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SHORT COMMUNICATION

Fluorinated NH-iminophosphonates in synthesis of biorelevant *α*-aminophosphonic acids derivatives

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Abstract: Reactions of (poly)fluoroalkylated NH-iminophosphonates with nitromethane, trimethylsilylcyanide, and diphenylphosphine oxide lead to respective fluorinated *β*-nitro-*α*-aminophosphonates, *α*-cyano-*α*-aminophosphonates, and heminal bisphosphonates. Reaction with 3-aminocrotonitrile **5** proceeds at the *β*-position of enamine. In the case of *α*-imino chlorodifluoroethylphosphonate **1c** the reaction is accompanied by an unusual nucleophilic substitution of the chlorine atom in CF_2Cl group with the formation of pyrroline bearing a difluoromethylated aminophosphonate moiety.

Keywords: iminophosphonates; aza-Henry reaction; cyanation; enamines; fluoroalkyl.

Introduction

α-Aminophosphonic acids are phosphorus analogs of *α*-amino acids in which the planar carboxylic group is replaced with a tetrahedral phosphonate moiety and because of this they can serve as surrogates of α-amino acids in peptides, modifying their properties [1]. They reveal a wide spectrum of biological activity and have numerous applications in medicinal and pharmaceutical sciences as haptens of catalytic antibodies, enzyme inhibitors, antibacterial agents as well as agrochemicals [1-6]. Of particular importance are fluorinated aminophosphonic acid derivatives. They are expected to be resistant to metabolic degradation. In addition, the presence of fluorine could improve the lipophilicity and pharmacokinetic profile [7]. Incorporation of the fluorinated group in organic molecules became almost a standard tool in the design and lead optimization of drug candidates in medicinal chemistry.

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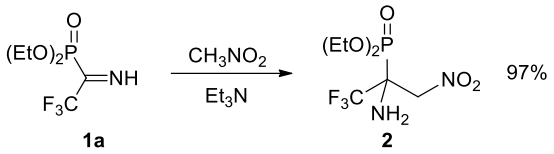
However, synthetic approaches to fluorinated aminophosphonic derivatives are few in number and of limited applicability. Most of the reported methods for preparation of aminophosphonates are based on the addition of phosphites to non-phosphorylated imines as the key step (Pudovik reaction or Kabachnik-Fields reaction). Despite seeming simplicity, these methods have some drawbacks such as purification of final compounds, and low reactivity, and are of limited utility for the preparation of fluoroalkyl substituted aminophosphonates. We have developed an alternative general approach based on the use iminophosphonates as starting compounds for construction of various functionalized aminophosponates [8, 9]. The fluorinated imidoylphosphonates with a free N-H group seem especially promising for this purpose due to enhanced reactivity and the possibility to prepare directly aminophosphonate with the unprotected amino group. Recently we have developed convenient synthetic methods for the fluorinated NH-iminophosphoante and demonstrated their potential as novel promising building blocks for the construction of acyclic and heterocyclic fluoroalkylated aminophosphonic acid derivatives [10, 11]. Of particular interest is the possibility to prepare in this way quaternary aminophosphonates as they are promising compounds for the construction of novel peptide sequences with tailor-made improved properties [6]. In the present work, we describe the synthesis of fluoroalkylated quaternary aminophosphonates based on reactions of fluoroalkylated iminophosphonates with some C-centered nucleophiles.

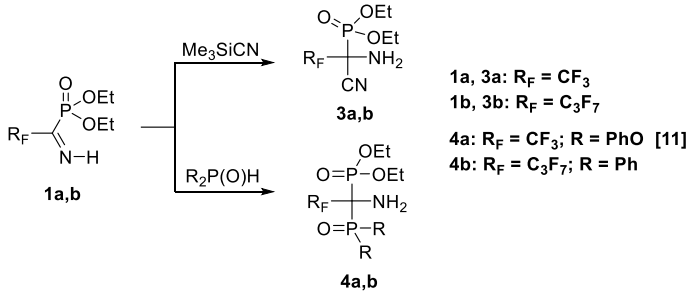
Results and Discussion

Reactions of imines with nitromethane is a powerful tool for the preparation of *β*-nitroamines and respective diamines. Recently, the Palacios group reported the enantioselective nucleophilic addition of nitromethane to C-arylated tosyliminophosphonates, catalyzed by cinchona alkaloids derived thioureas, affording non-racemic *β*-nitro-*α*-aminophosphonates [12]. Fluoroalkylated iminophosphonates were never utilized in the aza-Henry reaction. It is worth noting here that according to the publication [13] fluorinated aldimines exhibit a specific behavior in the aza-Henry reaction: in contrast to their non-fluorinated analogs, they do not react with nitromethane in the presence of organic or inorganic bases. It was concluded that the addition of nitroalkanes to the C=N bond of trifluoromethylaldimines occurs only upon catalysis by Lewis acids [14]. We have found that trifluoromethylated NH-iminophosphonate **1a** in the presence of triethylamine reacts with nitromethane at room temperature to afford *β*-nitro-*α*-aminotrifluoroethylphosphonate **2** in almost quantitative yield (Scheme 1).



Scheme 1. Synthesis of *β*-nitro-*α*-aminophosphonate.

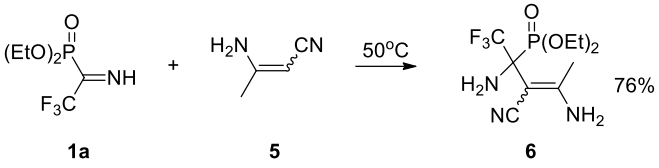
Next, we studied cyanation of polyfluoroalkylated NH-iminophosphonates **1a,b** with TMSCN. Addition of cyanides to C=N bond is widely used for the synthesis of α-aminonitriles, precursors of α-amino acids. We have found that iminophosphonates **1a,b** react with the commercially accessible trimethylsilyl cyanide in the presence of 10 mol.% triethylamine with the formation of *α*-amino-*α*-cyanopolyfluoroalkylphosphonates **3a,b** in high yields (Scheme 2).



Scheme 2. Addition of TMSCN and hydrophosphoryl compounds to the C=N bond of iminophosphonates.

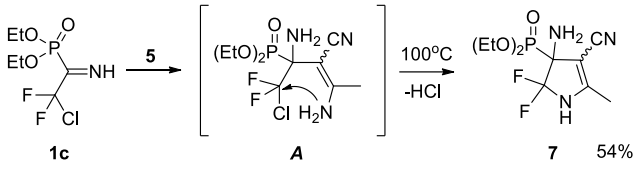
It is worth noting that C-arylated tosyliminophosphonates do not react with TMSCN in the presence of triethylamine and other various basic catalysts [15]. Effective enantioselective cyanation of C-arylated tosyiminophosphonates has only been achieved using MeCOCN, as cyanatimg agent, and Cinchona alkaloids, as chiral catalysts [15]. Thus, enhanced reactivity of fluorinated NH-iminophosphonates clearly reveals itself in cyanation reaction with TMSCN. Even without bases, NH-iminophosphonates **1a,b** at room temperature react with hydrophosphoryl compounds to afford fluorinated heminal diphosphorylated derivatives **4**. Compounds of such type are known to reveal a wide spectrum of biological activity.

α-Methyl-substituted push-pull enamines are other types of polyfunctional nucleophilic agents that are known to react with the involvement of nitrogen atom, *β*- or *β′*-position of enamine [16-18]. In particular, reactions with imines can lead to completely different products depending on the substituents at the C=N bond. Thus, the regioselectivity of the reactions of such enamines with NH-iminophopshonates remained unclear. We have found that NH-iminophosphonate **1a** reacts with enamine **5** with the involvement of only *β*-position of enamine to afford highly functionalized aminophosphonate **6** bearing an enamine moiety capable of further functionalization (Scheme 3). It should be noted that analogs of enamine **5** containing an alkoxycarbonyl substituent instead of a nitrile group react with iminopyruvates by a completely different scheme, involving the α-methyl group of enamine [17].



Scheme 3. Synthesis of enamine-derived aminophosphonate.

Reaction of enamine **5** with chlorodifluoromethylated analog **1c** does not stop at the formation of enamine *A*. The latter undergoes intramolecular condensation affording highly functionalized pyrroline **7** (Scheme 4). Rather unusual nucleophilic substitution of chlorine atom in CF_2Cl group is associated with the advantage of five-member ring formation and is promising for the construction of compounds combining in their structure biorelevant aminophosphonic fragment, difluoromethyl group, and pyrroline moiety in a single molecular platform.



Scheme 4. Synthesis of pyrroline-derived aminophosphonate.

Conclusions

(Poly)fluoroalkylated NH-iminophosphonates are convenient low-molecular starting compounds for the creation of substances incorporating biorelevant fluorinated aminophosphonic moiety. High reactivity of the compounds ensures C-C bond formation in reactions with nitromethane, trimethylsilylcyanide, and push-pull enamines providing easy access to highly functionalized tetrasubstituted aminophosphonates. The presence of an unprotected imine nitrogen atom in the iminophosphontes **1a-c** allows the direct synthesis of N-unprotected aminophosphonates.

Experimental section

NMR spectra were recorded with a Bruker Avance DRX 500 spectrometer with operating frequency 500 (^{1}H), 202 (^{31}P), 126 MHz (^{13}C), a Varian Unity Plus 400 instrument with operating frequency 400.4 MHz (^{1}H), and a Gemini 200 Varian spectrometer with operating frequency 80.95 MHz (^{31}P). Chemical shifts are reported relative to internal TMS (^{1}H, ^{13}C) and external 85%-H_3PO_4 (^{31}P) standards. The solvents were dried according to the standard procedures.

*(O,O)-Diethyl-1-amino-2,2,2-trifuoroethyl-1-(nitromethyl)-ethylphosphonate (**2**).*

A solution of triethylamine (130 mg, 0.18 mL, 1.29 mmol) and imine **1a** in nitromethane (1 mL) was left at room temperature overnight. The mixture was evaporated, washed with hexane and dried. Yellow oil. Yield: 370 mg, 97%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.90 (dd, $^2J_{H\text{-}H}$ 12.6, $^3J_{H\text{-}P}$ 8.1 Hz, 1H, CH_2NO$_2$), 4.78 (dd, $^2J_{H\text{-}H}$ 12.6, $^3J_{H\text{-}P}$ 6.6 Hz, 1H, CH_2NO$_2$), 4.23-4.33 (m, 4H, 2×CH_2O), 2.52 (br d, $^3J_{H\text{-}P}$ 15.6 Hz, 2H, NH_2), 1.38 (t, $^3J_{H\text{-}H}$ 7.1 Hz, 6H, 2×CH_3), ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 123.6 (qd, $^1J_{C\text{-}F}$ 285.9, $^2J_{C\text{-}P}$ 4.9 Hz, CF$_3$), 75.1 (s, CH$_2$), 64.9 (d, $^2J_{C\text{-}P}$ 7.1 Hz, CH$_2$O), 64.2 (d, $^2J_{C\text{-}P}$ 7.1 Hz, CH$_2$O), 59.8 (dq, $^1J_{C\text{-}P}$ 153.7, $^2J_{C\text{-}F}$ 28.9 Hz, CP), 15.61 (d, $^3J_{C\text{-}P}$ 5.9 Hz, CH$_3$), 15.55 (d, $^3J_{C\text{-}P}$ 5.9 Hz, CH$_3$), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -73.0 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 13.6 ppm; IR (neat) ν_{max}: 3430 (NH$_2$), 3340, 1575 (NO$_2$), 1270 (P=O), 1060 (POC), cm^{-1}; Calcd. For $C_7H_{14}F_3N_2O_5P$ (294.2): C 28.58; H 4.80; N 9.52; P 10.53. Found: C 28.54; H 4.80; N 9.50; P 10.50.

*General procedure for compounds **3a,b**.*

A mixture of imine **1a** or **1b** (0.64 mmol), trimethylsylilcyanide (190 mg, 0.24 mL, 1.92 mmol) and triethylamine (6.5 mg, 0.0089 mL, 0.064 mmol) in CH_3CN (1 mL) was refluxed for 3 hrs. After then 1 drop of methanol was added, the mixture was evaporated, washed with hexane and dried.

*(O,O)-Diethyl-1-amino-1-cyano-2,2,2-trifuoroethylphosphonate (**3a**).*

Brown oil. Yield: 160 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.31-4.47 (m, 4H, 2×CH_2O), 2.44 (br s, 2H, NH_2), 1.44 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), 1.42 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 121.6 (q, $^1J_{C\text{-}F}$ 285.0 Hz, CF$_3$), 113.5 (d, $^2J_{C\text{-}P}$ 7.2 Hz, CN), 66.2 (d, $^2J_{C\text{-}P}$ 7.4 Hz, CH$_2$O), 65.9 (d, $^2J_{C\text{-}P}$ 7.4 Hz, CH$_2$O), 56.1 (dq, $^1J_{C\text{-}P}$ 151.5, $^2J_{C\text{-}F}$ 33.3 Hz, CP), 15.8 (d, $^3J_{C\text{-}P}$ 5.9 Hz, CH$_3$), 15.7 (d, $^3J_{C\text{-}P}$ 5.9 Hz, CH$_3$), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -73.9 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 7.6 ppm; Calcd. For $C_7H_{12}F_3N_2O_3P$ (260.2): C 32.32; H 4.65; N 10.77; P 11.91. Found: C 32.29; H 4.64; N 10.74; P 11.92.

*(O,O)-Diethyl-1-amino-1-cyano-2,2,3,3,4,4,4-heptafluorobutylphosphonate (**3b**).*

Brown oil. Yield: 220 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.30-4.47 (m, 4H, 2×CH_2O), 2.40 (br s, 2H, NH_2), 1.42 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), 1.37 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -124.3 (m, J 290.1, 15.4 Hz, 1F, CF_2), -121.2 (m, J 290.1, 15.4 Hz, 1F, CF_2), -116.6 (m, ^2J 279.4 Hz, 1F, CF_2), -111.3 (m, ^2J 279.4 Hz, 1F, CF_2), -81.2 (m, 3F, CF_3), ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 8.3 ppm; IR (neat) ν_{max}: 1060 (POC), 1250 (P=O), 2200 (C≡N), 3220, 3340 (NH$_2$) cm^{-1}; Calcd. For $C_9H_{12}F_7N_2O_3P$ (360.2): 30.01; H 3.36; N 7.78; P 8.60. Found: C 29.95; H 3.33; N 7.80; P 8.60.

*(O,O)-Diethyl-1-amino-1-(diphenylphosphinoyl)-2,2,3,3,4,4,4-heptafluorobutylphosphonate (**4b**).*

A mixture of imine **1b** (100 mg, 0.31 mmol) and diphenylphosphine oxide (60 mg, 0.31 mmol) in Et_2O (2 mL) was left at room temperature overnight. The mixture was evaporated, the residue was triturated with hexane and dried. White crystals. Yield: 130 mg, 81%; mp 119-121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.35 (dd, $^3J_{H\text{-}H}$ 8.1, $^3J_{H\text{-}P}$ 10.5 Hz, 2H, H_{Ph}), 8.03 (dd, $^3J_{H\text{-}H}$ 8.1, $^3J_{H\text{-}P}$ 10.5 Hz, 2H, H_{Ph}), 7.46-7.54 (m, 6H, H_{Ph}), 4.17-4.29 (m, 1H, CH_2O), 3.95-4.09 (m, 1H, CH_2O), 3.77-3.90 (m, 1H, CH_2O), 3.55-3.69 (m, 1H, CH_2O), 2.72 (br s, 2H, NH_2), 1.26 (t, $^3J_{H\text{-}H}$ 7.1 Hz, 3H, CH_3), 1.04 (t, $^3J_{H\text{-}H}$ 7.1 Hz, 3H, CH_3), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -123.2 (m, $^2J_{F\text{-}F}$ 284.5 Hz, 1F, CF_2), -120.5 (m, $^2J_{F\text{-}F}$ 284.5 Hz, 1F, CF_2), -104.0 (m, $^2J_{F\text{-}F}$ 296.0 Hz, 1F, CF_2), -102.2 (m, $^2J_{F\text{-}F}$ 296.0 Hz, 1F, CF_2), -81.0 (m, 3F, CF_3), ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 30.6 (m, 1P, PPh), 13.9 (m, 1P, POEt), ppm; IR (KBr) ν_{max}: 3420 (NH$_2$), 1270 (P=O), 1220, 1065 (POC), cm^{-1}; Calcd. For $C_{20}H_{22}F_7NO_4P_2$ (535.3): C 44.87; H 4.14; N 2.62; P 11.57. Found: C 44.78; H 4.13; N 2.63; P 11.55.

*(O,O)-Diethyl-3-diamino-2-cyano-1-(trifluoromethyl)-but-2-en-1-yl]phosphonate (**6**).*

A mixture of imine **1a** (0.51 g, 2.2 mmol) and enamine **5** (0.18 g, 2.2 mmol) was heated at 50 ºC for 5 hrs. The product was purified by preparative TLC (EtOAc/MeOH 20:1) Rf 0.6. White crystals. Yield: 0.52 g, 76%; mp 104-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.18-4.33 (m, 4H, 2×CH_2O), 2.22 (s, 3H, =CCH_3), 2.12 (br, 2H, NH_2), 2.10 (br d, $^3J_{H\text{-}P}$ 15.3 Hz, 2H, NH_2), 1.39 (t, $^3J_{H\text{-}H}$ 6.9 Hz, 3H, CH_3), 1.37 (t, $^3J_{H\text{-}H}$ 6.9 Hz, 3H, CH_3), ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.2 (d, $^3J_{C\text{-}P}$ 5.2 Hz, =CNH$_2$), 124.8 (qd, $^1J_{C\text{-}F}$ 286.1, $^2J_{C\text{-}P}$ 13.1 Hz, CF$_3$), 120.4 (d, $^3J_{C\text{-}P}$ 4.9 Hz, CN), 67.6 (m, =CCN), 64.2 (d, $^2J_{C\text{-}P}$ 7.2 Hz, CH$_2$O), 64.0 (d, $^2J_{C\text{-}P}$ 7.2 Hz, CH$_2$O), 60.3 (dq, $^1J_{C\text{-}P}$ 156.8, $^2J_{C\text{-}F}$ 29.1 Hz, CP), 23.1 (d, $^4J_{C\text{-}P}$ 1.0 Hz, =CCH$_3$), 16.0 (d, $^3J_{C\text{-}P}$ 5.2 Hz, CH$_3$), 15.9 (d, $^3J_{C\text{-}P}$ 5.2 Hz, CH$_3$), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -73.9 ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.3 ppm; IR (KBr) ν_{max}: 3440 (NH^2), 3340, 2210 (C≡N), 1650 (C=C), 1260 (P=O), 1065 (POC), cm^{-1}. Calcd. For $C_{10}H_{17}F_3N_3O_3P$ (315.2): C 38.10; H 5.44; N 13.33; P 9.83. Found: C 37.98; H 5.42; N 13.36; P 9.81.

(O, O)-Diethyl- (3-amino-4-cyano-2,2-difluoro-5-methyl-2,3-dyhydro-1H-pyrrol-3-yl)phosphonate (7).

A mixture of imine **1c** (250 mg, 1 mmol) and enamine **5** (70 mg, 0.9 mmol) was heated at 100 ºC for 3 hrs. The mixture was triturated with Et_2O. Brown powder. Yield: 160 mg, 54%; mp 109-112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.18-4.34 (m, 4H, 2×CH_2O), 2.25 (s, 3H, CH_3), 2.20 (br d, $^3J_{H\text{-}P}$ 17.7 Hz, 2H, NH_2), 1.39 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), 1.36 (t, $^3J_{H\text{-}H}$ 7.2 Hz, 3H, CH_3), ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ: -56.9 (m, $^2J_{F\text{-}F}$ 159.9, 1*F*), -55.8 (m, $^2J_{F\text{-}F}$ 159.9 Hz, 1*F*), ppm; ^{31}P NMR (81 MHz, $CDCl_3$) δ: 16.6 ppm; IR (KBr) ν_{max}: 3450 (NH_2), 3310 (NH), 2210 (C≡N), 1650 (C=C), 1260 (P=O), 1065 (POC), cm^{-1}; Calcd. For $C_{10}H_{16}F_2N_3O_3P$ (295.2): C 40.68; H 5.46; N 14.23; P 10.49. Found: C 40.60; H 5.44; N 14.25; P 10.47.

Notes

The authors declare no conflict of interest.

References

1. Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and aminophosphinic acids. Chemistry and biological activity*; John Wiley & Sons: New York, NY, USA, 2000.
2. Kafarski, P.; Lejczak, B. Biological activity of aminophosphonic acids. *Phosphorus Sulfur Silicon Relat. Elem*. **1991**, *63*, 193-215.
3. Mucha, A.; Kafarski, P.; Berlicki, L. Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *J. Med. Chem*. **2011**, *54*, 5955-5980.
4. Orsini, F.; Sello, G.; Sisti, M. Aminophosphonic acids and derivatives. Synthesis and biological applications. *Curr. Med. Chem*. **2010**, 17, 264-289.
5. Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. An Overview of stereoselective synthesis of α-aminophosphonic acids and derivatives. *Tetrahedron* **2009**, *65*, 17-49.
6. Ordonez, M.; Sayago, F. J.; Cativiela, C. Synthesis of quaternary α-aminophosphonic acids. *Tetrahedron* **2012**, *68*, 6369-6412.
7. Smart, B. E. Fluorine substituent effects (on bioactivity). *J. Fluor. Chem.* **2001**, *109*, 3-11.
8. Onys'ko, P. P.; Rassukana, Yu. V.; Khomutnyk, Y. Y.; Yelenich, I. P.; Klukovsky, D. V.; Sinitsa, A. D. A new strategy for synthesis of compounds bearing biorelevant α-aminophosphonate functionalities. *Phosphorus Sulfur Silicon Relat. Elem*. **2015**, *190*, 725-728.
9. Rassukana, Y. V.; Onys'ko, P. P.; Kolotylo, M. V.; Sinitsa, A. D.; Lyzwa, P.; Mikolajczyk, M. A new strategy for asymmetric synthesis of aminophosphonic acid derivatives: the first enantioselective catalytic reduction of C-phosphorylated imines. *Tetrahedron Lett*. **2009**, *50*, 288-290.
10. Rassukana, Y. V.; Kolotylo, M. V.; Synytsya, O. A.; Pirozhenko, V. V.; Onys'ko, P. P. α-Iminotrifluoroethylphosphonates: the first representatives of N-H imidoyl phosphonates. *Synthesis* **2007**, *2007*, 2627-2630.
11. Rassukana, Y. V.; Yelenich, I. P.; Synytsya, A. D.; Onys'ko, P. P. Fluorinated NH-iminophosphonates and iminocarboxylates: novel synthons for the preparation of biorelevant α-aminophosphonates and carboxylates. *Tetrahedron* **2014**, *70*, 2928-2937.
12. Vicario, J.; Ortiz, P.; Ezpeleta, J. M.; Palacios, F. Asymmetric synthesis of functionalized tetrasubstituted α-aminophosphonates through enantioselective aza-Henry reaction of phosphorylated ketimines. *J. Org. Chem*. **2015**, 80, 156-164.
13. Fioravanti, S.; Pellacani, L.; Vergari, M. C. Fluorinated β-nitro amines by a selective ZrCl 4-catalyzed aza-Henry reaction of (E)-trifluoromethyl aldimines. *Org. Biomol. Chem*. **2012**, *10*, 8207-8210.
14. Pelagali, A.; Pellacani, L.; Fioravanti, S. In pursuit of β-amino-α-nitro-β-(trifluoromethyl) ketones: nitro-Mannich versus Mannich-type reactions. *Eur. J. Org. Chem.* **2017**, *2017*, 3373-3380.
15. Vicario, J.; Ezpeleta, J. M.; Palacios, F. Asymmetric cyanation of α-ketiminophosphonates catalyzed by cinchona alkaloids: enantioselective synthesis of tetrasubstituted α-aminophosphonic acid derivatives from trisubstituted α-aminophosphonates. *Adv. Synth. Catal*. **2012**, *354*, 2641-2647.
16. Onys'ko P. P.; Zamulko K. O.; Kyselyova O. I.; Shalimov O. O.; Rusanov E. B. Synthesis of α-CF_3-and α-CCl_3 substituted nitrogen heterocycles by aza-Diels-Alder and cyclocondensation reactions. *Tetrahedron* **2017**, *73*, 3513-3520.
17. Onys'ko P. P.; Khomutnyk Y. Y.; Kim T. V.; Kyselyova O. I.; Rassukana Yu. V.; Brovarets V. S.; Synytsya A. D. Novel synthetic approach for N-acyl imines of trichloropyruvate. *Synthesis* **2011**, *2011*, 65-68.
18. Sibgatulin D. A.; Volochnyuk D. M.; Rusanov E. B.; Kostyuk A. N. Aminoalkylation of 'push-pull' enamines having a methyl group at the α-position with imines of methyl 3,3,3-trifluoropyruvate. *Synthesis* **2006**, *2006*, 1625-1630.

Флуоровані NH-імінофосфонати в синтезі біологічно важливих похідних *α*-амінофосфонових кислот

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Резюме: Реакції (полі)флуороалкільованих NH-імінофосфонатів із нітрометаном, триметилсилілціанідом, та дифенілфосфіноксидом призводять до відповідних флуорованих *β*-нітро-*α*-амінофосфонатів, *α*-ціано-*α*-амінофосфонатів, та гемінальних бісфосфонатів. Взаємодія із 3-аміно-кротононітрилом здійснюється по *β*-положенню єнаміну. У випадку *α*-іміно хлородифлуороетилфосфонату **1c** реакція супроводжується незвичним нуклеофільним заміщенням атома хлору CF_2Cl групи з утворенням піроліну, що містить дифлуорометильований амінофосфонатний залишок.

Ключові слова: імінофосфонати; реакція аза-Генрі; ціанування; енаміни; флуороалкіл.