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Fluorinated NH-iminophosphonates and iminocarboxylates: novel synthons for the preparation of biorelevant α-aminophosphonates and carboxylates

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ABSTRACT

A convenient synthetic approach to previously unknown N–H α-iminophosphonates and iminotrifluoropropionates was developed. The synthetic potential of N–H iminophosphonates and iminotrifluoropropionates, existing as an equilibrium mixture of *E*/*Z*-isomers, was demonstrated by their easy functionalization to afford biorelevant fluorinated α-aminophosphonic and α-aminocarboxylic acid derivatives.

1. Introduction

The chemistry of α-amino acids and their phosphorus analogs has been extensively developed in recent years, first of all due to the wide spectrum of biological activity of these compounds. The rapidly expanding interest in the field of peptidomimetics has prompted chemists to develop novel and efficient approaches to unnatural amino acids. An extremely intriguing class of unnatural amino acids is represented by those incorporating one or more fluorine atoms. It is generally accepted that substitution of a hydrogen by a fluorine, or introduction of a trifluoromethyl group in place of a methyl, 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.[1,2] As a result, selectively fluorinated analogues of biologically active compounds can be considered to be valuable candidates for drug discovery. Specifically, α-trifluoromethylated amino acids are known to be potent inhibitors of pyridoxal phosphate-dependent enzymes, which catalyze transamination and decarboxylation processes.[3] Therefore, the development of methods for such compounds remains a challenging task. Fluorinated imidoyl phosphonates and carboxylates are attractive and promising building blocks for construction of functionalized aminophosponates and carboxylates for several reasons: (1) the compounds already contain the 'oxidized' fragment of the aminocarboxylic or aminophosphonic acid; (2) electron-withdrawing phosphonyl or alkoxycarbonyl groups and fluorinated substituents additionally activate the C=N bond leading to an increase in reactivity; (3) the compounds with a free N–H group seem especially promising for this purpose as they can be functionalized both by nucleophilic addition across the C=N bond, and electrophilic substitution at the nitrogen atom; (4) functionalization of NH-iminophosphonates and iminocarboxylates leads *directly* to *N*-unprotected aminophosphonates and aminocarboxylates; note that the removal of protecting groups in highly functionalized aminophosphonates and aminocarboxylates (especially in those, bearing electron-withdrawing groups) is often accompanied by the cleavage of C–P bond or decarboxylation. At the same time, *N*-unprotected α-iminophosphonates were unknown until recently.[4] On the other hand, attempts to synthesize α-iminotrifluoropyruvate by reaction of methyl trifluoropyruvate with hexamethyldisilazane failed.[5] In the present work, we propose new simple and effective approaches to fluorinated NH-iminophosphonates and carboxylates and reveal their synthetic potential as promising building blocks for the preparation of biorelevant fluorinated aminophosphonic and carboxylic acid derivatives.

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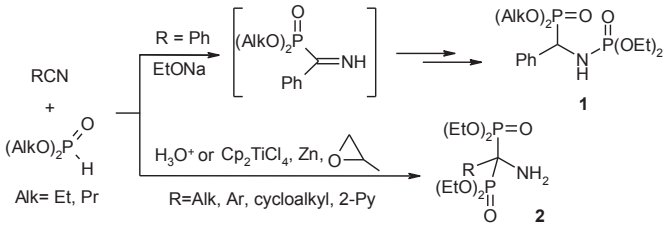
2. Results and discussion

2.1. Synthesis of fluorinated NH-iminophosphonates

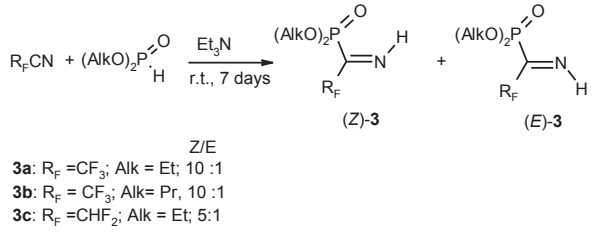
In the last decades, several methods to prepare imidoyl phosphonates bearing various substituents at the nitrogen atom were developed in our laboratory.[6] None of them, however, can be used for synthesis of NH-imidoyl phosphonates. Addition of hydrophosphoryl compounds to the triple bond of nitriles represents the most straightforward route to such compounds. Analysis of the literature data shows, however that in reactions of nitriles with dialkyl phosphites, the respective iminophosphonates were never isolated or even detected as reaction intermediates.[7] Thus, sodium salts of dialkyl phosphites react with nitriles to yield phosphorylamino phosphonates **1**.[7a] In the presence of acids,[7b,c] or under free radical conditions[7d] aminobisphosphonates **2**, as the main products, were reported to form in low to moderate yields (Scheme 1).



Scheme 1.

Most probably, the reactions in Scheme 1 do involve initial formation of the iminophosphonate followed by fast addition of a second molecule of phosphite resulting in aminobisphosphonates **2**. Formation of phosphorylamino phosphonates **1** was explained by *C,N*-phosphoryl shift in intermediate aminobisphosphonates[7a] (cf. Ref. 8). It was claimed that for ordinary nitriles addition of dialkyl phosphites under conditions of base catalysis is not characteristic.[7b] We believed that in the case of highly electrophilic fluorinated acetonitriles the reaction could be stopped at the first stage due to the higher reactivity of the C≡N bond and the mild reaction conditions.

Indeed, we have found that dialkyl phosphites react with difluoro- or trifluoroacetonitriles in the presence of a catalytic amount of nitrogen base at room temperature to form iminophosphonates **3** in high yields (Scheme 2). Formation of the P–C bond is confirmed by ^{13}C NMR spectra of compounds **3** in which the imine C-atom signal (δ 167–171 ppm) with a large direct C–P coupling constant (J_{CP} 150–164 Hz) was identified. It is worthwhile noting that the less electrophilic fluoroacetonitrile, CH_2FCN, does not react with hydrophosphoryl compounds under the same conditions.

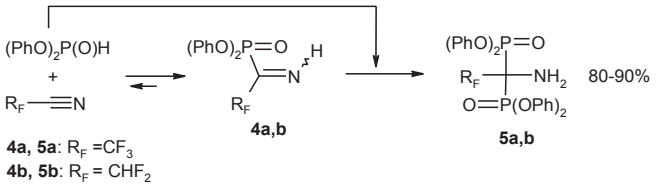


Scheme 2.

In solution, imidoyl phosphonates **3** exist as an equilibrium mixture of *Z*/*E*-isomers, the more sterically hindered *Z*-configuration being thermodynamically preferable. The *Z*/*E* ratio essentially depends on the fluorinated substituent at C=N bond, but it is practically independent of the nature of the phosphonyl group. Identification of *Z*,*E*-isomers is based mainly on the significant difference in coupling constants of the N–H proton and phosphorus atom (37–39 and 58–60 Hz, respectively). The dynamic equilibrium between geometrical isomers was substantiated by the fact that on heating imine **3a** in toluene-d_8 solutions, the N–H proton signals of the *Z*/*E*-isomers first broaden then coalesce (~100 °C). On cooling to rt the starting state is recovered.

Less nucleophilic diphenyl phosphite reacts with fluorinated nitriles in the same manner to afford imidoyl phosphonates **4**, as a dynamic mixture of *Z*/*E*-isomers. This reaction, *unexpectedly*, proceeds essentially faster than with its dialkyl analogs, and is completed in less than 1 h at room temperature. Note that in the three-component Kabachnik–Fields reaction, diphenyl phosphite reacted slower than diethyl phosphite.[9]

It turned out that iminophosphonates **4**, on storage at room temperature, undergo partial dissociation to the starting compounds. Diphenyl phosphite, formed upon dissociation, quickly adds to the activated C=N bond of starting iminophosphonates **4a**,**b** to form stable geminal bisphosphonates **5a**,**b**, which are the final products of this reaction (Scheme 3). The reversibility of iminophosphonate formation was verified experimentally by direct observation of low intensity NMR signals of the starting nitrile and phosphite upon dissolution of pure **4a** in deuterochloroform, and also by cross-experiment: addition of diethyl phosphite to imine **4a** results in partial formation of iminophosphonate **3a**, detected by ^{31}P NMR spectroscopy.



Scheme 3.

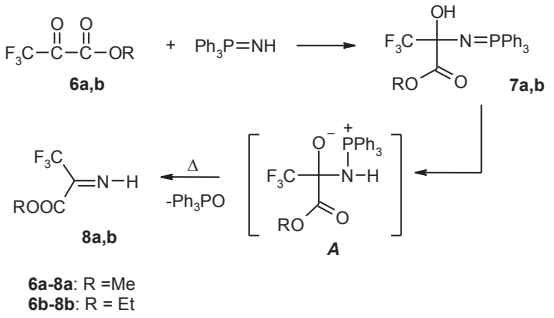
Thus, the iminophosphonates **4** are products of kinetic control, and bisphosphonates **5**—the products of thermodynamic control.

The presented scheme offers an excellent preparative approach to biorelevant fluorinated aminobisphosphonates **5**. It is worthwhile noting that peptidomimetics bearing a *diaryl* aminophosphonate fragment exhibit high activity as serine protease inhibitors, due to the possibility of covalent binding with the enzyme by means of substitution of an aroxy group at the phosphorus atom.[10] The diverse biomedical potential of diaryl α-aminophosphonates for the treatment of various pathologies, such as cancer and metastasis, inflammatory diseases, emphysema, hypertension, type 2 diabetes, infections, immunological and fibrogenic disorders, has been discussed.[10,11a]

2.2. Synthesis of α-iminotrifluoropropionates

An essentially different methodology, namely the aza-Wittig reaction of commercially available trifluoropyruvates with triphenylphosphine imide, was used for the synthesis of N–H imines of trifluoropyruvate.[12] It is noteworthy that at rt the reaction leads initially to a mixture (~1:10) of the respective imine **8** and phosphine imide **7** (δ_F −80.2 to −80.4 ppm, δ_P 4.2–4.6 ppm). The latter results from nucleophilic addition of the imino N–H function of triphenylphosphine imide across the highly electrophilic C=O bond of **6**. Imides **7** are stable at rt in ethereal or benzene solutions, but upon heating or thermal distillation they cleanly convert into

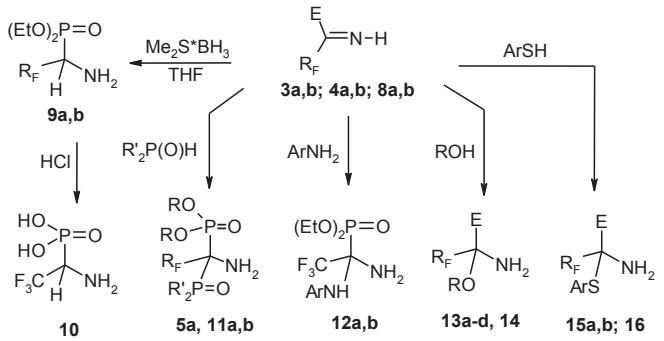
imines **8**. We believe that the transformation **7**→**8** involves 1,3-proton transfer followed by elimination of triphenylphosphine oxide in the classical aza-Wittig reaction intermediate *A* (Scheme 4). Compounds **8** are quite stable in dry, inert atmospheres and can be easily purified by distillation. In solution, iminocarboxylates **8**, like their phosphorus analogs **3** and **4**, exist as equilibrium mixture of the *E*/*Z*-isomers (*E*/*Z*≈10:1 at 25 °C). Identification of *E*,*Z*-isomers is based on a comparison of ^{1}H, ^{19}F NMR spectroscopic characteristics with those of the respective iminophosphonates **3**, **4**.



Scheme 4.

2.3.1. Reduction and addition of X–H nucleophiles. Reduction of the C=N bond of iminophosphonates **3a**,**b** with $BH_3 \cdot Me_2S$ in toluene solution quantitatively leads to fluorinated aminophosphonates **9a**,**b**. Compound **9a** was hydrolyzed under acidic conditions to afford α-aminotrifluoroethylphosphonic acid **10** (Scheme 5).[4] Both iminophosphonates **3**,**4** and iminocarboxylates **8** readily react with P-, N-, O-, and S-centered X–H nucleophiles to give biorelevant highly functionalized fluorinated aminophosphonates and aminocarboxylates **5**, **11**–**16**. The unusual stability of aminals **11**–**16** is most likely caused by the presence of the electron-withdrawing phosphonyl or alkoxycarbonyl group and fluorinated substituents. At the same time, adducts **13** in $CDCl_3$ solutions, according to NMR spectroscopy, partially (about 5–10%) dissociate into the starting phosphonyl or alkoxycarbonyl groups being in the *syn*-position with the =NH hydrogen atom. At the same time the =C–P bond in the iminophosphonates is prone to scission. This peculiarity reveals itself in partial dissociation of compounds **4** and their subsequent transformations (Scheme 3). That is why iminophosphonates **4a**,**b** were not isolated in analytically pure state, and should be used in synthesis immediately after preparation.

The feasibility of transforming imines **3**, **4**, **8** into aminophosphonic or aminocarboxylic acid derivatives possessing fluoroalkyl group are demonstrated by their reduction, addition reactions or cyclocondensations with bifunctional reagents.



9: R_F = CF_3 (a), CHF_2 (b); **11**: R = Et, R_F = CF_3, R′ = Ph (a), PhO (b); **12**: Ar = 4-$MeOC_6H_4$ (a), 4-MeC_6H_4 (b); **13**: E = $P(O)(OEt)_2$, R_F = CF_3, R = Me (a), Et (b), 2-$PyCH_2$ (c), R_F = CHF_2, R = Me (d); **14**: E = COOMe, R_F =CF_3, R = Me; **15**: E = $P(O)(OEt)_2$, R_F = CF_3, Ar = 4-$CH_3C_6H_4$ (a), 4-FC_6H_4 (b); **16**: E = COOMe, R_F =CF_3, Ar = 4-$CH_3C_6H_4$ (a), 4-FC_6H_4 (b)

Scheme 5.

2.3. Chemical reactivity

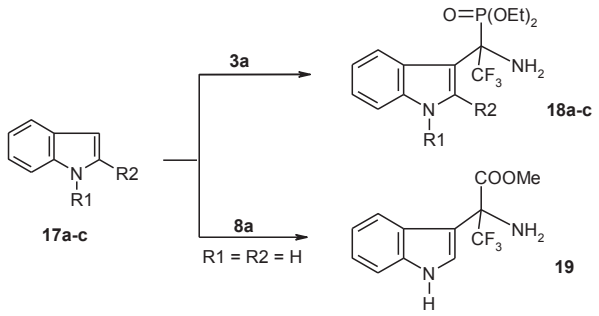
Iminophosphonates **3**,**4** and iminocarboxylates **8** contain a polarized azomethyne group and are promising building blocks in the synthesis of aminophosphonic and aminocarboxylic acid derivatives with a fluoroalkyl group. Two electron-withdrawing groups at the imine carbon atom essentially activate the C=N bond allowing, addition of nucleophilic reagents under mild and neutral conditions. As alkoxycarbonyl and phosphonyl groups have close electronic parameters [σ_p 0.45 and 0.52 for COOEt and $(EtO)_2PO$ substituents, respectively],[13] one would expect similar reactivity for the respective iminophosphonates and iminocarboxylates. In addition, the compounds have similar geometry: preferential *Z*-configuration for iminophosphonates **3**,**4** and *E*-configuration for iminocarboxylates **8**, in both cases the more bulky compounds. Hence, adducts **13** serve as masked sources of the corresponding imines **3**: we have successfully explored this property for the improvement of the enantiomeric excess in catalytic asymmetric reduction by maintaining a beneficial catalyst/imine ratio during the course of a reaction.[14]

The simple preparative access to fluorinated heminal diphosphorylated derivatives of the type **5**, **11**, bearing the same or different phosphorus groups at the α-carbon atom, is of special importance when taken into consideration the wide spectrum of biological activity exhibited by compounds containing a P–C–P triad, in particular by aminomethylenebisphosphonates. The drugs on their bases are widely used in the treatment of diseases caused by a disorder in calcium or phosphate exchange (Paget's disease, bone metastasis, myeloma, osteoporosis, steroid-induced osteogenesis), inflammations, and so on.[11] The pharmacological effect of

the drugs essentially depends on the lipophilic and electronic characteristics of the substituents at the C and N atoms.

It is noteworthy that all these reactions occur at room temperature, almost quantitatively, and do not require base or acid catalysis.

2.3.2. Aminoalkylation of electron-rich heterocycles. Reactions of fluorinated NH-iminocarboxylates and iminophosphonates with electron-rich heterocycles offers a novel approach to direct C–C bond formation, and introduction of an aminophosphonic or aminocarboxylic fragment into the heterocyclic nucleus. Aminoalkylation of indoles **17a**–**c**, independently of the R1 and R2 substituents, proceeds regioselectively into the 3-position of the heterocycle (Scheme 6).



17, 18: R1= R2 = H (a), R1 =H, R2 = Me (b); R1 = Me, R2 = H (c)

Scheme 6.

In contrast, regioselectivity of pyrroles aminoalkylation is controlled by the N-substituent in the heterocycle (Scheme 7). Thus, pyrrole and 2,4-dimethylpyrrole give exclusively α-substituted products **20** and **21**, whereas N-*tert*-butyl pyrrole is aminoalkylated at the β-position. Different regioselectivity was observed for the reaction of iminophosphonate **3a** and iminocarboxylate **8a** with *N*-methylpyrrole: the first reacts non-selectively to give a mixture (4:1) of 2- and 3-pyrrolylaminophosphonates **22** and **24**, respectively, whereas the latter under the same conditions affords only 2-pyrrolylaminocarboxylate **23** (Scheme 7).

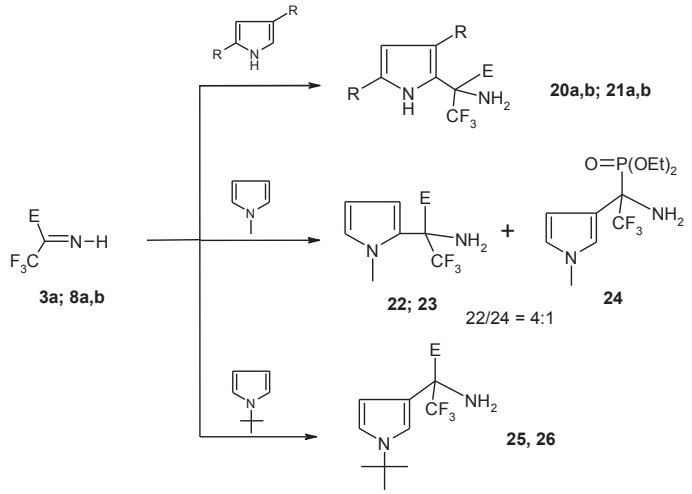
We believe that the steric influence of the substituent is mainly responsible for the change in regioselectivity of pyrrole aminoalkylation. In the absence of steric shielding (N–H pyrroles) the reaction proceeds as expected in the α-position, whereas a bulky *tert*-butyl substituent favors β-aminoalkylation. In line with this, differences in regioselectivity for phosphonate **3a** and carboxylate **8a** can be accounted for by reduced steric requirements of the less bulky COOMe group in **8a** (as compared with the $(EtO)_2PO$ substituent in **3a**). Steric control of the regiochemistry of electrophilic substitution in pyrroles was observed earlier in the example of electrophilic phosphorylation with phosphorus(III) halides.[15]

2.3.3. Cyclocondensations and dipolar cycloaddition. Cycloconden sations with bifunctional compounds—thioglycolic, 3-mercapto propionic, or 2-mercaptobenzoic acid—allow the preparation of biologically promising thiazolidone **27**, **28**, thiazinanone **29**, **30** or benzothiazine derivatives **31** and **32** bearing a polyfluorinated aminophosphonic or aminocarboxylic acid fragment as part of a five- or six-membered heterocycle (Scheme 8).

Primary adducts *A* resulting from reactions of **3a** with thioglycolic (Scheme 8) acid can be detected only spectroscopically. Even at room temperature, they undergo intramolecular ring closure to give the previously unknown *C*-phosphorylated thiazolidones **27**. The ease of cyclization is explained by the steric accessibility of the unsubstituted *N*-nucleophilic center in adduct *A* and beneficial five-membered ring formation.

Synthetic advantages of N–H imines clearly reveal themselves in the reaction with salicylic aldehyde. In this case, both the electrophilic imine carbon and the nucleophilic N–H function are involved in the process (Scheme 9).

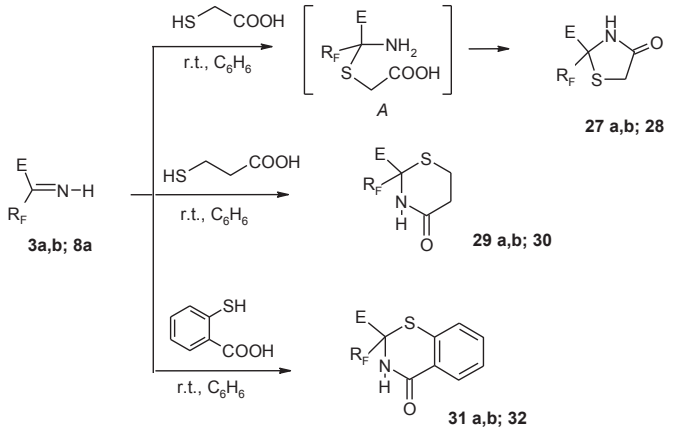
This interesting reaction proceeds via addition of the O–H group across C=N bond of imines **3**, **8**. Subsequent creation of a novel C=N bond by means of the intramolecular condensation of amino group thus formed, with the carbonyl moiety leads to benzoxazines **33**, **34** bearing a fluoroalkyl and phosphonate or methoxycarbonyl function. Note that the latter reaction is possible only for imines with a free N–H function.



20: E = P(O)(OEt)$_2$, R = H (a), Me (b); **21**: E = COOEt, R = H (a), E = COOMe, R = Me (b);

22, 25: E = P(O)(OEt)$_2$; **23, 26**: E = COOMe

Scheme 7.

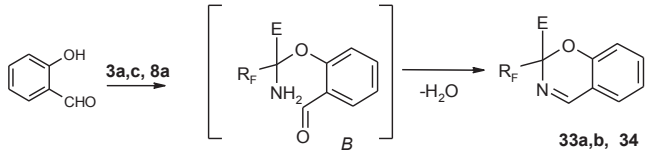


27a, 29a, 31a: E = P(O)(OEt)$_2$, R_F = CF_3

27b, 29b, 31b: E= P(O)(OEt)$_2$, R_F = CHF_2

28, **30**, **32**: E = COOMe, R_F = CF_3

Scheme 8.



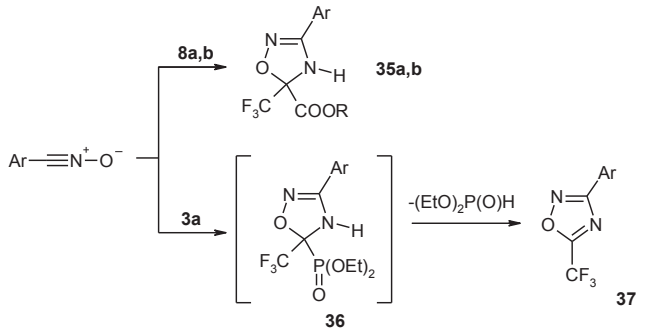
33a: E = P(O)(OEt)$_2$, R_F = CF_3

33b: E = P(O)(OEt)$_2$, R_F = CHF_2

34: E = COOMe, R_F = CF_3

Scheme 9.

In reactions with dipolar compounds, NH-iminocarboxylates and iminophosphonates behave as dipolarophiles. Thus, reaction of **8a** with nitrile oxides, generated from the respective hydroxymoyl chlorides, affords oxadiazolines **35**, bearing a fragment of trifluoroalanine. Reaction with iminophosphonate **3a** also leads initially to the unstable [3+2]-cycloaddition product **36**, which even at room temperature undergoes fast elimination of diethyl phosphite to form trifluoromethylated oxadiazole **37** (Scheme 10). Intermediate oxadiazoline **36** was detected by ^{31}P and ^{19}F NMR spectroscopy within 10 min after the onset of the reaction [δ_P=7 ppm, δ_F=−64.7 (3F, $ArCF_3$) and −81.6 (3F, 5-CF_3) ppm]. The



35a: Ar = 4-ClC_6H_4, R= Me

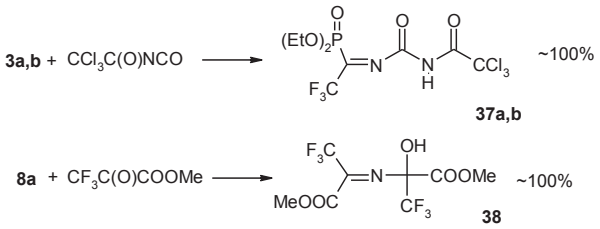
35b: Ar = 4-$CF_3C_6H_4$, R= Et

36, 37: Ar = 4-$CF_3C_6H_4$

Scheme 10.

transformation **36**→**37** is completed within 30 min at room temperature. Note that analogs of NH-diazoline **36**, bearing a XC_6H_4 group at the N-4 atom, are quite stable compounds and have close chemical shifts (δ_P=6.7–8.3 ppm).[16] The differences in stability of oxadiazolines **35** and their phosphorus analog **36** can be accounted for by a higher nucleofugicity of the $(EtO)_2PO$ substituent.

2.3.4. Electrophilic functionalization at nitrogen atom. The presence of two electron-withdrawing groups results in reduced nucleophilicity of the imine nitrogen atom in compounds **3**, **8**, therefore they can react only with strong electrophiles. The possibility for functionalization at the nitrogen atom is exemplified by reaction of **3a** with trichloroacetyl isocyanate, leading to a new type of synthetically promising activated *C*-phosphorylated *N*-acylimine **37**.[4] Iminocarboxylate **8a** reacts with methyl trifluoropyruvate also without involvement of the C=N bond to afford highly functionalized imine **38** resulting from addition of the N–H function across the highly electrophilic C=O bond (Scheme 11).[12]



Scheme 11.

3. Conclusions

In summary, we have developed a simple and efficient synthesis of previously unknown fluorinated N–H α-iminophosphonates **3**,**4** and iminotrifluoropropionates **8,** and demonstrated their considerable potential as novel convenient building blocks in the design and synthesis of biorelevant α-aminophosphonates, α-aminobisphosphonates, and α-aminocarboxylates bearing a trifluoromethyl or difluoromethyl group. The electron-deficient nature of the imines makes them promising substrates for the preparation of various functionalized acyclic and heterocyclic derivatives with an aminophosphonic or aminocarboxylic fragment by the use of reductive nucleophilic addition reactions, direct aminoalkylation of electron-rich heterocycles, cyclocondensations, and dipolar cycloaddition reactions. The presence of an unprotected imine nitrogen atom in the imines **3**, **4**, and **8** allows the direct synthesis of *N*-unprotected aminophosphonates and aminocarboxylates.

4. Experimental section

4.1. General

IR spectra were obtained on an UR-20 instrument. NMR spectra were recorded on a Varian VXR-300 spectrometer (operating frequency 299.95 MHz), ^{19}F NMR and ^{31}P NMR spectra—on Gemini 200 Varian (188.14 and 80.95 MHz, respectively) and Varian VXR-300 instrument (282.2 and 121.42 MHz, respectively). ^{13}C NMR spectra were obtained on Bruker Avance DRX 500 spectrometer operating at 125.76 MHz. Chemical shifts are reported relative to internal TMS (^1H) 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. Compounds **3a**,**b**, **9a**, **10**, **11a**, **13a**–**c**, **27a**, **37a**,**b**,[4] **7a**, **8a**, **19**, **28**, **30**, **32**, **34**, **35a**, and **38**[12] were described in our preliminary communications. Elemental analysis was carried out in the analytical laboratory of Institute of Organic Chemistry, NAS of Ukraine.

4.2. Iminophosphonates

4.2.1. Diethyl (2,2-difluoroethanimidoyl)phosphonate ***3c***. A mixture of difluoroacetonitrile (1.91 g, 24.8 mmol), Et_3N (0.45 mL, 0.33 g, 3.3 mmol), and diethyl phosphite (2.28 g, 16.5 mmol) was kept in ampoule at 15 °C for 5 days and evaporated in vacuo, keeping temperature below 20 °C, to give iminophosphonate **3c** of 90% purity, which was used in synthesis without further purification. Yield ~100%, light yellow oil. The compound can be kept at 5 °C under inert atmosphere for about 5 days.

IR (neat) ν: 1080 (POC), 1260 (P=O), 1720 (C=N), 3200, 3230 (NH) cm^{-1}. ^1H NMR (299.95 MHz, C_6D_6) δ: 0.95 (m, 6H, CH_3CH_2), 3.69–4.18 (m, 4H, OCH_2), 5.90 (td, $^2J_{HF}$=55.0 Hz, $^3J_{HP}$=6.5 Hz, 1H, CHF_2, *E*-isomer), 6.08 (td, $^2J_{HF}$=54.5 Hz, $^3J_{HP}$=11.3 Hz, 1H, CHF_2, *Z*-isomer), 12.00 (br d, $^3J_{HP}$=59.5 Hz, 1H, NH, *E*-isomer), 12.52 (br d, $^3J_{HP}$=39.0 Hz, 1H, NH, *Z*-isomer) ppm. ^{13}C NMR for major isomer (125.76 MHz, C_6D_6) δ: 15.7 (d, $^3J_{CP}$=5.5 Hz, CH_3), 63.3 (d, $^2J_{CP}$=5.8 Hz, OCH_2), 113.7 (td, $^1J_{CF}$=246 Hz, $^2J_{CP}$=34.7 Hz, CHF_2), 171.0 (dt, $^1J_{CP}$=150 Hz, $^2J_{CF}$=30 Hz, C=N) ppm. ^{19}F NMR (188 MHz, C_6D_6) δ: −121.5 ppm (d, $^2J_{FH}$=55 Hz) (*Z*-isomer) and −127.2 ppm (d, $^2J_{FH}$=55 Hz) (*E*-isomer, *Z*/*E* 5:1). ^{31}P NMR (81 MHz, C_6D_6) δ: 0.5 ppm (m, $^3J_{PH}$=39 Hz) (*Z*-isomer) and 3.3 ppm (m, $^3J_{PH}$=59.5 Hz) (*E*-isomer, *Z*/*E* 5:1).

4.2.2. Diphenyl (2,2,2-trifluoroethanimidoyl)phosphonate ***4a***. Trifluoroacetonitrile (*Caution*! CF_3CN is a highly toxic gas and should be handled with care) was bubbled for 15 min through a cooled to −55 °C solution of diphenyl phosphite (1.00 g, 0.82 mL, 4.27 mmol) and triethylamine (0.09 g, 0.12 mL, 0.85 mmol) in diethyl ether (7.5 mL). The mixture was stirred for 0.5 h and allowed to warm to rt, the solvent was evaporated under reduced pressure to give phosphonate **4a** as a colorless oil, yield 1.4 g (~100%), *Z*/*E*~10:1. The compound is unstable (see Scheme 3) and should be used in synthesis immediately after preparation. IR (neat) ν: 1170 (POC), 1280 (P=O), 1720 (C=N), 3220, 3240 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.12–7.26 (m, 6H, Ar), 7.32–7.36 (m, 4H, Ar), 12.38 (br d, $^3J_{HP}$=63.8 Hz, 1H, NH, *E*-isomer) and 12.83 (br d, $^3J_{HP}$=40 Hz, 1H, NH, *Z*-isomer) ppm (*Z*/*E* ~10:1). ^{19}F NMR (188 MHz, $CDCl_3$) δ: −69.9 (*Z*) and −72.8 (*E*-isomer, *Z*/*E* ~10:1). ^{31}P NMR (81 MHz, $CDCl_3$) δ: −10.5 ppm (m, $^3J_{PH}$=40 Hz) (*Z*-isomer) and −8.9 ppm (m, $^3J_{PH}$=63.8 Hz) (*E*-isomer, *Z*/*E* ~10:1).

4.2.3. Tetraphenyl 1-amino-2,2,2-trifluoroethylidenebis(phosphonate) ***5a***. Iminophosphonate **4a** (0.63 g, 1.9 mmol) was dissolved in ether. After 3 days the precipitated solid was collected by filtration to afford bisphosphonate **5a**. White solid, yield 0.54 g (96%), mp: 123–125 °C. IR (KBr) ν: 1165 (POC), 1290 (P=O), 3305, 3355 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.60 (br s, 2H, NH_2), 7.07–7.15 (m, 12H, Ar), 7.19–7.30 (m, 8H, Ar) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 62.9 (tq, $^1J_{CP}$=145.6 Hz, $^2J_{CF}$=29.4 Hz, CP), 120.2 (br, C^2_{Ph}), 123.3 (q, $^1J_{CF}$=286.5 Hz, CF_3), 125.40 and 125.46 (C^4_{Ph}), 129.44 and 129.50 (C^3_{Ph}), 149.8 and 149.9 (two doublets, $^2J_{CP}$=8.8 Hz, POC) ppm. ^{19}F NMR (282.2 MHz, $CDCl_3$) δ: −68.2 (t, $^3J_{FP}$=4.5 Hz) ppm. $^{31}P\{H\}$ NMR (121.42 MHz, $CDCl_3$) δ: 5.5 (q, $^3J_{PF}$=4.5 Hz) ppm. Anal. Calcd for $C_{26}H_{22}F_3NO_6P_2$ (563.4): C 55.43; H 3.94; N 2.49; P 11.00. Found: C 55.25; H 3.88; N 2.45; P 11.08.

4.2.4. Reaction of difluoroacetonitrile with diphenyl phosphite. Diphenyl phosphite (0.69 g, 0.56 mL, 2.94 mmol) was added to a cooled to −5 °C solution of difluoroacetonitrile (0.11 g, 1.47 mmol) and triethylamine (0.03 g, 0.04 mL, 0.29 mmol) in diethyl ether (2 mL), then the reaction mixture was allowed to warm to room temperature. ^{31}P and ^{19}F NMR spectra show the formation of **4b** and unreacted starting compounds [**4b**/$(PhO)_2POH$/CHF_2CN 2:1:1]. *Diphenyl (2,2-difluoroethanimidoyl)phosphonate* ***4b***, *Z*/*E* ~4:1. ^{19}F NMR (188 MHz, Et_2O) δ: −121.9 (d, $^2J_{FH}$=50.8 Hz) ppm (*Z*) and −127.5 (d, $^2J_{FH}$=50.6 Hz) ppm (*E*). ^{31}P NMR (121 MHz, Et_2O) δ: −8.4 (m, $^3J_{PH}$=40.1 Hz, $^3J_{PF}$=15.3 Hz) ppm (*Z*) and −5.2 (m, $^3J_{PH}$=70.0 Hz) ppm (*E*). The reaction mixture was left overnight at rt. The precipitated product **5b** was isolated by filtration. *Tetraphenyl 1-amino-2,2-difluoroethylidenebisphosphonate* ***5b***. White solid, yield 0.70 g (88%), mp: 113–115°C. IR (KBr) ν: 1168 (POC), 1275 (P=O), 3315, 3370 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.46 (t, $^3J_{HP}$=14.8 Hz, 2H, NH_2), 6.46 (tt, $^2J_{HF}$=55.2 Hz, $^3J_{HP}$=8.8 Hz, 1H, CHF_2), 7.16–7.21 (m, 12H, Ar), 7.26–7.31 (m, 8H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −122.8 (dt, $^2J_{FH}$=55.2 Hz, $^3J_{FP}$=8.5 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 8.1 (m, $^3J_{PCNH}$=14.8 Hz, $^3J_{PCCH}$=8.8 Hz, $^3J_{PF}$=8.5 Hz) ppm. Anal. Calcd for $C_{26}H_{23}F_2NO_6P_2$ (545.4): C, 57.26; H, 4.25; N, 2.57; P, 11.36. Found: C, 57.34; H, 4.15; N, 2.51; P, 11.25.

4.3. Iminotrifluoropropionates

4.3.1. Ethyl 3,3,3-trifluoro-2-iminopropionate ***8b***. Ethyl 3,3,3-trifluoro-2-iminopropionate **8b** (*E*/*Z*≈10:1 at 25 °C) was prepared by the same procedure as **8a**,[12] yellow liquid, yield 84%, bp: 118–120 °C. IR (neat): 1725, 1755 (C=N, C=O), 3250, 3280 (NH) cm^{-1}. (*E*)-**8b**: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 4.34 (q, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 12.13 (br s, 1H, NH). ^{19}F NMR (188 MHz, $CDCl_3$): δ −71.2 ppm. (*Z*)-**8b**: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3), 4.35 (q, $^3J_{HH}$=7.2 Hz, 2H, CH_2), 11.70 (br s, 1H, NH). ^{19}F NMR (188 MHz, $CDCl_3$) δ: −73 ppm. Anal. Calcd for $C_5H_6F_3NO_2$ (169.1): C, 35.51; H, 3.58; N, 8.28. Found: C, 35.67; H, 3.52; N, 8.31.

4.4. General procedure for the preparation of aminophosphonates 9a,b

$BH_3 \cdot Me_2S$ (2 M solution in toluene, 0.65 mL, 1.3 mmol) was added at −20 °C to a stirred solution of the respective imidoyl phosphonate **3** (1 mmol) in THF (10 mL). The reaction mixture was stirred at −20 °C for 1 h then allowed to warm to rt, quenched with aq NH_4Cl (10 mL), and extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give aminophosphonate **9a**[4] or **9b**, yields 95 and 84%, respectively. *Diethyl 1-amino-2,2-difluoroethylphosphonate* ***9b***, colorless oil. IR (neat) ν: 1080 (POC), 1265 (P=O), 2970 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, $^3J_{HH}$=7.2 Hz, 6H, CH_3CH_2), 3.39–3.51 (m, 1H, CHP), 3.48 (br s, 2H, NH_2), 4.13–4.20 (m, 4H, OCH_2), 6.01 (t, $^2J_{HF}$=56 Hz, 1H, CHF_2) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): *AB* system, δ_A −124.6 ppm, δ_B −128.5 ppm, $^2J_{AB}$=285 Hz, $^2J_{FH}$=56 Hz. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 18.6 ppm. Anal. Calcd for $C_6H_{14}F_2NO_3P$ (217.1): C, 33.19; H, 6.50; N, 6.45; P, 14.26. Found: C, 33.23; H, 6.42; N, 6.33; P, 14.21.

4.5. *O,O*-Diethyl-*O′,O′*-diphenyl 1-amino-2,2,2-trifluoroethyli denebis(phosphonate) 11b

A mixture of imidoyl phosphonate **3a** (0.23g, 1.00 mmol) and diphenyl phosphite (0.23 g, 0.20 mL, 1.00 mmol) was maintained at rt for 5 days and triturated with hexane to give compound **11b** as colorless viscous oil, yield 0.45 g (96%). IR (neat) ν: 1040, 1180 (POC), 1280 (P=O), 3220, 3310 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.35 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.46 (br s, 2H, NH_2), 4.13–4.38 (m, 4H, OCH_2), 7.14–7.22 (m, 6H, Ar), 7.27–7.34 (m, 4H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −67.9 (t, $^3J_{FCPOEt} \approx {}^3J_{FCPOPh} \approx 4.8$ Hz) ppm. $^{31}P\{H\}$ NMR (121.42 MHz, $CDCl_3$) δ: 5.9 (qd, $^3J_{PF}$=4.8 Hz, $^2J_{PP}$=2.3, 1P, POPh), 12.1 (qd, $^3J_{PF}$=4.8 Hz, $^2J_{PP}$=2.3, 1P, POEt) ppm. Anal. Calcd for $C_{18}H_{22}F_3NO_6P_2$ (467.3): C, 46.26; H, 4.75; N, 3.00; P, 13.26. Found: C, 46.10; H, 4.64; N, 2.93; P, 13.20.

4.6. General procedure for the synthesis of compounds 12a,b

The solution of imine **3a** (0.60 mmol) and respective aniline (0.60 mmol) in Et_2O (2 mL) was left to react at room temperature for 3 days. The solvent was evaporated under reduced pressure and the residue was washed with petroleum ether.

*4.6.1. Diethyl 1-amino-2,2,2-trifluoro-1-(4-methoxyphenylamino) ethylphosphonate **12a**.* Yellow oil, yield 0.14 g (67%). IR (neat) ν: 1070 (POC), 1265 (P=O), 3330, 3380, 3420 (NH, NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.00 (br, 2H, NH_2), 3.50 (br, 1H, NH), 3.76 (s, 3H, OCH_3), 4.19–4.33 (m, 4H, OCH_2), 6.80 (d, $^3J_{HH}$=8.7 Hz, 2H, Ar), 7.02 (d, $^3J_{HH}$=8.7 Hz, 2H, Ar) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 15.9 (d, $^3J_{CP}$=6.3 Hz, OCH_2CH_3), 55.0 (s, OCH_3), 63.8 (d, $^2J_{CP}$=7.2 Hz, OCH_2CH_3), 64.1 (d, $^2J_{CP}$=7.2 Hz, OCH_2CH_3), 71.8 (dq, $^1J_{CP}$=172.9 Hz, $^2J_{CF}$=29.2 Hz, CP), 113.7, 114.4, 116.0, 126.2 (Ar), 123.9 (qd, $^1J_{CF}$=287 Hz, $^2J_{CP}$=12.1 Hz, CF_3) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −76.2 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 15 ppm. Anal. Calcd for $C_{13}H_{20}F_3N_2O_4P$ (356.3): C, 43.83; H, 5.66; N, 7.86; P, 8.69. Found: C, 43.64; H, 5.60; N, 7.77; P, 8.58.

*4.6.2. Diethyl 1-amino-2,2,2-trifluoro-1-(4-methylphenylamino)ethylphosphonate **12b**.* Yellow oil, yield 0.14 g (70%). IR (neat) ν: 1070 (POC), 1275 (P=O), 3230, 3390, 3425 (NH, NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.35 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.05 (br, 2H, NH_2), 2.28 (s, 3H, ArCH_3), 3.55 (br, 1H, NH), 4.16–4.31 (m, 4H, OCH_2), 6.96 (d, $^3J_{HH}$=8.2 Hz, 2H, Ar), 7.05 (d, $^3J_{HH}$=8.2 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −76.3 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 15.3 ppm. Anal. Calcd for $C_{13}H_{20}F_3N_2O_3P$ (340.3): C, 45.89; H, 5.92; N, 8.23; P, 9.10. Found: C, 45.58; H, 5.86; N, 8.15; P, 9.00.

4.7. General procedure for the preparation of compounds 13, 14

A solution of respective imine **3** or **8b** (1.0 mmol) in anhydrous methanol (4 mL) was left at rt for 10 h. The solvent was evaporated and the residue was washed with hexane.

*4.7.1. Diethyl 1-amino-2,2-difluoro-1-methoxyethylphosphonate **13d**.* Pale yellow oil, yield 0.21 g (84%). IR (neat) ν: 1075 (POC), 1250 (P=O), 3235, 3320 (NH_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25–1.31 (m, 6H, CH_3CH_2), 2.27 (br, 2H, NH_2), 3.38 (s, 3H, OCH_3), 4.12–4.20 (m, 4H, OCH_2), 5.78 (t, $^2J_{HF}$=56.4 Hz, 1H, CHF_2) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): *AB* system, δ_A −131.4 (dd, $^2J_{AB}$=286.5 Hz, $^2J_{AH}$=56.4 Hz), δ_B −135.9 (ddd, $^2J_{AB}$=286.5 Hz, $^2J_{BH}$=56.4 Hz, $^3J_{BP}$=13.1 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 14.5 ppm. Anal. Calcd for $C_7H_{16}F_2NO_4P$ (247.2): C, 34.01; H, 6.52; N, 5.67; P, 12.53. Found: C, 34.12; H, 6.48; N, 5.57; P, 12.37.

*4.7.2. Ethyl 2-amino-2-methoxy-3,3,3-trifluoropropionate **14**.* Colorless oil, yield 0.20 g (99%). IR (neat) ν: 1760 (C=O), 3390, 3460 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.42 (br, 2H, NH_2), 3.34 (s, 3H, OCH_3), 4.30–4.41 (m, 2H, OCH_2) ppm. ^{19}F (188 MHz, $CDCl_3$) δ: −81 ppm. Anal. Calcd for $C_6H_{10}F_3NO_3$ (201.2): C, 35.83; H, 5.01; N, 6.96. Found: C, 35.48; H, 4.97; N, 6.78.

4.8. General procedure for the preparation of compounds 15, 16

To a stirred solution of imine **3a** or **8a** (1.00 mmol) in Et_2O (2 mL) was added respective thiophenol (1.00 mmol), the mixture was kept at room temperature for 10 h, the solvent was evaporated under reduced pressure and the residue was washed with petroleum ether.

*4.8.1. Diethyl 1-amino-2,2,2-trifluoro-1-(4-methylphenylthio)ethylphosphonate **15a**.* Colorless oil, yield 0.35 g (98%). IR (neat) ν: 1070 (POC), 1265 (P=O), 3400 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.42 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.76 (br, 2H, NH_2), 2.38 (s, 3H, ArCH_3), 4.25–4.35 (m, 2H, OCH_2), 4.36–4.43 (m, 2H, OCH_2), 7.20 (d, $^3J_{HH}$=8 Hz, 2H, Ar), 7.48 (d, $^3J_{HH}$=8 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −72.9 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 14.2 ppm. Anal. Calcd for $C_{13}H_{19}F_3NO_3PS$ (357.3): C, 43.70; H, 5.36; N, 3.92; P, 8.67; S, 8.97. Found: C, 43.63; H, 5.32; N, 3.88; P, 8.59; S, 8.93.

*4.8.2. Diethyl 1-amino-2,2,2-trifluoro-1-(4-fluorophenylthio)ethylphosphonate **15b**.* White crystals, yield 0.35 g (97%), mp: 36–38 °C. IR (KBr) ν: 1070 (POC), 1265 (P=O), 3235, 3420 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH_2), 1.42 (t, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH_2), 1.76 (br, 2H, NH_2), 4.25–4.34 (m, 2H, OCH_2), 4.35–4.43 (m, 2H, OCH_2), 7.10 (dd, $^3J_{HH}$=8.7 Hz, $^3J_{HF}$=8.7 Hz, 2H, Ar), 7.61 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HF}$=5.4 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.2 (3F, CF_3), −111.2 (1F, ArF) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 13.5 ppm. Anal. Calcd for $C_{12}H_{16}F_4NO_3PS$ (361.3): C, 39.89; H, 4.46; N, 3.88; P, 8.57; S, 8.87. Found: C, 39.78; H, 4.32; N, 3.83; P, 8.49; S, 8.90.

*4.8.3. Methyl 3,3,3-trifluoro-2-(4-methylphenylthio)propionate **16a**.* Yellow crystals, yield 0.27 g (97%), mp: 38–40 °C. IR (KBr) ν: 1765 (C=O), 3420, 3440 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.01 (br, 2H, NH_2), 2.38 (s, 3H, ArCH_3), 3.84 (s, 3H, OCH_3), 7.21 (d, $^3J_{HH}$=8 Hz, 2H, Ar), 7.36 (d, $^3J_{HH}$=8 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.8 ppm. Anal. Calcd for $C_{11}H_{12}F_3NO_2S$ (279.3): C, 47.31; H, 4.33; N, 5.02; S, 11.48. Found: C, 47.11; H, 4.28; N, 4.88; S, 11.34.

*4.8.4. Methyl 3,3,3-trifluoro-2-(4-fluorophenylthio)propionate **16b**.* Yellow oil, yield 0.27 g (96%). IR (neat) ν: 1770 (C=O), 3370, 3450 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.04 (br, 2H, NH_2), 3.83 (s, 3H, OCH_3), 7.10 (dd, $^3J_{HH}$=8.7 Hz, $^3J_{HF}$=8.7 Hz, 2H, Ar), 7.48 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HF}$=5.4 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.7 (3F, CF_3), −109.3 (1F, ArF) ppm. Anal. Calcd for $C_{10}H_9F_4NO_2S$ (283.3): C, 42.41; H, 3.20; N, 4.95; S, 11.32. Found: C, 42.32; H, 3.14; N, 5.03; S, 11.24.

4.9. General procedure for the synthesis of compounds 18, 22–26

A mixture of iminophosphonate **3a** (1.00 mmol) and respective indole or pyrrole (1.00 mmol) was heated at 80 °C for 4 h, cooled, and triturated with hexane.

*4.9.1. Diethyl 1-amino-2,2,2-trifluoro-1-(indol-3-yl)ethylphosphonate **18a**.* Colorless viscous oil, yield 0.34 g (97%). IR (neat) ν: 1060 (POC), 1260 (P=O), 3270 (NH), 3390 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.30 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.32 (br, 2H, NH_2), 3.58–3.72 (m, 1H, OCH_2), 3.89–4.02 (m, 1H, OCH_2), 4.11–4.24 (m, 2H, OCH_2), 7.10 (t, $^3J_{HH}$=7.5 Hz, 1H, Het), 7.16 (t, $^3J_{HH}$=7.5 Hz, 1H, Het), 7.34 (d, $^3J_{HH}$=7.5 Hz, 1H, Het), 7.44 (s, 1H, Het), 8.23 (d, $^3J_{HH}$=7.5 Hz, 1H, Het), 9.49 (br s, 1H, NH) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74 ppm. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 16.7 ppm. Anal. Calcd for $C_{14}H_{18}F_3N_2O_3P$ (350.3): C, 48.01; H, 5.18; N, 8.00; P, 8.84. Found: C, 47.78; H, 5.12; N, 7.86; P, 8.73.

*4.9.2. Diethyl 1-amino-2,2,2-trifluoro-1-(2-methylindol-3-yl)ethylphosphonate **18b**.* Orange crystals, yield 0.35 g (96%), mp:

49–51 °C. IR (KBr) ν: 1050 (POC), 1240 (P=O), 3260 (NH), 3300 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.10 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.28 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.38 (br s, 2H, NH_2), 2.67 (s, 3H, CH_3), 3.71–3.85 (m, 1H, OCH_2), 3.93–4.04 (m, 1H, OCH_2), 4.10–4.24 (m, 2H, OCH_2), 7.06 (t, $^3J_{HH}$=7.8 Hz, 1H, Het), 7.11 (t, $^3J_{HH}$=7.8 Hz, 1H, Het), 7.25 (d, $^3J_{HH}$=7.8 Hz, 1H, Het), 8.23 (br s, 1H, NH), 8.30 (d, $^3J_{HH}$=7.8 Hz, 1H, Het) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.4 (s, CH_3), 16.2 (d, $^3J_{CP}$=5.5 Hz, OCH_2CH_3), 16.3 (d, $^3J_{CP}$=5.5 Hz, OCH_2CH_3), 63.0 (dq, $^1J_{CP}$=154.8 Hz, $^2J_{CF}$=29.7 Hz, CP), 63.8 (d, $^2J_{CP}$=7.8 Hz, OCH_2CH_3), 64.1 (d, $^2J_{CP}$=7.8 Hz, OCH_2CH_3), 101.8 (d, $^2J_{CP}$=5.2 Hz, Het), 110.4, 119.5, 121.0, 122.3 (Het), 125.8 (qd, $^1J_{CF}$=285 Hz, $^2J_{CP}$=13.8 Hz, CF_3),135.0, 135.4 (Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −72.2 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.9 ppm. Anal. Calcd for $C_{15}H_{20}F_3N_2O_3P$ (364.3): C, 49.45; H, 5.53; N, 7.69; P, 8.50. Found: C, 49.52; H, 5.44; N, 7.54; P, 8.67.

4.9.3. Diethyl 1-amino-2,2,2-trifluoro-1-(1-methylindol-3-yl)ethylphosphonate ***18c***. Orange crystals, yield 0.35 g (96%), mp: 55–57 °C. IR (neat) ν: 1050 (POC), 1250 (P=O), 3200 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.09 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.30 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.31 (br s, 2H, NH_2), 3.62–3.75 (m, 1H, OCH_2), 3.77 (s, 3H, NCH_3), 3.91–4.04 (m, 1H, OCH_2), 4.11–4.24 (m, 2H, OCH_2), 7.13 (t, $^3J_{HH}$=7.8 Hz, 1H, Het), 7.24 (t, $^3J_{HH}$=7.8 Hz, 1H, Het), 7.31 (d, $^3J_{HH}$=7.8 Hz, 1H, Het), 7.43 (d, $^4J_{HP}$=2.7 Hz, 1H, Het), 8.24 (d, $^3J_{HH}$=7.8 Hz, 1H, Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.1 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.2 ppm. Anal. Calcd for $C_{15}H_{20}F_3N_2O_3P$ (364.3): C, 49.45; H, 5.53; N, 7.69; P, 8.50. Found: C, 49.74; H, 5.47; N, 7.81; P, 8.36.

4.9.4. Diethyl 1-amino-2,2,2-trifluoro-1-(1-methylpyrrol-2-yl)ethylphosphonate ***22***. Diethyl 1-amino-2,2,2-trifluoro-1-(1-methyl pyrrol-2-yl)ethylphosphonate **22** was isolated from the mixture with isomer **24** by TLC (silica gel, EtOAc/hexane, 10:1, R_f=0.74). Orange crystals, yield 0.21 g (70%), mp: 53–55 °C. IR (neat) ν: 1060 (POC), 1270 (P=O), 3400, 3460 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.29 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.91 (br s, 2H, NH_2), 3.87–3.99 (m, 1H, OCH_2), 3.96 (s, 3H, NCH_3), 4.00–4.18 (m, 3H, OCH_2), 6.08 (dd, $^3J_{HH}$ 3.9 and 3.3 Hz, 1H, Het), 6.52–6.54 (m, 1H, Het), 6.62–6.64 (m, 1H, Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −73.7 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.6 ppm. Anal. Calcd for $C_{11}H_{18}F_3N_2O_3P$ (314.2): C, 42.04; H, 5.77; N, 8.91; P, 9.86. Found: C, 41.57; H, 5.61; N, 9.11; P, 10.01.

4.9.5. Methyl 3,3,3-trifluoro-2-(1-methylpyrrol-2-yl)propionate ***23***. Brown viscous oil, yield 0.23 g (97%). IR (neat) ν: 1770 (C=O), 3350, 3440 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.16 (br s, 2H, NH_2), 3.61 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 6.08 (t, $^3J_{HH}$=3.3 Hz, 1H, Het), 6.30 (m, 1H, Het), 6.62 (m, 1H, Het) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 35.0 (NCH_3), 53.8 (OCH_3), 64.7 (q, $^2J_{CF}$=29.1 Hz, CCF_3), 106.7 (Het), 110.0 (q, J_{CF}=2.5 Hz, Het), 124.5 (d, $^1J_{CF}$=286.9 Hz, CF_3), 124.6, 125.1 (Het), 168.7 (C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.9 ppm. Anal. Calcd for $C_9H_{11}F_3N_2O_2$ (236.2): C, 45.77; H, 4.69; N, 11.86. Found: C, 45.52; H, 4.64; N, 11.72.

4.9.6. Diethyl 1-amino-2,2,2-trifluoro-1-(1-methylpyrrol-3-yl)ethylphosphonate ***24***. Diethyl 1-amino-2,2,2-trifluoro-1-(1-methyl pyrrol-3-yl)ethylphosphonate **24** was isolated from the mixture with isomer **22** by preparative TLC (silica gel, EtOAc/hexane, 10:1, R_f=0.43). Orange crystals, yield 0.05 g (16%), mp: 61–63 °C. IR (neat) ν: 1060 (POC), 1270 (P=O), 3390, 3410 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.32 (br, 2H, NH_2), 3.66 (s, 3H, NCH_3), 3.75–3.88 (m, 1H, OCH_2), 3.99–4.09 (m, 1H, OCH_2), 4.09–4.24 (m, 2H, OCH_2), 6.32–6.34 (m, 1H, Het), 6.59 (t, $^3J_{HH}$=$^4J_{HH}$=2.3 Hz, 1H, Het), 6.85–6.87 (m, 1H, Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −75.6 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.4 ppm. Anal. Calcd for $C_{11}H_{18}F_3N_2O_3P$ (314.2): C, 42.04; H, 5.77; N, 8.91; P 9.86. Found: C, 41.83; H, 5.68; N, 9.08; P, 9.99.

4.9.7. Diethyl 1-amino-1-(1-tert-butylpyrrol-3-yl)-2,2,2-trifluoroethylphosphonate ***25***. Orange viscous oil, yield 0.35 g (98%). IR (neat) ν: 1060 (POC), 1250 (P=O), 3400 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.14 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.30 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.51 (s, 9H, *t*-Bu), 2.93 (br, 2H, NH_2), 3.62–3.75 (m, 1H, OCH_2), 3.93–4.03 (m, 1H, OCH_2), 4.08–4.18 (m, 2H, OCH_2), 6.34–6.36 (m, 1H, Het), 6.81 (dd, $^3J_{HH}$=2.7 Hz, $^3J_{HH}$=2.7 Hz, 1H, Het), 7.05 (dd, $^4J_{HH}$ 4.5 and 2.7 Hz, 1H, Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −76.2 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.8 ppm. Anal. Calcd for $C_{14}H_{24}F_3N_2O_3P$ (356.3): C, 47.19; H, 6.79; N, 7.86; P, 8.69. Found: C, 47.32; H, 6.67; N, 7.72; P, 8.53.

4.9.8. Methyl 2-(1-tert-butylpyrrol-3-yl)-3,3,3-trifluoropropionate ***26***. Yellow viscous oil, yield 0.27 g (97%). IR (neat) ν: 1760 (C=O), 3430 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.51 (s, 9H, *t*-Bu), 2.24 (br, 2H, NH_2), 3.84 (s, 3H, OCH_3), 6.25–6.26 (m, 1H, Het), 6.78 (dd, J_{HH} 3.0 and 2.3 Hz, 1H, Het), 6.97–6.99 (m, 1H, Het) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −76.7 ppm. Anal. Calcd for $C_{12}H_{17}F_3N_2O_2$ (278.3): C, 51.80; H, 6.16; N, 10.07. Found: C, 52.06; H, 6.13; N, 10.15.

4.10. General procedure for the synthesis of compounds 20, 21

A mixture of pyrrole or 2,4-dimethylpyrrole (1.00 mmol) and respective imine **3a** or **8** (1.00 mmol) was left at room temperature overnight and triturated with hexane to afford aminoalkylation product **20** or **21**.

4.10.1. Diethyl 1-amino-2,2,2-trifluoro-1-(pyrrol-2-yl)ethylphosphonate ***20a***. White crystals, yield 0.29 g (97%), mp: 62–64 °C. IR (KBr) ν: 1040 (POC), 1260 (P=O), 3320, 3420 (NH, NH_2) cm^{-1}. ^1H (300 MHz, $CDCl_3$) δ: 1.16 (t, $^3J_{HH}$=6.9 Hz, 3H, CH_3CH_2), 1.34 (t, $^3J_{HH}$=6.9 Hz, 3H, CH_3CH_2), 2.12 (br s, 2H, NH_2), 3.60–3.73 (m, 1H, OCH_2), 3.93–4.05 (m, 1H, OCH_2), 4.12–4.22 (m, 2H, OCH_2), 6.22 (dd, $^3J_{HH}$=6.2 Hz, $^4J_{HH}$=2.9 Hz, 1H, Het), 6.42 (m, 1H, Het), 6.85 (m, 1H, Het), 9.16 (br s, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.1 (d, $^3J_{CP}$=5.5 Hz, OCH_2CH_3), 16.2 (d, $^3J_{CP}$=5.5 Hz, OCH_2CH_3), 59.5 (dq, $^1J_{CP}$=153.2 Hz, $^2J_{CF}$=29.7 Hz, CP), 63.9 (d, $^2J_{CP}$=7.3 Hz, OCH_2CH_3), 64.3 (d, $^2J_{CP}$=7.3 Hz, OCH_2CH_3), 108.6 (s, C_{Het}), 108.7 (d, J_{CP}=1.8 Hz, C_{Het}), 119.2 (d, J_{CP}=1.5 Hz, C_{Het}), 121.9 (d, J_{CP}=6 Hz, C^2_{Het}), 124.5 (qd, $^1J_{CF}$=284.3 Hz, $^2J_{CP}$=10.1 Hz, CF_3) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.2 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.3 ppm. Anal. Calcd for $C_{10}H_{16}F_3N_2O_3P$ (300.2): C, 40.01; H, 5.37; N, 9.33; P, 10.32. Found: C, 39.73; H, 5.28; N, 9.44; P, 10.25.

4.10.2. Diethyl 1-amino-1-(3,5-dimethylpyrrol-2-yl)-2,2,2-trifluoroethylphosphonate ***20b***. Brown oil, yield 0.32 g (98%). IR (neat): 1070 (POC), 1260 (P=O), 3220 (NH), 3340, 3390 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.16 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.09 (br d, $^3J_{HP}$=13.2 Hz, 2H, NH_2), 2.19 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.66–3.79 (m, 1H, OCH_2), 3.96–4.09 (m, 1H, OCH_2), 4.16–4.26 (m, 2H, OCH_2), 5.67 (s, 1H, H^4), 8.82 (br s, 1H, NH) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ: 12.9 (=CCH_3), 13.0 (=CCH_3), 16.2 (d, $^3J_{CP}$=5.2 Hz, OCH_2CH_3), 16.3 (d, $^3J_{CP}$=5.2 Hz, OCH_2CH_3), 61.1 (dq, $^1J_{CP}$=149.1 Hz, $^2J_{CF}$=29.5 Hz, CP), 63.8 (d, $^2J_{CP}$=7.2 Hz, OCH_2CH_3), 64.2 (d, $^2J_{CP}$=7.2 Hz, OCH_2CH_3), 110.8 (d, J_{CP}=1.4 Hz, C_{Het}), 113.7 (d, J_{CP}=6.4 Hz, C_{Het}), 120.2 (d, J_{CP}=8.2 Hz, C_{Het}), 124.8 (qd, $^1J_{CF}$=284.8 Hz, $^2J_{CP}$=13.5 Hz, CF_3), 127.5 (d, J_{CP}=1.8 Hz, CHet) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.8 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.9 ppm. Anal. Calcd for $C_{12}H_{20}F_3N_2O_3P$

(328.3): C, 43.91; H, 6.14; N, 8.53; P, 9.44. Found: C, 43.53; H, 6.22; N, 8.40; P, 9.29.

*4.10.3. Ethyl 3,3,3-trifluoro-2-(pyrrol-2-yl)propionate **21a**.* Yellow oil, yield 0.23 g (97%). IR (neat) ν: 1755 (C=O), 3280 (NH), 3360, 3430 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 2.33 (br s, 2H, NH_2), 4.25–4.40 (m, 2H, OCH_2), 6.22 (dd, $^3J_{HH}$ 6.0 and 2.7 Hz, 1H, Het), 6.41–6.43 (m, 1H, Het), 6.81–6.83 (m, 1H, Het), 9.1 (br, 1H, NH) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −77.3 ppm. Anal. Calcd for $C_9H_{11}F_3N_2O_2$ (236.2): C, 45.77; H, 4.69; N, 11.86. Found: C, 45.59; H, 4.63; N, 11.74.

*4.10.4. Methyl 2-(3,5-dimethylpyrrol-2-yl)-3,3,3-trifluoropropionate **21b**.* Methyl 2-(3,5-dimethylpyrrol-2-yl)-3,3,3-trifluoropropionate **21b** was purified by column chromatography (hexane/EtOAc=5:1). Brown crystals, yield 0.24 g (96%), mp: 59–62 °C. IR (KBr) ν: 1765 (C=O), 3330, 3420 (NH, NH_2) cm^{-1}. ^1H (300 MHz, $CDCl_3$) δ: 2.02 (s, 3H, CCH_3), 2.10 (br, 2H, NH_2), 2.21 (s, 3H, CCH_3), 3.86 (s, 3H, OCH_3), 5.70 (s, 1H, Het), 8.45 (br, 1H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7 (CCH_3), 12.8 (CCH_3), 53.4 (OCH_3), 63.7 (q, $^2J_{CF}$=29.1 Hz, CCF_3), 110.5, 116.5, 118.8 (Het), 124.4 (d, $^1J_{CF}$=285.1 Hz, CF_3), 127.2 (Het), 169.5 (C=O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −76.5 ppm. Anal. Calcd for $C_{10}H_{13}F_3N_2O_2$ (250.2): C, 48.00; H, 5.24; N, 11.20. Found: C, 47.45; H, 5.18; N, 11.10.

4.11. General procedure for the synthesis of compounds 27, 29

Mercaptoacetic or 3-mercaptopropionic acid (1.00 mmol) was added to a stirred solution of the iminophosphonate **3** (1.0 mmol for **3a** and 1.10 mmol for **3b**) in benzene (2 mL). The mixture was refluxed for 4 h, the solvent was evaporated in vacuum and the residue was triturated with hexane.

*4.11.1. Diethyl [2-(difluoromethyl)-4-oxo-1,3-thiazolidin-2-yl]phosphonate **27b**.* White crystals, yield 0.27 g (93%), mp: 54–56 °C. IR (KBr) ν: 1090 (POC), 1240 (P=O), 1700 (C=O), 3190, 3220 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2), 3.52 (d, $^2J_{HAHB}$=15.2 Hz, 1H, SCH_AH_B), 3.61 (dd, $^2J_{HBHA}$=15.2 Hz, $^4J_{HBP}$=5.4 Hz, 1H, SCH_AH_B), 4.21–4.32 (m, 4H, OCH_2), 5.97 (td, $^2J_{HF}$=55.5 Hz, $^3J_{HP}$=4 Hz, 1H, CHF_2), 7.62 (br, 1H, NH) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): *AB* system, δ_A −125.8 (dd, $^2J_{AB}$=280.1 Hz, $^2J_{AH}$=55.5 Hz, 1F), δ_B −128.5 (dd, $^2J_{AB}$=280.1 Hz, $^2J_{BH}$=55.5 Hz, 1F) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 13.4 ppm. Anal. Calcd for $C_8H_{14}F_2NO_4PS$ (289.2): C, 33.22; H, 4.88; N, 4.84; P, 10.71; S, 11.09. Found: C, 33.13; H, 4.78; N, 4.79; P, 10.75; S, 11.01.

*4.11.2. Diethyl [4-oxo-2-(trifluoromethyl)-1,3-thiazinan-2-yl]phosphonate **29a**.* White crystals, yield 0.28 g (88%), mp: 97–99 °C. IR (KBr) ν: 1045 (POC), 1265 (P=O), 1680 (C=O), 3100, 3200 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, $^3J_{HH}$=6.6 Hz, 6H, CH_3CH_2), 2.66–2.74 (m, 2H, SCH_2CH_2), 2.95–3.09 (m, 2H, SCH_2CH_2), 4.17–4.30 (m, 4H, OCH_2), 6.50 (br, 1H, NH) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.5 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 10.2 ppm. Anal. Calcd for $C_9H_{15}F_3NO_4PS$ (321.3): C, 33.65; H, 4.71; N, 4.36; P, 9.64; S, 9.98. Found: C, 33.26; H, 4.68; N, 4.25; P, 9.48; S, 9.85.

*4.11.3. Diethyl [2-(difluoromethyl)-4-oxo-1,3-thiazinan-2-yl]phosphonate **29b**.* Yellow viscous oil, yield 0.25 g (83%). IR (neat) ν: 1080 (POC), 1250 (P=O), 1680 (C=O), 3200 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, $^3J_{HH}$=6.8 Hz, 3H, CH_3CH_2), 1.35 (t, $^3J_{HH}$=6.8 Hz, 3H, CH_3CH_2), 2.70–2.75 (m, 2H, SCH_2CH_2), 3.05–3.10 (m, 2H, SCH_2CH_2), 4.19–4.33 (m, 4H, OCH_2), 5.94 (td, $^2J_{HF}$=55.5 Hz, $^3J_{HP}$=2.4 Hz, 1H, CHF_2), 6.74 (br s, 1H, NH) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): AB system, δ_A −121.5 (dd, $^2J_{AB}$=278 Hz, $^2J_{AH}$=55.5 Hz, 1F), δ_B −127.8 (ddd, $^2J_{AB}$=278 Hz, $^2J_{BH}$=55.5 Hz, $^3J_{BP}$=14.1 Hz, 1F) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 13.3 ppm. Anal. Calcd for $C_9H_{16}F_2NO_4PS$ (303.3): C, 35.65; H, 5.32; N, 4.62; P, 10.21; S, 10.57. Found: C, 35.34; H, 5.29; N, 4.53; P, 10.25; S, 10.43.

4.12. General procedure for the synthesis of compounds 31

Thiosalicylic acid (1.00 mmol) was added to a stirred solution of respective iminophosphonate **3** (1.0 mmol for **3a** and 1.1 mmol for **3b**) in THF (2 mL) and was allowed to react for 24 h. The solvent was evaporated in vacuum and the residue was triturated with hexane.

*4.12.1. Diethyl (4-oxo-2-trifluoromethyl-3,4-dihydro-2H-1,3-benzothiazin-2-yl)phosphonate **31a**.* Yellow crystals, yield 0.32 g (87%), mp: 104–105 °C. IR (KBr) ν: 1050 (POC), 1280 (P=O), 1680 (C=O), 3190 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.38 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 4.34 (m, 4H, OCH_2), 6.65 (br, 1H, NH), 7.22 (d, $^3J_{HH}$=7.6 Hz, 1H, Ar), 7.27 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar), 7.43 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar), 8.14 (d, $^3J_{HH}$=7.6 Hz, 1H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −74.4 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 8.7 ppm. Anal. Calcd for $C_{13}H_{15}F_3NO_4PS$ (369.3): C, 42.28; H, 4.09; N, 3.79; P, 8.39; S, 8.68. Found: C, 42.12; H, 4.01; N, 3.84; P, 8.44; S, 8.57.

*4.12.2. Diethyl [2-(difluoromethyl)-4-oxo-3,4-dihydro-2H-1,3-benzothiazin-2-yl]phosphonate **31b**.* Yellow crystals, yield 0.29 g (83%), mp: 103–105 °C. IR (KBr) ν: 1080 (POC), 1260 (P=O), 1660 (C=O), 3190 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.39 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 4.21–4.37 (m, 4H, OCH_2), 6.07 (td, $^2J_{HF}$=55.2 Hz, $^3J_{HP}$=3.3 Hz, 1H, CHF_2), 6.73 (br, 1H, NH), 7.24 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar), 7.28 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar), 7.43 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar), 8.16 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): AB system, δ_A −120.9 (dd, $^2J_{AB}$=278 Hz, $^2J_{AH}$=55.5 Hz), δ_B −127.8 (ddd, $^2J_{BA}$=278 Hz, $^2J_{BH}$=55.5 Hz, $^3J_{BP}$=14.1 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 11.9 ppm. Anal. Calcd for $C_{13}H_{16}F_2NO_4PS$ (351.3): C, 44.45; H, 4.59; N, 3.99; P, 8.82; S, 9.13. Found: C, 44.24; H, 4.50; N, 3.91; P, 8.79; S, 9.06.

4.13. General procedure for the synthesis of compounds 33

A mixture of salicylaldehyde (2.50 mmol) and iminophosphonate **3** (2.50 mmol for **3a** and 2.75 mmol for **3b**) was left at room temperature for 24 h. After addition of benzene (5 mL) and $TsOH \cdot H_2O$ (20 mg), the mixture was refluxed for 3 h, the solvent was evaporated in vacuum, and the residue was purified by chromatography.

*4.13.1. Diethyl [2-(trifluoromethyl)-2H-1,3-benzoxazin-2-yl]phosphonate **33a**.* Diethyl [2-(trifluoromethyl)-2*H*-1,3-benzoxazin-2-yl] phosphonate **33a** was purified by column chromatography (silica gel, CH_2Cl_2). Yellow oil, yield 0.57 g (68%). IR (neat) ν: 1040 (POC), 1270 (P=O), 1650 (C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 1.31 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 4.14–4.29 (m, 4H, OCH_2), 6.80 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar), 6.95 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar), 7.14 (d, $^3J_{HH}$=7.8 Hz, 1H, Ar), 7.34 (t, $^3J_{HH}$=7.8 Hz, 1H, Ar), 8.22 (d, $^3J_{HP}$=4.4 Hz, 1H, CH=N) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −79.2 ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 6.1 ppm. Anal. Calcd for $C_{13}H_{15}F_3NO_4P$ (337.2): C, 46.30; H, 4.48; N, 4.15; P, 9.18. Found: C, 46.20; H, 4.39; N, 4.07; P, 9.11.

*4.13.2. Diethyl [2-(difluoromethyl)-2H-1,3-benzoxazin-2-yl]phosphonate **33**.* Diethyl [2-(difluoromethyl)-2*H*-1,3-benzoxazin-2-yl] phosphonate **33** was purified by column chromatography (silica gel, EtOAc). Yellow oil, yield 0.57 g (72%). IR (neat) ν: 1040 (POC), 1270 (P=O), 1650 (C=N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, $^3J_{HH}$=6.8 Hz, 3H, CH_3CH_2), 1.32 (t, $^3J_{HH}$=6.8 Hz, 3H, CH_3CH_2), 4.16–4.29 (m, 4H, OCH_2), 6.10 (t, $^2J_{HF}$=54.2 Hz, 1H, CHF_2), 6.81 (d, $^3J_{HH}$=7.6 Hz, 1H, Ar), 6.94 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar), 7.13 (d,

$^3J_{HH}$=7.6 Hz, 1H, Ar), 7.34 (t, $^3J_{HH}$=7.6 Hz, 1H, Ar), 8.21 (d, $^3J_{HP}$=4 Hz, 1H, CH=N) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −133.4 (d, $^2J_{FH}$=54.2 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$) δ: 10.6 ppm. Anal. Calcd for $C_{13}H_{16}F_2NO_4P$ (319.2): C, 48.91; H, 5.05; N, 4.39; P, 9.70. Found: C, 48.66; H, 4.98; N, 4.30; P, 9.54.

4.14. Ethyl 5-trifluoromethyl-3-(4-trifluoromethylphenyl)-4,5-dihydro-1,2,4-oxadiazole-5-carboxylate 35b

4-Trifluoromethylbenzenecarbohydroxymoyl chloride (0.33g, 1.5 mmol) was added to a stirred at −30 °C solution of the imino-carboxylate **8b** (0.21 g, 1.24 mmol) and triethylamine (0.15 g, 0.21 mL, 1.5 mmol) in diethyl ether (5 mL). After stirring at room temperature for 3 h, the precipitated solid was separated by filtration, the solvent was evaporated in vacuum, and the residue was crystallized from hexane. Yield 0.38 g (86%), white crystals, mp: 96–98 °C. IR (KBr) ν: 1765 (C=O, C=N), 3240, 3270 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (t, $^3J_{HH}$=7.2 Hz, 3H, CH_3CH_2), 4.35–4.52 (m, 2H, OCH_2), 5.92 (br, 1H, NH), 7.73 (d, $^3J_{HH}$=8.1 Hz, 2H, Ar), 7.88 (d, $^3J_{HH}$=8.1 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −63.6 (3F, $ArCF_3$), −82.3 (3F, CF_3) ppm. Anal. Calcd for $C_{13}H_{10}F_6N_2O_3$ (356.2): C, 43.83; H, 2.83; N, 7.86. Found: C, 43.69; H, 2.80; N, 7.75.

4.15. 5-Trifluoromethyl-3-(4-trifluoromethylphenyl)-1,2,4-oxadiazole 37

4-Trifluoromethylbenzenecarbohydroxymoyl chloride (0.29g, 1.3 mmol) was added to a stirred solution of the imine **3a** (0.25 g, 1.1 mmol) and triethylamine (0.13 g, 0.18 mL, 1.3 mmol) in diethyl ether (10 mL) at −30 °C. The reaction mixture was stirred at rt for 30 min, washed with water (5 mL), and 2 N NaOH (5 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give compound **37** as colorless viscous oil, yield 0.19 g (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, $^3J_{HH}$=8.1 Hz, 2H, Ar), 8.23 (d, $^3J_{HH}$=8.1 Hz, 2H, Ar) ppm. ^{19}F NMR (188 MHz, $CDCl_3$) δ: −64.5 (3F, $ArCF_3$), −66.7 (3F, CF_3) ppm. Anal. Calcd for $C_{10}H_4F_6N_2O$ (282.2): C, 42.57; H, 1.43; N, 9.93. Found: C, 42.21; H, 1.41; N, 9.75.

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