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Facile synthesis of cyclic α-perfluoroalkyl-α-aminophosphonates

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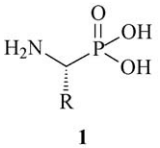
ABSTRACT

Addition of diethylphosphite to cyclic α-perfluoalkyl substituted imines in the presence of boron trifluoride etherate as a catalyst presents an efficient route for racemic saturated cyclic α-perfluoroalkyl-α-aminophosphonates. Hydrolysis of latter compounds gives the corresponding α-aminoalkanephosphonic acids existing as the corresponding zwitterions according IR and X-ray data.

1. Introduction

α-Aminophosphonates and the corresponding α-aminophosphonic acids attract persistent attention during several decades due to the high and diverse biological activity determining their practical applications and the permanent search and investigations of novel structures of such type [1]. Some of them are natural products, such as (R)-phosphotyrosine **1** with R = *p*-$CH_2C_6H_4OH$ which is a key component of two hypotensive tripeptides [2]. Being analogous to amino acids they found applications as antibiotics [2], proteolytic enzyme inhibitors [3], anti-cancer agents [4], and herbicides [5]. α-Aminophosphonates are also of undoubted interest as ligands in homogeneous [6,7] or organic [8,9] catalysis.



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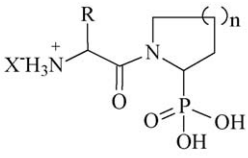

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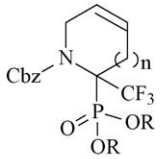

3 (n=1,2)

It is well known that cyclic or heterocyclic rings introduced into the molecular skeleton increase its rigidity and modify electronic effects. Thus many cyclic α-aminophosphonic acids bearing the exocyclic amino group were prepared mostly in racemic series [10–14]. However, among α-aminophosphonates those containing nitrogen as a ring heteroatom are scarce. Nevertheless, a series of dipeptides which contained phosphonate analogs **2** of proline and piperidine-2-carboxylic acid (homoproline) have been reported as potential therapeutic agents to prevent the rejection of transplanted tissues [15].

In this connection it should be mentioned that synthetic routes to cyclic α-aminophosphonates containing the nitrogen as a ring heteroatom, are limited mostly by addition of hydrophosphoryl compounds to triazine derivatives [16–18], lactame alkylation using dialkyl phosphite sodium salts [19] or multistep asymmetric synthesis [20] developed for non-substituted 5- and 6-membered compounds, and some procedures developed for aziridine phosphonates [21–23].

At the same time fluorine introduction in a biomolecule may change the "normal" route of its interaction with a biological target or the direction of binding. That is why fluorine is more and more popular in the construction of new pharmaceutical and biochemical tools. However, in contrast to the rather well developed aminophosphonic and aminophosphinic acids area, only limited representatives of fluorine containing α-aminophosphonates are currently known [24–32]. The compounds with linear scaffold were obtained in few steps starting from fluorinated acetic acid [25], generated *in situ* fluorinated aldehydes [26] or fluorinated *N*-acyl hemiaminals [27] or aluminum iminoderivates obtained in turn by reduction of nitriles with DIBAL [28]. As for cyclic α-CF_3-substituted aminophosphonates, till now only unsaturated compounds, namely analogs of

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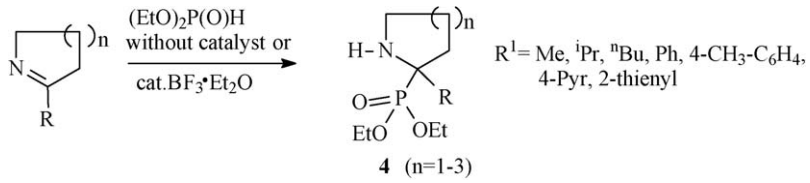


Scheme 1. Synthesis of non-fluorinated α-substituted cyclic α-aminophosphonates.

dehydropipecolinic and tetrahydroazepin-2-carboxylic acids **3** [32], were obtained *via* the ring closing metathesis strategy starting from α-CF_3-substituted α-amino phosphonates with two alkene chains, 1,7-dienes and 1,8-dienes, obtained in turn by nucleophilic addition of dialkyl phosphites to highly electrophilic imines Cbz-N = $C(CF_3)P(O)(OR)_2$ [31].

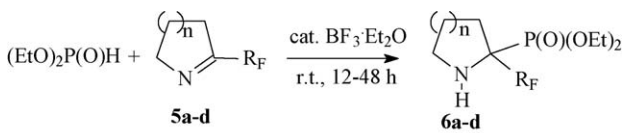
2. Results and discussion

It should be mentioned, that the most convenient approach to build phosphonate P–C–N systems comprises a nucleophilic addition of dialkyl phosphites to the C=N double bond of Schiff bases. Depending on the structure and electrophilicity of a Schiff base, dialkyl phosphites are known to add to the C=N bond under thermal [33], ultrasonic [34] or microwave [35] initiation, in the presence of strong bases [36] or Lewis acids [35,37] to give racemic α-aminophosphonates. Using this strategy, recently we developed the effective synthesis of cyclic α-substituted-α-aminophosphonates **4** with different cyclic size based on the diethylphosphite addition to the C=N double bond of easily available α-substituted cyclic imines (Scheme 1) [38]. The reaction proceeds smoothly in ether or THF as a solvent at room temperature without any catalyst (ca 30 h for R = Alk and 3–5 days for R = Ar, Het), however boron trifluoride etherate (20 mol%) can be advantageously used to accelerate the reaction (reaction time was 12–18 h depending on the starting substrate).

Taking into account our continuous investigations of cyclic imines reactivity [38–43] and having now in hands α-trifluoromethyl- and α-pentafluoroethyl-substituted 3,4-dihydropyrroles and 2,3,4,5-tetrahydropiperidines [42,43], it seems reasonable to apply the similar methodology for the formation of saturated cyclic α-amino-α-perfluoroalkylphosphonates. Although electron-withdrawing properties of fluorinated substituents might inhibit the reactivity of C=N double bond, in the case of success such approach would provide easy access to previously unknown fluorinated cyclic aminophosphonates with saturated structure.

Indeed, in contrast to the addition of cyclic imines bearing either alkyl or aryl substituent at the carbon atom of C=N double bond, the addition of diethyl phosphite to perfluoralkyl-substituted cyclic imines **5** did not proceed in the absence of a catalyst. However, when boron trifluoride etherate was used as a catalyst (20 mol%) the reaction proceeded smoothly to give the desired fluorinated aminophosphonates as only reaction products (Scheme 2). Moreover, under catalysis the fluorinated compounds **6a–d** were obtained even in higher yields (>90%) than their non-fluorinated analogues mentioned above.

The formation of 5-membered aminophosphonates **6a** and **6b** proceeds faster comparing with those having the 6-membered



Scheme 2. Synthesis α-perfluoroalkylsubstituted cyclic α-aminophosphonates.

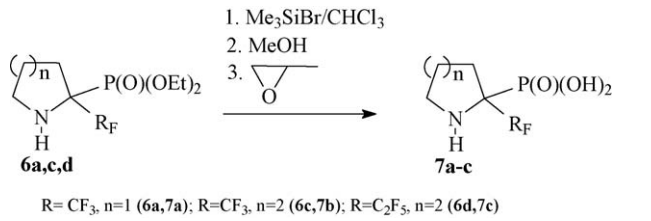
ring. As steric hindrances decrease the reaction rate, compounds **6a** and **6d** bearing trifluoromethyl group are formed more readily that those having the pentafluroethyl moiety. After simple work-up procedure (see experimental) aminophosphonates **6a–c** were isolated in high yields and more than 99% purity (according the NMR data) while **6d** still contained unreacted starting imine and required additional purification by column chromatography. All compounds present colorless viscous liquids and their structures were unambiguously confirmed by NMR and IR spectral data along with elemental analysis data. The scaling up of the reaction does not affect the reaction course.

The fundamental mechanism by which a Lewis acid promotes reaction at an organic functional group is through electrophilic activation [44]. In other words, the binding of electron-deficient catalyst to the nonbonding lone pair of a functional group such as C=N functionality, polarizes the adjacent bonds, activating them toward nucleophilic attack. Moreover, the binding of boron trifluoride with the oxygen atom of the hydroxyl group in nucleophilic three-coordinate phosphorus tautomeric form of diethyl phosphite may also contribute to increased reaction rate.

As mentioned above, the developed procedure opens easy access to racemic α-perfluoroalkylsubstituted cyclic α-aminophosphonates. At the same time, asymmetric Brønsted acids are known to be powerful organocatalysts for asymmetric nucleophilic addition reactions to achiral imines due to hydrogen bonding of acidic protons with the nitrogen atom of imine moiety and preventing access to a single prochiral substrate face [45]. Application of this approach for hydrophosphonylation reaction resulted in highly enantiomerically enriched linear α-aminophosphonates using chiral thiourea derivatives [46] and binaphthylphosphoric acids [47] as catalysts. Guided by these results, we estimated the possibility of asymmetric hydrophosphonylation of cyclic imines **5** using the most active imine **5a** as a representative example.

However, due to poor reactivity of fluorinated imine the reaction was very sluggish in the presence of unsubstituted (R)-binaphthylphosphoric acid derived from (R)-BINOL (20 mol%) instead of $BF_3{\cdot}Et_2O$ and completed over approximately 1 month. The desired aminophosphonate **6a** was isolated in 92% yield but in low enatiomeric excess of 11%. Despite the slow reaction rate and poor enantioselectivity achieved under such conditions, these results highlighted the strategy of detailed search of optimized conditions and catalyst among chiral Brønsted acids for the synthesis of individual enantiomers of such compounds being of undoubted interest for further biochemical study.

Finally, in spite of the presence of strong electron-withdrawing perfluorinated substituent, aminophosphonates **6** can be converted to the corresponding α-amino phosphonic acids *via* the reaction with trimethylbromosilane in chloroform followed by treatment with aq.MeOH of the intermediate trimethylsilyl ester formed. At that, the reaction time was more prolonged in comparison with the similar reaction in non-fluorinated series. As the cyclic phosphonic aminoacids easily undergo quaternization by HBr formed in result of the hydrolysis of Me_3SiBr, they are obtained as the corresponding hydrobromides while further treatment with propylene oxide afforded free aminoacids **7a–c** as illustrated on Scheme 3.



Scheme 3. Synthesis α-perfluoroalkylsubstituted cyclic α-aminophosphonic acids.

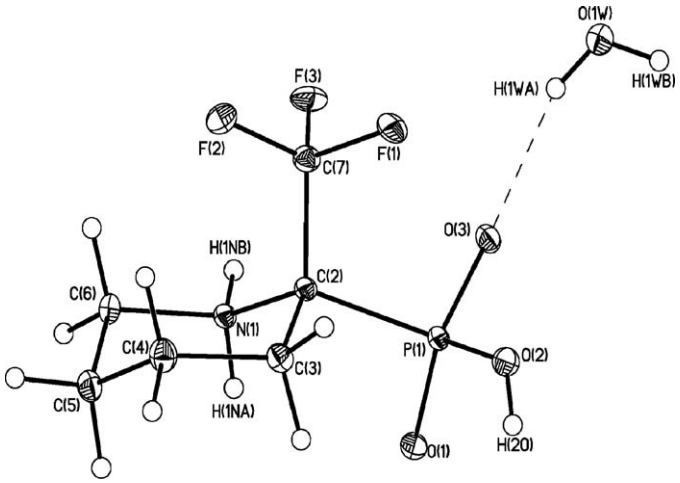


Fig. 1. The general view of **7b** atoms represented by thermal ellipsoids at 50% probability level.

The high-melting points and the presence in the IR spectra of acids **7a–c** of an absorption at 1618–1625 cm^{-1} which are characteristic [48] for ammonium species $>NH_2^+$ allow one to suggest that these compounds exist as the corresponding zwitter ions. Indeed, according to X-ray diffraction analysis performed for trifluoromethyl substituted phosphonous acid **7b**, it crystallizes in zwitterionic form with one solvate water molecule (Fig. 1). In general, the geometry of **7b** is close to the expected one for aminophosphonates, however, we can mention a significant elongation of P(1)–C(2) bond up to 1.887(1) Å due to the presence of CF_3 group. For example, the same bond is only 1.842 Å in 1-amino-1-methylethyl-phosphonic acid [49]. In crystal molecules of **7b** are assembled in layers by a number of O–H. . .O and N–H. . .O bonds with hydrophobic coating formed by CF_3 and methylene groups.

3. Conclusions

In summary, starting from available fluorinated cyclic imines we elaborated a convenient approach to racemic saturated cyclic α-amino-α-perfluoroalkylphosphonates, which along the free phosphonic acids obtained on their base are of undoubted interest as potent biologically active substances.

4. Experimental

4.1. General

NMR spectra were recorded with a Bruker Avance-300 (^1H, 300.13, ^{31}P, 121.49 and ^{13}C, 75.47 MHz) and Avance 400 (^1H, 400.13, ^{31}P, 161.97 and ^{13}C, 100.61 MHz) spectrometers using residual proton signals of deuterated solvent as an internal standard (^1H, ^{13}C), $CFCl_3$ (^{19}F) and H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the JMODECHO mode; the signals for the C atom bearing odd and even numbers of protons have opposite polarities. Melting points are uncorrected. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. IR spectra were recorded in KBr pellets on a Fourier-spectrometer "Magna-IR750" (Nicolet), resolution 2 cm^{-1}, 128 scans. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). The rotation angle was determined on PerkinElmer 341 instrument, cavity 10 cm, wavelength 589 nm. The analytical HPLC of the compound **6a** was performed using Chiralpac AD column 250 mm × 4.6 mm, the mixture hexane/i-PrOH 1000/1 as an eluent at flow rate 0.4 mL/min, 230 nm.

The starting cyclic imines **5a–d** were obtained according to known procedures [42,43]. (R)-binaphthylphosphoric acid was obtained from (R)-BINOL *via* the literature procedure [47]. Other reactants were purchased from Aldrich and used without further purification.

4.2. Diethyl (2-perfluoroalkyl-2-pyrrolidinyl)-phosphonates and diethyl (2-perfluoroalkyl-2-piperidinyl)-phosphonates 6a–d (general procedure).

To a solution of the corresponding cyclic imine **5** (5 mmol) and diethylphosphite (10 mmol) in ca. 2 mL of anhydrous diethyl ether boron trifluoride etherate (1 mmol) was slowly added *via* syringe. The mixture was stirred at room temperature with monitoring of the reaction course *via* the ^{31}P NMR spectra. Dichloromethane (10 mL) was added and the mixture was extracted by diluted hydrochloric acid. The organic layer was discarded, pH of the water phase was adjusted up to 10 with 20% NaOH and this mixture was extracted by CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, dichloromethane was evaporated in vacuum to give the target phosphonates **6a–d**. Compounds **6a–c** had more than 99% purity according the NMR data while compound **6d** was additionally purified by silica gel column chromatography (gradient elution hexane–acetone from 100:1 to 100:10).

4.2.1. Diethyl 2-(trifluoromethyl)-2-pyrrolidinylphosphonate 6a

Yield 94%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 20.47 (q, $^3J_{P-F}$ = 6.2 Hz). ^{19}F NMR (282.40 MHz, $CDCl_3$): δ −73.32 (d, $^3J_{P-F}$ = 6.2 Hz).^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 6H, CH_3, $^3J_{H-H}$ = 7.1 Hz), 1.87 (quintet, 2H, $^3J_{H-H}$ = 6.8 Hz), 2.22 (br.s, 1H, NH), 2.05–2.15 (m, 1H, CH_2), 2.24–2.36 (m, 1H, CH_2) overlapped with 2.22 (br.s, 1H, NH), 3.02–3.12 (m, 2H, NCH_2), 4.10–4.25 (m, 4H, OCH_2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 15.55 (br.s, $\underline{C}H_3CH_2O$), 24.80 (d, C^4, $^3J_{P-C}$ = 4.3 Hz), 29.03 (C^3), 46.70 (d, C^5, $^3J_{P-C}$ = 4.3), 62.41 (d, $POCH_2$, $^2J_{P-C}$ = 7.5 Hz), 62.75 (d, $POCH_2$, $^2J_{P-C}$ = 6.9 Hz), 64.85 (dq, C^2, $^2J_{C-F}$ = 27.9 Hz, $^1J_{P-C}$ = 158.6 Hz), 125.63 (dt, CF_3, $^1J_{C-F}$ = 282.5 Hz, $^2J_{P-C}$ = 17.7 Hz). IR (thin layer) ν, cm^{-1}: 586, 971, 1025 and 1053 (P–O–C), 1165, 1260 (P═O), 2872, 2984 (NH), 3325. Calcd. for $C_9H_{17}F_3NO_3P$: C, 39.28; H, 6.23; F, 20.71; P 11.25. Found: C, 39.36; H, 6.26; F, 20.64; P 11.15.

Enantiomerically enriched 2-pyrrolidinylphosphonate **6a** was obtained *via* the similar procedure excluding usage of (R)-binaphthylphosphoric acid instead of boron trifluoride etherate. Spectral data of this sample coincide with those for racemic compound, $[\alpha]_L^{25} = +0.2$ (c = 1 M, CH_2Cl_2), *ee* 11% as determined by HPLC.

4.2.2. Diethyl 2-(pentafluoroethyl)-2-pyrrolidinylphosphonate 6b

Yield 90%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 20.61 (br). ^{19}F NMR (282.40 MHz, $CDCl_3$): δ −78.45 (s, 3F, CF_3), −115.93 (F_A), −115.68 (F_B) (AB-system, CF_2, $^2J_{FF}$ = 342.6 Hz, $^3J_{P-F(A)} = {}^3J_{P-F(B)}$ = 8.0 Hz). ^1H NMR (400 MHz, $CDCl_3$): δ 1.309 and 1.31 (both t, 6H, CH_3, $^3J_{H-H}$ = 7.0 Hz), 1.80–1.95 (m, 2H, CH_2), 2.20–2.42 (m, 3H,

CH_2 + NH), 3.05–3.15 (m, 2H, NCH_2), 4.10–4.25 (m, 4H, OCH_2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 15.91 (d, $\underline{C}H_3CH_2O$, $^3J_{P-C}$ = 6.5), 15.98 (d, $\underline{C}H_3CH_2O$, $^3J_{P-C}$ = 8.0), 24.85 (C^4), 29.23 (C^3), 47.00 (C^5), 62.80 (d, $POCH_2$, $^2J_{P-C}$ = 7.6 Hz), 63.27 (d, $POCH_2$, $^2J_{P-C}$ = 7.3 Hz), 65.69 (dt, C^2, $^2J_{C-F}$ = 22.9 Hz, $^1J_{P-C}$ = 157.7 Hz), 112.00–127.7 (m, C_2F_5). IR (thin layer) ν, cm^{-1}: 971, 1025 and 1040 (P–O–C), 1115, 1140, 1165, 1194, 1218, 1254 (P=O), 2874, 2936, 2985 (NH), 3334. Calcd. for $C_{10}H_{17}F_5NO_3P$: C, 36.93; H, 5.27; F, 29.21; P 9.52. Found: C, 37.01; H, 5.28; F, 29.15; P 9.48.

4.2.3. Diethyl 2-(trifluoromethyl)-2-piperidinylphosphonate **6c**

Yield 92%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 19.65 (q, $^3J_{P-F}$ = 8.2 Hz). ^{19}F NMR (282.40 MHz, $CDCl_3$): δ −68.50 (d, $^3J_{P-F}$ = 8.20 Hz). ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 and 1.33 (both d, 6H, CH_3, $^3J_{H-H}$ = 7.62 Hz), 1.48–1.68 (m, 2H, CH_2), 1.71–1.81 (m, 2H, CH_2), 1.95–2.10 (m, 2H, CH_2), 2.16 (br.s, 1H, NH), 2.94–3.05 (m, 2H, NCH_2), 4.15–4.25 (m, 4H, OCH_2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 15.34 and 15.42 (both d, $\underline{C}H_3CH_2O$, $^3J_{P-C}$ = 7.4 Hz), 18.47 (d, C^3, $^2J_{P-C}$ = 10.2 Hz), 23.25 (C^4), 23.52 (br.s, C^5), 40.26 (d, C^6, $^3J_{P-C}$ = 12.0), 58.37 (dq, C^2, $^2J_{C-F}$ = 24.9 Hz, $^1J_{P-C}$ = 155.7 Hz), 62.09 (d, $POCH_2$, $^2J_{P-C}$ = 6.9 Hz), 63.05 (d, $POCH_2$, $^2J_{P-C}$ = 6.9 Hz), 125.83 (dt, CF_3, $^1J_{C-F}$ = 289.3 Hz, $^2J_{P-C}$ = 11.8 Hz). IR (thin layer) ν, cm^{-1}: 943, 971, 1025 and 1055 (P–O–C), 1164, 1194, 1235, 1258 (P=O), 2877, 2937, 2980 (NH), 3319. Calcd. for $C_{10}H_{19}F_3NO_3P$: C, 41.53; H, 6.62; F, 19.71; P 10.71. Found: C, 41.36; H, 6.67; F, 19.57; P 10.64.

4.2.4. Diethyl 2-(pentafluoroethyl)-2-piperidinylphosphonate **6d**

Yield 87% (crude, purity 93%), 54% (after column chromatography), oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 20.61 (br). ^{19}F NMR (282.40 MHz, $CDCl_3$): δ −77.41 (s, 3F, CF_3), −111.96 (F_A), −113.02 (F_B) (AB-system, CF_2, $^2J_{FF}$ = 384.0 Hz, $^3J_{P-F(A)}$ = 12.6, $^3J_{P-F(B)}$ = 9.2). ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 and 1.32 (both d, 6H, CH_3, $^3J_{H-H}$ = 7.1 Hz), 1.46–1.55 (m, 2H, CH_2), 1.57–1.68 (m, 1H, CH2), 1.79–1.92 (m, 1H, CH_2), 2.01–2.09 (m, 2H, $^3J_{P-H}$ = 6.2 Hz), 2.10 (br.s, 1H, NH), 2.90–3.05 (m, 2H, NCH_2), 4.12–4.25 (m, 4H, OCH_2). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 15.34 and 15.42 (both d, $\underline{C}H_3CH_2O$, $^3J_{P-C}$ = 7.4 Hz), 18.47 (d, C^3, $^2J_{P-C}$ = 10.2 Hz), 23.59 (br., C^4), 23.81 (br., C^5), 41.00 (d, C^6, $^3J_{P-C}$ = 3.7), 59.67 (dt, C^2, $^2J_{C-F}$ = 20.5 Hz, $^1J_{P-C}$ = 146.7.6 Hz), 62.38 (d, $POCH_2$, $^2J_{P-C}$ = 8.1 Hz), 63.30 (d, $POCH_2$, $^2J_{P-C}$ = 7.3 Hz), 113.51–123.56 (m, C_2F_5). IR (thin layer) ν, cm^{-1}: 617, 969, 1025 and 1052 (P–O–C), 1131, 1145, 1177, 1219, 1250 (P=O), 2877, 2937, 2984 (NH), 3323. Calcd. for $C_{11}H_{19}F_5NO_3P$: C, 38.95; H, 5.65; F, 28.00; P 9.13. Found: C, 38.80; H, 5.82; F, 27.87; P 9.04.

4.3. 2-Perfluoroalkyl-2-pyrrolidinyl- and 2-perfluoroalkyl-2-piperidinyl-phosphonic acids **7a–c** *(general procedure)*

A solution of trimethylsilyl bromide (5 mmol) in 2 mL of $CHCl_3$ was added dropwise to a solution of the corresponding aminophosphonate **6** (2 mmol) in 5 mL of $CHCl_3$. A reaction mixture was allowed to stir at r.t. overnight for **6a** and **c** and for 24 h for **6b**, then solvent was removed under reduced pressure (rotor evaporator) and the residue was dissolved in 5 mL of EtOH. To this solution ca 0.5 mL of propylene oxide were added *via* syringe and the mixture was kept under ambient conditions overnight. The solvent was evaporated to half of the initial volume, Et_2O was added (2 mL) and the precipitated phosphonic acid was filtered off and dried in vacuo.

4.3.1. (2-Trifluoromethyl-2-pyrrolidinyl)phosphonic acid **7a**

Yield 89%, white solid, m.p. 274–275 °C. ^{31}P NMR (161.97 MHz, D_2O): δ. 6.04 (q, $^3J_{P-F}$ = 3.9 Hz). ^1H NMR (400 MHz, D_2O): δ 1.93–2.13 (m, 2H, CH_2), 2.24–2.46 (m, 2H, CH_2), 3.26–3.43 (m, 2H, NCH_2). ^{19}F NMR (282.4 MHz, D_2O): δ −70.29 (d, $^3J_{P-F}$ = 3.9 Hz). IR (KBr) ν, cm^{-1}: 574, 940, 1098, 1118, 1144, 1199, 1215, 1229 (P=O), 1618 (NH_2^+), 2299, 2423, 2678, 2742, 2917, 2979 (NH).Calcd. for $C_5H_9F_3NO_3P$: C, 27.41; H, 4.14; N, 6.39; P, 14.14. Found: C, 27.25; H, 4.14; N, 6.26; P, 13.91.

4.3.2. (2-Trifluoromethyl-2-piperidinyl)phosphonic acid **7b**

Yield 84%, white solid, m.p. 253–254 °C. ^{31}P NMR (161.97 MHz, D_2O): δ. 5.00 (q, $^3J_{P-F}$ = 3.3 Hz). ^1H NMR (400 MHz, D_2O): δ 1.63–1.80 (m, 3H, CH_2), 1.82–1.94 (m, 1H, CH_2), 1.96–2.17 (m, 2H, CH_2), 3.15–3.22 (m, 1H, NCH_2), 3.36–3.42 (m, 1H, NCH_2). ^{19}F NMR (282.40 MHz, D_2O): δ −68.85 (d, $^3J_{P-F}$ = 3.3 Hz). IR (KBr) ν, cm^{-1}: 572, 936, 952, 1059, 1090, 1128, 1163, 1178, 1205, 1250 (P=O), 1625 (NH_2^+), 2443, 2545, 2723, 2954, 2979 (NH). Calcd. for $C_6H_{11}F_3NO_3P$: C, 30.91; H, 4.76; N, 6.01; P, 13.29. Found: C, 30.99; H, 4.85; N, 5.81; P, 12.84.

4.3.3. (2-Pentafluoromethyl-2-piperidinyl)phosphonic acid **7c**

Yield 92%, white solid, m.p. 210–211 °C. ^{31}P NMR (121.49 MHz, D_2O): δ. 4.53 (br.). ^1H NMR (400 MHz, D_2O): δ 1.62–1.86 (m, 2H, CH_2), 1.86–2.10 (m, 1H, CH_2), 2.10–2.33 (m, 3H, CH_2), 3.23–3.34 (m, 1H, NCH_2), 3.54–3.63 (m, 1H, NCH_2). IR (KBr) ν, cm^{-1}: 573, 938, 952, 1050, 1096, 1120, 1156, 1205, 1248 (P=O), 1622 (NH_2^+), 2343, 2540, 2720, 2958, 2976 (NH). Calcd. for $C_6H_{11}F_3NO_3P$: C, 30.91; H, 4.76; N, 6.01; P, 13.29. Found: C, 30.99; H, 4.85; N, 5.81; P, 12.84.

4.4. X-ray crystallography

Single crystal of compound **7b** suitable for X-ray diffraction analysis was obtained by slow evaporation of the acetonitrile/water solution. Crystallographic data for **7b** ($C_6H_{13}F_3NO_4P$, FW = 251.14): crystals are triclinic, space group P-1, at 100 K: a = 6.5082(7) Å, b = 8.1097(9) Å, c = 9.7316(11) Å, α = 108.501(2)°, β = 93.020(2)°, γ = 99.944(2)°, V = 476.58(9) Å^3, Z = 1, d_{calc} = 1.750 g cm^{-3}, λ(Mo Kα) = 3.32 cm^{-1}, F(0 0 0) = 260. The refinement of **7b** using 2534 independent reflections ($2\theta < 58°$, R_{int} = 0.0167) is converged to wR2 = 0.0818, GOF = 1.049 and R1 = 0.0277 (for 2367 observed reflections with $I > 2\sigma(I)$). Further details are available from CCDC 718664.

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