A One-Pot, Three-Step Synthesis of α-Aminophosphonic Acids

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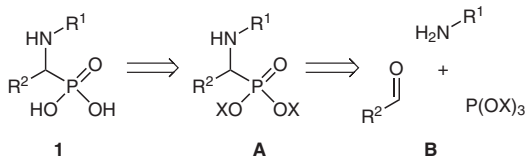
Abstract: A total of 20 α-aminophosphonic acids are synthesized in 73–89% yields via a one-pot, three-step procedure involving chlorotrimethylsilane-promoted condensation of carbonyl compounds and primary amines yielding azomethine intermediates, subsequent reaction with tris(trimethylsilyl) phosphite to give the corresponding trimethylsilylphosphonic esters and finally, mild cleavage with methanol–water. The wide scope and simple set-up and work-up procedures of the reported method allow the synthesis of a diverse set of α-aminophosphonic acids possessing two different functional groups.

Key words: α-aminophosphonic acids, aldehydes, amines, chlorotrimethylsilane, tris(trimethylsilyl) phosphite, one-pot synthesis

α-Aminophosphonic acids **1** (Scheme 1) are analogues of α-amino acids in which the carboxylic group is replaced with a dihydroxyphosphoryl functionality.[1] α-Aminophosphonic acids possess a wide spectrum of biological activity.[2] For example, oligopeptides incorporating an α-aminophosphonic acid group are excellent inhibitors of proteolytic enzymes.[3] Additionally, many derivatives of α-aminophosphonic acids have been shown to possess antibacterial,[4] antiviral[5] and antifungal[6] activities. Some α-aminophosphonic acids, such as glyphosate, glufosinate and bilanafos are environmentally friendly commercial herbicides.[7] In connection with the important applications of the title structures, a range of synthetic pathways to α-aminophosphonic acids has been developed. Previously reported synthetic routes to α-aminophosphonic acids are summarized in Scheme 1.



Scheme 1 A basic retrosynthetic analysis of α-aminophosphonic acids

A few synthetic methodologies have been developed to vary the nature of the R^1 and R^2 groups in order to influence the biological activity of the α-aminophosphonic acids. For example, N-substituted α-aminomethanephosphonic acids were synthesized in one step through a Mannich-type reaction of a primary amine (R^1NH_2), formaldehyde (CH_2O) and phosphonic acid (H_3PO_3).[8] Both the R^1 and R^2 groups can be varied via a two-step approach comprising the synthesis and hydrolysis of α-aminophosphonates **A** (Scheme 1). Compounds **A** were prepared through either a one-pot Kabachnik–Fields reaction[9] of carbonyl compounds, primary amines, and a dialkyl phosphonate [$(AlkO)_2P(O)H$] (Scheme 1), or via hydrophosphonylation of azomethines with a dialkyl phosphonate.[10] A mild Lewis acid catalyzed hydrophosphonylation of azomethines afforded α-aminophosphonates in high yields.[11] Dialkyl α-aminophosphonates of type **A** were prepared in 85–98% yields through a one-pot chlorotrimethylsilane-promoted reaction of aldehydes with primary amines, followed by a lithium perchlorate ($LiClO_4$) activated reaction with a trialkyl phosphite [$P(OAlk)_3$].[12] Compounds **A** were also converted into α-aminophosphonic acids through an acid-catalyzed hydrolysis[13] or, in the case of dibenzylphosphonates, by catalytic hydrogenation.[14] The reaction of α-aminophosphonates with bromotrimethylsilane (Me_3SiBr)[15] or iodotrimethylsilane (Me_3SiI)[16] resulted in the corresponding trimethylsilyl esters, which were then hydrolyzed with methanol–water. To avoid the transesterification step, trimethylsilylphosphonates were obtained directly through an Abramov-type reaction of tris(trimethylsilyl) phosphite [$(Me_3SiO)_3P$] with various electrophilic reagents. For example, the reaction of tris(trimethylsilyl) phosphite with carbonyl compounds followed by mild hydrolysis afforded α-hydroxyphosphonic acids,[17] whereas treatment of acid chlorides or anhydrides with two molar equivalents of tris(trimethylsilyl) phosphite gave the corresponding hydroxymethylene bisphosphonic acids.[18] Trimethylsilyl esters of α-aminophosphonic acids were also synthesized through the reactions of tris(trimethylsilyl) phosphite with aminoacetals[19] and azomethines.[20]

However, the procedures mentioned above cannot be used for the parallel synthesis of α-aminophosphonic acids on account of either a narrow scope, or technical complications with the two-step procedures, such as the isolation

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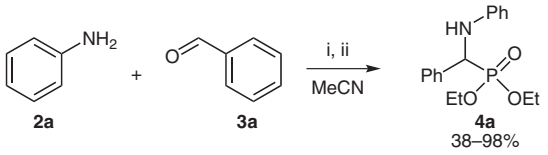
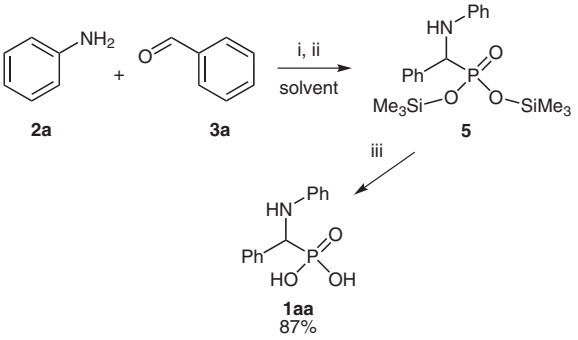
and purification of intermediates. In this contribution, we describe a one-pot, three-step synthesis of α-aminophosphonic acids. The process involves: (1) the chlorotrimethylsilane-promoted generation of azomethines from various aldehydes and amines, (2) reaction with tris(trimethylsilyl) phosphite to give trimethylsilylphosphonate intermediates, and (3) mild hydrolysis to afford the target α-aminophosphonic acids.

We previously reported a chlorotrimethylsilane-promoted combinatorial synthesis of azomethines from various amines and carbonyl compounds.[21] In this connection, our attention was drawn by the aforementioned high-yielding, one-pot preparation of dialkyl α-aminophosphonates via the chlorotrimethylsilane/lithium perchlorate mediated reaction of aldehydes, primary amines, and a trialkyl phosphite.[12] The large excess of lithium perchlorate used in the reported procedure to facilitate the addition of the trialkyl phosphite to the azomethine intermediate complicated the isolation and purification steps. This fact makes the procedure, to a large degree, impractical from the combinatorial synthesis standpoint. In an attempt to optimize the one-pot preparation of α-aminophosphonates, we carried out a series of model experiments in which, as shown in Scheme 2, aniline (**2a**) was reacted with an equimolar amount of benzaldehyde (**3a**) in the presence of different quantities of chlorotrimethylsilane and lithium perchlorate in acetonitrile. After sonication of the solution containing **2a**, **3a**, chlorotrimethylsilane and lithium perchlorate at room temperature for two hours, triethyl phosphite [$P(OEt)_3$] was added and the mixture was sonicated for another two hours. The formation of product **4a** was monitored by ^{31}P NMR spectroscopy of the reaction mixture.



Scheme 2 Preparation of diethyl α-aminophosphonate **4a**. *Reagents and conditions*: (i) Me_3SiCl, $LiClO_4$, r.t.; (ii) $P(OEt)_3$, r.t. See text for details.

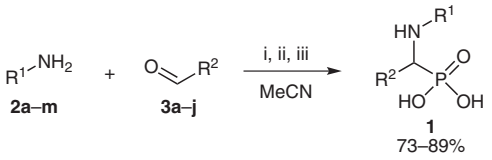
The first experiment in which **2a**, **3a**, chlorotrimethylsilane and lithium perchlorate were mixed in a molar ratio of 1:1:1:10 showed a moderate conversion of 38%. Interestingly, the exclusion of lithium perchlorate in a second experiment, while leaving all the other reagents and conditions unchanged, led to the formation of nearly the same amount of **4a** (42%). This observation seemed to indicate that chlorotrimethylsilane not only promoted the formation of the azomethine intermediate, but also the addition of triethyl phosphite to the latter. Therefore, it was envisaged that addition of a larger amount of chlorotrimethylsilane would lead to an increase in the conversion. Indeed, the use of two and three equivalents of chlorotrimethylsilane (with respect to **2a** or **3a**) afforded compound **4a** in high (81%) and nearly quantitative (98%) conversions, respectively. Consequently, the optimization studies revealed that a 1:1:3 ratio of reactants (**2a**:**3a**:Me_3SiCl) in acetonitrile at room temperature were the best conditions for the synthesis of compound **4a**. Our subsequent attempts at cleavage of the ethyl groups of **4a** in the same reaction pot, by the action of bromotrimethylsilane and varying the reaction temperature were unsuccessful. On the basis of the obtained results and those reported in the literature (see the introductory section), we reasoned that the use of tris(trimethylsilyl) phosphite instead of triethyl phosphite should not influence the yield of the corresponding trimethylsilyl analogue of **4a** (Scheme 2). At the same time, trimethylsilylphosphonates are known to hydrolyze smoothly, thereby simplifying the preparation of the α-aminophosphonic acids in the same reaction pot.



Scheme 3 Preparation of aminophosphonic acid **1aa**. *Reagents and conditions*: (i) Me_3SiCl, r.t.; (ii) $P(OSiMe_3)_3$, r.t.; (iii) $MeOH–H_2O$.

The one-pot, three-step synthesis of α-aminophosphonic acids was optimized using the reaction of aniline (**2a**) and benzaldehyde (**3a**) (Scheme 3) as a model system, by varying the solvent and the quantity of chlorotrimethylsilane. In a series of experiments similar to those carried out with the use of triethyl phosphite (see Scheme 2), it was found that addition of tris(trimethylsilyl) phosphite to the azomethine intermediate proceeded smoothly in the presence of three equivalents of chlorotrimethylsilane (with respect to **2a** or **3a**) in acetonitrile, 1,4-dioxane or THF to give α-aminophosphonate **5** (Scheme 3). Compound **5** was hydrolyzed in situ by simply triturating with methanol–water. It was found that the use of a 1:1:3:1 ratio of reactants [**2a**:**3a**:Me_3SiCl:$P(OSiMe_3)_3$] in anhydrous acetonitrile gave the highest yield of **1aa** (optimized conditions). It is noteworthy that the simultaneous addition of **2a**, **3a**, chlorotrimethylsilane and tris(trimethylsilyl) phosphite under the optimized conditions, followed by triturating the reaction mixture with methanol–water gave an inseparable mixture of **1aa** (70%) and the corresponding α-hydroxyphosphonic acid (30%). It was proved in a separate experiment [by the reaction of **3a** with $P(OSiMe_3)_3$ in the presence of Me_3SiCl)] that the latter compound stemmed from a chlorotrimethylsilane-mediated addition of tris(trimethylsilyl) phosphite to aldehyde **3a**. Therefore, it is important to ensure complete conversion of **2a** and **3a** into the azomethine intermediate prior to the addition of tris(trimethylsilyl) phosphite. The opti-

mization studies showed that a reaction time of two hours was sufficient for complete generation of the azomethine. As shown in Scheme 4, the optimum reaction conditions were applied to primary amines **2a**–**m** (Figure 1) and carbonyl compounds **3a**–**j** (Figure 2) to afford 20 α-aminophosphonic acids **1** in 73–89% yields. Compounds **1** normally precipitated from the reaction mixtures at room temperature. They were purified by filtering and washing with methanol. When precipitates did not form, the reaction mixtures were reduced in volume through partial evaporation of the solvent and crude compounds **1** were triturated with methanol, filtered, and washed with cold methanol. These simple work-up procedures afforded compounds **1** in >95% purity according to the NMR and LC–MS analyses.



Scheme 4 Preparation of aminophosphonic acids **1** using the optimized conditions: (i) Me_3SiCl, r.t., sonication, 2 h; (ii) $P(OSiMe_3)_3$, r.t., sonication, 2 h; (iii) MeOH–H_2O work-up.

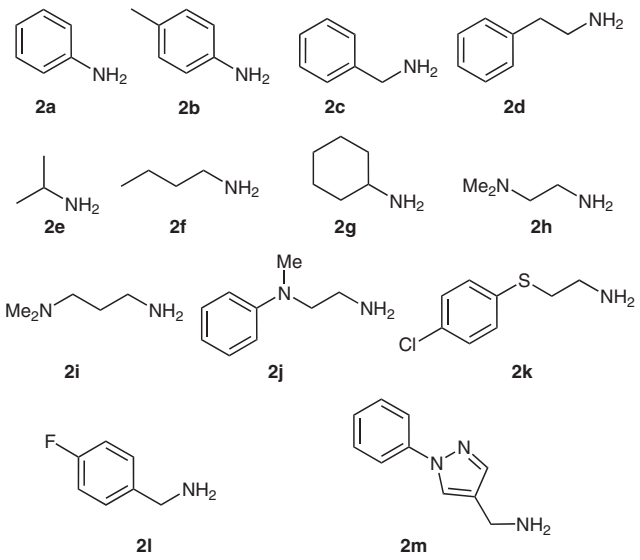


Figure 1 The selection of amines used for the synthesis of α-aminophosphonic acids **1**

The structures and compositions of compounds **1** were confirmed by ^1H, ^{13}C and ^{31}P NMR spectroscopy, LC–MS and elemental analysis. The ^1H NMR spectra of α-aminophosphonic acids **1** derived from aldehydes contained signals for the R^1 and R^2 groups and a pronounced doublet ($^2J_{H,P}$ = 15–25 Hz) at 4.1–5.3 ppm for the methine proton at the α-position relative to the phosphonate group. The ^1H NMR (DMSO-d_6) signals of the protons due to the NH and OH groups of compounds **1** were difficult to observe, presumably on account of their mutual exchange. Interestingly, seven out of the 20 phosphonic acids reported here have been prepared before by other methods, and the reported melting regions for these compounds were often quite different to those obtained here (see the Supporting Information for details). The differences found in the reported and observed melting regions might be due to the different isolation procedures.

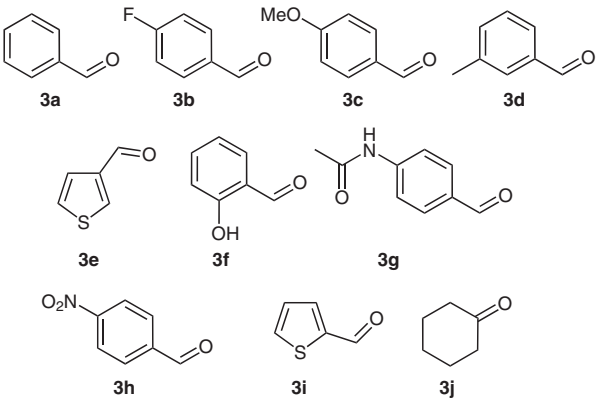


Figure 2 The selection of carbonyl compounds used for the synthesis of α-aminophosphonic acids **1**

In conclusion, the described one-pot, three-step synthetic procedure was validated by preparing 20 structurally diverse α-aminophosphonic acids. The main benefits of the described method are easily available reagents, ambient conditions for all three reaction steps, and simple reaction work-up and product purification. These advantages indicate that the method should be easily adaptable for the parallel synthesis of sizable collections of α-aminophosphonic acids.

Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Merck or Fluka. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) silica gel as the stationary phase. A VWR USC 500 T ultrasonic bath was used for sonication. Melting points were measured on a Buchi melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (500 MHz for ^1H and NOE, 125 MHz for ^{13}C and 202 MHz for ^{31}P), and a Varian Unity Plus 400 spectrometer (400.4 MHz for ^1H), using TMS as the internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (CI) and Agilent 5890 Series II 5972 GC–MS instrument (EI). Elemental analyses were carried out on a Vario MICRO Cube (Elementar) Elemental Micro-Analyzer.

α-Aminophosphonic Acids 1; General Procedure

Me_3SiCl (0.432 g, 4 mmol) was added dropwise to a solution of amine **2** (1 mmol) and carbonyl compound **3** (1 mmol) in anhydrous MeCN (1.5–2 mL), and the resulting mixture was sonicated for 2 h at r.t. $P(OSiMe_3)_3$ (0.328 g, 1.1 mmol) was added dropwise and the mixture was sonicated for another 2 h at r.t. The mixture was diluted with MeOH (5 mL) and H_2O (0.1 mL, 5 mmol). Dilution normally caused precipitation of the product. The precipitated product was filtered and washed with MeOH (1 mL). In cases where no precipitation occurred, the mixture was further sonicated for 2 h and then left to stand for 24 h at 0 °C. Alternatively, the solvents were removed under reduced pressure and the residue was triturated with cold MeOH (2 mL) and filtered.

[Phenyl(phenylamino)methyl]phosphonic Acid (1aa)
Yield: 0.23 g (87%); colorless crystals; mp 115–117 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.67 (d, $^2J_{P,H}$ = 24.2 Hz, 1 H), 6.52 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H), 6.68 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H), 7.02 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H), 7.20 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H), 7.28 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H), 7.47 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 56.7 (d, $^1J_{C,P}$ = 142 Hz), 114.1, 117.3, 127.2, 128.2, 128.7 (d, $^3J_{C,P}$ = 5 Hz), 129.1, 138.7, 147.6 (d, $^2J_{C,P}$ = 14 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 18.6.

MS (APSI): m/z = 262 $[M - 1]^+$.

Anal. Calcd for $C_{13}H_{14}NO_3P$: C, 59.32; H, 5.36; N, 5.32. Found: C, 59.47; H, 5.27; N, 5.42.

[Phenyl(*p*-tolylamino)methyl]phosphonic Acid (1ba)
Yield: 0.22 g (85%); colorless crystals; mp 139–141 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.10 (s, 3 H), 4.63 (d, $^2J_{P,H}$ = 24.5 Hz, 1 H), 6.58 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 6.82 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 7.19 (t, $^3J_{H,H}$ = 7.1 Hz, 1 H), 7.27 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H), 7.45 (d, $^3J_{H,H}$ = 7.1 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.5, 56.9 (d, $^1J_{C,P}$ = 145 Hz), 114.2, 125.8, 127.1, 128.2, 128.6 (d, $^3J_{C,P}$ = 5 Hz), 129.6, 138.8, 145.3 (d, $^2J_{C,P}$ = 14 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 18.9.

MS (APSI): m/z = 276 $[M - 1]^+$.

Anal. Calcd for $C_{14}H_{16}NO_3P$: C, 60.65; H, 5.82; N, 5.05. Found: C, 60.52; H, 5.69; N, 5.12.

[(Benzylamino)(Phenyl)methyl]phosphonic Acid (1ca)
Yield: 0.21 g (78%); colorless crystals; mp 238–240 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.09 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.15 (d, $^2J_{H,H}$ = 13.4 Hz, 1 H), 4.27 (d, $^2J_{P,H}$ = 17.0 Hz, 1 H), 7.30–7.35 (m, 8 H), 7.45 (d, $^3J_{H,H}$ = 6.3 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.3 (d, $^3J_{C,P}$ = 5 Hz), 57.7 (d, $^1J_{C,P}$ = 147 Hz), 128.6, 128.7, 129.1 (d, $^3J_{C,P}$ = 2 Hz), 129.3, 129.8, 129.9, 130.8, 131.1 (d, $^2J_{C,P}$ = 5 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 11.5.

MS (APSI): m/z = 276 $[M - 1]^+$.

Anal. Calcd for $C_{14}H_{16}NO_3P$: C, 60.65; H, 5.82; N, 5.05. Found: C, 60.55; H, 5.70; N, 5.16.

[(Phenethylamino)(phenyl)methyl]phosphonic Acid (1da)
Yield: 0.22 g (75%); colorless crystals; mp 263–265 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.89–3.00 (m, 2 H), 3.00–3.10 (m, 1 H), 3.14–3.22 (m, 1 H), 4.51 (d, $^2J_{P,H}$ = 17.0 Hz, 1 H), 7.05 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H), 7.12 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.31–7.38 (m, 3 H), 7.52 (d, $^3J_{H,H}$ = 6.8 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 31.5, 48.4, 59.2 (d, $^1J_{C,P}$ = 144 Hz), 126.9, 128.6, 128.7, 128.8, 129.1, 129.7 (d, $^2J_{C,P}$ = 6 Hz), 131.3 (d, $^3J_{C,P}$ = 5 Hz), 137.2.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 11.9.

MS (APSI): m/z = 290 $[M - 1]^+$.

Anal. Calcd for $C_{15}H_{18}NO_3P$: C, 61.85; H, 6.23; N, 4.81. Found: C, 61.64; H, 6.10; N, 4.84.

[(Isopropylamino)(phenyl)methyl]phosphonic Acid (1ea)
Yield: 0.18 g (79%); colorless crystals; mp 241–243 °C.

^{1}H NMR (500 MHz, CF_3COOD): δ = 1.56 (t, $^3J_{H,H}$ = 7.6 Hz, 6 H), 3.50–3.74 (m, 1 H), 5.02 (d, $^2J_{P,H}$ = 14.7 Hz, 1 H), 7.63 (s, 5 H).

^{13}C NMR (125 MHz, CF_3COOD): δ = 17.6, 19.6, 48.8 (d, $^3J_{C,P}$ = 4 Hz), 59.2 (d, $^1J_{C,P}$ = 145 Hz), 126.8, 128.4, 129.7, 130.6.

^{31}P NMR (202 MHz, CF_3COOD): δ = 14.4.

MS (APSI): m/z = 228 $[M - 1]^+$.

Anal. Calcd for $C_{10}H_{16}NO_3P$: C, 52.40; H, 7.04; N, 6.11. Found: C, 52.32; H, 6.89; N, 6.27.

[(Butylamino)(phenyl)methyl]phosphonic Acid (1fa)
Yield: 0.17 g (73%); colorless crystals; mp 231–233 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.76 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 1.10–1.24 (m, 2 H), 1.53–1.67 (m, 2 H), 2.74–2.79 (m, 1 H), 2.87–2.95 (m, 1 H), 4.46 (d, $^2J_{P,H}$ = 16.9 Hz, 1 H), 7.34–7.38 (m, 3 H), 7.52 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 12.9, 19.4, 27.1, 47.0 (d, $^3J_{C,P}$ = 5 Hz), 59.6 (d, $^1J_{C,P}$ = 144 Hz), 128.7, 129.0, 129.7 (d, $^2J_{C,P}$ = 5 Hz), 131.5 (d, $^3J_{C,P}$ = 4 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 12.0.

MS (APSI): m/z = 242 $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.46; N, 5.76. Found: C, 54.18; H, 7.55; N, 5.88.

[(Cyclohexylamino)(phenyl)methyl]phosphonic Acid (1ga)
Yield: 0.20 g (78%); colorless crystals; mp 192–194 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.90–1.11 (m, 3 H), 1.21–1.39 (m, 2 H), 1.48–1.58 (m, 1 H), 1.63–1.69 (m, 2 H), 1.95–2.08 (m, 1 H), 2.89–2.97 (m, 1 H), 4.51 (d, $^2J_{P,H}$ = 17.1 Hz, 2 H), 7.40 (s, 3 H), 7.55 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.6, 23.7, 27.4, 30.1 (d, $^3J_{C,P}$ = 4 Hz), 57.4 (d, $^1J_{C,P}$ = 145 Hz), 126.6, 128.5 (d, $^2J_{C,P}$ = 6 Hz), 129.7, 130.7.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 12.1.

MS (APSI): m/z = 268 $[M - 1]^+$.

Anal. Calcd for $C_{13}H_{20}NO_3P$: C, 57.99; H, 7.49; N, 5.20. Found: C, 57.82; H, 7.35; N, 5.28.

({[2-(Dimethylamino)ethyl]amino}[phenyl]methyl)phosphonic Acid (1ha)
Yield: 0.21 g (82%); colorless crystals; mp 162–163 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.48 (s, 6 H), 2.67–2.81 (m, 1 H), 2.84–2.96 (m, 1 H), 3.06–3.16 (m, 2 H), 4.08 (d, $^2J_{P,H}$ = 18.1 Hz, 1 H), 7.25–7.37 (m, 1 H), 7.53–7.62 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 42.9, 44.5, 55.5 (d, $^3J_{C,P}$ = 4 Hz), 61.5 (d, $^1J_{C,P}$ = 137 Hz), 127.4, 128.3, 129.5, 137.5 (d, $^2J_{C,P}$ = 5 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 11.7.

MS (APSI): m/z = 257 $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{19}N_2O_3P$: C, 51.16; H, 7.42; N, 10.85. Found: C, 51.03; H, 7.38; N, 11.01.

({[3-(Dimethylamino)propyl]amino}[phenyl]methyl)phosphonic Acid (1ia)
Yield: 0.23 g (82%); colorless crystals; mp 156–158 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.12–2.22 (m, 2 H), 2.68 (s, 6 H), 2.83–2.90 (m, 1 H), 3.01–3.21 (m, 3 H), 4.51 (d, $^2J_{P,H}$ = 16.5 Hz, 1 H), 7.37–7.47 (m, 3 H), 7.58–7.67 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.8, 42.3, 44.4, 53.9, 60.2, (d, $^1J_{C,P}$ = 138 Hz), 128.8, 128.9, 130.0 (d, $^3J_{C,P}$ = 5 Hz), 132.8 (d, $^2J_{C,P}$ = 4 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 10.8.

MS (APSI): m/z = 271 $[M - 1]^+$.

Anal. Calcd for $C_{12}H_{21}N_2O_3P$: C, 52.93; H, 7.77; N, 10.29. Found: C, 52.80; H, 7.72; N, 10.34.

[({2-[Methyl(phenyl)amino]ethyl}amino)(phenyl)methyl]phosphonic Acid (1ja)
Yield: 0.28 g (89%); colorless crystals; mp 222–224 °C.

^{1}H NMR (500 MHz, CF_3COOD): δ = 3.48 (s, 3 H), 3.47–3.57 (m, 2 H), 4.26–4.38 (m, 2 H), 4.86 (d, $^2J_{P,H}$ = 17.2 Hz, 1 H), 7.45–7.62 (m, 7 H), 7.62–7.67 (m, 3 H).

^{13}C NMR (125 MHz, CF_3COOD): δ = 42.5, 46.8, 54.8, 62.2 (d, $^1J_{C,P}$ = 143 Hz), 119.9, 125.9, 128.4 (d, $^3J_{C,P}$ = 6 Hz), 129.8, 131.1, 131.3, 131.9, 138.1 (d, $^2J_{C,P}$ = 9 Hz).

^{31}P NMR (202 MHz, CF_3COOD): δ = 12.5, 12.6.

MS (APSI): *m*/*z* = 319 $[M - 1]^+$.

Anal. Calcd for $C_{16}H_{21}N_2O_3P$: C, 59.99; H, 6.61; N, 8.75. Found: C, 59.87; H, 6.54; N, 8.80.

[({2-[(4-Chlorophenyl)thio]ethyl}amino)(phenyl)methyl]phosphonic Acid (1ka)
Yield: 0.30 g (82%); colorless crystals; mp 258–260 °C.

^{1}H NMR (500 MHz, CF_3COOD): δ = 3.23–3.32 (m, 3 H), 3.41–3.51 (m, 1 H), 4.86 (d, $^2J_{P,H}$ = 17.8 Hz, 1 H), 7.18–7.30 (m, 4 H), 7.38–7.48 (m, 4 H), 7.48–7.62 (m, 1 H).

^{13}C NMR (125 MHz, CF_3COOD): δ = 29.8, 46.2, 61.1 (d, $^1J_{C,P}$ = 144 Hz), 126.3, 128.3 (d, $^3J_{C,P}$ = 5 Hz), 129.4, 129.5, 129.7, 130.7, 132.1, 134.8.

^{31}P NMR (202 MHz, CF_3COOD): δ = 13.5.

MS (APSI): *m*/*z* = 356 $[M - 1]^+$.

Anal. Calcd for $C_{15}H_{17}ClNO_3PS$: C, 50.35; H, 4.79; N, 3.91. Found: C, 50.22; H, 4.71; N, 4.04.

[(4-Fluorophenyl)(phenylamino)methyl]phosphonic Acid (1ab)
Yield: 0.24 g (84%); colorless crystals; mp 187–189 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.70 (d, $^2J_{P,H}$ = 24.4 Hz, 1 H), 6.53 (t, $^3J_{H,H}$ = 7.1 Hz, 1 H), 6.67 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H), 7.01 (t, $^3J_{H,H,F}$ = 8.0 Hz, 2 H), 7.11 (t, $^3J_{H,H,F}$ = 8.0 Hz, 2 H), 7.45–7.55 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.7 (d, $^1J_{C,P}$ = 146 Hz), 113.8, 115.0 (d, $^2J_{C,F}$ = 22 Hz), 117.1, 129.2, 130.5 (m), 135.1, 147.8 (d, $^2J_{C,P}$ = 14 Hz), 161.2 (d, $^1J_{C,F}$ = 243 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 16.8.

MS (APSI): *m*/*z* = 280 $[M - 1]^+$.

Anal. Calcd for $C_{13}H_{13}FNO_3P$: C, 55.52; H, 4.66; N, 4.98. Found: C, 55.43; H, 4.50; N, 5.08.

[(4-Methoxyphenyl)(phenylamino)methyl]phosphonic Acid (1ac)
Yield: 0.22 g (77%); colorless crystals; mp 162–163 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.71 (s, 3 H), 4.58 (d, $^2J_{P,H}$ = 17.4 Hz, 1 H), 6.51 (t, $^3J_{H,H}$ = 7.8 Hz, 1 H), 6.66 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H), 6.85 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H), 7.00 (t, $^3J_{H,H}$ = 7.8 Hz, 2 H), 7.37 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.5 (d, $^1J_{C,P}$ = 147 Hz), 55.6, 113.7, 116.9, 129.1, 129.7 (d, $^3J_{C,P}$ = 5 Hz), 130.7 (d, $^3J_{C,P}$ = 3 Hz), 148.1 (d, $^2J_{C,P}$ = 15 Hz), 159.2.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 19.3.

MS (APSI): *m*/*z* = 292 $[M - 1]^+$.

Anal. Calcd for $C_{14}H_{16}NO_4P$: C, 57.34; H, 5.50; N, 4.78. Found: C, 57.17; H, 5.43; N, 4.88.

[(Phenylamino)(*m*-tolyl)methyl]phosphonic Acid (1ad)
Yield: 0.23 g (82%); colorless crystals; mp 130–132 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 4.60 (d, $^2J_{H,P}$ = 15.2 Hz, 1 H), 6.52 (t, $^3J_{H,H}$ = 7.1 Hz, 1 H), 6.57 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 6.98–7.06 (m, 3 H), 7.18 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.25 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.29 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 21.6, 56.5 (d, $^1J_{C,P}$ = 149 Hz), 113.7, 116.9, 125.8 (d, $^3J_{C,P}$ = 5 Hz), 127.9 (d, $^3J_{C,P}$ = 3 Hz), 128.1, 129.1, 129.2, 137.1, 138.9 (d, $^3J_{C,P}$ = 2 Hz), 148.1 (d, $^2J_{C,P}$ = 14 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 19.0.

MS (APSI): *m*/*z* = 276 $[M - 1]^+$.

Anal. Calcd for $C_{14}H_{16}NO_3P$: C, 60.65; H, 5.82; N, 5.05. Found: C, 60.57; H, 5.70; N, 5.18.

[(Phenylamino)(thien-3-yl)methyl]phosphonic Acid (1ae)
Yield: 0.24 g (88%); colorless crystals; mp 132–133 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.82 (d, $^2J_{P,H}$ = 23.5 Hz, 1 H), 6.56 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H), 6.74 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H), 7.02 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H), 7.16–7.22 (m, 1 H), 7.38–7.42 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 52.7 (d, $^1J_{C,P}$ = 147 Hz), 114.0, 117.5, 123.1 (d, $^3J_{C,P}$ = 8 Hz), 125.5, 128.7 (d, $^3J_{C,P}$ = 4 Hz), 129.2, 139.6, 147.6 (d, $^2J_{C,P}$ = 13 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 18.4.

MS (APSI): *m*/*z* = 268 $[M - 1]^+$.

Anal. Calcd for $C_{11}H_{12}NO_3PS$: C, 49.07; H, 4.49; N, 5.20. Found: C, 48.95; H, 4.44; N, 5.31.

[(2-Hydroxyphenyl)(phenylamino)methyl]phosphonic Acid (1af)
Yield: 0.20 g (75%); colorless crystals; mp 131–134 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.01 (d, $^2J_{P,H}$ = 24.3 Hz, 1 H), 6.51 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H), 6.68 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 6.72 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H), 6.89 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H), 6.96–7.05 (m, 3 H), 7.36 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.2 (d, $^1J_{C,P}$ = 150 Hz), 113.4, 115.8, 116.9, 119.4, 125.5, 128.1 (d, $^3J_{C,P}$ = 6 Hz), 128.9 (d, $^3J_{C,P}$ = 4 Hz), 129.1, 148.8 (d, $^2J_{C,P}$ = 15 Hz), 155.7 (d, $^3J_{C,P}$ = 6 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 20.4.

MS (APSI): *m*/*z* = 278 $[M - 1]^+$.

Anal. Calcd for $C_{13}H_{14}NO_4P$: C, 55.92; H, 5.05; N, 5.02. Found: C, 55.87; H, 4.94; N, 5.17.

[(4-Acetamidophenyl)(benzylamino)methyl]phosphonic Acid (1cg)
Yield: 0.26 g (77%); colorless solid; mp 272–274 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.05 (s, 3 H), 3.72 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H), 3.80 (d, $^2J_{H,P}$ = 15.9 Hz, 1 H), 4.13 (d, $^2J_{H,H}$ = 11.3 Hz, 1 H), 7.30–7.45 (m, 7 H), 7.51–7.61 (m, 2 H), 10.18 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.2, 49.3, 59.3 (d, $^1J_{C,P}$ = 134 Hz), 119.1, 129.0, 129.1 (d, $^3J_{C,P}$ = 5 Hz), 130.3 (d, $^2J_{C,P}$ = 8 Hz), 132.7, 134.6, 139.4, 162.8, 168.9.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 9.1.

MS (APSI): *m*/*z* = 333 $[M - 1]^+$.

Anal. Calcd for $C_{16}H_{19}N_2O_4P$: C, 57.48; H, 5.73; N, 8.38. Found: C, 57.57; H, 5.80; N, 8.26.

{[(4-Fluorobenzyl)amino](4-nitrophenyl)methyl}phosphonic Acid (1lh)
Yield: 0.27 g (79%); colorless crystals; mp 244–246 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.14–4.21 (m, 2 H), 4.51 (d, $^2J_{P,H}$ = 17.1 Hz, 1 H), 7.13 (t, $^3J_{H,H,F}$ = 8.5 Hz, 2 H), 7.50 (t, $^3J_{H,H,F}$ = 6.0 Hz, 2 H), 7.79 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 8.20 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.7, 58.2 (d, $^1J_{C,P}$ = 134 Hz), 115.7 (d, $^2J_{C,F}$ = 22 Hz), 123.7, 128.1 (d, $^3J_{C,F}$ = 3 Hz), 131.1 (d,

$^3J_{C,P}$ = 4 Hz), 133.4 (d, $^2J_{C,P}$ = 11 Hz), 140.9, 147.7, 162.4 (d, $^1J_{C,F}$ = 55 Hz).

^{31}P NMR (202 MHz, DMSO-d_6): δ = 10.2.

MS (APSI): m/z = 339 $[M - 1]^+$.

Anal. Calcd for $C_{14}H_{14}FN_2O_5P$: C, 49.42; H, 4.15; N, 8.23. Found: C, 49.49; H, 4.26; N, 8.11.

({[(1-Phenyl-1*H*-pyrazol-4-yl)methyl]amino}(thien-2-yl)methyl)phosphonic Acid (1mi)
Yield: 0.29 g (82%); colorless crystals; mp 246–247 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.43 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 4.57 (d, $^2J_{H,H}$ = 13.7 Hz, 1 H), 5.32 (d, $^2J_{P,H}$ = 17.6 Hz, 1 H), 7.14–7.22 (m, 1 H), 7.43 (br s, 1 H), 7.50–7.74 (m, 6 H), 8.56 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 40.1, 57.1 (d, $^1J_{C,P}$ = 147 Hz), 114.1, 122.5, 126.2 (d, $^3J_{C,P}$ = 5 Hz), 125.1, 129.9, 130.5, 132.2 (d, $^2J_{C,P}$ = 7 Hz), 132.4, 133.5, 136.8, 137.4.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 11.6.

MS (APSI): m/z = 348 $[M - 1]^+$.

Anal. Calcd for $C_{15}H_{16}N_3O_3PS$: C, 51.57; H, 4.62; N, 12.03. Found: C, 51.73; H, 4.73; N, 11.87.

[1-(Phenylamino)cyclohexyl]phosphonic Acid (1aj)
Yield: 0.19 g (74%); colorless crystals; mp 161–164 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16–1.24 (m, 1 H), 1.37–1.52 (m, 5 H), 1.68–1.76 (m, 2 H), 2.12–2.18 (m, 2 H), 6.74 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H), 7.10 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H), 7.16 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.4 (d, $^3J_{C,P}$ = 4 Hz), 25.4 (d, $^2J_{C,P}$ = 8 Hz), 29.6, 57.2 (d, $^1J_{C,P}$ = 158 Hz), 119.2, 119.5, 128.6, 144.4.

^{31}P NMR (202 MHz, DMSO-d_6): δ = 24.9.

MS (APSI): m/z = 254 $[M - 1]^+$.

Anal. Calcd for $C_{12}H_{18}NO_3P$: C, 56.47; H, 7.11; N, 5.49. Found: C, 56.38; H, 7.00; N, 5.62.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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