Synthesis of New (3-Aminopyrrolidin-3-yl)phosphonic Acid – A Cucurbitine Analogue – and (3-Aminotetrahydrothiophen-3-yl)phosphonic Acid via Phosphate Addition to Heterocyclic Hydrazones

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Abstract: Hydrazones were prepared by condensation of carbocyclic and heterocyclic ketones with benzoyl- and tosylhydrazines. These hydrazones underwent nucleophilic addition with phosphate to provide efficiently (3-hydrazinopyrrolidin-3-yl)-, (3-hydrazinotetrahydrothiophen-3-yl)-, (3-hydrazinotetrahydrofururan-3-yl)-, and (1-hydrazinocyclopentyl)phosphonates. Cleavage of the hydrazine N–N bonds followed by acidic hydrolysis of the phosphonate functions of the (3-aminothiophenyl)cyclic phosphonates gave the new (3-aminopyrrolidin-3-yl)- and (3-aminothiophenyl)phosphonic acids. This synthesis was achieved in a four-step sequence from the appropriate ketones.

Key words: phosphonic acids, heterocycles, amines, cucurbitine analogue, nucleophilic additions

Several α-aminophosphonic acids show activity as enzyme inhibitors, antibacterials, herbicides, or plant growth regulators. These acid derivatives, in which the tetrahydropyran moiety acts as a transition-state analogue of peptide bond cleavage, selectively inhibit peptidases and proteinases (e.g., HIV protease, serine protease). Thus, in recent years, many cyclic α-aminophosphonic acids have been prepared, and when from cycloalkanones, mainly by Mannich-type reactions.

Very few examples of heterocyclic α-aminophosphonic acids 1 or the corresponding phosphonates have been reported; only the 4-aminobutyric acid (GABA) analogue 1a, the tetrahydropyranylphosphonate derivative of 1b, and tetrahydrothiopyranylphosphonate derivative of 1c are described (Figure 1).16 In all these synthetic approaches, the Kabatschek–Fields reaction was used from heterocyclohexanones, to provide α-aminophosphonates in moderate to good yields.

Figure 1 Heterocyclic α-aminocarboxylic and phosphonic acids

Herein, we report our efforts towards the synthesis of phosphonocucurbitine 3a and related compounds 3b,c (Figure 1). We decided to first apply our methodology involving the addition of a phosphate to iminium intermediate 6 as a key step (Scheme 2). Unfortunately, we realized that for the five-membered-ring heterocyclic ketones 7–9 (X = NCO2Et, O, or S), the failure of formation of iminiums 6 limited the formation of the corresponding aminophosphonates 10–12 (Scheme 2). Attempts to isolate and characterize such imine intermediates (corresponding to iminiums 6) also failed (Scheme 2).

In addition, we tried different conditions for the phosphate additions to 3-pyrrolidinone 7 [P(OEt)3, HP(OEt)3 under acidic conditions, or LiP(O)(OEt)2 under basic conditions] (Scheme 2). However, none of these conditions
Ketones 7–9 and 13 (Scheme 3).

Hydrazide formation was carried out under mild conditions. Ketones 725 and 826 as well as commercially available ketones 9 and 13, reacted with tosylhydrazide 22a and benzoylhydrazide 22b in ethanol at 50 °C, to give the desired E/Z-configured hydrazones 14–17 in good yields (72–89%) (Scheme 4, Table 1). The thus obtained hydrazones 14–17 were used in the next step without further purification.

The standard reactions (Scheme 5) of pyrrolidin-3-one hydrazones 14a,b with diethyl phosphate, used as solvent and reagent, in the presence of 0.3 equivalents trifluoroacetic acid in dichloromethane at room temperature for 18–24 hours (method B), furnished the expected hydrazinophosphonates 18b, 19b, and 20b, respectively, in slightly increased yields (Table 2, entries 4, 6 and 8). Likewise, cyclopentanone hydrazones 17a21a and 17b27b by methods A and B, respectively, gave hydrazinophosphonates 21a and 21b, respectively, in the same yields obtained for the pyrrolidine derivatives (Table 2, cf. entries 1 and 9; and entries 4 and 10).

On the other hand, the reactions of benzylohydrzones 14b, 15b, and 16b with triethyl phosphate (1.1 equiv) in the presence of 0.5 equivalents trifluoromethanesulfonic acid in dichloromethane at room temperature for 18–24 hours (method B), furnished the expected hydrazinophosphonates 18b, 19b, and 20b, respectively, in slightly increased yields (Table 2, entries 4, 6 and 8). Likewise, cyclopentanone hydrazones 17a21a and 17b27b by methods A and B, respectively, gave hydrazinophosphonates 21a and 21b, respectively, in the same yields obtained for the pyrrolidine derivatives (Table 2, cf. entries 1 and 9; and entries 4 and 10).

We next tried to obtain the aminophosphonates starting from other imine analogues (such as oximes or phosphanes), which are known to be easily cleaved in the final sequence affording free amines. Thus, imine 23, prepared from cyclopentanone oxime and chlorodiphenylphosphine,28 reacted with triethyl phosphate to give the desired aminophosphonate 24 in low yield and with a mixture of unidentified products (Scheme 6). Similarly, the addition of diethoxyphosphorylpotassium in the presence of three equivalents of boron trifluoride–diethyl ether complex to the easily prepared carbonylic and heterocyclic oximes 25a and 25b30 yielded the expected aminophosphonates 26a and 26b, respectively, in only 30% and 24% yields, respectively, with 30–55% recovered starting materials (Scheme 6). Finally, optically active hydrazone 27, prepared from (R)-(−)-1-amino-2-(methoxymethyl)pyrro-

Table 1: Preparation of Hydrazones 14–17 from Ketones 7–9 and 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone 7–9</th>
<th>X</th>
<th>Hydrazine 22</th>
<th>R1</th>
<th>Hydrazone 14–17</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>NCO2Et</td>
<td>22a</td>
<td>Ts</td>
<td>14a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>NCO2Et</td>
<td>22b</td>
<td>Bz</td>
<td>14b</td>
<td>89</td>
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<tr>
<td>3</td>
<td>8</td>
<td>O</td>
<td>22b</td>
<td>Bz</td>
<td>15b</td>
<td>74</td>
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<td>4</td>
<td>9</td>
<td>S</td>
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<td>Bz</td>
<td>16b</td>
<td>84</td>
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<td>CH3</td>
<td>22a</td>
<td>Ts</td>
<td>17a</td>
<td>88</td>
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<tr>
<td>6</td>
<td>13</td>
<td>CH3</td>
<td>22b</td>
<td>Bz</td>
<td>17b</td>
<td>72</td>
</tr>
</tbody>
</table>

*See Scheme 4. Reaction conditions: ketone 7, 8, or 13, hydrazine 22a or 22b (1 equiv), EtOH, 50 °C, 2 h.
dine (RAMP) and heterocyclic ketone 7, reacted with a phosphonate in the presence of titanium(IV) chloride to provide an inseparable diastereomeric mixture of amino-phosphonates 28 in moderate yield (Scheme 7). Because of these unsatisfactory results, aminophosphonates 24, 26a, 26b, and 28 are not used for the next steps.

We then subjected (benzoylhydrazino)phosphonates 18b–21b to cleavage of the hydrazine N–N bonds (Scheme 8, Table 3). Reaction of hydrazinophosphonate 18b under the mild conditions of 2.2 equivalents samarium(II) iodide in tetrahydrofuran–methanol 30 at 0 °C resulted in cleavage of the N–N bond, affording free aminophosphonate 29 in low yield (Table 3, entry 1). Although the reaction as monitored by TLC gave the desired aminophosphonate 29 cleanly, the workup and purification on silica gel seem to be the limiting step for this reaction. Use of hexamethylphosphoramide as cosolvent, known to increase the reduction power of the samarium(II) iodide solution towards functional groups, 31 did not improve the yield (20%). Attempt to cleave the N–N bond of tosylhydrazine 18a under the same conditions (SmI2, MeOH) failed. The best result was obtained when the cleavage reaction of 18b was carried out with sodium/ammonia in ethanol, 32 giving the free amine 29 in 55% yield (Table 3, entry 2). Unexpectedly, this reduction step required 35 equivalents of sodium for complete N–N bond cleavage. Furthermore, other reduction agents, such as Raney nickel/hydrogen in ethanol, 32 hydrogen/palladium(II) hydroxide/carbon in acetic acid, hydrogen/platinum(IV) oxide in acetic acid, 33a zinc/acetic acid/trifluoroacetic acid, 33b sodium borohydride/nickel(II) were not successful.

### Table 2  Preparation of Hydrazinophosphonates 18–21 from Hydrazones 14–17

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R1</th>
<th>Hydrazone</th>
<th>Conditions</th>
<th>Phosphonate 18–21</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCO₂Et</td>
<td>Ts</td>
<td>14a</td>
<td>A</td>
<td>18a</td>
<td>96</td>
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<tr>
<td>2</td>
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<td>14a</td>
<td>A</td>
<td>18a</td>
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<tr>
<td>3</td>
<td>NCO₂Et</td>
<td>Bz</td>
<td>14b</td>
<td>A</td>
<td>18b</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>NCO₂Et</td>
<td>Bz</td>
<td>14b</td>
<td>B</td>
<td>18b</td>
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<td>Bz</td>
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<td>B</td>
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<td>40</td>
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</tr>
<tr>
<td>10</td>
<td>CH₂</td>
<td>Bz</td>
<td>17b</td>
<td>B</td>
<td>21b</td>
<td>61</td>
</tr>
</tbody>
</table>

We then subjected (benzoylhydrazino)phosphonates 18b–21b to cleavage of the hydrazine N–N bonds (Scheme 8, Table 3). Reaction of hydrazinophosphonate 18b under the mild conditions of 2.2 equivalents samarium(II) iodide in tetrahydrofuran–methanol 30 at 0 °C resulted in cleavage of the N–N bond, affording free aminophosphonate 29 in low yield (Table 3, entry 1). Although the reaction as monitored by TLC gave the desired aminophosphonate 29 cleanly, the workup and purification on silica gel seem to be the limiting step for this reaction. Use of hexamethylphosphoramide as cosolvent, known to increase the reduction power of the samarium(II) iodide solution towards functional groups, 31 did not improve the yield (20%). Attempt to cleave the N–N bond of tosylhydrazine 18a under the same conditions (SmI₂, MeOH) failed. The best result was obtained when the cleavage reaction of 18b was carried out with sodium/ammonia in ethanol, 32 giving the free amine 29 in 55% yield (Table 3, entry 2). Unexpectedly, this reduction step required 35 equivalents of sodium for complete N–N bond cleavage. Furthermore, other reduction agents, such as Raney nickel/hydrogen in ethanol, 32 hydrogen/palladium(II) hydroxide/carbon in acetic acid, hydrogen/platinum(IV) oxide in acetic acid, 33a zinc/acetic acid/trifluoroacetic acid, 33b sodium borohydride/nickel(II) were not successful.
chloride in ethanol, and sodium bis(2-methoxyethoxy)aluminum hydride in toluene at reflux, did not cleave hydrazinophosphonates 21b.

Cleavage of (benzoylhydrazino)phosphonate 19b (a furan derivative) under the same conditions afforded a mixture of degradation products (Table 3, entry 3). In contrast, the tetrahydrothiophene derivative 21b reacted with samarium(II) iodide to furnish the desired free aminophosphonates 31 and 32 in the acceptable yields of 50% and 32%, respectively (Table 3, entries 4 and 5). In addition, 21b was reduced by sodium/ammonia or tributylstannane to give 32 in 15% yield (Table 3, entry 6) or to form degradation products, respectively.

These results are probably explained by the formation of the radical 33 in the presence of samarium(II) iodide or sodium/ammonia, which by fragmentation gives radical 34 (Scheme 9). By hydrogen abstraction, free amines 29–32 form (Scheme 9). Although we were not able to isolate any byproducts, the possible ring-opening rearrangement of heterocyclic radical 34 cannot be excluded.

Subsequent phosphonate hydrolysis and methoxycarbonyl group deprotection of 29 was accomplished simultaneously in six molar hydrochloric acid at reflux, to give the new amino acid hydrochloride 3a·2HCl (a cucurbitine analogue) quantitatively (Scheme 10). Hydrolysis of aminophosphonates 31 and 32 with six molar hydrochloric acid at reflux, followed by treatment with propylene oxide, provided the new (3-aminotetrahydrothiophen-3-yl)phosphonic acid (3c) and (1-aminocyclopentyl)phosphonic acid (3d), in quantitative yields (Scheme 10). Additionally, hydrolysis of 32 was also achieved with trimethylsilyl iodide, followed by treatment with propylene oxide. 34

In summary, we have developed an easy and efficient four-step synthesis of new (3-amino-3-heterocyclopentyl)phosphonic acids 3a and 3c and (aminocyclopentyl)phosphonic acid 3d. Thus, starting from readily available 3-heterocyclic ketones 7–9 and commercially available cyclopentanone (13), we have demonstrated that the hydrazones formed from these ketones undergo nucleophilic addition of phosphites to give the heterocyclic aminophosphonates 18–21 in good to acceptable yields. Subsequent cleavage of the N–N bonds with sodium/liquid ammonia or samarium(II) iodide was accomplished in acceptable yields. Finally, acid hydrolysis of the phosphonate functions provided amino-substituted phosphonic acids in quantitative yields. This new approach to the synthesis of aminophosphonates from five-membered heterocyclic ketones and hydrazines constitutes an interesting and useful alternative to our previously reported method on six-membered-ring heterocycles. This series of experiments confirms that the reactivity of five-membered-ring compounds is very often different from that of the six-membered analogues.

All reactions were carried out under an argon atmosphere and under magnetic stirring. rac-α-Methylbenzylamine, tosylhydrazine (22a), benzoylhydrazine (22b), RAMP, AcOH, TIOH, cyclcopentanone (13), dihydrothiophen-3-one (9), TFA, BF3·OEt2, Pd(OH)2/C (20%), Pd(OEt)3, H2Pd(OEt)2, (MeO)2P(O)TMS, KHMS, and propylene oxide were purchased from Aldrich. Dihydroxyprolidin-3-one (7), dihydrofuran-3-one (8), and SmI2 were prepared by literature procedures. P(OEt)2, and HP(OEt)2, were distilled under reduced pressure and stored over 4Å molecular sieves under argon. DMF, toluene, DMSO, HMPA, and CH2Cl2 were freshly distilled over Na/Hg under argon before use. TLC (source of reported Rf) was carried out on 0.25-mm silica gel plates (Merck F254). Flash chromatography was performed on silica gel 60 (0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except where noted. IR spectra were recorded on a Perkin-Elmer (spectrum one) spectrophotometer. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected. 1H and 13C NMR spectra were measured on a Bruker DRX250 (1H, 250 MHz; 13C, 62.9 MHz) or Bruker AC360 (1H, 300 MHz; 13C, 75.5 MHz).
Synthesis of Pyrrolidinyl- and Tetrahydrothiophenylphosphonic Acids


N'-(E/Z)-Dihydrofuran-3(2H)-ylidene)benzohydrazide (15b) Yield: 74%; mp 159 °C; Rf = 0.29 (MeOH–Et2O–aq NH3, 5:9:5.0). IR (neat): 3195, 2955, 1635, 1600, 1576, 1530, 1300, 1137, 1044 cm⁻¹.


Anal. Calcd for C10H16O2Na: C, 64.69; H, 5.92, N, 13.72. Found: C, 64.33; H, 5.84; N, 13.82.

N'-[(E)-Dihydrothiophen-3(2H)-ylidene)benzohydrazide (16b) Yield: 84%; white solid; mp 191.0 °C; Rf = 0.39 (MeOH–Et2O–aq NH3, 5:9:5.0).

IR (film): 3210, 3048, 3003, 1650, 1640, 1578, 1530, 1286, 907 cm⁻¹.


N'-Cyclopentylidene-4-toluenesulfonylhydrazide (17a) Compound 17a was prepared according to the procedure in ref. 27a. Yield: 88%; white solid.

1H NMR (360 MHz, CDCl3): δ (E/Z) = 1.81–2.21 (m, 4 H), 2.95 (t, J1/H2 = 7.2 Hz, 2 H, 4-H, E), 3.71–3.75 (m, 2 H, 5-H, Z), 4.38 (br s, 2 H, 2-H, Z), 7.63–7.86 (m, 3 H, Hαm), 8.02 (s, 1 H, NH, Z), 8.19 (s, 1 H, NH, E).


Anal. Calcd for C18H17O2N2: C, 80.38; H, 5.75; N, 11.92. Found: C, 80.44; H, 5.74; N, 11.94.

N'-Cyclopentylidenebenzoylhydrazide (17b) Yield: 70%; mp 150.1 °C; Rf = 0.45 (MeOH–Et2O–aq NH3, 10:9:0.5).

1H NMR spectral data were in accord with the literature values, but 13C NMR data were not previously reported.

1H NMR (250 MHz, CDCl3): δ (E/Z) = 1.70–1.88 (m, 2 H, 2-H, E), 2.92–3.05 (m, 2 H, 4-H, E), 4.45–4.57 (m, 2 H, 5-H, Z), 5.24–5.34 (m, 2 H, 2-H, Z), 7.35–7.62 (m, 3 H, Hαm), 7.63–7.96 (m, 2 H, Hαm), 8.51 (br s, 1 H, NH).

Hydrazinophosphonates 18–21 by Method A; General Procedure

**TIOH** (55 µL, 0.6 mmol, 0.5 equiv) was added to a solution of a hydrazone 14–17 (2 mmol) in **HP(OEt)2** (2.06 mL, 16 mmol, 8 equiv) at 0 °C. The mixture was warmed to r.t. for 4 h, and then concentrated to dryness in vacuo. The residue was mixed with sat. aq NaHCO3 (5 mL), the reaction mixture was extracted with CH2Cl2 (3 × 30 mL). The organic layers were dried (MgSO4), filtered, and then concentrated in vacuo to give the crude phosphonate. Purification by flash chromatography (silica gel, MeOH–Et2O, 5:95) gave pure hydrazinophosphonates 18–21; yields: 29–96%.

Hydrazinophosphonates 18–21 by Method B; General Procedure

**P(OEt)2** (380 µL, 2.2 mmol) and TIOH (76 µL, 0.5 equiv) were added successively to a solution of a hydrazone 14–17 (2 mmol) in CH2Cl2 (15 mL) at 0 °C. The mixture was then stirred at r.t. for 12–24 h. After addition of sat. aq NaHCO3 (5 mL), the reaction mixture was extracted with CH2Cl2 (2 × 30 mL). The organic layer was dried, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (silica gel); this gave pure hydrazinophosphonates 18–21; yields: 37–68%.

**Diethyl [1-(Ethoxycarbonyl)-3-(2-tosylhydrazino)pyrrolidin-3-yl]phosphonate (18a)**

Prepared by Method A.

**Yield: 96%; colorless viscous oil;** Rf = 0.33 (MeOH–Et2O–aq NH3, 5:95:0.5).

**IR (neat):** 3437, 3560, 3121, 2982, 1682, 1348, 1330, 1230, 1160, 1050 cm–1.

**1H NMR (250 MHz, CDCl3):** 6.96 (d, 1 H, JHH = 2.7 Hz, 3 H, CH3), 3.92 (d, 3 H, CH2OP), 2.37–2.50 (m, 2 H, Harom), 8.85 (d, 3 H, JHH = 8.2 Hz, 1 H, HNCO).

**Found: C, 52.30; H, 6.83; N, 10.16.**


**Anal. Calcd for C18H28N3O6P. C: 52.50; H: 6.83; N: 10.16.**

**Diethyl [3-(Benzoylhydrazino)tetrahydrofuran-3-yl]phosphonate (19b)**

Prepared by Method B.

**Yield: 37%; colorless oil;** Rf = 0.35 (MeOH–Et2O–aq NH3, 5:95:0.5).

**IR (neat):** 3497, 3298, 3057, 2983, 1682, 1602, 1581, 1277, 1216, 1048, 1020, 968 cm–1.

**1H NMR (250 MHz, CDCl3):** 6.71 (t, JHH = 7.0 Hz, 6 H, 2 CH2CHO), 2.03–2.35 (m, 2 H, 4–H, 3-H, 2-H and 1-H), 3.79–4.00 (m, 3 H, 2.5-H and 2-H), 4.46–4.75 (m, 2 H, 3-H, 2-H), 3.99–4.24 (m, 4 H, 2 CH2OP), 3.91–4.16 (m, 5 H, 2 CH2OP and 2-H), 5.35–5.61 (m, 3 H, CH2OP and 2-H), 8.75–8.97 (d, JHH = 8.7 Hz, 1 H, Harom), 7.75–7.87 (d, JHH = 8.0 Hz, 2 H, Harom).

**Found: C, 51.83; H, 6.91; N, 9.86.**
Diethyl [1-(2-Tosylhydrazino)cyclopentyl]phosphonate (21a)
Prepared by Method A.
Yield: 90%; white solid; mp 121.5 °C; Rf = 0.27 (MeOH–CH2Cl2–aq NH4, 5:95:0.5).
IR (film): 3425, 3300, 2958, 1596, 1439, 1330, 1220, 1162, 1041, 1022, 966 cm−1.

1H NMR (360 MHz, CDCl3): δ = 1.34 (t, 3 JHH = 7.2 Hz, 6 H, 2 CH2(CH3)O), 1.40–1.90 (m, 8 H, 2 H,C(3,5)), 2.44 (s, 3 H, CH3), 3.71 (s, 1 H, NH), 4.00–4.20 (m, 4 H, 2 CH2OP), 6.49 (s, 1 H, NH2O), 7.31 (d, 3 JHH = 8.0 Hz, 2 H, H arom), 7.79 (d, 3 JHH = 8.0 Hz, 2 H, H arom).

13C NMR (101.25 MHz, CDCl3):

Phosphinic amide 23 was prepared according to a literature procedure. A soln of crude cyclopentane oxime (640 mg, 6.46 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C and then successively treated with Et3N (1.012 mL, 7.26 mmol) and Ph3PCH2I (1.60 g, 7.26 mmol). The mixture was stirred at −78 °C for 3 h. Sat. aq NH4Cl (10 mL) was added to the reaction mixture, which was then extracted with CH2Cl2 (3 × 70 mL). The organic layer was dried (MgSO4), filtered, and concentrated. Purification (silica gel, CH2Cl2–MeOH–PE: 20:80) afforded amide 23.

Yield: 1.39 g (76%); viscous oil; Rf = 0.24 (Et2O–PE, 80:20).
IR (neat): 3230, 3057, 1699, 1635, 1591, 1438, 1184, 1125 cm−1.

1H NMR (300 MHz, CDCl3): δ = 1.70 (m, 4 H, 2 H-C-3 and 2 H-4), 2.54–2.60 (m, 4 H, 2 H-2 and 2 H-5), 7.29–7.38 (m, 6 H, H arom).

13C NMR (90.56 MHz, CDCl3):

Phosphinic amide 25a was prepared by a general procedure from pyrrolidine 7 (353 mg, 2.25 mmol), H2NOBn-HCl (358 mg, 2.25 mmol), and K2CO3 (310 mg, 2.25 mmol) in EtOH (10 mL). Purification by chromatography (silica gel, Et2O–PE, 90:10) gave an E/Z mixture of oxime 25a.

ESI-HRMS: m/z [M + Na]+ calcd for C15H23N2O4PS: 381.1008; found: 381.1009.

Diethyl [1-[(Diphenylphosphoryl)amino]cyclopentyl]phosphonate (24)
Prepared by Method B (as for preparation of phosphonates 18–21) from amide 23.
Yield: 36% (triple purification on silica gel from a mixture of undifferentiated products); colorless oil; Rf = 0.40 (MeOH–Et2O–aq NH4, 9:5).

1H NMR (300 MHz, CDCl3): δ = 1.33 (t, J = 7.0 Hz, 6 H, CH3), 1.46–1.70 (m, 2 H), 1.70–1.88 (m, 2 H), 1.88–2.18 (m, 4 H), 3.35 (dd, J = 6.4 Hz, J = 3.0 Hz, 3 H, NH), 4.17 (q, J = 7.0 Hz, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 7.12–7.58 (m, 6 H, 2 H arom).

13C NMR (101.25 MHz, CDCl3): δ = 18.6 (C-2), 29.8 (C-3), 30.1 (C-4), 32.3 (C-5), 63.0 (d, JPC = 148.3 Hz, C-1). [6 P, C-2, C-3, C-4, C-5] 128.1 (2 CH), 129.1 (2 CH). 135.0 (C-CH2), 143.4 (C-SO2)].

13P NMR (101.25 MHz, CDCl3): δ = 30.15.

Diethyl [1-[Benzylhydrazino]cyclopentyl]phosphonate (21b)
Prepared by Method B.
Yield: 61%; colorless oil; Rf = 0.70 (MeOH–Et2O–aq NH4, 10:90:0.5).
IR (neat): 3480, 3274, 3061, 2977, 1652, 1603, 1580, 1455, 1225, 1049, 1026, 966 cm−1.

1H NMR (360 MHz, CDCl3): δ = 1.32 (t, 3 JHH = 7.0 Hz, 6 H, 2 CH2(CH3)O), 1.66 (sharp m, 2 H, H2v), 1.68–2.10 (m, 6 H, H2v), 4.07–4.24 (m, 4 H, 2 CH2OP), 5.01 (dd, 3 JHH = 7.0 Hz, 3 JHP = 27.0 Hz, 1 H, NH), 7.30–7.50 (m, 3 H, H arom), 7.70–7.90 (m, 2 H, H arom).

13C NMR (101.25 MHz, CDCl3): δ = 28.81.

HRMS data could not be obtained. 

-N-Cyclopentylidene-P-P-diphenylphosphinic Amide (23)
Cyclopentanone oxime was prepared by a general procedure from cyclopentanone (13, 555 mg, 6.6 mmol), H2NOBn-HCl (459 mg, 6.6 mmol), and K2CO3 (312 mg, 2.25 mmol) in EtOH (10 mL). This gave crude cyclopentanone oxime, which was used without further purification; yield: 643 mg (98%).

Phosphinic amide 23 was prepared according to a literature procedure. A soln of crude cyclopentanone oxime (640 mg, 6.46 mmol) in CH2Cl2 (10 mL) was cooled to −78 °C and then successively treated with Et3N (1.012 mL, 7.26 mmol) and Ph3PCH2I (1.60 g, 7.26 mmol). The mixture was stirred at −78 °C for 3 h. Sat. aq NH4Cl (10 mL) was added to the reaction mixture, which was then extracted with CH2Cl2 (3 × 70 mL). The organic layer was dried (MgSO4), filtered, and concentrated. Purification (silica gel, CH2Cl2–MeOH–PE: 20:80) afforded amide 23.

Yield: 1.39 g (76%); viscous oil; Rf = 0.24 (Et2O–PE, 80:20).
IR (neat): 3230, 3057, 1699, 1635, 1591, 1438, 1184, 1125 cm−1.
Diethyl [1-(Benzyloxyl)amino)cyclopentyl]phosphonate (26b)

Phosphonate 26b was prepared from benzylxime 25b39 by the procedure described above for the preparation of 26a.

Yield: 24%; colorless oil; \( R_f = 0.74 \) (MeOH–Et\(_2\)O–aq NH\(_3\), 5:95:0.5).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.27 \) (t, \( J = 7.0 \) Hz, 6 H, CH\(_3\)), 1.62/1.84 (m, 6 H, H\(_{15}\)), 1.91–2.08 (m, 2 H, CH\(_2\)H\(_2\) and H-5), 4.04–4.24 (m, 4 H, CH\(_2\)OP), 4.74 (s, 2 H, CH\(_2\)ON), 5.81–5.90 (br s, 1 H, NH), 7.31–7.39 (m, 5 H).

\(^13\)C NMR (75.1 MHz, CDCl\(_3\)): \( \delta = 127.7 \) (2 CH), 128.2 (2 CH), 128.5 (2 CH), 137.4 (C\( = \)).

**Free Aminophosphonate 29 by Cleavage of the Hydrazine N–N Bond with Sodium/Ammonia**

Liquid NH\(_3\) (4 mL) was condensed into a solution of hydrazinophosphonate 18b (0.6 mmol) in THF (1 mL) and absolute EtOH (1 mL) cooled to −78 °C. Then Na (485 mg, 35 equiv) was added in small portions. The mixture was warmed to −50 °C and stirred at this temperature for 1 h. Then the reaction mixture was degassed at r.t. with argon to remove the excess liquid NH\(_3\). The resulting residue was quenched with solid NH\(_4\)Cl (1 g) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH–Et\(_2\)O–aq NH\(_3\), 10:90:0.5): this provided a free aminophosphonate 29.

Yield: 97 mg (55%).

**Free Aminophosphonates 29–32 by Cleavage of the Hydrazine N–N Bond with Samarium(II) Iodide30 (Method A); General Procedure**

A 1.2 M solution of SmI\(_2\) in THF (3.6 mmol) was added to a solution of one of the hydrazinophosphonates 18b–21b (0.43 mmol) in MeOH (3 mL) at 0 °C. The mixture was stirred for 20 min at the same temperature and then concentrated under reduced pressure to remove the solvents. The residue was extracted with 1 M HCl (2 × 5 mL) and the aqueous layers were washed with Et\(_2\)O (8 mL), made alkaline with 1 M aq NaOH, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H\(_2\)O (2 × 1 mL) and brine (2 × 2 mL), dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, MeOH–Et\(_2\)O–aq NH\(_3\), 10:90:0.5); this afforded free aminophosphonates 29, 31, and 32; yields: 20–50%.

**Diethyl [3-Amino-1-(Ethoxycarbonyl)pyrrolidin-3-ylidene]-2-(methoxycarbonyl)pyrrolidin-1-amine (27)**

Pyrrolidin-1-amine 27 was prepared by a general procedure from pyrrolidone 7 (277 mg, 1.76 mmol) and RAMP (235 mg, 1.76 mmol) in EtOH (4 mL) at 50 °C for 2 h. After purification by chromatography (silica gel, MeOH–Et\(_2\)O, 10:90) gave an inseparable diastereomeric mixture of hydrazonophosphonate 27 was obtained.

Yield: 300 mg (63%); \( R_f = 0.66 \) and 0.53 (Z/E), (MeOH–Et\(_2\)O–aq NH\(_3\), 10:90:0.5).

IR (neat): 2974, 2926, 2875, 1705, 1625, 1424, 1113 cm\(^{-1}\).

\(^13\)C NMR (62.9 MHz, CDCl\(_3\)): \( \delta = 14.6 \) (CH\(_3\)), 22.4 (C-4 RAMP), 26.3/26.6 (C-3 RAMP–EIZ), 28.5/29.1 (C-2, Z), 30.3/31.8 (C-4), 43.1/44.4 (C-5, EIZ), 47.0/47.3 (C-2, Z), 49.7 (C-2, E), 54.0/54.5 (C-5 RAMP–EIZ), 59.0 (C-2 RAMP–EIZ), 61.0 (CH\(_2\)OCO), 66.3 (CH\(_3\)O), 75.1/75.6 (CH\(_3\)CH\(_2\)OP), 124.9 (COO), 159.9 (COO), 159.9 (COO).

**Dimethyl [(R/S)-1-(Ethoxycarbonyl)-3-[(R)-2-(methoxycarbonyl)-1-azabicyclo[3.2.1]oct-3-en-3-ylidene]-2-(methoxycarbonyl)pyrrolidin-1-yl]phosphonate (28)**

A solution of hydrazone 27 (122 mg, 0.453 mmol) in CH\(_2\)Cl\(_2\) (1.5 mL) was added to a 1 M solution of TiCl\(_4\) in CH\(_2\)Cl\(_2\) (906 \( \mu \)L) at −78 °C. After the mixture had stirred for 15 min at −78 °C, Et\(_2\)O (200 \( \mu \)L) was added, and 15 min later, (MeO\(_2\)PO)\(_2\)TMS (130 \( \mu \)L, 0.68 mmol) was added. The stirred reaction mixture was warmed slowly from −78 °C to r.t. over 3 h. After hydrolysis with a sat. aq soln of KF/NH\(_4\)Cl, the mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). Concentration of the organic layer and purification (silica gel, MeOH–Et\(_2\)O, 10:90) gave an inseparable diastereomeric mixture of hydrazinophosphonates 28.

Yield: 100 mg (54%); colorless oil; \( R_f = 0.33 \) (MeOH–Et\(_2\)O–aq NH\(_3\), 10:90:0.5).

\(^1\)H NMR (360 MHz, CDCl\(_3\), 320 K): \( \delta = 1.27/1.28 \) (t, \( J = 7.2 \) Hz, 6 H, CH\(_3\)), 1.48–1.65 (m, 1 H, H\(_{\text{RAMP}}\)), 1.83–2.00 (m, 1 H, H\(_{\text{RAMP}}\)), 2.17–2.37 (m, 2 H, H-4), 2.37–2.64 (m, 1 H), 2.64–2.88 (m, 1 H), 3.00 (s, 1 H, NH), 3.25–3.40 (m, 1 H), 3.32/3.35 (s, OCH\(_3\), b/a), 3.40–3.68 (m, 5 H), 3.68–3.95 (m, 5 H), 3.78 (s, 3 H, CH\(_3\)OP, b), 3.80 (s, 3 H, CH\(_2\)OP, a), 3.83 (s, 3 H, CH\(_2\)OP, a), 4.15/4.16 (q, \( J = 7.2 \) Hz, 2 H, CH\(_2\)OCO, a/b).

\(^{31}\)P NMR (121.49 MHz, CDCl\(_3\)): \( \delta = 299/29.40 \) (b/a); \( \delta = 320 \) K = 29.31 (a and b).

\[ 1^1 \text{H NMR (250 MHz, CDCl}_3\]): \delta = 1.38 (t, J_{P,H} = 7.0 \text{ Hz, } 3 \text{ H}, \text{CH}_3), 1.60 (br s, 2 \text{H, NH}_2), 2.03–2.23 (m, 2 \text{H, 4-H}), 2.72 (dd, J = 11.0, 1.5 \text{ Hz, } 1 \text{H, 2-H}), 3.02 \text{(ddd, } J = 2.5, 7.2, 9.8 \text{ Hz, } 1 \text{H, 5-H}), 3.14 \text{(dd, } J = 7.2, 9.8, 10.7 \text{ Hz, } 1 \text{H, 5-H}), 3.32 \text{(dd, } J_{P,H} = 11.0 \text{ Hz, } 2 \text{J}_{P,H} = 7.5 \text{ Hz, } 1 \text{H, 2-H}), 4.21 \text{(dq, } J_{P,H} = 1.8 \text{ Hz, } 2 \text{J}_{P,H} = 7.0 \text{ Hz, } 2 \text{H, CH}_2O), 4.24 \text{(dq, } J_{P,H} = 1.8 \text{ Hz, } 2 \text{J}_{P,H} = 7.0 \text{ Hz, } 2 \text{H, CH}_2O) \]

\[ 1^3 \text{C NMR (62.9 MHz, D}_2\text{O}): \delta = 12.43 \text{ (d, } J_{P,C} = 7.5 \text{ Hz, } 2 \text{H, CH}_2O) \]

(1-Aminocyclopentyl)phosphonic Acid (3d)

Hydrolysis of aminophosphonate with TMSI according to our previously reported method: TMSI (150 mg, 107 \mu\text{mol}) was added dropwise to a stirred soln of diethyl phosphate (32 mg, 0.25 mmol) in CH2Cl2 (3 mL) and stirring was continued at r.t. for 6 h. The volatiles were then removed in vacuo and a mixture of EtOH (2 mL) and an excess of propylene oxide (1 mL) were added, followed by stirring for 18 h. Once precipitation of pure aminophosphonic acid was complete, it was collected by filtration and dried under high vacuum.

Yield: 40 mg (100%); white solid; mp 243.5 °C (crystallized from H2O–EtOH); \( R_f = 0.45 \) (aq NH4–MeOH, 20:80).

\[ 1^1 \text{H NMR (360 MHz, D}_2\text{O}): \delta = 1.70–1.90 \text{ (m, } 6 \text{H, H}_\text{cycle}), 2.10–2.38 \text{ (m, } 2 \text{H, H}_\text{cycle}) \]

Analytical data were in accord with the literature values.

Diethyl phosphonate (3c·2HCl)

A soln of diethyl phosphonate (3a·2HCl) was dissolved in a min-

\[ 1^3 \text{P NMR (101.25 MHz, CDCl}_3\): \delta = 24.71 \text{ (d, } J_{P,C} = 17.1 \text{ Hz, C-3}) \]

HRMS data could not be obtained.

References


(7) For cyclopentyl derivatives, see: Guéguen, C.; About-Jaudet, E.; Collignon, V.


For microwave assistance, see: Kabachnick, M. M.; Zobina, E. V.; Belatskaya, I. P. Synlett 2005, 1393; and references cited therein.


(a) Louaisil, N.; Rabasso, N.; Fadel, A. Synthesis 2008, 505.

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Unfortunately, HRMS could not be carried out despite use of various kinds of methods, including ESI, EI, or CI.