**Abstract:** A convenient synthetic approach to previously unknown N–H imidoyl phosphonates, based on addition of dialkyl phosphites to trifluoroacetonitrile, has been developed. The synthetic potential of such imines, which exist as equilibrium mixtures of E/Z-isomers, was demonstrated by their easy reduction and functionalization with O- and P-centered nucleophiles, to afford derivatives of α-aminophosphonic acids containing a trifluoromethyl group. Furthermore, interaction with mercaptoacetic acid proceeds with intramolecular cyclization of the intermediate adduct to produce a novel 2-phosphorylated N–H thiazolidine. Identification of the N–H imines and trifluoroacetylisocyanate leads to novel, reactive, phosphorylated α-amino acids.

**Key words:** imidoyl phosphonates, N–H imines, trifluoroacetylisocyanate, phosphorylated aminophosphonates, E/Z-isomerism

Imidoyl phosphonates are valuable new building blocks for the synthesis of a range of functionalized aminophosphonic acid derivatives. Compounds with a free NH group seem especially promising as they can be functionalized with both nucleophilic (at the imine carbon atom) and electrophilic agents (at the nitrogen atom). However, to the best of our knowledge, the N–H imidoyl phosphonates have not been characterized, although they have been postulated as intermediates.

We have developed a convenient synthetic approach to imines of type 1, which constitute the first N–H imidoyl phosphonates reported (Scheme 1). Addition of dialkyl phosphites to the C≡N bond of the highly electrophilic trifluoroacetonitrile, in the presence of a catalytic amount of a nitrogen base, occurs at room temperature and leads to phosphonates 1 in high yields.

**Scheme 1**

Formation of the P–C bond was confirmed by the 13C NMR spectra of compounds 1, in which the imine carbon signal (δ = 166.8–166.9 ppm) with a large, direct C–P coupling constant (J_{C–P} = 164 Hz, J_{C–F} = 36–37 Hz) was identified.

It is noteworthy that N–H imines, with a few exceptions, have been reported to be inherently unstable, leading to difficulties in their isolation. Phosphorylated imines 1, however, are quite stable under a dry, inert atmosphere and can be easily purified by distillation. In solutions (CDCl3, toluene-d8), imidoyl phosphonates 1 exist as an equilibrium mixture of Z/E isomers (Z/E = ~10:1 at 25 °C). Identification of Z/E-isomers is based mainly on the significant difference in the coupling constants of the NH proton and the phosphorus atom (J = 37–38 Hz and J = 58–59 Hz, respectively). Selected NMR spectral characteristics for the Z/E-isomers of imines 1 are represented in Figure 1. The spectral distinctions found are important since they can be used for assignment of geometrical isomers in related systems.

**Figure 1**

The dynamic equilibrium between geometrical isomers 1 was substantiated by the fact that on heating 1a or 1b in deuterated toluene solutions, the NH proton signals of the Z/E-isomers in the 1H NMR spectrum first broaden and then coalesce (~100 °C); on cooling to room temperature the starting state was recovered. The presence of a phenyl group at the imine carbon atom seems to be crucial in defining the geometry of trifluoroethyl ketimines. Analogous to parent imines 1, N-alkyl-substituted analogs were also found to exist mainly in the Z-configuration. However, for non-phosphorylated ketimines [CF3C(Ar)=NH], the isomer with cis-configuration of CF3 group and NH hydrogen atom dominates.

Since imines of type 1 contain a polarized imine group and are promising building blocks in the synthesis of aminophosphonic acid derivatives with a trifluoroethyl group, they could become the basis of a new strategy for aminophosphonic acid synthesis. In the most widely used
methods, the phosphorus function is introduced to the C=N bond of an imine in a key step. In our approach, the phosphorus moiety already exists in the starting imine and this opens new possibilities for functionalization. In particular, the phosphoryl group additionally activates the C=N bond, allowing for the introduction of weakly nucleophilic functional groups. In this context, the possibility of functionalization at the nitrogen atom of N–H imines is exemplified by the reaction with trichloroacetyl isocyanate, which leads to a new type of synthetically promising, activated C-phosphorylated N-acylimines 7 (Scheme 3).

\[ (RO)_{2}P=O \quad \text{CCl}_{3}CONCOR \]

**Scheme 3**

Compounds such as 7 display a characteristic $^{31}$P NMR signal in the region between $\delta = -3.5$ and $-4.9$ ppm, which is characteristic for N-acylthioalacetimidoylphosphonates.

In summary, we have developed a simple and efficient synthesis of N–H trifluoroacacetimidoyl phosphonates of type 1 and demonstrated their synthetic potential for the preparation of functionalized acyclic and heterocyclic derivatives possessing $\alpha$-aminoalkylphosphoryl or bisphosphoryl fragments.

IR spectra were obtained with an UR-20 instrument. $^1$H NMR spectra were recorded on a Varian VXR-300 spectrometer (operating frequency 300 MHz). $^1$F NMR and $^{31}$P NMR spectra were recorded on a Gemini 200 Varian instrument operating at 188.14 and 80.95 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 ($^1$H, $^{13}$C), CFCl$_3$ ($^{19}$F) and external 85% H$_3$PO$_4$ ($^{31}$P). APCI MS spectra were recorded using an Agilent 1100 instrument. Melting points are uncorrected. Solvents were dried before use according to standard methods. All reactions were carried out under an atmosphere of argon in oven-dried glassware.

Diethyl Trifluoroacetimidoyl Phosphonate (1a)

An autoclave (50 mL) was filled with diethyl phosphite (14 g, 0.101 mol), Et$_3$N (1 mL, 0.007 mol) and trifluoroacetonitrile (10 g, 0.105 mol) and the mixture was allowed to react at r.t. for 3 d. $^{31}$P and $^{19}$F NMR spectra of the reaction mixture showed the quantitative formation of 1a and the solution was subsequently used without further purification. An analytical sample was obtained after distillation.

Yield: 20.3 g (87%); colorless liquid; bp 51–53 °C/0.03 mmHg. IR (CCl$_4$): 1060 (POCl), 1270 (P=O), 1700 (C=N), 3200, 3240 (NH) cm$^{-1}$.

(Z)-1a

$^1$H NMR (CDCl$_3$): $\delta = 1.39$ (t, $J_{H,F} = 7.2$ Hz, 6 H, CH$_3$), 4.15–4.32 (m, 4 H, CH$_2$), 12.47 (dd, $J_{H,P} = 37.2$ Hz, $J_{F,H} = 1.2$ Hz, 1 H, NH). $^1$F NMR (CDCl$_3$): $\delta = 69.7$ (dd, $J_{F,H} = 1.9$ Hz, $J_{H,F} = 1.2$ Hz). $^{31}$P NMR (CDCl$_3$): $\delta = -1.4$ (m, $J_{P,F} = 37.2$ Hz, $J_{F,P} = 1.9$ Hz).

$^1$C NMR (CDCl$_3$): $\delta = 15.9$ (d, $J_{C,F} = 5$ Hz, CH$_3$), 64.3 (d, $J_{C,F} = 6.3$ Hz, CH$_2$), 119.1 (dq, $J_{C,F} = 279$ Hz, $J_{F,C} = 44$ Hz, CF$_3$), 166.8 (dq, $J_{C,F} = 163.5$ Hz, $J_{F,C} = 36.5$ Hz, C=O).

(£)-1a

$^1$H NMR (CDCl$_3$): $\delta = 1.40$ (t, $J_{H,F} = 7.2$ Hz, 6 H, CH$_3$), 4.15–4.32 (m, 4 H, CH$_2$), 12.01 (dd, $J_{H,P} = 58.2$ Hz, $J_{F,H} = 0.6$ Hz, 1 H, NH). $^1$F NMR (CDCl$_3$): $\delta = -72.4$ (dd, $J_{F,H} = 1.5$ Hz, $J_{H,F} = 0.6$ Hz).
The solvent was evaporated to leave analytically pure oily adducts 5.

5a

Yield: 0.267 g (100%).

1H NMR (CDCl3): δ = 1.36 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 2.41 (br s, 1 H, NH), 3.47 (s, 3 H, CH2O), 4.19–4.31 (m, 4 H, CH2).

19F NMR (CDCl3): δ = -76.7.

13P NMR (CDCl3): δ = 11.9.


5b

Yield: 0.279 g (100%).

1H NMR (CDCl3): δ = 1.25 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 1.36 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 1.37 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 2.46 (br s, 2 H, NH2), 3.71 (m, 1 H, CH3), 3.84 (m, 1 H, CH3), 4.19–4.32 (m, 4 H, CH2).

19F NMR (CDCl3): δ = -77.9.

13P NMR (CDCl3): δ = 12.7.


Compound 5c

A mixture of 2-hydroxymethylpyridine (0.094 g, 0.86 mmol) and imidoyl phosphonate (1a; 0.2 g, 0.86 mmol) was allowed to react at r.t. for 10 h, to produce the oily adduct 5c.

Yield: 0.294 g (100%).

IR (nujol): 1060 (POCl), 1270 (P=O), 3300 (NH2) cm⁻¹.

1H NMR (CDCl3): δ = 1.35 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 1.36 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 2.98 (br s, 2 H, NH2), 4.18–4.32 (m, 4 H, CH2), 4.91 (d, J_{H-H} = 13.8 Hz, 1 H, CH3CH2Py), 4.98 (d, J_{H-H} = 13.8 Hz, 1 H, CH3CH2Py), 7.21 (dd, J_{H-H} = 5.1 Hz, 7.8 Hz, 1 H, Py), 7.51 (d, J_{H-H} = 5.1 Hz, 1 H, Py), 7.72 (t, J_{H-H} = 7.8 Hz, 1 H, Py), 8.54 (d, J_{H-H} = 5.1 Hz, 1 H, Py).

19F NMR (CDCl3): δ = -78.0.

13P NMR (CDCl3): δ = 11.9.

Anal. Calcd for C8H15F3NO3P: C, 42.11; H, 5.30; N, 8.18; P, 9.05. Found: C, 42.23; H, 5.27; N, 8.14; P, 9.12.

Compound 6

Mercaptoacetic acid (0.11 g, 1.2 mmol) or methyl thioglycolate (0.13 g, 1.2 mmol) were added to a stirred solution of the imidoyl phosphonate (1a; 0.28 g, 1.2 mmol) in benzene (2 mL). After reacting at r.t. for 3 h (R = H) or 3 d (R = Me), the solvent was evaporated under vacuum and the residue was triturated with hexane.

Yield: 84% (R = H) and 80% (R = Me); colorless solid; mp 76–78 °C.

IR (KBr): 1060 (POCl), 1270 (P=O), 3140 (NH) cm⁻¹.

1H NMR (CDCl3): δ = 1.38 (t, J_{H-H} = 7.2 Hz, 3 H, CH3), 3.57 (d, J_{H-H} = 15.3 Hz, 1 H, SCH3H2), 3.71 (dd, J_{H-H} = 15.3 Hz, J_{H-H} = 5.4 Hz, 1 H, SCH3H2), 4.21–4.39 (m, 4 H, CH2O), 8.91 (s, 1 H, NH).

19F NMR (CDCl3): δ = -74.7.

13P NMR (CDCl3): δ = 12.4.

13C NMR (CDCl3): δ = 16.2 (d, J_{C-P} = 5 Hz, CH3), 16.3 (d, J_{C-P} = 5 Hz, CH2), 32.0 (s, CH2O), 64.7 (dq, J_{C-P} = 169.8 Hz, J_{C-P} = 34 Hz, C–P), 65.5 (d, J_{C-P} = 7.5 Hz, CH2O), 65.6 (d, J_{C-P} = 7.5 Hz, CH2O), 123.9 (qd, J_{C-P} = 283 Hz, J_{C-P} = 18.9 Hz, CF2), 174.7 (d, J_{C-P} = 7.5 Hz, CF2).
MS (APCI): m/z (%) = 306 (100%) [M – 1].

Anal. Calcd for C11H15Cl3F3N2O5P: C, 29.39; H, 3.36; Cl, 23.66; N, 6.23; P, 6.89. Found: C, 29.48; H, 3.39; Cl, 23.79; N, 6.31; P, 7.02.

Compounds 7a and 7b: General Procedure
Trichloroacetyl isocyanate (0.19g, 1 mmol) was added to imidoyl phosphonate (1 mmol). After reacting for 3 h at r.t. the oily residue was crystallized from hexane.

7a
Yield: 0.41 g (98%); colorless solid; mp 65–66 ºC (hexane).
IR (nujol): 1060 (POC), 1270 (P=O), 1740 (C=N, C=O), 3260 (NH)
1H NMR (CDCl3): δ = 1.39 (t, J_H-H = 7.2 Hz, 6 H, CH3), 4.22–4.32 (m, 4 H, CH2), 9.00 (s, 1 H, NH).
19F NMR (CDCl3): δ = –70.1.
31P NMR (CDCl3): δ = 0.97 (t, J_H-H = 7.2 Hz, 6 H, CH3), 1.76 (sext, J_H-H = 7.2 Hz, 4 H, CH2), 4.09–4.27 (m, 4 H, CH2O), 9.12 (s, 1 H, NH).

7b
Yield: 0.44 g (96%); colorless solid; mp 64–65 ºC (hexane).
IR (nujol): 1060 (POC), 1275 (P=O), 1740 (C=O), 3270 (NH)
1H NMR (CDCl3): δ = 0.97 (t, J_H-H = 7.2 Hz, 6 H, CH3), 1.76 (sext, J_H-H = 7.2 Hz, 4 H, CH2), 4.09–4.27 (m, 4 H, CH2O), 9.12 (s, 1 H, NH).
19F NMR (CDCl3): δ = –70.1.
31P NMR (CDCl3): δ = –3.5.

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