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α-(Imino)pyridyldifluoroethyl Phosphonates: Novel Promising Building Blocks in Synthesis of Biorelevant Aminophosphonic Acids Derivatives

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Abstract: A convenient synthetic approach to previously unknown NH-iminophosphonates bearing 2-, 3-, and 4-pyridyldifluoromethyl groups at the imine carbon atom was developed. The synthetic potential of these novel building blocks was demonstrated by their conversion into highly functionalized acyclic and heterocyclic aminophosphonates and phosphonic acids combining in their structure biorelevant aminophosphonic fragment, difluoromethyl group, and pyridyl, piperidyl, thiazolidin-4-one, or thiazidinan-4-one heterocyclic moieties in a single molecular platform.

Keywords: iminophosphonates; aminophosphonates; NH-imines; nitriles; difluoromethyl; pyridine; piperidine; E-Z isomerism

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1. Introduction

α-Aminophosphonates are phosphorus analogs of amino acids in which the planar carboxylic group is replaced with a tetrahedral bioisosteric phosphonic unit. They exhibit a wide range of biological activity and play a significant role in the development of antibiotics, antiviral, antihypertensive, antitumor agents and other bioactive substances [1–5]. Of particular interest are fluorinated aminophosphonates. Modification of organic molecule with fluorine has become almost a standard tool in modern drug design. It is generally accepted that introduction of a fluorine containing group may improve the pharmacodynamic and the pharmacokinetic profiles of the compound by concomitant alteration of its electronic, lipohilic, and steric characteristics as well as its metabolic stability [6–9].

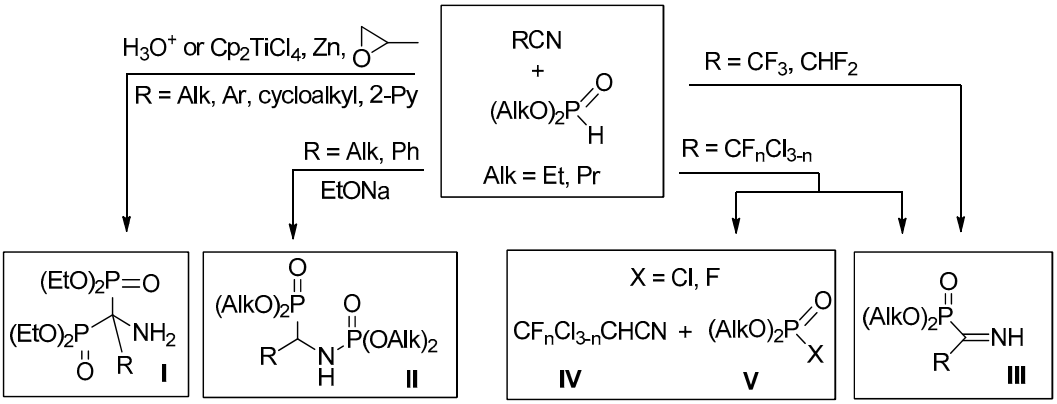
α-Iminophosphonates, i.e., the compounds bearing $(RO)_2P(O)C{=}N$-fragment, are valuable precursors of α-aminophosphonates. Unprotected NH-iminophosphonates are especially promising in this respect. They show enhanced reactivity and allow straightforward preparation of aminophosphonates with a free NH_2 group avoiding tedious N-deprotection step. Recently we have prepared the first representatives of NH-iminophosphonates and demonstrated their potential for the introduction of pharmacophore α-fluoroalkylated aminophosphonic unit into various structures.

NH-Iminophosphonates incorporating heterocyclic residue were unknown so far. In the present work we report the synthesis of NH-iminophosphonates bearing α-, β-, or γ-pyridyldifluoromethyl group at the imine carbon atom and their use for the preparation of aminophosphonic acids derivatives bearing difluoromethyl group and heterocyclic residue. Note, that compounds with 2-pyridyldifluoromethyl fragment were used for the development of effective thrombin and trypsin inhibitors [10] and highly selective antifungal agents [11]. The presence of a pyridine ring offers additional synthetic possibilities connected with the hydrogenation of heterocyclic ring and preparation of compounds

containing aminophosphonic unit, difluoromethyl group and piperidine fragment in the same molecule. It is worth of noting that according to [12] piperidine and pyridine are most frequent nitrogen heterocycles in U.S. FDA approved drugs.

2. Results and Discussion

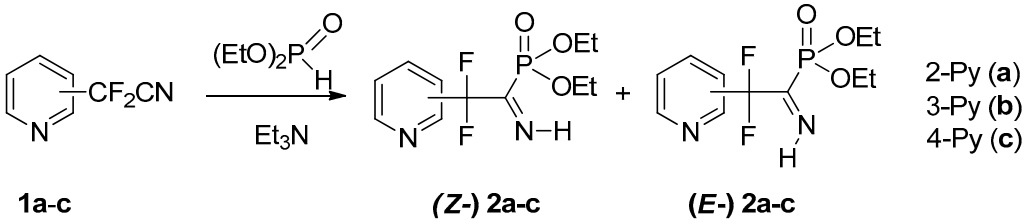
Analysis of the literature data shows that hydrophosphoryl compounds can react with nitriles by different schemes. Thus, reaction of dialkylphosphites with alkyl, cycloalkyl, aryl, or pyridyl nitriles in the presence of acids [13,14] or under free radical conditions [15] leads to aminobisphosphonates **I**, as the main products, formed in low to moderate yields (Scheme 1). At the same time, under basic conditions benzonitrile reacts with dialkyl or diphenyl phosphites to form phosphorylamino phosphonates **II** [16]. Recently we have shown that highly electrophilic polyfluoroalkylated nitriles in the reactions with dialkyl or diphenyl phosphite afford first representatives of NH-iminophosphonates **III** [17,18]. At the same time, mixed perfluoro(chloro) acetonitriles react with $(RO)_2POH$ (R = Et, Ph) by two competitive routes: addition to the C≡N bond affording the respective N-unprotected iminophosphonates **III**, or reductive dehalogenation leading to chloro(fluoro) acetonitriles IV and the respective halogenophosphates **V** [19].



Scheme 1. Reactions of nitriles with hydrophosphoryl compounds.

Thus, the results of reactions of hydrophosphoryl compounds with nitriles depend on reactants structure and conditions.

We have found that all three isomeric pyridyldifluoroacetonitriles **1a–c** react with diethyl phosphite under mild conditions (20 mol.% Et_3N, r.t.) to afford respective NH-iminophosphonates **2a–c** (Scheme 2). It should be noted that 2-pyridyl nitrile **1a** reacts much more slowly than the 3- and 4-isomers **1b**,**c**: under the same conditions the reaction is completed within 120 and 12 h, respectively. Similar differences have previously been noted for pKa values of the isomeric pyridineacetic acids [20] which may be associated with the specific effect of the α-nitrogen atom.



Scheme 2. Synthesis of pyridyldifluoromethylated NH-iminophosphonates.

Formation of the P-C=N-H fragment is confirmed by ^{13}C NMR spectra of compounds **2**, in which the imine C-atom signal (δ_C171–173 ppm) with a large direct C-P coupling

constant ($^1J_{CP}$ 153–154 Hz for *Z*-izomers **2a–c**; 210 Hz for *E*-isomer **2a**) was identified, and ^{1}H, ^{31}P NMR spectra showing characteristic spin-spin interaction of the N-H proton and phosphorus atom ($^3J_{P\text{-}C\text{-}N\text{-}H}$ 40–62 Hz).

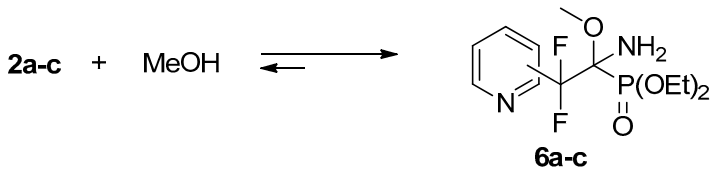
Iminophosphonates **2a–c** are formed as an equilibrium mixture of *Z*/*E* isomers and, similarly to other fluoroalkylated NH-iminophosphonates, a more sterically hindered *Z* configuration is preferred. We have shown previously that substituent at the C=N bond of iminophosphonates markedly affect *E*/*Z* isomeric ratio: C-trifluoromethylated iminophosphonates exist preferentially in *Z* configuration, whereas for their C-arylated analogs *E*-configuration prevails [21,22]. Table 1 shows the values of equilibrium *Z*/*E* ratios and phosphorus chemical shifts for pyridyldifluoromethylphosphonates **2a–c** and some other related iminophosphonates. It is seen that ^{31}P NMR data and *Z*/*E* ratios for iminophosphonates **2b**,**c** are very close and markedly differ from those for isomer **2a**. It is very interesting to note from analysis of Table 1 that imines **2b**,**c** bearing more strong electron withdrawing 3- and 4-pyridyl substituent (σ_p 0.25 and 0.44, respectively [23] are in this respect more similar to trifluoromethylated analog **3**, whereas isomer **2a** with less electron withdrawing 2-pyridyl group (σ_p 0.17) is more like benzimidoyl phosphonates **4**, **5**.

Table 1. *Z*/*E* isomeric ratio and selected ^{13}C, ^{31}P NMR data of the compounds **2** and some related iminophosphonates.

Compound	*Z*/*E*	δ_P ($^3J_{P\text{-}C\text{=}N\text{-}H}$)		$\delta_{C=N}$ ($^1J_{CP}$)	
	($CDCl_3$)	*Z*	*E*	*Z*	*E*
2a	2:1	5.9 (39.9)	6.6 (61.6)	173.2 (153)	170.8 (210)
2b	6:1	1.2 (39.6)	3.0 (61.2)	173 (154)	-
2c	7:1	0 (39.5)	1.8 (62.2)	172.9 (154)	-
$CF_3CP(O)(OEt)_2$=NH (**3**)	10:1	−1.4 (37.2)	0.7 (58.2)	166.8 (163.5)	-
$PhCP(O)(OEt)_2$=NH (**4**)	3:1	3.9 (46)	6.5 (75)	-	-
$PhCP(O)(OEt)_2$=NMe (**5**)	1:17	2.3	6.9	-	169.3 (220)

Identification of *Z*,*E*-isomers **2a–c** is based mainly on the significant difference in coupling constants of the N-H proton and phosphorus atom ($^3J_{P\text{-}C\text{-}N\text{-}H}$ ~40 and ~61–62 Hz, respectively) and high-field shift of phosphorus signals of *Z*-isomers in ^{31}P NMR spectra, previously noted for other α-iminophosphonates [17,18,21,22].

Iminophosphonates **2** contain a polarized C=N bond activated by the presence of electron-withdrawing group at the imine carbon atom. Thus, imines **2a–c** readily add methanol across the C=N bond to afford adduct **6a–c** (Scheme 3). The reactivity decreases in the order **2a** > **2b**,**c**: after 8 h the conversion is 100%, 44%, and 46%, respectively. The complete conversion of **2b**,**c** proceeds within 2 days.



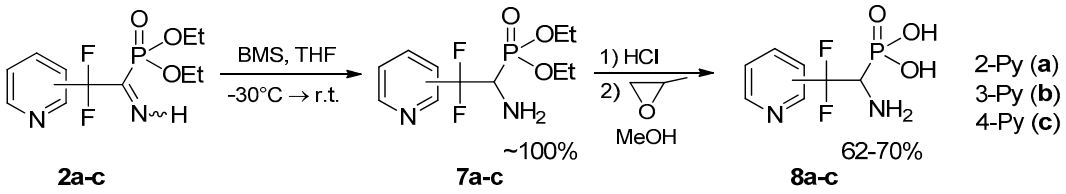
Scheme 3. Reversible reaction of iminophosphonates **2** with methanol.

Similar to trifluoromethylated analogs [17,18,21], compounds **6a–c** in $CDCl_3$ solution partially (~15–20%) dissociate to the starting compounds. This property of NH-imine adducts was successfully explored for the improvement of the enantiomeric excess in catalytic asymmetric reduction [24].

It is very interesting to note, that addition of methanol to iminophosphonates **2** is accompanied by the change in the *Z*/*E* ratio of the starting compounds and *Z*-*E* equilibrium is established very quickly. Thus, immediately after dissolution of imines **2a–c** in methanol, *Z*/*E* ratios of imines **2a–c**, according to ^{31}P, ^{19}F NMR data, are 1:1, 2.5:1, and 2:1, respectively.

Evaporation of methanol and dissolution in deuterochloroform leads to recovery of *Z*/*E* isomeric ratios, presented in Table 1, i.e., 2:1, 6:1, and 7:1, respectively. Similar increase of *E*-isomer content on going from aprotic to protic solvent was shown recently for the sodium salts of N-methyliminophosphonates, bearing aryl or hetaryl substituents at the imine carbon atom [22].

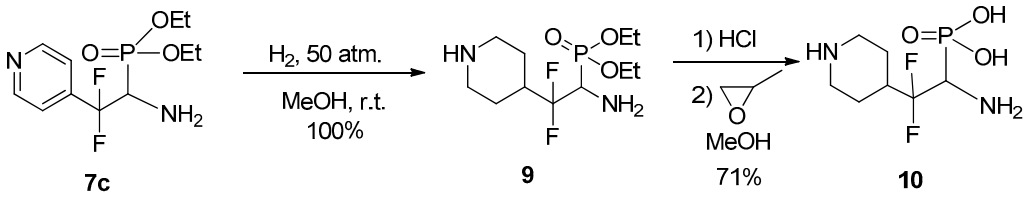
Synthesis of biorelevant pirydyldifluoroemethylated aminophosphonates and aminophosphonic acids. We have found that selective reduction of the C=N bond in iminophosphonates **2a–c** with borane-dimethylsulfide (BMS) proceeds under mild conditions to give aminophosphonates **7a–c** incorporating pyridyldifluoromethyl residue (Scheme 4). Free aminophosphonates **7a–c** are not very stable (the stability decreases in the order **7c** > **7b** > **7a**) and should be stored at the reduced temperature in refrigerator.



Scheme 4. Selective reduction of the C=N bond in the iminophosphonates **2a–c**.

Preparation of heterocycle-containing aminophosphonic acids from their esters are often complicated by side processes. It was found that hydrolysis of aminophosphonates **7a–c** with conc. HCl proceeds cleanly and affords the first representatives of fluoroalkylated aminophosphonic acids **8a–c,** incorporating heterocyclic moiety in the β-position.

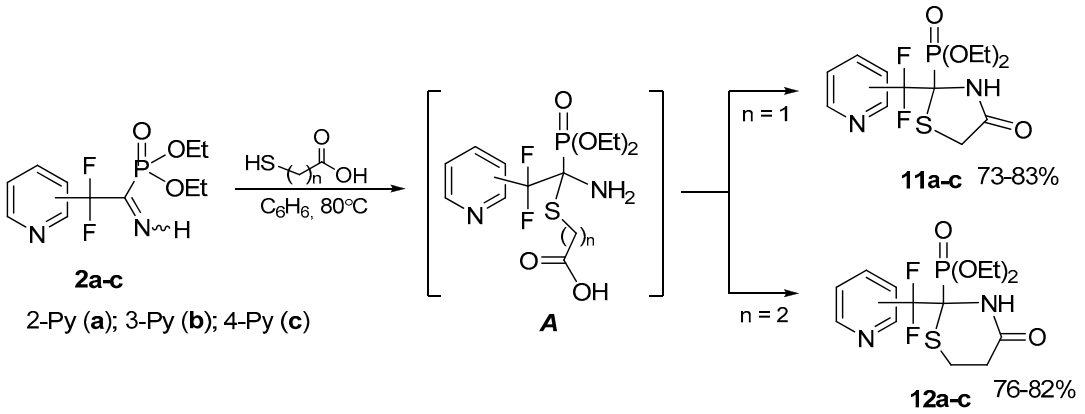
The possibility of reducing the pyridine ring was studied using compound **7c** as the most stable pyridyl substituted aminophosphonate. It was found that catalytic hydrogenation of **7c** leads to complete reduction of pyridine ring to afford 4-piperidyl substituted aminophosphonate **9** (Scheme 5).



Scheme 5. Catalytic hydrogenation of the aminophosphonate **7c**.

The latter should be stored at a reduced temperature, since under ordinary conditions it gradually decomposes, most likely undergoing O-N transfer of the ethyl group. More stable free aminophosphonic acid **10** was obtained by hydrolysis of **9** followed by treatment with propylene oxide.

Cyclocondensation with mercaptocarboxylic acids. Highly polarized azomethyne bond in the imines **2** can be readily functionalized by the reactions with the bifunctional compounds. Thus, cyclocondensation of iminophosphonates **2a–c** with thioglycolic or 3-mercaptopropionic acid leads to highly functionalized thiazolidin-4-ones **11a–c** or thiazidinan-4-ones **12a–c**, respectively (Scheme 6). Obviously, the reaction proceeds via primary nucleophilic addition to the C=N bond followed by intramolecular ring closure in the intermediate ***A***. The ease of cyclization of the latter is due to the spatial accessibility of the unsubstituted N-nucleophilic center, and the experimentally found noticeably faster formation of thiazolidinones **11** as compared to thiazinanones **12** is explained by the proximity of the reaction centers upon creation of the 5-membered cycle. We were able to detect by ^{31}P NMR adduct ***A*** (Scheme 6, n = 2) resulting from addition of 3-mercaptopropionic acid (δ_P 16 ppm).



Scheme 6. Cyclocondensation with mercaptocarboxylic acids.

3. Conclusions

In summary, the triethylamine catalyzed addition of diethyl phosphite to isomeric pyridyldifluoroacetonitriles leads to α-iminopyridyldifluoroethyl phosphonates, existing as equilibrium mixture of *E*-*Z* isomers. The synthetic potential of these novel electrophilic building blocks was demonstrated by their reduction to biorelevant compounds combining in their structure aminophosphonic residue, difluoromethyl group and isomeric pyridine or piperidine moiety. Cyclocondensation with mercaptocarboxylic acids allow preparation of hybrid molecules bearing two bioactive heterocyclic moieties (pyridine and thiazolidine or thiazinane) and aminophosphonic fragment in a single molecular platform. These reactions proceed under mild neutral conditions and lead directly to N-unprotected aminophosphonic derivatives.

4. Materials and Methods

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded using Bruker Avance NMR spectrometers operating at 302, 400 and 499.8 ^{1}H frequencies; 75.8, 125.7 and 150.8 MHz for ^{13}C experiments; 188, 376.5 and 470.3 MHz for ^{19}F; 81 and 202.3 MHz for ^{31}P. Chemical shifts are reported relative to internal TMS (^{1}H) or $CFCl_3$ (^{19}F) and external 85%-H_3PO_4 (^{31}P) standards. Melting points are uncorrected. Solvents were dried before use according to standard methods. Elemental analysis was carried out in the analytical laboratory of Institute of Organic Chemistry, NAS of Ukraine. See the Supplementary File for the ^{1}H, ^{19}F, and ^{13}C NMR spectra of compounds synthesized.

4.1. Synthesis of Diethyl (2,2-Difluoro-1-imino-2-(pyridinyl)ethyl)phosphonates **2a**–**c***: General Procedure*

To equimolar mixture of pyridinylacetonitrile **1** (0.45 g, 2.9 mmol) and diethyl phosphite (0.4 g, 2.9 mmol) was added triethylamine (0.58 mmol, 0.059 g). After 12 h for **2b**,**c** and 120 h for **2a** triethylamine was removed under vacuum.

4.1.1. Diethyl (2,2-Difluoro-1-imino-2-(pyridin-2-yl)ethyl)phosphonate **2a**

Yield 0.85 g (100%); light brown oil. *Z*/*E* = 2:1. *Z*-isomer: ^{1}H NMR (499.8 MHz, $CDCl_3$) δ (ppm): 1.33 (t, $^{3}J_{HH}$ = 7.2 Hz, 6H, CH_3), 4.16–4.22 (m, 4H, CH_2), 7.40 (t, $^{3}J_{HH}$ = 7.9 Hz, 1H, Py), 7.74 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, Py), 7.84–7.88 (m, 1H, Py), 8.66 (d, $^{3}J_{HH}$ = 4.9 Hz, 1H, Py), 12.27 (d, $^{3}J_{HP}$ = 39.9 Hz, 1H, NH).

^{13}C NMR (75.8 MHz, $CDCl_3$) δ (ppm): 16.0 (d, $^{3}J_{CP}$ = 6 Hz, CH_3), 63.8 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 116.1 (td, $^{1}J_{CF}$ = 246 Hz, $^{2}J_{CP}$ = 33 Hz, CF_2), 120.9 (t, $^{3}J_{CF}$ = 4 Hz, C_{Py}), 125.1 (s, C_{Py}), 136.9 (s, C_{Py}), 149.3 (s, C_{Py}), 152.8 (t, $^{2}J_{CF}$ = 28.5 Hz, $\underline{C}CF_2$), 173.2 (dt, $^{1}J_{CP}$ = 153 Hz, $^{2}J_{CF}$ = 33 Hz, C=N).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −100.2.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 5.9 (m, $^{3}J_{PH}$ = 39.9 Hz).

E-isomer: ^{1}H NMR (499.8 MHz, $CDCl_3$) δ (ppm): 1.26 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 4.10–4.15 (m, 4H, CH_2), 7.40 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H, Py), 7.80–7.84 (m, 2H, Py), 8.6 (d, $^{3}J_{HH}$ = 4.9 Hz, 1H, Py), 11.97 (dt, $^{3}J_{HP}$ = 61.6 Hz, $^{4}J_{HF}$ = 4.0 Hz, 1H, NH).

^{13}C NMR (75.8 MHz, $CDCl_3$) δ (ppm): 16.2 (d, $^{3}J_{CP}$ = 6 Hz, CH_3), 63.7 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 113.9 (td, $^{1}J_{CF}$ = 249 Hz, $^{2}J_{CP}$ = 42 Hz, CF_2), 120.8 (t, $^{3}J_{CF}$ = 4 Hz, C_{Py}), 125.4 (s, C_{Py}), 137.3 (s, C_{Py}), 149.1 (s, C_{Py}), 151.5 (t, $^{2}J_{CF}$ = 29 Hz, $\underline{C}CF_2$), 170.8 (dt, $^{1}J_{CP}$ = 210 Hz, $^{2}J_{CF}$ = 30 Hz, C=N).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −103.5.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 6.6 (m, $^{3}J_{PH}$ = 61.6 Hz).

Anal. Calc. for $C_{11}H_{15}F_2N_2O_3P$: C, 45.21; H, 5.17; N, 9.59. Found: C, 45.38; H, 5.29; N, 9.67.

4.1.2. Diethyl (2,2-Difluoro-1-imino-2-(pyridin-3-yl)ethyl)phosphonate **2b**

Yield 0.85 g (100%); yellow oil. *Z*/*E* = 6:1. *Z*-isomer: ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.27 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 3.93–4.20 (m, 4H, CH_2), 7.29 (dd, $^{3}J_{HH}$ = 8.1 Hz, $^{3}J_{HH}$ = 5.1 Hz, Py), 7.81 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, Py), 8.63 (d, $^{3}J_{HH}$ = 5.1 Hz, 1H, Py), 8.74 (s, 1H, Py), 12.17 (d, $^{3}J_{HP}$ = 39.6 Hz, 1H, NH).

^{13}C NMR (75.8 MHz, $CDCl_3$) δ (ppm): 16.1 (d, $^{3}J_{CP}$ = 6 Hz, CH_3), 63.9 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 117.3 (td, $^{1}J_{CF}$ = 246 Hz, $^{2}J_{CP}$ = 35 Hz, CF_2), 122.9 (s, C_{Py}), 129.9 (t, $^{2}J_{CF}$ = 27 Hz, $\underline{C}CF_2$), 133.8 (t, $^{3}J_{CF}$ = 6 Hz, C_{Py}), 147.3 (t, $^{3}J_{CF}$ = 6.5 Hz, C_{Py}), 151.6 (s, C_{Py}), 173.0 (dt, $^{1}J_{CP}$ = 154 Hz, $^{2}J_{CF}$ = 35 Hz, C=N).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −97.5.

^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 1.2 (m, $^{3}J_{PH}$ = 39.6 Hz).

E-isomer: ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.15 (t, $^{3}J_{HH}$ = 6.9 Hz, 6H, CH_3), 3.93–4.20 (m, 4H, CH_2), 7.30–7.35 (m, 1H, Py), 7.85 (d, $^{3}J_{HH}$ = 6.7 Hz, 1H, Py), 8.66 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H, Py), 8.78 (s, 1H, Py), 11.85 (d, $^{3}J_{HP}$ = 61.2 Hz, 1H, NH).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −100.5.

^{31}P NMR (81 MHz, $CDCl_3$) δ (ppm): 2.9 (m, $^{3}J_{PH}$ = 61.2 Hz).

Anal. Calc. for $C_{11}H_{15}F_2N_2O_3P$: C, 45.21; H, 5.17; N, 9.59. Found: C, 45.46; H, 5.04; N, 9.43.

4.1.3. Diethyl (2,2-Difluoro-1-imino-2-(pyridin-4-yl)ethyl)phosphonate **2c**

Yield 0.85 g (100%); light orange oil. *Z*/*E* = 7:1. *Z*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.34 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 4.14–4.27 (m, 4H, CH_2), 7.50 (d, $^{3}J_{HH}$ = 6 Hz, 2H, Py), 8.74 (d, $^{3}J_{HH}$ = 6 Hz, 2H, Py), 12.21 (d, $^{3}J_{HP}$ = 39.5 Hz, 1H, NH).

^{13}C NMR (75.8 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^{3}J_{CP}$ = 6 Hz, CH_3), 64.1 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 116.9 (td, $^{1}J_{CF}$ = 246 Hz, $^{2}J_{CP}$ = 34 Hz, CF_2), 120.4 (t, $^{3}J_{CF}$ = 6 Hz, $2C_{Py}$), 142.2 (td, $^{2}J_{CF}$ = 27 Hz, $^{3}J_{CP}$ = 6 Hz, $\underline{C}CF_2$), 150.2 (s, $2C_{Py}$), 172.9 (dt, $^{1}J_{CP}$ = 154 Hz, $^{2}J_{CF}$ = 35 Hz, C=N).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −99.4.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 0.1 (m, $^{3}J_{PH}$ = 39.5 Hz).

E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H, CH_3), 4.05–4.13 (m, 4H, CH_2), 7.45 (d, $^{3}J_{HH}$ = 5 Hz, 2H, Py), 8.76 (d, $^{3}J_{HH}$ = 5 Hz, 2H, Py), 11.81 (d, $^{3}J_{HP}$ = 60.9 Hz, 1H, NH).

^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −102.4.

^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 1.8 (m, $^{3}J_{PH}$ = 60.9 Hz).

Anal. Calc. for $C_{11}H_{15}F_2N_2O_3P$: C, 45.21; H, 5.17; N, 9.59. Found: C, 45.03; H, 5.23; N, 9.41.

4.2. Reactions of Iminophosphonates **2a**–**c** *with Methanol*

Iminophosphonates **2a**–**c** (0.02 g, 0.07 mmol) were dissolved in methanol (0.6 mL) at room temperature. According to ^{31}P, ^{19}F NMR the reaction was completed after 8 h (**2a**) or 2 days (**2b**,**c**). The spectral data are similar to those of methanol adduct with trifluoromethyl analog [17].

Spectral data for adduct **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30–1.34 (m, 6H, CH_3), 3.21 (s, 3H, OCH_3), 4.20–4.30 (m, 4H, CH_2), 7.36 (dd, $^{3}J_{HH}$ = 8.1 Hz, $^{3}J_{HH}$ = 3.9 Hz, 1H, Py), 7.68 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, Py), 7.78 (t, $^{3}J_{HH}$ = 8.1 Hz, 1H, Py), 8.60 (d, $^{3}J_{HH}$ = 3.9 Hz, 1H, Py). ^{19}F NMR (470.3 MHz, MeOH) δ (ppm): −103.0 (d, $^{2}J_{FAFB}$ = 255 Hz), −110.5 (d, $^{2}J_{FBFA}$= 255 Hz). ^{31}PNMR (202.3 MHz, MeOH) δ (ppm): 15.1.

Spectral data for adduct **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (t, $^{3}J_{HH}$ = 7.5 Hz, 3H, CH_3), 1.27 (t, $^{3}J_{HH}$ = 7.6 Hz, 3H, CH_3), 2.40 (d, $^{3}J_{HP}$ = 20 Hz, 2H, NH_2), 3.37 (s, 3H, OCH_3), 3.94–4.08 (m, 2H, OCH_2), 4.13–4.18 (m, 2H, OCH_2), 7.30 (dd, $^{3}J_{HH}$ = 7.3 Hz, $^{3}J_{HH}$ = 4.2 Hz, 1H, Py), 7.87 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H, Py), 8.63 (d, $^{3}J_{HH}$ = 4.2 Hz, 1H, Py), 8.77 (s, 1H, Py). ^{19}F NMR (470.3 MHz, MeOH) δ (ppm): −103.9 (d, $^{2}J_{FAFB}$ = 257 Hz), −106.6 (dd, $^{2}J_{FBFA}$ = 257 Hz, $^{3}J_{FP}$ = 7 Hz). ^{31}PNMR (202.3 MHz, MeOH) δ (ppm): 14.8 (m, $^{3}J_{PF}$ = 7 Hz).

Spectral data for adduct **6c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.13 (t, $^{3}J_{HH}$ = 6.9 Hz, 3H, CH_3), 1.30 (t, $^{3}J_{HH}$ = 6.6 Hz, 3H, CH_3), 2.40 (d, $^{3}J_{HP}$ = 22.5 Hz, 2H, NH_2), 3.38 (s, 3H, OCH_3), 3.97–4.12 (m, 2H, OCH_2), 4.13–4.21 (m, 2H, OCH_2), 7.49 (d, $^{3}J_{HH}$ = 5.3 Hz, 2H, Py), 8.66 (d, $^{3}J_{HH}$ = 5.3 Hz, 2H, Py). ^{19}F NMR (470.3 MHz, MeOH) δ (ppm): −106.4 (d, $^{2}J_{FAFB}$ = 254 Hz), −108.4 (dd, $^{2}J_{FBFA}$= 254 Hz, $^{3}J_{FP}$ = 7 Hz). ^{31}PNMR (202.3 MHz, MeOH) δ (ppm): 13.1 (m, $^{3}J_{PF}$ = 7 Hz).

4.3. Synthesis of Diethyl (1-Amino-2,2-difluoro-2-(pyridinyl)ethyl)phosphonates **7a**–**c***: General Procedure*

To a solution of respective iminophosphonate **2** (0.65 g, 2.22 mmol) in THF (8 mL) borane-dimethyl sulfide complex (0.25 g, 3.34 mmol) was added dropwise at −30 °C in argon atmosphere. The reaction mixture was kept at this temperature for 0.5 h and allowed to warm to r.t. After that the reaction mixture was quenched with methanol (2 mL) and stirred for 15 min. Then solvents were evaporated under reduced pressure and residue was dried in vacuo.

4.3.1. Diethyl (1-Amino-2,2-difluoro-2-(pyridin-2-yl)ethyl)phosphonate **7a**

Yield 0.65 g (100%); yellow crystals; mp 52–53 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$) δ (ppm): 1.22 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CH_3), 1.25 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, CH_3), 1.85 (br s, 2H, NH_2), 4.18–4.00 (m, 4H, CH_2), 4.23 (m, 1H, CH), 7.37 (dd, $^{3}J_{HH}$ = 7.8, $^{3}J_{HH}$ = 4.8 Hz, 1H, Py), 7.7 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H, Py), 7.81 (t, $^{3}J_{HH}$ = 7.8 Hz, 1H, Py), 8.64 (d, $^{3}J_{HH}$ = 4.8 Hz, 1H, Py). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm):16.3 (d, $^{3}J_{CP}$ = 5.9 Hz, CH_3), 16.4 (d, $^{3}J_{CP}$ = 6.1 Hz, CH_3), 53.7 (dt, $^{1}J_{CP}$ = 154.9 Hz, $^{2}J_{CF}$ = 28 Hz, CH), 62.7 (d, $^{2}J_{CP}$ = 6.9Hz, CH_2), 63.0 (d, $^{2}J_{CP}$ = 6.7 Hz, CH_2), 120.2 (td, $^{1}J_{CF}$ = 248 Hz, $^{2}J_{CP}$ = 5 Hz, CF_2), 121.0 (t, $^{3}J_{CF}$ = 4.8 Hz, C_{Py}), 124.9 (s, C_{Py}), 137.0 (s, C_{Py}), 149.2 (s, C_{Py}), 153.6 (t, $^{2}J_{CF}$ = 29 Hz, $\underline{C}CF_2$). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): -103.8 (ddd, $^{2}J_{FAFB}$ = 256.5 Hz, $^{3}J_{FH}$ = 15.4 Hz, $^{3}J_{FP}$ = 15.4 Hz), −106.3 (dd, $^{2}J_{FBFA}$ = 256.5 Hz, ^{3}J = 15.1 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 19.8. Anal. Calc. for $C_{11}H_{17}F_2N_2O_3P$: C, 44.90; H, 5.82; N, 9.52. Found: C, 44.67; H, 5.73; N, 9.41.

4.3.2. Diethyl (1-Amino-2,2-difluoro-2-(pyridin-3-yl)ethyl)phosphonate **7b**

Yield 0.65 g (100%); white-yellow oil. ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.13–1.43 (m, 6H, CH_3), 1.85 (br s, 2H, NH_2), 3.62 (m, 1H, CH), 4.00–4.25 (m, 4H, CH_2), 7.54–7.64 (m, 1H, Py), 8.15 (d, $^{3}J_{HH}$ = 8.1 Hz, 1H, Py), 8.68 (d, $^{3}J_{HH}$ = 5.8 Hz, 1H, Py), 8.82 (s, 1H, Py). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ (ppm): 16.0 (d, $^{3}J_{CP}$ = 5 Hz, CH_3), 16.2 (d, $^{3}J_{CP}$ = 5 Hz, CH_3), 53.8 (dt, $^{1}J_{CP}$ = 150 Hz, $^{2}J_{CF}$ = 29 Hz, CH), 62.0 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 62.5 (d, $^{2}J_{CP}$ = 6 Hz, CH_2), 119.8 (td, $^{1}J_{CF}$ = 248 Hz, $^{2}J_{CP}$ = 6 Hz, CF_2), 125.8 (s, C_{Py}), 133.6 (td, $^{2}J_{CF}$ = 28 Hz, $^{3}J_{CP}$ = 4 Hz, $\underline{C}CF_2$), 138.0 (t, $^{3}J_{CF}$ = 6 Hz, C_{Py}), 144.8 (t, $^{3}J_{CF}$ = 6 Hz, C_{Py}), 148.4 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −100.0 (ddd, $^{2}J_{FAFB}$ = 259.1 Hz, $^{3}J_{FH}$ = 11.8 Hz, $^{3}J_{FP}$ = 11.8 Hz), −100.8 (ddd, $^{2}J_{FBFA}$ = 259.1 Hz, $^{3}J_{FH}$ = 12.4Hz, $^{3}J_{FP}$ = 12.4Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 18.8. Anal. Calc. for $C_{11}H_{17}F_2N_2O_3P$: C, 44.90; H, 5.82; N, 9.52. Found: C, 44.71; H, 5.74; N, 9.39.

4.3.3. Diethyl (1-Amino-2,2-difluoro-2-(pyridin-4-yl)ethyl)phosphonate **7c**

Yield 0.65 g (100%); white-yellow powder; mp 105–107 °C. ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.12–1.48 (m, 6H, CH_3), 1.81 (br s, 2H, NH_2), 3.60 (m, 1H, CH), 4.00–4.23 (m, 4H, CH_2), 7.70 (d, $^{3}J_{HH}$ = 6 Hz, 2H, Py), 8.70 (d, $^{3}J_{HH}$ = 6 Hz, 2H, Py). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^{3}J_{CP}$ = 5.9 Hz, CH_3), 16.4 (d, $^{3}J_{CP}$ = 5.9 Hz, CH_3), 53.4 (dt, $^{1}J_{CP}$ = 151.3 Hz, $^{2}J_{CF}$ = 29.2 Hz, CH), 63.2 (d, $^{2}J_{CP}$ = 6.8 Hz, CH_2), 63.5 (d, $^{2}J_{CP}$ = 6.8 Hz, CH_2), 119.0 (td, $^{1}J_{CF}$ = 248 Hz, $^{2}J_{CP}$ = 5.7 Hz, CF_2), 123.0 (t, $^{3}J_{CF}$ = 5.9 Hz, C_{Py}), 146.5 (t, $^{2}J_{CF}$ = 28.2 Hz, $\underline{C}CF_2$), 147.5 (s, C_{Py}). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −102.4 (ddd, $^{2}J_{FAFB}$ = 249.4 Hz, $^{3}J_{FH}$ = 11.4 Hz, $^{3}J_{FP}$ = 11.4 Hz), −102.7 (ddd, $^{2}J_{FBFA}$ = 249.4 Hz, $^{3}J_{FH}$ = 11.8 Hz, $^{3}J_{FP}$ = 11.8 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 17.95 (m, $^{2}J_{PH}$ = 18.2, $^{3}J_{PF}$ = 8.6 Hz). Anal. Calc. for $C_{11}H_{17}F_2N_2O_3P$: C, 44.90; H, 5.82; N, 9.52. Found: C, 44.78; H, 5.68; N, 9.43.

4.4. Synthesis of (1-Amino-2,2-difluoro-2-(pyridinyl)ethyl)phosphonic Acids **8a**–**c***: General Procedure*

To respective aminophosphonate **7** (0.3 g, 1.02 mmol) was added concentrated HCl (2 mL), the reaction mixture was heated at 110 °C for 2.5 h. After that HCl/H_2O was evaporated, the residue was dissolved in MeOH (2 mL), and treated with propylene oxide (0.35 g, 6.12 mmol). After 24 h the precipitate formed was separated by filtration, washed with MeOH (2 mL) and dried in vacuo.

4.4.1. (1-Amino-2,2-difluoro-2-(pyridin-2-yl)ethyl)phosphonic Acid **8a**

Yield 0.17 g (70%); white powder; mp 235–237 °C (decomp.). ^{1}H NMR (499.8 MHz, D_2O) δ (ppm): 4.13–4.30 (m, 1H, CH), 7.58–7.64 (m, 1H, Py), 7.86 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py), 8.04 (t, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py), 8.64 (d, $^{3}J_{HH}$ = 4.9 Hz, 1H, Py). ^{13}C NMR (75.8 MHz, D_2O) δ (ppm): 53.8 (dt, $^{1}J_{CP}$ = 126.5 Hz, $^{2}J_{CF}$ = 27.8 Hz, CH), 119.1 (td, $^{1}J_{CF}$ = 247 Hz, $^{2}J_{CP}$ = 6.0 Hz, CF_2), 121.4 (s, C_{Py}), 126.3 (s, C_{Py}), 138.7 (s, C_{Py}), 149.3 (s, C_{Py}), 151.3 (t, $^{2}J_{CF}$ = 27.5 Hz, $\underline{C}CF_2$). ^{19}F NMR (470.3 MHz, D_2O) δ (ppm): −93.6 (d, $^{2}J_{FAFB}$ = 257 Hz), −110.0 (dd, $^{2}J_{FBFA}$ = 257 Hz, ^{3}J = 21.5 Hz). ^{31}P NMR (202.3 MHz, D_2O) δ (ppm): 3.9. Anal. Calc. for $C_7H_9F_2N_2O_3P$: C, 35.31; H, 3.81; N, 11.76. Found: C, 35.13; H, 3.66; N, 11.55.

4.4.2. (1-Amino-2,2-difluoro-2-(pyridin-3-yl)ethyl)phosphonic Acid **8b**

Yield 0.15 g (62%); white powder; mp 210–125 °C (decomp.). ^{1}H NMR (499.8 MHz, D_2O) δ (ppm): 3.62 (m, 1H, CH), 7.66 (dd, $^{3}J_{HH}$ = 8.2 Hz, $^{3}J_{HH}$ = 5.1 Hz, 1H, Py), 8.18 (d, $^{3}J_{HH}$ = 8.2 Hz, 1H, Py), 8.72 (d, $^{3}J_{HH}$ = 5.1 Hz, 1H, Py), 8.83 (s, 1H, Py). ^{13}C NMR (75.8 MHz, D_2O) δ (ppm): 54.8 (dt, $^{1}J_{CP}$ = 132.7 Hz, $^{2}J_{CF}$ = 24.1 Hz, CH), 119.3 (t, $^{1}J_{CF}$ = 248 Hz, CF_2), 124.5 (s, C_{Py}), 130.2 (td, $^{2}J_{CF}$ = 26 Hz, $^{3}J_{CP}$ = 4.6 Hz, $\underline{C}CF_2$), 136.3 (t, $^{3}J_{CF}$ = 5.7 Hz, C_{Py}), 145.6 (t, $^{3}J_{CF}$ = 7.9 Hz, C_{Py}), 150.4 (s, C_{Py}). ^{19}F NMR (470.3 MHz, D_2O) δ (ppm): −86.1 (dd, $^{2}J_{FAFB}$ = 253 Hz, ^{3}J = 24.7 Hz), −110.1 (dd, $^{2}J_{FBFA}$ = 253 Hz, ^{3}J = 24.5 Hz). ^{31}P NMR (202.3 MHz, D_2O) δ (ppm): 2.8 (d, $^{2}J_{PH}$ = 24.3 Hz). Anal. Calc. for $C_7H_9F_2N_2O_3P$: C, 35.31; H, 3.81; N, 11.76. Found: C, 35.04; H, 3.72; N, 11.59.

4.4.3. (1-Amino-2,2-difluoro-2-(pyridin-4-yl)ethyl)phosphonic Acid **8c**

Yield 0.16 g (67%); white powder; mp 218–220 °C (decomp.). ^{1}H NMR (499.8 MHz, D_2O) δ (ppm): 4.08 (m, 1H, CH), 7.73 (d, $^{3}J_{HH}$ = 5.3 Hz, 2H, Py), 8.72 (d, $^{3}J_{HH}$ = 5.3 Hz, 2H, Py). ^{13}C NMR (75.8 MHz, D_2O) δ (ppm): 54.3 (ddd, $^{1}J_{CP}$ = 129.6 Hz, $^{2}J_{CFA}$ = 27.6 Hz, $^{2}J_{CFB}$ = 20.1 Hz, CH), 119.0 (td, $^{1}J_{CF}$ = 247.3 Hz, $^{2}J_{CP}$ = 2.8 Hz, CF_2), 121.4 (dd, $^{3}J_{CFA}$ = 7.3 Hz, $^{3}J_{CFB}$ = 4.8 Hz, C_{Py}), 143.3 (t, $^{2}J_{CF}$ = 26.2 Hz, $\underline{C}CF_2$), 148.8 (s, C_{Py}). ^{19}F NMR (470.3 MHz, D_2O) δ (ppm): −89.8 (d, $^{2}J_{FAFB}$ = 250 Hz), −110.2 (dd, $^{2}J_{FBFA}$ = 250 Hz, ^{3}J = 23.3 Hz). ^{31}P NMR (202.3 MHz, D_2O) δ (ppm): 3.3. Anal. Calc. for $C_7H_9F_2N_2O_3P$: C, 35.31; H, 3.81; N, 11.76. Found: C, 35.12; H, 3.77; N, 11.63.

4.5. Diethyl (1-Amino-2,2-difluoro-2-(piperidin-4-yl)ethyl)phosphonate **9**

To a solution of aminophosphonate **7c** (0.3 g, 1.02 mmol) in MeOH (10 mL) was added Rh/Al_2O_3 (0.1 g, 10%), the mixture was hydrogenated under 50 atm. of H_2 for 10 h. After completion of the reaction, the catalyst was filtered off, the solvent was evaporated to give 0.31 g of **9** (yield 100%) as colorless oil. ^{1}H NMR (302 MHz, DMSO-d_6) δ (ppm): 1.09–1.29 (m, 6H, CH_3), 1.30–1.93 (m, 4H, CH_2), 2.69–2.85 (m, 2H, CH_2), 2.87–3.07 (m, 1H), 3.15–3.30 (m, 2H, CH_2), 3.47 (m, 1H, CHP), 3.93–4.17 (m, 4H, OCH_2), 8.39 (s, 1H, NH). ^{13}C NMR (75.8 MHz, DMSO-d_6) δ (ppm): 16.1 (d, $^3J_{CP}$ = 5.2 Hz, CH_3), 16.2 (d, $^3J_{CP}$ = 5.2 Hz, CH_3), 21.4 (t, $^3J_{CF}$ = 4.1 Hz, $CF_2CH\underline{C}H_2$), 22.0 (t, $^3J_{CF}$ = 4.7 Hz, $CF_2CH\underline{C}H_2$), 37.3 (td, $^2J_{CF}$ = 23.7 Hz, $^3J_{CP}$ = 4.2 Hz, $\underline{C}HCF_2$), 42.8 (s, $2CH_2$), 50.7 (dt, $^1J_{CP}$ = 147.3 Hz, $^2J_{CF}$ = 28.4 Hz, CHP), 61.8 (d, $^2J_{CP}$ = 6.8 Hz, OCH_2), 62.1 (d, $^2J_{CP}$ = 6.7 Hz, OCH_2), 124.0 (td, $^1J_{CF}$ = 248 Hz, $^2J_{CP}$ = 30 Hz, CF_2).^{19}F NMR (470.3 MHz, DMSO-d_6) δ (ppm): −111.2 (m), −111.5 (m). ^{31}P NMR (202.3 MHz, DMSO-d_6) δ (ppm): 21.3. Anal. Calc. for $C_{11}H_{23}F_2N_2O_3P$: C, 44.00; H, 7.72; N, 9.33. Found: C, 44.21; H, 7.65; N, 9.28.

4.6. (1-Amino-2,2-difluoro-2-(piperidin-4-yl)ethyl)phosphonic Acid **10**

To aminophosphonate **9** (0.29 g, 0.97 mmol) was added concentrated HCl (1 mL), the reaction mixture was heated at 110 °C for 2.5 h. After completion of reaction HCl/H_2O was evaporated, the residue was dissolved in MeOH (1 mL), and treated with propylene oxide (0.23 g, 4 mmol). After 24 h the precipitate formed was separated by filtration, washed with MeOH (2 mL) and dried to give 0.17 g of **10** (yield 71%) as white powder; mp 250 °C (decomp.). ^{1}H NMR (499.8 MHz, D_2O) δ (ppm): 1.65–1.91 (m, 4H), 2.19 (t, $^2J_{HH}$ = 14.9 Hz, 2H), 3.07 (t, $^2J_{HH}$ = 14.1 Hz, 2H), 3.48–3.58 (m, 2H), 3.70–3.78 (m, 1H, CH). ^{13}C NMR (150.8 MHz, D_2O) δ (ppm): 27.4 (s, CH_2), 28.3 (s, CH_2), 37.4 (t, $^2J_{CF}$ = 22.4 Hz, $\underline{C}HCF_2$), 42.8 (s, CH_2), 43.1 (s, CH_2), 52.0 (d, $^1J_{CP}$ = 125.6 Hz, CH), 122.5 (t, $^1J_{CF}$ = 248 Hz, CF_2).^{19}F NMR (470.3 MHz, D_2O) δ (ppm): −107.3 (ddd, $^2J_{FAFB}$ = 246 Hz, $^3J_{FH}$ = 26.5 Hz, $^3J_{FP}$ = 26.5 Hz), −111.6 (dd, $^2J_{FBFA}$ = 246 Hz, ^3J = 26.5 Hz). ^{31}P NMR (202.3 MHz, D_2O) δ (ppm): 3.5. Anal. Calc. for $C_7H_{15}F_2N_2O_3P$: C, 34.43; H, 6.19; N, 11.47. Found: C, 34.17; H, 6.07; N, 11.63.

4.7. Synthesis of Diethyl (2-(Difluoro(pyridinyl)methyl)-4-oxothiazolidin-2-yl)phosphonates **11a**–**c***: General Procedure*

To solution of respective iminophosphonate **2** (0.12 g, 0.41 mmol) in benzene (1 mL) was added mercaptoacetic acid (0.04 g, 0.41 mmol). The reaction mixture was refluxed for 2 h, the solvent was evaporated in vacuum and the residue was triturated with hexane.

4.7.1. Diethyl (2-(Difluoro(pyridin-2-yl)methyl)-4-oxothiazolidin-2-yl)phosphonate **11a**

Yield 0.11 g (73%); yellow oil. ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.11–1.30 (m, $^3J_{HH}$ = 7.1 Hz, 6H, CH_3), 3.44 (dd, $^2J_{HAHB}$ = 15.1 Hz, $^4J_{HAP}$ = 5.8 Hz, 1H, $SC\underline{H_A}H_B$), 3.6 (d, $^2J_{HBHA}$ = 15.1 Hz, 1H, $SCH_A\underline{H_B}$), 3.93–4.22 (m, 4H, OCH_2), 7.45 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, Py), 7.74 (d, $^3J_{HH}$ = 7.9 Hz, 1H, Py), 7.86 (t, $^3J_{HH}$ = 7.9 Hz, 1H, Py), 8.20 (s, 1H, NH), 8.65 (d, $^3J_{HH}$ = 4.9 Hz, 1H, Py). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^3J_{CP}$ = 5.9 Hz, CH_3), 16.4 (d, $^3J_{CP}$ = 5.6 Hz, CH_3), 32.1 (s, SCH_2), 64.8 (d, $^2J_{CP}$ = 7.7 Hz, OCH_2), 65.2 (d, $^2J_{CP}$ = 7.6 Hz, OCH_2), 68.5 (dt, $^1J_{CP}$ = 170.7 Hz, $^2J_{CF}$ = 32.6 Hz, CP), 116.0 (td, $^1J_{CF}$ = 254 Hz, $^2J_{CP}$ = 21 Hz, CF_2), 121.7 (t, $^3J_{CF}$ = 4.5Hz, C_{Py}),125.6 (s, C_{Py}), 137.5 (s, C_{Py}), 149.0 (s, C_{Py}), 152.2 (t, $^2J_{CF}$ = 30Hz, $\underline{C}CF_2$), 174.1 (d, $^3J_{CP}$ = 5.2 Hz, C(O)). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −98.5 (dd, $^2J_{FAFB}$ = 260 Hz, $^3J_{FP}$ = 12 Hz), −108.4 (d,$^2J_{FBFA}$ = 260 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm):13.5. Anal. Calc. for $C_{13}H_{17}F_2N_2O_4PS$: C, 42.62; H, 4.68; N, 7.65; S, 8.75. Found: C, 42.44; H, 4.53; N, 7.51; S, 8.62.

4.7.2. Diethyl (2-(Difluoro(pyridin-3-yl)methyl)-4-oxothiazolidin-2-yl)phosphonate **11b**

Yield 0.125 g (83%); white powder; mp 162–164 °C. ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.30 (t, $^3J_{HH}$ = 6.8 Hz, 6H, CH_3), 3.05 (dd, $^2J_{HAHB}$ = 15.3 Hz, $^4J_{HAP}$ = 5.9 Hz, 1H, $SC\underline{H_A}H_B$), 3.39 (d, $^2J_{HBHA}$ = 15.3 Hz, 1H, $SCH_A\underline{H_B}$), 4.09–4.45 (m, 4H, OCH_2), 7.38 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, Py), 7.99 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Py), 8.73 (d, $^3J_{HH}$ = 4.9 Hz,

1H, Py), 8.73 (s, 1H, NH), 8.91 (s, 1H, Py). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^3J_{CP}$ = 6 Hz, CH_3), 16.4 (d, $^3J_{CP}$ = 6 Hz, CH_3), 32.1 (s, SCH_2), 65.0 (d, $^2J_{CP}$ = 8 Hz, OCH_2), 65.1 (d, $^2J_{CP}$ = 8 Hz, OCH_2), 68.0 (dt, $^1J_{CP}$ = 167 Hz, $^2J_{CF}$ = 32 Hz, CP), 120.7 (td, $^1J_{CF}$ = 255 Hz, $^2J_{CP}$ = 12 Hz, CF_2), 122.7 (s, C_{Py}), 128.2 (td, $^2J_{CF}$ = 27 Hz, $^3J_{CP}$ = 4 Hz, $\underline{C}CF_2$), 136.0 (t, $^3J_{CF}$ = 7 Hz, C_{Py}), 148.6 (t, $^3J_{CF}$ = 5 Hz, C_{Py}), 151.4 (s, C_{Py}), 174.8 (d, $^3J_{CP}$ = 7 Hz, C(O)). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): −96.7 (d, $^2J_{FAFB}$ = 255.5 Hz), −101.9 (d, $^2J_{FBFA}$ = 255.5 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm):13.4. Anal. Calc. for $C_{13}H_{17}F_2N_2O_4PS$: C, 42.62; H, 4.68; N, 7.65; S, 8.75. Found: C, 42.47; H, 4.73; N, 7.41; S, 8.58.

4.7.3. Diethyl (2-(Difluoro(pyridin-4-yl)methyl)-4-oxothiazolidin-2-yl)phosphonate **11c**

Yield 0.116 g (77%); white powder; mp 80–82 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$) δ (ppm): 1.31 (t, $^3J_{HH}$ = 7 Hz, 6H, CH_3), 3.1 (dd, $^2J_{HAHB}$ = 15.2 Hz, $^4J_{HAP}$ = 5.6 Hz, 1H, $SC\underline{H}_AH_B$), 3.4 (d, $^2J_{HBHA}$ = 15.2 Hz, 1H, $SCH_A\underline{H}_B$), 4.12–4.33 (m, 4H, OCH_2), 7.58 (d, $^3J_{HH}$ = 5.3 Hz, 2H, Py), 8.26 (s, 1H, NH), 8.73 (d, $^3J_{HH}$ = 5.3 Hz, 2H, Py).^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.3 (d, $^3J_{CP}$ = 5.7 Hz, CH_3), 16.4 (d, $^3J_{CP}$ = 5.7 Hz, CH_3), 32.1 (s, SCH_2), 65.0 (d, $^2J_{CP}$ = 7.3 Hz, OCH_2), 65.2 (d, $^2J_{CP}$ = 7.3 Hz, OCH_2), 67.6 (dt, $^1J_{CP}$ = 167.1 Hz, $^2J_{CF}$ = 34.2 Hz, CP), 120.2 (td, $^1J_{CF}$ = 253 Hz, $^2J_{CP}$ = 11.6 Hz, CF_2), 122.4 (t, $^3J_{CF}$ = 5.6 Hz, $2C_{Py}$), 140.7 (td, $^2J_{CF}$ = 27.6 Hz, $^3J_{CP}$ = 2.8 Hz, $\underline{C}CF_2$), 149.3 (s, $2C_{Py}$), 174.8 (d, $^3J_{CP}$ = 6.5 Hz, CO). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −98.9 (d, $^2J_{FAFB}$ = 252 Hz), −104.0 (d,$^2J_{FBFA}$ = 252 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 13.2.Anal. Calc. for $C_{13}H_{17}F_2N_2O_4PS$: C, 42.62; H, 4.68; N, 7.65; S, 8.75. Found: C, 42.39; H, 4.56; N, 7.48; S, 8.64.

4.8. Synthesis of Diethyl (2-(Difluoro(pyridinyl)methyl)-4-oxo-1,3-thiazinan-2-yl)phosphonates **12a**–**c***: General Procedure*

To a solution of respective iminophosphonate **2** (0.13 g, 0.44 mmol) in benzene (1 mL) was added 3-mercaptopropionic acid (0.05 g, 0.44 mmol). The reaction mixture was refluxed for 8 h, the solvent was evaporated in vacuum and the residue was triturated with Et_2O.

4.8.1. Diethyl (2-(Difluoro(pyridine-2-yl)methyl)-4-oxo-1,3-thiazinan-2-yl)phosphonate **12a**

Yield 0.13 g (76%); yellow oil. ^{1}H NMR (302 MHz, $CDCl_3$) δ (ppm): 1.13 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 2.73–2.84 (m, 2H, CH_2), 2.91–3.01 (m, 1H, CH), 3.22–3.35 (m, 1H, CH), 3.96–4.28 (m, 4H, $2OCH_2$), 7.46 (dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 7.70 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.86 (t, $^3J_{HH}$ = 7.9 Hz, 1H), 8.09 (s, 1H, NH), 8.70 (d, $^3J_{HH}$ = 5.1 Hz, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm):16.2 (d, $^3J_{CP}$ = 6 Hz, CH_3), 16.3 (d, $^3J_{CP}$ = 5 Hz, CH_3), 23.5 (s, SCH_2), 33.3 (s, $\underline{C}H_2CO$), 64.7 (d, $^2J_{CP}$ = 7.7 Hz, OCH_2), 65.3 (d, $^2J_{CP}$ = 7.6 Hz, OCH_2), 66.6 (dm, $^1J_{CP}$ = 168.7 Hz, CP), 116.0 (td, $^1J_{CF}$ = 256.2 Hz, $^2J_{CP}$ = 15 Hz, CF_2), 122.1 (s, C_{Py}),125.5 (s, C_{Py}), 137.2 (s, C_{Py}), 148.8 (s, C_{Py}), 152.2 (td, $^2J_{CF}$ = 30 Hz, $^3J_{CP}$ = 2.5 Hz, $\underline{C}CF_2$), 170.9 (d, $^3J_{CP}$ = 3.1 Hz, CO). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −99 (dd, $^2J_{FAFB}$ = 255 Hz, $^3J_{FP}$ = 9 Hz), −106.4 (d,$^2J_{FBFA}$ = 255 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 13.2 (m, ^3J = 9 Hz). Anal. Calc. for $C_{14}H_{19}F_2N_2O_4PS$: C, 44.21; H, 5.04; N, 7.37; S, 8.42. Found: C, 44.39; H, 4.91; N, 7.43; S, 8.34.

4.8.2. Diethyl (2-(Difluoro(pyridine-3-yl)methyl)-4-oxo-1,3-thiazinan-2-yl)phosphonate **12b**

Yield 0.14 g (82%); white powder; mp 158–160 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 6H, CH_3), 2.32–2.44 (m, 2H, CH_2), 2.53–2.68 (m, 1H, CH_2), 2.80–2.89 (m, 1H, CH_2), 4.10–4.35 (m, 4H, OCH_2), 6.72 (s, 1H, NH), 7.37 (dd, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, Py), 7.92 (d, $^3J_{HH}$ = 8.1Hz, 1H, Py), 8.72 (d, $^3J_{HH}$ = 4.9 Hz, 1H, Py), 8.87 (s, 1H, Py). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.40 (d, $^3J_{CP}$ = 5.7 Hz, CH_3), 16.43 (d, $^3J_{CP}$ = 5.6 Hz, CH_3), 23.4 (s, SCH_2), 33.4 (s, $\underline{C}H_2CO$), 65.0 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2), 65.2 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2), 65.5 (dt, $^1J_{CP}$ = 161.2 Hz, $^2J_{CF}$ = 29.5 Hz, CP), 120.5 (td, $^1J_{CF}$ = 255.7 Hz, $^2J_{CP}$ = 7.4 Hz, CF_2), 122.5 (s, C_{Py}), 128.3 (td, $^2J_{CF}$ = 26.7 Hz, $^3J_{CP}$ = 3.6 Hz, $\underline{C}CF_2$), 135.9 (t, $^3J_{CF}$ = 5.9 Hz, C_{Py}), 148.9 (t, $^3J_{CF}$ = 6.4 Hz, C_{Py}), 151.5 (s, C_{Py}), 170.4 (d, $^3J_{CP}$ = 3.1Hz, C(O)). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): -98.8 (d, $^2J_{FAFB}$ = 253.6 Hz),

−102.2 (d,$^2J_{FBFA}$ = 253.6 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 13.5. Anal. Calc. for $C_{14}H_{19}F_2N_2O_4PS$: C, 44.21; H, 5.04; N, 7.37; S, 8.42. Found: C, 44.08; H, 4.97; N, 7.48; S, 8.31.

4.8.3. Diethyl (2-(Difluoro(pyridine-4-yl)methyl)-4-oxo-1,3-thiazinan-2-yl)phosphonate **12c**

Yield 0.13 g (76%); white powder; mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.27–1.38 (m, $^3J_{HH}$ = 7.4 Hz, 6H, CH_3), 2.41–2.53 (m, 2H, CH_2), 2.56–2.67 (m, 1H, CH), 2.84–2.92 (m, 1H, CH), 4.19–4.31 (m, 4H, OCH_2), 6.39 (s, 1H, NH), 7.65 (d, $^3J_{HH}$ = 5.1 Hz, 2H, Py), 8.76 (d, $^3J_{HH}$ = 5.1Hz, 2H, Py). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ (ppm): 16.4 (br d, $^3J_{CP}$ = 5.7 Hz, CH_3), 23.4 (s, SCH_2), 33.4 (s, $\underline{C}H_2CO$), 65.2 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2), 65.2 (dt, $^1J_{CP}$ = 161.4 Hz, $^2J_{CF}$ = 30.8 Hz, CP), 65.3 (d, $^2J_{CP}$ = 7.5 Hz, OCH_2), 119.9 (td, $^1J_{CF}$ = 257 Hz, $^2J_{CP}$ = 8 Hz, CF_2), 122.4 (t, $^3J_{CF}$ = 5.7 Hz, $2C_{Py}$), 140.8 (td, $^2J_{CF}$ = 28.1 Hz, $^3J_{CP}$ = 4.8 Hz, $\underline{C}CF_2$), 149.3 (s, $2C_{Py}$), 170.6 (d, $^3J_{CP}$ = 2.7 Hz, CO). ^{19}F NMR (470.3 MHz, $CDCl_3$) δ (ppm): −100.4 (d, $^2J_{FAFB}$ = 251 Hz), −103.5 (d,$^2J_{FBFA}$ = 251 Hz). ^{31}P NMR (202.3 MHz, $CDCl_3$) δ (ppm): 12.9. Anal. Calc. for $C_{14}H_{19}F_2N_2O_4PS$: C, 44.21; H, 5.04; N, 7.37; S, 8.42. Found: C, 44.48; H, 4.88; N, 7.28; S, 8.28.

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