** can be readily converted into interesting objects for synthetic chemistry, for example, the corresponding alcohols **9a-c** and acids **10a-c** (Scheme 5). It should be noted that *β*- and *γ*-pyridinyldifluoroacetic acids **10b-c** were unknown so far, α-isomer **10a** was obtained previously in low yield [10].

On the other hand, fluorinated nitriles **2a-c** can serve as a basis for the synthesis of bifunctional nucleophilic systems, convenient pre-

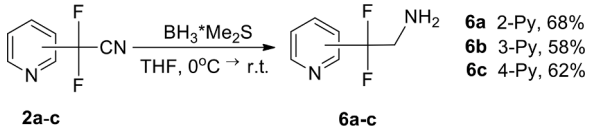


1a-c **2a-c**

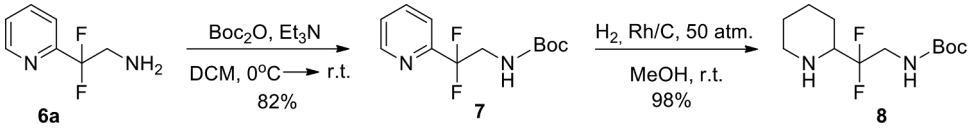
Scheme 1. xxx



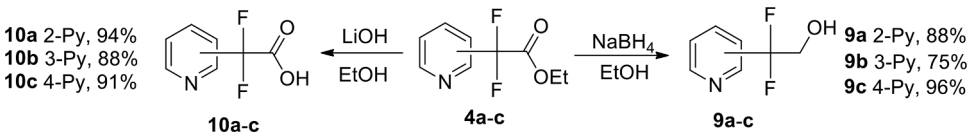
Scheme 2. xxx



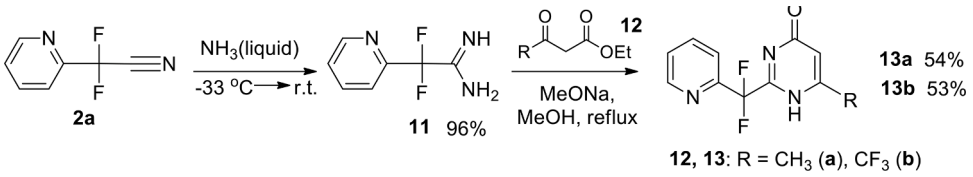
Scheme 3. xxx



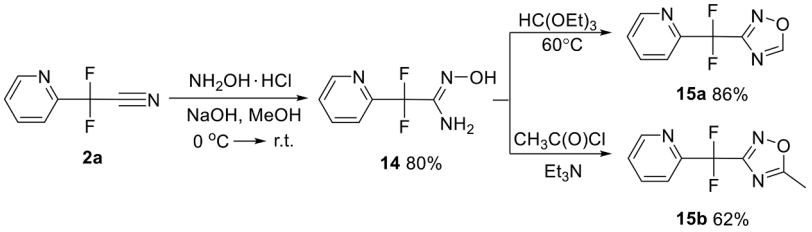
Scheme 4. xxx



Scheme 5. xxx



Scheme 6. xxx



Scheme 7. xxx

cursors of nitrogen-containing heterocycles modified with a difluoromethylpyridinyl group. For example, the addition of ammonia to C≡N triple bond of the nitrile **2a,** proceeding under mild conditions, leads to pyridinylacetamidine **11**, promising substrate for the synthesis of biologically important pyrimidinones. Thus, cyclocondensations of pyridinylacetamidine **11** with acetoacetate (**12a**) or trifluoroacetoacetate (**12b**) in the presence of a base afford biorelevant 2-substituded difluoropyridinylmethyl pyrimidones **13a-b** with preparative yields (Scheme 6).

The reaction of α-difluoropyridinylacetonitrile **2a** with hydroxylamine leads to the fluorinated pyridinyl-containing amidoxime **14**, a typical building block for the construction of the oxadiazole ring. For instance, condensation of amidoxime **14** with triethyl orthoformate or acetyl chloride allows preparing of oxadiazoles **15a,b** with preparative yields (Scheme 7).

3. Conclusions

In summary, we have developed a simple and efficient synthesis of all isomers of previously unknown fluorinated pyridinylacetonitriles, and demonstrated their considerable potential as novel convenient building blocks in design and synthesis of biologically important amines, diamines, nitrogen-containing heterocycles etc.

4. Experimental

4.1. General

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded using Bruker Avance NMR spectrometers operating at 301.5, 400 and 499.8 MHz ^{1}H frequencies (75.8, 100.6, 125.7 and 150.8 MHz for ^{13}C, 188, 376.5 and 470.3 MHz for ^{19}F). Chemical shifts are reported in ppm relative to internal TMS (^{1}H) or $CFCl_3$ (^{19}F) standards. Melting points are uncorrected. Solvents were dried according to standard methods. Elemental analysis was carried out in the analytical laboratory of Institute of Organic Chemistry, NAS of Ukraine.

4.2. Synthesis of difluoropyridinylacetonitriles **2a-c**

4.2.1. Synthesis of difluoropyridinylacetonitriles **2a-c** from pyridinylacetonitriles **1a-c** (method A)

To a solution of respective pyridinylacetonitrile **1** (1.18 g, 10 mmol) in THF (30 mL) *t*-BuLi (1.7 M in pentane, 12.9 mL, 22 mmol) was slowly added at –78°C. The reaction mixture was kept at –78°C for 0.5 h, and a solution of N-fluorobenzenesulfonimide (6.94 g, 22 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at –78°C for 12 hours and allowed to warm to room temperature. The reaction mixture was neutralized with an aqueous solution of citric acid (5%, 30 mL), the solvent was evaporated, and the residue was extracted with EtOAc (3 × 30 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4, evaporated under reduced pressure, the residue was distilled.

4.2.2. Synthesis of fluorinated pyridinylacetonitriles **2a-c** from pyridinylacetamides **5a-c** (method B)

To a solution of respective amide **5** (4.3 g, 25 mmol) in MeCN (80 mL) phosphorus pentoxide (7.1 g, 50 mmol) was slowly added. The mixture was refluxed for 10 hrs, the solvent was evaporated under reduced pressure, the residue was dissolved in water (50 mL), and neutralized with $NaHCO_3$. The product was extracted with EtOAc (3 × 30 mL), the organic layers were combined and washed with brine (30 mL), dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was distilled *in vacuo*.

4.2.3. 2,2-Difluoro-2-(pyridin-2-yl)acetonitrile **2a**

Yield 1.17 g (76%, *method A*); yield 2.12 g (55%, *method B*); colorless liquid; bp 78°C (10 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (dd, $^{3}J_{HH}$ = 7.9 Hz, $^{3}J_{HH}$ = 4.8 Hz, 1H), 7.72 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H), 7.93 (t, $^{3}J_{HH}$ = 7.9 Hz, 1H), 8.77 (d, $^{3}J_{HH}$ = 4.8 Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 108.2 (t, $^{1}J_{CF}$ = 245 Hz, CF_2), 112.0 (t, $^{2}J_{CF}$ = 45 Hz, CN), 119.9 (t, $^{3}J_{CF}$ = 3 Hz, C_{Py}), 127.1 (t, $^{4}J_{CF}$ = 2 Hz, C_{Py}), 138.0 (s, C_{Py}), 149.1 (t, $^{2}J_{CF}$ = 28 Hz, $\underline{C}CF_2$), 150.1 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –87.4 (s). Anal. Calc. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.18. Found: C, 54.61; H, 2.60; N, 18.21.

4.2.4. 2,2-Difluoro-2-(pyridin-3-yl)acetonitrile **2b**

Yield 0.85 g (55%, *method A*); yield 2.39 g (62%, *method B*); colorless liquid; bp 82-84°C (12 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (dd, $^{3}J_{HH}$ = 8.0 Hz, $^{3}J_{HH}$ = 3.8 Hz, 1H), 7.97 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H), 8.86 (d, $^{3}J_{HH}$ = 3.8 Hz, 1H), 8.94 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 107.8 (t, $^{1}J_{CF}$ = 244 Hz, CF_2), 111.8 (t, $^{2}J_{CF}$ = 50.5 Hz, CN), 123.7 (s, C_{Py}), 127.5 (t, $^{2}J_{CF}$ = 26.5 Hz, $\underline{C}CF_2$), 133.1(t, $^{3}J_{CF}$ = 4.5 Hz, C_{Py}), 146.6 (t, $^{3}J_{CF}$ = 5.5 Hz, C_{Py}), 153.7 (t, $^{5}J_{CF}$ = 1.5 Hz, C_{Py}). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –84.9(s). Anal. Calc. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.18. Found: C, 54.43; H, 2.64; N, 18.16.

4.2.5. 2,2-Difluoro-2-(pyridin-4-yl)acetonitrile **2c**

Yield 0.8 g (52%, *method A*); yield 2.66 g (69%, *method B*); colorless liquid; bp 55°C (12 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, $^{3}J_{HH}$ = 4.7 Hz, 2H), 8.88 (d, $^{3}J_{HH}$ = 4.7 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 107.4 (t, $^{1}J_{CF}$ = 245 Hz, CF_2), 111.5 (t, $^{2}J_{CF}$ = 50.5 Hz, CN), 119.0 (t,

$^3J_{CF}$ = 5 Hz, C_{Py}), 139.1 (t, $^2J_{CF}$ = 26.5 Hz, $\underline{C}CF_2$), 151.2 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –87.1(s). Anal. Calc. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.18. Found: C, 54.50; H, 2.68; N, 18.24.

4.3. Synthesis of difluoropyridinylacetates **4a-c**: general procedure

To a solution of respective pyridinylacetic acid ester **3** (8.25 g, 50 mmol) in THF (80 mL) LiHMDS (1.1 M in THF/heptane/ethylbenzene, 100 mL, 110 mmol) was slowly added at -78°C. The reaction mixture was kept at –78°C for 40 minutes, and then a solution of NFSI (34.65 g, 110 mmol) in THF (150 mL) was added. The mixture was stirred at -78°C for 8 hrs, and was allowed to warm to 0°C. The mixture was neutralized with an aqueous solution of citric acid (5%, 30 mL), the solvent was evaporated, and the residue was extracted with ethyl acetate (3 × 50 mL). The organic phase was washed with water (50 mL), saturated aqueous NH_4Cl solution (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure, the residue was distilled.

4.3.1. Ethyl 2,2-difluoro-2-(pyridin-2-yl)acetate **4a**

Yield 9.2 g (92%); yellow liquid; bp 85-87°C (0.5 Torr). Other physicochemical and spectral data were identical to literature data [4].

4.3.2. Ethyl 2,2-difluoro-2-(pyridin-3-yl)acetate **4b**

Yield 8.6 g (86%); yellow liquid; bp 72°C (0.3 Torr). Other physicochemical and spectral data were identical to literature data [11].

4.3.3. Ethyl 2,2-difluoro-2-(pyridin-4-yl)acetate **4c**

Yield 8.9 (89%); yellow liquid; bp 45°C (0.3 Torr). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.7 (s, CH_3), 63.5 (s, CH_2), 111.9 (t, $^1J_{CF}$ = 254 Hz, CF_2), 119.7 (m, $^3J_{CF}$ = 6 Hz, C_{Py}), 140.8 (t, $^2J_{CF}$ = 26 Hz, $\underline{C}CF_2$), 151.4 (s, C_{Py}), 162.9 (t, $^2J_{CF}$ = 34 Hz, C(O)). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –106.5(s). Other spectral data were identical to literature data [12].

4.4. Synthesis of difluoropyridinacetamides **5a-c**: general procedure

To a solution of respective ester **4** (5.03 g, 25 mmol) in MeOH (20 mL) was added NH_3/MeOH (20 mL). The reaction mixture was kept at r. t. for 6 hrs, the solvent was evaporated under reduced pressure, and the solid residue was washed with hexane (2 × 50mL) and dried.

4.4.1. 2,2-Difluoro-2-(pyridin-2-yl)acetamide **5a**

Yield 4.3 g (100%); white powder; mp 162-164°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.35 (br s, 2H, NH_2), 7.41 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 7.57 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.86 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 8.55 (d, $^3J_{HH}$ = 4 Hz, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 114.1 (t, $^1J_{CF}$ = 254 Hz, CF_2), 120.8 (t, $^3J_{CF}$ = 4 Hz, C_{Py}), 124.8 (s, C_{Py}), 137.3 (s, C_{Py}), 149.2 (s, C_{Py}), 155.4 (t, $^2J_{CF}$ = 28 Hz, $\underline{C}CF_2$), 165.4 (t, $^2J_{CF}$ = 27 Hz, C(O)). ^{19}F NMR (376.5 MHz, DMSO-d_6) δ: –102.5(s). Anal. Calc. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 48.96; H, 3.42; N, 16.1.

4.4.2. 2,2-Difluoro-2-(pyridin-3-yl)acetamide **5b**

Yield 4.3 g (100%); white powder; mp 160-162°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.58 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 8.00 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 8.2 (br s, 2H, NH_2), 8.76 (d, $^3J_{HH}$ = 4.1 Hz, 1 H), 8.79 (s, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 114.3 (t, $^1J_{CF}$ = 253 Hz, CF_2), 124.2 (s, C_{Py}), 129.7 (t, $^3J_{CF}$ = 26 Hz, $\underline{C}CF_2$), 133.8 (t, $^3J_{CF}$ = 5.5 Hz, C_{Py}), 146.6 (t, $^3J_{CF}$ = 6 Hz, C_{Py}), 152.4 (s, C_{Py}), 165.1 (t, $^2J_{CF}$ = 30 Hz, C(O)). ^{19}F NMR (376.5 MHz, DMSO-d_6) δ: –103.2(s). Anal. Calc. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 48.71; H, 3.64; N, 16.11.

4.4.3. 2,2-Difluoro-2-(pyridin-4-yl)acetamide **5c**

Yield 4.3 g (100%); white powder; mp 182-184°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.58 (d, $^3J_{HH}$ = 5.1 Hz, 2H), 8.35 (br s, 2H, NH_2), 8.77 (d, $^3J_{HH}$ = 5.1 Hz, 2H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 113.9 (t, $^1J_{CF}$ = 253 Hz, CF_2), 120.2 (t, $^3J_{CF}$ = 6 Hz, C_{Py}), 141.7 (t, $^3J_{CF}$ = 28 Hz, $\underline{C}CF_2$), 150.9 (s, C_{Py}), 164.7 (t, $^2J_{CF}$ = 30 Hz, C(O)).^{19}F NMR (376.5 MHz, DMSO-d_6) δ: –105.3 (s). Anal. Calc. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 48.92; H, 3.43; N, 16.38.

4.5. Synthesis of difluoropyridinylethanamines **6a-c**: general procedure

To a solution of respective nitrile **2** (0.1 g, 0.65 mmol) in THF (2 mL) a borane-dimethyl sulfide complex (0.053 g, 0.7 mmol) was added dropwise at –40°C. The reaction mixture was kept at this temperature for 0.5 h and allowed to warm to r.t., and then the mixture was refluxed for 2 hours. After cooling to r.t., the reaction mixture was diluted with water and neutralized with 6N HCl (2mL). Stirred for 1 hour at room temperature and added dry NaOH to pH~12. The organic layer was separated, and the aqueous was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and the solvents were evaporated under reduced pressure.

4.5.1. 2,2-Difluoro-2-(pyridin-2-yl)ethanamine **6a**

Yield 0.07 g (68%); yellow oil. Other physicochemical and spectral data were identical to literature data [3]. Anal. Calc. for $C_7H_8F_2N_2$: C, 53.16; H, 5.10; N, 17.71. Found: C, 53.27; H, 5.01; N, 17.83.

4.5.2. 2,2-Difluoro-2-(pyridin-3-yl)ethanamine **6b**

Yield 0.06 g (58%); yellow oil. ^1H NMR (499.8 MHz, $CDCl_3$) δ: 1.74 (br s, 2H, NH_2), 3.20 (t, $^3J_{HF}$ = 14.6 Hz, 2H, CH_2), 7.37 (dd, $^3J_{HH}$ = 8 Hz, $^3J_{HH}$ = 3 Hz, 1H), 7.80 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 8.69 (d, $^3J_{HH}$ = 3 Hz, 1H), 8.74 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 49.3 (t, $^2J_{CF}$ = 30 Hz, CH_2), 120.7 (t, $^1J_{CF}$ = 243 Hz, CF_2), 123.3 (s, C_{Py}), 131.4 (t, $^2J_{CF}$ = 28 Hz, $\underline{C}CF_2$), 133.2 (t, $^3J_{CF}$ = 6 Hz, C_{Py}), 146.9 (t, $^3J_{CF}$ = 7 Hz, C_{Py}), 151.3 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –106.0 (t, $^3J_{FH}$ = 14.6 Hz). Anal. Calc. for $C_7H_8F_2N_2$: C, 53.16; H, 5.10; N, 17.71. Found: C, 53.03; H, 5.26; N, 17.59.

4.5.3. 2,2-Difluoro-2-(pyridin-4-yl)ethanamine **6c**

Yield 0.064 g (62%); yellow crystals; mp 165-167°C. ^1H NMR (400 MHz, DMSO-d_6) δ: 3.33 (br s, 2H, NH_2), 3.66 (m, $^3J_{HF}$ = 15.8 Hz, 2H, CH_2), 7.61 (d, $^3J_{HH}$ = 4 Hz, 2H), 8.78 (d, $^3J_{HH}$ = 4 Hz, 2H). ^{13}C NMR (150.8 MHz, DMSO-d_6) δ: 43.8 (t, $^2J_{CF}$ = 28.0 Hz, CH_2), 119.2 (t, $^1J_{CF}$ = 244 Hz, CF_2), 120.3 (t, $^3J_{CF}$ = 5.5 Hz, C_{Py}), 141.5 (t, $^2J_{CF}$ = 26 Hz, $\underline{C}CF_2$), 150.9 (s, C_{Py}). ^{19}F NMR (470.3 MHz, DMSO-d_6) δ: –102.0 (t, $^3J_{FH}$ = 15.8 Hz). Anal. Calc. for $C_7H_8F_2N_2$: C, 53.16; H, 5.10; N, 17.71. Found: C, 53.07; H, 5.15; N, 17.9.

4.6. tert-Butyl (2,2-difluoro-2-(pyridin-2-yl)ethyl)carbamate **7**

To a solution of amine **6a** (0.21 g, 1.33 mmol) in DCM (3 mL) NEt_3 (0.2 g, 2 mmol), and Boc_2O (0.29 g, 1.33 mmol) in DCM (3 mL) were added with ice cooling. The reaction mixture was stirred at r.t. for 16 h. Then it was quenched with water (2 mL), layers were separated and aqueous layer was extracted with DCM (3 × 10mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 0.28 g (yield 82%) of **7** as white powder; mp 130-132°C. ^1H NMR (301.5 MHz, $CDCl_3$) δ: 1.41 (s, 9H, $C(CH_3)_3$), 3.98 (t, $^3J_{HF}$ = 14 Hz, 2H, CH_2), 5.09 (br s, 1H, NH), 7.38 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 7.67 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.82 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 8.64 (d, $^3J_{HH}$ = 4.6 Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.2 (s, $C(\underline{C}H_3)_3$), 44.7 (t, $^2J_{CF}$ = 30 Hz, CH_2), 79.8 (s, $\underline{C}(CH_3)_3$), 118.6 (t, $^1J_{CF}$ = 243 Hz, CF_2), 120.6 (s, C_{Py}), 125.0 (s, C_{Py}), 137.2 (s, C_{Py}), 149.2 (s, C_{Py}), 153.3 (t, $^2J_{CF}$ = 31 Hz, $\underline{C}CF_2$), 155.6 (s, C(O)). ^{19}F NMR (188 MHz, $CDCl_3$) δ: –108.3 (t, $^3J_{FH}$ = 14 Hz). Anal. Calc. for $C_{12}H_{16}F_2N_2O_2$: C, 55.81; H, 6.24; N, 10.85. Found: C, 55.59; H, 6.13; N, 10.66.

4.7. tert-Butyl (2,2-difluoro-2-(piperidin-2-yl)ethyl)carbamate **8**

The autoclave (50 mL) was filled with a solution of Boc-amine **7** (0.1 g, 0.39 mmol) in MeOH (5 mL), and 10% Rh/C (10 mg) was added. The mixture was hydrogenated under 50 atm. of H_2 for 16 h. After completion of the reaction, the catalyst was filtered off, and the solvent was evaporated to give 0.1 g of **8** (yield 98%) as white solid; mp 184-186°C. ^{1}H NMR (301.5 MHz, $CDCl_3$) δ: 1.36-1.41 (m, 1H, CH), 1.46 (s, 9H, $C(CH_3)_3$), 1.47-1.69 (m, 2H), 1.91 (d, $^2J_{HH}$ = 12.1 Hz, 2H, CH_2), 2.68 (td, $^2J_{HH}$ = 12.1 Hz, 1H, CH), 2.95-3.17 (m, 2H, CH, NH), 3.28 (d, $^2J_{HH}$ = 12.4 Hz, 2H, CH_2), 3.63 (tt, $^3J_{HF}$ = 14 Hz, 2H, CF_2CH_2), 5.35 (t, $^3J_{HH}$ = 6.5 Hz, 1H, NHCO). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 22.6 (s, CH_2), 23.6 (s, CH_2), 23.9 (s, CH_2), 28.1 (s, $C\underline{C}H_3)_3$), 41.6 (t, $^2J_{CF}$ = 28 Hz, $CF_2\underline{C}H_2$), 45.6 (s, CH_2), 57.4 (t, $^2J_{CF}$ = 24 Hz, $\underline{C}HCF_2$), 78.4 (s, $\underline{C}(CH_3)_3$), 121.6 (t, $^1J_{CF}$ = 246 Hz, CF_2), 155.8 (s, C(O)). ^{19}F NMR (188 MHz, $CDCl_3$) δ: –115.8 (dd, $^2J_{FAFB}$ = 254 Hz, $^3J_{FH}$ = 10.6 Hz, 1F), –117.7 (dd, $^2J_{FBFA}$ = 254 Hz, $^3J_{FH}$ = 12.8 Hz, 1F). Anal. Calc. for $C_{12}H_{22}F_2N_2O_2$: C, 54.53; H, 8.39; N, 10.60. Found: C, 54.39; H, 8.47; N, 10.65.

4.8. Synthesis of difluoropyridinylethanoles **9a-c**: general procedure

To a solution of respective ester **4** (1 g, 5 mmol) in EtOH (10 mL) was slowly added $NaBH_4$ (0.29 g, 7.5 mmol) at –10°C. The reaction mixture was stirred at r. t. for 18 hrs, the solvent was evaporated under reduced pressure, the residue was neutralized with saturated NH_4Cl solution (2mL), dissolved in 10 mL of EtOAc, washed by brine (5 mL), dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give **9**.

4.8.1. 2,2-Difluoro-2-(pyridin-2-yl)ethanol **9a**

Yield 0.7 g (88%); white crystals; mp 69-72°C (lit. mp 67-69°C [4]). Anal. Calc. for $C_7H_7F_2NO$: C, 52.83; H, 4.43; N, 8.80. Found: C, 52.68; H, 4.51; N, 8.93.

4.8.2. 2,2-Difluoro-2-(pyridin-3-yl)ethanol **9b**

Yield 0.6 g (75%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.0 (t, $^3J_{HF}$ = 13.2 Hz, 2H), 4.72 (br s, 1H, OH), 7.40 (dd, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 3.9 Hz, 1H), 7.88 (d, $^3J_{HH}$ = 7.4 Hz, 1H), 8.63 (d, $^3J_{HH}$ = 3.9 Hz, 1H), 8.7 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 65.1 (t, $^2J_{CF}$ = 34 Hz, CH_2), 119.9 (t, $^1J_{CF}$ = 244 Hz, CF_2), 123.6 (s, C_{Py}), 131.4 (t, $^2J_{CF}$ = 27 Hz, $\underline{C}CF_2$), 134.4 (t, $^3J_{CF}$ = 6 Hz, C_{Py}), 146.7 (t, $^3J_{CF}$ = 6.5 Hz, C_{Py}), 150.56 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –106.7 (t, $^3J_{FH}$ = 13.2 Hz). Anal. Calc. for $C_7H_7F_2NO$: C, 52.83; H, 4.43; N, 8.80. Found: C, 52.71; H, 4.38; N, 8.91.

4.8.3. 2,2-Difluoro-2-(pyridin-4-yl)ethanol **9c**

Yield 0.76 g (96%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.98 (t, $^3J_{HF}$ = 13.2 Hz, 2H), 4.27 (br s, 1H, OH), 7.45 (d, $^3J_{HH}$ = 5.5 Hz, 2H), 8.6 (d, $^3J_{HH}$ = 5.5 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 64.8 (t, $^2J_{CF}$ = 32.5 Hz, CH_2), 119.5 (t, $^1J_{CF}$ = 245 Hz, CF_2), 120.8 (t, $^3J_{CF}$ = 6 Hz, C_{Py}), 144.1 (t, $^2J_{CF}$ = 27.5 Hz, $\underline{C}CF_2$), 149.4 (s, C_{Py}). ^{19}F NMR (376.5 Hz, $CDCl_3$) δ: –109.5 (t, $^3J_{FH}$ = 13.2 Hz). Anal. Calc. for $C_7H_7F_2NO$: C, 52.83; H, 4.43; N, 8.80. Found: C, 52.94; H, 4.39; N, 8.88.

4.9. Synthesis of difluoropyridinylacetic acids **10a-c**: general procedure

To a solution of respective ester **4** (0.2 g, 1 mmol) in EtOH (10 mL) was added LiOH (0.024 g, 1 mmol). The mixture was stirred at r.t. for 12 h, neutralized with MeOH/HCl (5 mL), the solvents were evaporated under reduced pressure. The residue was dissolved in THF (3 mL), and treated with propylene oxide (0.17 g, 3 mmol). The solvent was evaporated under reduced pressure; the dry residue was washed with THF (1 mL), dried under vacuum.

4.9.1. 2,2-Difluoro-2-(pyridin-2-yl)acetic acid **10a**

Yield 0.16 g (94%); white powder; mp 134-138°C. ^{1}H NMR (499.8 MHz, DMSO-d_6) δ: 7.4 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 7.57 (d, $^3J_{HH}$ = 7.7 Hz, 1 H), 7.85 (t, $^3J_{HH}$ = 7.7 Hz 1H), 8.54 (d, $^3J_{HH}$ = 4.8 Hz, 1H). ^{13}C NMR (150.8 MHz, DMSO-d_6) δ: 114.1 (t, $^1J_{CF}$ = 253 Hz, CF_2), 120.9 (t, $^3J_{CF}$ = 4.5 Hz, C_{Py}), 124.7 (s, C_{Py}), 137.2 (s, C_{Py}), 149.0 (s, C_{Py}), 155.6 (t, $^2J_{CF}$ = 27.5 Hz, $\underline{C}CF_2$), 164.8 (t, $^2J_{CF}$ = 27 Hz, C(O)). Other physicochemical and spectral data were identical to literature data [9]. Anal. Calc. for $C_7H_5F_2NO_2$: C, 48.57; H, 2.91; N, 8.09. Found: C, 48.48; H, 2.97; N, 8.21.

4.9.2. 2,2-Difluoro-2-(pyridin-3-yl)acetic acid **10b**

Yield 0.15 g (88%); white powder; mp 193-195°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 7.89 (d, $^3J_{HH}$ = 7.9 Hz, 1 H), 8.62 (d, $^3J_{HH}$ = 4.7 Hz, 1 H), 8.69 (s, 1H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 114.9 (t, $^1J_{CF}$ = 254 Hz, CF_2), 123.7 (s, C_{Py}), 133.1 (t, $^3J_{CF}$ = 27 Hz, $\underline{C}CF_2$), 133.7 (t, $^3J_{CF}$ = 4.5 Hz, C_{Py}), 146.9 (t, $^3J_{CF}$ = 4.5 Hz, C_{Py}), 150.80 (s, C_{Py}), 164.9 (t, $^2J_{CF}$ = 27.5 Hz, C(O)). ^{19}F NMR (376.5 Hz, DMSO-d_6) δ: –103.3 (s). Anal. Calc. for $C_7H_5F_2NO_2$: C, 48.57; H, 2.91; N, 8.09. Found: C, 48.63; H, 2.99; N, 7.99.

4.9.3. 2,2-Difluoro-2-(pyridin-4-yl)acetic acid **10c**

Yield 0.155 g (91%); white powder; mp 230-240°C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45 (d, $^3J_{HH}$ = 4.5 Hz, 2H), 8.61 (d, $^3J_{HH}$ = 4.5 Hz, 2H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 114.6 (t, $^1J_{CF}$ = 254 Hz, CF_2), 120.5 (t, $^3J_{CF}$ = 5.5 Hz, C_{Py}), 145.7 (t, $^3J_{CF}$ = 27.5 Hz, $\underline{C}CF_2$), 150.0 (s, C_{Py}), 164.2 (t, $^2J_{CF}$ = 26.5 Hz, C(O)). ^{19}F NMR (376.5 MHz, DMSO-d_6) δ: –102.0 (s). Anal. Calc. for $C_7H_5F_2NO_2$: C, 48.57; H, 2.91; N, 8.09. Found: C, 48.68; H, 2.79; N, 8.23.

4.10. 2,2-Difluoro-2-(pyridin-2-yl)acetimidamide **11**

Nitrile **2a** (2 g, 13 mmol) was added dropwise to the ammonia (40 mL) condensed in a three-necked reactor, maintaining the temperature at about –33°C. The reaction mixture was kept at this temperature for 4 hrs, and then warmed to room temperature. The residue was dried *in vacuo* to give 2.13 g of 11 (yield 96%) as white solid; mp 130-132°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (br s, 3H, NH_2, NH), 7.44 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 7.70 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.85 (t, $^3J_{HH}$ = 7.7 Hz, 1H), 8.69 (d, $^3J_{HH}$ = 4.8 Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 112.9 (t, $^1J_{CF}$ = 248 Hz, CF_2), 120.3 (s, C_{Py}), 125.49 (s, C_{Py}), 137.4 (s, C_{Py}), 149.7 (s, C_{Py}), 152.17 (t, $^2J_{CF}$ = 29 Hz), 160.3 (t, $^2J_{CF}$ = 28.5 Hz). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –105.2 (s). Anal. Calc. for $C_7H_7F_2N_3$: C, 49.12; H, 4.12; N, 24.55. Found: C, 49.23; H, 4.01; N, 24.63.

4.11. Synthesis of difluoro(pyridin-2-yl)methyl)pyrimidin-4(1H)-ones **13a-b**: general procedure

To a solution of amidine **11** (0.17 g, 1 mmol) in methanol (5 ml) were added sodium methoxide (0.16 g, 3 mmol) and respective ketoester **12** (1 mmol). The reaction mixture was refluxed for 24 hrs. After completion of the reaction, the solvent was evaporated, the residue was dissolved in water, and 1N HCl was added until pH=7. The aqueous solution was extracted with ethyl acetate (3 × 20 mL), and then the organic extract was washed with brine. The solvent was dried over Na_2SO_4 and evaporated under reduced pressure.

4.11.1. 2-(Difluoro(pyridin-2-yl)methyl)-6-methylpyrimidin-4(1H)-one **13a**

Yield 0.13 (54%); gray solid; mp 170-174°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, CH_3), 6.32 (s, C_{pyrim}), 7.46 (dd, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 4.2 Hz 1H), 7.85-7.92 (m, 2H), 8.66 (d, $^3J_{HH}$ = 4.2 Hz, 1H). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ: 21.6 (s, Me), 110.5 (t, $^1J_{CF}$ = 248.5 Hz, CF_2), 111.8 (s, CH_{pyrim}), 118.5 (t, $^3J_{CF}$ = 4 Hz, C_{Py}), 123.5 (s, C_{Py}), 126.1 (s, C_{pyrim}-Me), 135.3 (s, C_{Py}), 147.4 (s, C_{Py}), 149.5 (t, $^2J_{CF}$ = 28.5 Hz, $\underline{C}CF_2$), 150.4 (t, $^2J_{CF}$ = 29 Hz, $CF_2\underline{C}$=N), 162.63 (s, C(O)). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –103.8 (s). Anal. Calc. for $C_{11}H_9F_2N_3O$: C, 55.70; H, 3.82; N, 17.71. Found: C, 55.59; H, 3.89; N, 17.58.

4.11.2. 2-(Difluoro(pyridin-2-yl)methyl)-6-(trifluoromethyl)pyrimidin-4(1H)-one **13b**

Yield 0.15 (53%); yellow solid; mp 150-154°C. ^{1}H NMR (499.8 MHz, $CDCl_3$) δ: 6.86 (s, H_{pyrim}), 7.51 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 7.88 (d, $^3J_{HH}$ = 8.0 Hz, 1 H), 7.94 (t, $^3J_{HH}$ = 8 Hz, 1H), 8.67 (d, $^3J_{HH}$ = 5 Hz, 1H). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ): 112.3 (t, $^1J_{CF}$ = 249 Hz, CF_2), 114.9 (s, CH_{pyrim}), 120.0 (q, $^1J_{CF}$ = 275 Hz, CF_3), 120.9 (t, $^3J_{CF}$ = 4 Hz, C_{Py}), 126.1 (s, C_{Py}), 137.8 (s, C_{Py}), 149.6 (s, C_{Py}), 151.1 (t, $^2J_{CF}$ = 28.5 Hz, $\underline{C}_{Py}CF_2$), 152.7 (q, $^2J_{CF}$ = 36.5 Hz, $\underline{C}CF_3$), 155.5 (t, $^2J_{CF}$ = 32 Hz, $CF_2\underline{C}$=N), 160.9 (s, CO). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –71.4 (s, CF_3), –103.1 (s, CF_2). Anal. Calc. for $C_{11}H_9F_2N_3O$: C, 45.37; H, 2.08; N, 14.43. Found: C, 45.21; H, 2.15; N, 14.34.

4.11.3. 2,2-Difluoro-N'-hydroxy-2-(pyridin-2-yl)acetimidamide **14**

To a solution of hydroxylamine hydrochloride (0.23 g, 3.3 mmol) in methanol (1 mL) was added sodium hydroxide (0.13 g, 3.3 mmol) with ice cooling. The reaction mixture was stirred for 0.5 h, then the precipitate was filtered off, and the solution of nitrile **2a** (0.462 g, 3 mmol) in MeOH (1 mL) was added to the filtrate with ice cooling. The reaction mixture was kept at r. t. for 6 hrs, then the solvent was evaporated, the residue was washed with hexane to give 0.45 g of **14** (yield 80%) as white solid; mp 95-97°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.51 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 7.64 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.93 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 8.64 (d, $^3J_{HH}$ = 4.7 Hz, 1H).^{13}C NMR (125.7 MHz, DMSO-d_6) δ: 115.5 (t, $^1J_{CF}$ = 242 Hz, CF_2), 121.1 (t, $^3J_{CF}$ = 4 Hz, C_{Py}), 125.1 (s, C_{Py}), 137.0 (s, C_{Py}), 148.4 (m, $^2J_{CF}$ = 29 Hz, ($\underline{C}$N)CF_2), 148.9 (s, C_{Py}), 152.5 (m, $^2J_{CF}$ = 26 Hz, $^2J_{CF}$ = 28 Hz, $\underline{C}CF_2$). ^{19}F NMR (376.5 MHz, DMSO-d_6) δ: –100.6 (s). Anal. Calc. for $C_7H_7F_2N_3O$: C, 44.92; H, 3.77; N, 22.45. Found: C, 44.81; H, 3.88; N, 22.57.

4.12. 3-(Difluoro(pyridin-2-yl)methyl)-1,2,4-oxadiazole **15a**

The mixture of amidoxime **14** (0.19 g, 1 mmol) and 0.8 mL of ethyl orthoformate (0.74 g, 5 mmol) was heated at 60 °C for 72 hrs. After the completion of the reaction, ethyl orthoformate was evaporated, and the residue was washed with hexane to give 0.17 g of **15** (yield 86%) as white solid; mp 55-57°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (dd, $^3J_{HH}$ = 7 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 7.88-7.90 (m, 2H), 8.67 (d, $^3J_{HH}$ = 4.2 Hz, 1H), 8.84 (s, 1H). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ: 113.6 (t, $^1J_{CF}$ = 244 Hz, CF_2), 120.6 (t, $^3J_{CF}$ = 3.5 Hz, C_{Py}), 125.8 (s, C_{Py}), 137.5 (s, C_{Py}), 149.7 (s, C_{Py}), 151.8 (t, $^2J_{CF}$ = 28.5 Hz, $\underline{C}CF_2$), 165.7 (t, $^2J_{CF}$ = 32.5 Hz, C=N), 166.0 (s, $C_{oxadiaz.}$). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –99.5 (s). Anal. Calc. for $C_8H_5F_2N_3O$: C, 48.74; H, 2.56; N, 21.31. Found: C, 48.55; H, 2.67; N, 21.48.

4.13. 3-(Difluoro(pyridin-2-yl)methyl)-5-methyl-1,2,4-oxadiazole **15b**

To a solution of amidoxime **14** (0.06 g, 0.32 mmol) in DCM (3 mL) was added NEt_3 (0.036 g, 0.35 mmol), and acetyl chloride (0.028 g, 0.35 mmol) in DCM (3 mL) with ice cooling. The reaction mixture was stirred at r.t. for 2 hrs. Then water (2 mL) was added, layers were separated and aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was heated at 100 °C for 6 h. After completion of the reaction the residue was dissolved in EtOAc (5 mL). The mixture was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 0.042 g of **15b** (yield 62%) as white solid; mp 57-58°C. ^{1}H NMR (301.5 MHz, $CDCl_3$) δ: 2.65 (s, 3H, CH_3), 7.44 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 7.83-7.92 (m, 2H), 8.66 (d, $^3J_{HH}$ = 4.6 Hz, 1H). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ: 12.3 (s, CH_3), 113.6 (t, $^1J_{CF}$ = 244 Hz, CF_2), 120.5 (t, $^3J_{CF}$ = 4 Hz, C_{Py}), 125.6 (t, $^5J_{CF}$ = 1.5 Hz, C_{Py}), 137.3 (s, C_{Py}), 149.7 (s, C_{Py}), 152.1 (t, $^2J_{CF}$ = 28 Hz, $\underline{C}CF_2$), 166.3 (t, $^2J_{CF}$ = 32 Hz, C=N), 178.1 (s, $C_{oxadiaz.}$). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ: –99.6 (s). Anal. Calc. for $C_9H_7F_2N_3O$: C, 51.19; H, 3.34; N, 19.90. Found: C, 49.98; H, 3.12; N, 19.76.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2021.109792.

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