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Synthesis of P,N-Heterocycles from ω -Amino-*H*-Phosphinates: Conformationally Restricted α -Amino Acid Analogs

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Abstract

P,N-Heterocycles (3-hydroxy-1,3-azaphospholane and 3-hydroxy-1,3-azaphosphorinane-3-oxide) are synthesized in moderate yield from readily available ω -amino-*H*-phosphinates and aldehydes or ketones via an intramolecular Kabachnik-Fields reaction. The products are conformationally restricted phosphinic analogs of α -amino acids. The multi-gram scale syntheses of the $H_2N(CH_2)_nPO_2H_2$ phosphinic precursors ($n = 1, 2, 3$) and some derivatives are also described.

Introduction

Analogues of α -amino acids for use in peptidomimetics are an important and well-studied area of research. The reason rests in the importance of peptidomimetics for the design of medically useful compounds.¹ At the same time, the Kabachnik-Fields reaction, which is the “phosphamannich” reaction of phosphinylidene $[P(O)H]$ compounds, has been investigated and used extensively since its initial discovery in the early nineteenfifties.² However, applications of the reaction to intramolecular cases is surprisingly lacking. In addition, very few P,N-heterocycles have been described in the literature and there are only two known examples of simple 3-hydroxy-1,3-azaphospholane and 3-hydroxy-1,3-azaphosphorinane-3-oxides (both P-O esters, **1** and **2**, respectively, Figure 1).³ Other related heterocycles **3** – **5** have been reported.⁴ In terms of simple ring systems, aminophosphines react with carbonyl compounds to provide heterocycles **6** and **7** in a lower oxidation state than compound **2** (Figure 1).⁵ In general, these syntheses are lengthy and/or inconvenient, and proceed in low overall yields.

Over the past several years, we have developed various methodologies for the synthesis of *H*-phosphinates,⁶ and we became interested in the preparation of ω -amino-*H*-phosphinates which have value in their own right.⁷ Herein, we describe the syntheses of three ω -amino-*H*-phosphinates, and prompted by the availability of these precursors, their reactions with carbonyl compounds.

Results and Discussion

Synthesis of the ω -amino-*H*-phosphinates precursors

Since ω -amino-*H*-phosphinates have potential value for various applications, the multi-gram syntheses of the three precursors **8** – **10** (Figure 2) were developed. Several literature preparations of protected versions of **8** have appeared,⁸ because of the utility of the synthons for phosphinopeptide synthesis.⁹ A synthesis of aminomethyl-*H*-phosphinic acid **8** and some derivatives is described in the Supporting Information.

2-Aminoethyl-*H*-phosphinic acid

2-Aminoethyl-*H*-phosphinic acid **9** was synthesized using our hydrophosphinylation of *N*-vinylphthalimide with hypophosphorous acid H_3PO_2 (Scheme 1).¹⁰

Phthalimide reacted with vinyl acetate according to the literature procedure.¹¹ Palladium-catalyzed hydrophosphinylation with H_3PO_2 using our reusable polymer-supported catalyst¹⁰ gave phosphinic acid **11** in 60–70% yield. When the homogeneous catalyst (0.25 mol% Pd/xantphos) was used, **11** was obtained in 72–87% yield. Simple acid hydrolysis of phthalimide **11** gave hydrochloride **9** as a white solid. Other syntheses of 2-aminoethyl-*H*-phosphinic acid **9** and some derivatives have been reported previously.¹² Kafarski reported^{8c} a nice preparation of **9** via Hoffman degradation (NaOH , Br_2 , -15°C , 77% yield after propylene oxide treatment) of $\text{H}_2\text{PO}_2\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$ itself prepared by thermal conjugate addition of H_3PO_2 with acrylamide.¹³

3-Aminopropyl-*H*-phosphinic acid

We¹⁴ and other¹⁵ have reported previously the preparation of the biologically-active GABA analog 3-aminopropyl-*H*-phosphinic acid and related compounds. For the present study, we opted for a simple synthesis using our Pd-catalyzed hydrophosphinylation on ethyl *N*-allylcarbamate **12** in place of the more expensive benzyl and *tert*-butyl carbamates, since acid hydrolysis would ultimately be employed to form compound **10**. Scheme 2 shows the preparation of **10** from allylamine. As with *N*-vinylphthalimide, this reusable polymer catalyst¹⁰ was employed to directly deliver *H*-phosphinic acid **13**. Hydrolysis then provided hydrochloride **10**. If the synthesis of **10** is desired, alternate routes via other intermediates¹⁴ are more expensive, atom-wasteful, and lower-yielding in the case of **14**.^{14a}

Overall, compounds **8** – **10** were synthesized in reasonable yields and on a multi-gram scale, using some methodologies we have developed previously. The syntheses are generally simpler than comparable literature approaches, and ion-exchange chromatography is avoided in all cases. With the compounds in hand, we then set out to study their reactions with carbonyl compounds for the formation of P,N-heterocycles (eq 1). Yiotakis, Dive, and co-workers have recently reported a different approach toward phosphinic peptidomimetics where the phosphorus atom is exocyclic, also using *H*-phosphinic acids, amines, and aldehydes (eq. 2),^{9a} however in their case the aldehyde and amine functionalities are linked with a tether, whereas in our case, the amine and *H*-phosphinic acid are linked by a tether.

(1)

(2)

Reactions of ω -amino-*H*-phosphinates **8** – **10** with aldehydes and ketones

The intramolecular Kabachnik-Fields reaction of synthons **8** – **10** was investigated with aldehydes and ketones. Maybe not surprisingly, the reaction of aminomethylphosphinate **8** resulted in intractable mixtures of products, although ^{31}P -NMR peaks in the phosphetanic acid¹⁶ range (δ 28 ppm) may indicate some cyclization. The results are not unexpected since the 3-hydroxy-1,3-azaphosphetane oxide ring system is apparently unknown. There are, however, a few 4-membered P,N-heterocycles which have been described.¹⁷ Instead, focus was shifted on the more promising 5- and 6-membered ring precursors **9** and **10**.

2-Substituted 3-hydroxy-1,3-azaphospholane-3-oxides

The reaction of 2-aminoethyl-*H*-phosphinate **9** with carbonyl compounds took place smoothly, in acceptable yields (Table 1). Although the isolated yields are relatively low, the compounds were obtained directly as pure solids by precipitation from the reaction mixtures (entries 1 – 4), or after chromatography on silica gel for the phosphinic esters (entries 5 – 7). Reaction with benzaldehyde under method B provided the butyl ester which could be isolated after acetylation (entry 5). In general, prior esterification of **9** via azeotropic water-removal in a Dean-Stark trap gave better results than the direct reaction, however direct heating of **9** with benzaldehyde (entry 1b, Method C) gave an improved yield of heterocycle **15**, although this was not true with other substrates. Thus, minor changes in the reaction conditions sometimes resulted in significant differences in isolated yields depending on the carbonyl compounds. Method B was employed with ketones because method A failed to deliver the phosphinic acids as precipitates in these cases. Thus, in order to isolate the products **19**, **20**, and **21**, it was necessary to preserve the butyl ester.

2-Substituted 3-hydroxy-1,3-azaphosphorinane-3-oxides

Not surprisingly, *H*-Phosphinate **10** also reacted with aldehydes to form 6-membered heterocycles (Table 2). Again, the yields ranged from low to medium, but the compounds were easily isolated pure in all cases through simple filtration. Unfortunately, ketones failed to provide the desired products.

Method C did not result in a good yield of heterocycle **22** (Table 2, entry 1a), nor did methods A and B. However, changing the thermal heating used for the 5-membered rings (Table 1) with microwave heating gave acceptable results with the 6-membered rings, and in some cases, simply heating the reagents in BuOH provided the products (entries 1c and 7). Again, as it was the case with the 1,3-azaphospholanes, small variations in conditions resulted in large changes in yield for the 1,3-azaphosphorinanes. One key to the success of these reactions is the use of butanol as a solvent. This allowed the precipitation of the heterocycles from the reaction mixture. While the reactions are intrinsically higher yielding than the isolated yields reflect, the conditions are adjusted to directly provide the products as solids and to avoid lengthy purification procedures. No attempt was made at purifying the filtrate in these reactions.

The 1,3-azaphosphorinanes were obtained simply via an intramolecular Kabachnik-Fields reaction as shown in eq. 1. Because the aminopropyl-*H*-phosphinate starting material **10** can easily be prepared on a multi-gram scale, the heterocycles shown in Table 2 are still readily accessible.

Conclusions

Using our own methodologies, we have prepared three ω -amino-*H*-phosphinic acids ($\text{H}_2\text{N}(\text{CH}_2)_n\text{PO}_2\text{H}_2$, $n = 1, 2, 3$) and some variously protected derivatives. Previously unknown phosphinic P,N-heterocycles (3-hydroxy-1,3-azaphospholane- and 3-hydroxy-1,3-azaphosphorinane-3-oxides) were prepared directly from amino-*H*-phosphinates **9** and **10** and aldehydes or ketones using an intramolecular Kabachnik-Fields reaction, under thermal or microwave heating. Although the yields are low to moderate, the heterocycles are generally isolated easily as pure solids from readily available starting materials. These heterocycles are novel analogs of α -amino acids, and as such might be useful in the preparation of peptidomimetics. Other heterocyclic ring systems should be accessible using other amino-*H*-phosphinic acids as precursors and this will be the object of future studies.

Experimental

2-(Phthalimido)ethyl-*H*-phosphinic acid **11** (Scheme 1).¹⁰

Pd_2dba_3 (0.132 g, 0.14 mmol, 0.25 mol% of Pd) and xantphos (0.2 g, 0.34 mmol, 0.3 mol%) were added to a solution of N-vinyl phthalimide (20 g, 115 mmol) and concentrated H_3PO_2 (15.2 g, 2 equiv, 231 mmol) in distilled CH_3CN (230 mL) under nitrogen. The mixture was refluxed for 3 h. On cooling, a brown powder appeared. This precipitate was filtered, washed with CH_3CN (3×50 mL) and dried in vacuo to afford **11** (21.3 g, 77%) as a tan powder: ^1H NMR (D_2O , 300 MHz) δ 7.60–7.70 (m, 4H), 6.92 (d, $J = 538$ Hz, 1H), 3.70–3.80 (m, 2H), 1.80–1.94 (m, 2H); ^{13}C NMR (D_2O , 75.45 MHz) δ 168.3, 135.0, 132.4, 123.7, 31.4, 29.5 (d, $J_{\text{PC}} = 89$ Hz); ^{31}P NMR (D_2O , 121.47 MHz) δ 29.9 (dm, $J = 538$ Hz).

2-Aminoethyl-*H*-phosphinic acid hydrochloride **9** (Scheme 1).¹²

Hydrochloric acid (12 N, 400 mL) was added to (2-phthalimidoethyl)phosphinic acid **11** (20 g, 83.7 mmol). After 16 h of reflux, the mixture was concentrated under high vacuum. The residue was diluted with water and washed with ethyl acetate (3×50 mL). Concentration of the aqueous layer afforded product **9** (7 g, 77%) as a yellow oil: ^1H NMR (D_2O , 300 MHz) δ 6.91 (d, $J = 531$ Hz, 1H), 3.15–3.25 (m, 2H), 1.82–1.98 (m, 2H); ^{13}C NMR (D_2O , 75.45 MHz) δ 33.6, 28.0 (d, $J_{\text{PC}} = 100$ Hz); ^{31}P NMR (D_2O , 121.47 MHz) δ 24.1 (dm, $J = 531$ Hz); HRMS (EI^+) calc for $\text{C}_2\text{H}_8\text{NO}_2\text{P}$ 110.0371, found 110.0377.

(3-Ethoxycarbonylamino-propyl)-*H*-phosphinic acid **13** (Scheme 2)

$\text{Pd}(\text{OAc})_2$ (0.348 g, 1.55 mmol, 1 mol% of Pd) and nixantphos (4.37 g, 1.705 mmol, 1.1 mol %) were added to a solution of (ethylcarbamate)allyl amine (20 g, 155 mmol) and concentrated H_3PO_2 (20.5 g, 2 equiv, 310 mmol) in distilled CH_3CN (300 mL) under nitrogen. The mixture was refluxed for 6 h. After cooling and filtration the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate then washed with brine (2 x). Drying and concentration afforded product **13** as an oil (16.6 g, 55%): ^1H NMR (CDCl_3 , 300 MHz) δ 7.12 (d, $J = 548$ Hz, 1H), 4.02–4.20 (m, 2H), 3.20–3.40 (m, 2H), 1.65–1.95 (m, 2H), 1.24 (t, $J = 7$ Hz, 3H); ^{13}C NMR (D_2O , 75.45 MHz) δ 159.0, 61.9, 40.8 (d, $J_{\text{PCC}} = 18$ Hz), 26.7 (d, $J_{\text{PC}} = 91$ Hz), 20.9, 13.9; ^{31}P NMR (D_2O , 121.47 MHz) δ 37.7 (d, $J = 548$ Hz); HRMS (EI^+) calc for $\text{C}_6\text{H}_{14}\text{NO}_4\text{P}$ 196.0738, found 196.0729.

3-Aminopropyl-*H*-phosphinic acid hydrochloride **10** (Scheme 2).^{14a}

Hydrochloric acid (12 N, 400 mL) was added to 3-ethoxycarbonylaminoethyl-*H*-phosphinic acid **13** (16 g, 81.9 mmol). After 16 h of reflux, the mixture was concentrated under high vacuum. The residue was diluted with water and washed with ethyl acetate (3×50 mL). Concentration of the aqueous layer afforded product **10** as a yellow oil (10.5 g, 80%): ^1H NMR (D_2O , 300 MHz) δ 6.86 (d, $J = 535$ Hz, 1H), 2.91 (t, $J = 7$ Hz, 2H), 1.50–1.80 (m, 4H); ^{13}C

NMR (D₂O, 75.45 MHz) δ 39.9 (d, $J_{\text{PCCC}} = 19$ Hz), 26.7 (d, $J_{\text{PC}} = 91$ Hz), 19.0; ³¹P NMR (D₂O, 121.47 MHz) δ 33.2 (dm, $J = 535$ Hz); HRMS (EI⁺) calc for C₃H₁₀NO₂P 124.0527, found 124.0527.

General procedure for the cyclizations (Tables 1 and Table 2)

Method A—Compound **9** was dissolved in a mixture of HCl (1 N, 1.5 – 2.0 equiv) and *n*-butanol (0.1 M). Under strong stirring, the solution is refluxed with a Dean-Stark for 12 h. After cooling to room temperature, the solution is used as is: ³¹P NMR δ 34.2 (dm). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added one equivalent of the aldehyde. The mixture was refluxed for 12–18 h. After cooling, the precipitate was filtered and washed with *n*-butanol, then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method B—Compound **9** was dissolved in a mixture of HCl (1 N, 1.5 – 2.0 equiv) and *n*-butanol (0.1 M). Under vigorous stirring, the solution is refluxed with a Dean-Stark trap for 12 h. After cooling at room temperature, the solution is used as is: ³¹P NMR δ 34.2 (dm). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added one equivalent of diethylamine and one equivalent of the aldehyde. After a brief stirring at room temperature, the mixture was irradiated by microwaves for 3 min at 200 °C. Concentration under high vacuum and purification by silica gel chromatography (EtOAc / Et₃N 100:0.5, v/v to EtOAc / EtOH / Et₃N 90:10:0.5, v/v) afforded the product as a colorless oil.

Method C—To a solution of compound **9** (1 mmol) in hydrochloric acid (12 N, 10 mL) was added one equivalent of the aldehyde. The mixture was refluxed for 16 h. After cooling, the mixture was concentrated. After precipitation in *n*-butanol, the solid was dried under high vacuum to yield the expected compound as a white solid.

Method D—Dry HCl(g) was bubbled through a solution of compound ethyl (3-tert-butoxycarbonylamino-propyl)-*H*-phosphinate (2.4 g, 9.6 mmol) in 50 mL of distilled dichloromethane for 1 h 30. The solution was then stirred for 12 h at room temperature. After concentration, the residue was diluted with 47 mL of *n*-butanol (0.1 M) and refluxed overnight with a Dean-Stark system. This solution is used directly for the cyclization step (³¹P NMR δ 37.5). To that solution (10 mL, 0.1 M, 1 mmol) in *n*-butanol was added one equivalent of the aldehyde. The mixture was irradiated by microwaves 3 min at 200 °C. After cooling, the precipitate was filtered and washed with *n*-butanol then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method E—To a solution of compound **10** (1 mmol) in *n*-butanol (0.2 M) was added one equivalent of the aldehyde. The mixture was refluxed for 16 h. After cooling, the precipitate was filtered and washed with *n*-butanol then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

Method F—To a solution of compound **10** (1 mmol) in *n*-butanol (0.2 M) was added one equivalent of the aldehyde. The mixture was irradiated by microwaves 10 min at 200 °C. After cooling, the precipitate was filtered and washed with *n*-butanol then with diethyl ether and dried under high vacuum to yield the expected compound as a white solid.

3-Hydroxy-2-(4-methoxy-phenyl)-1,3-azaphospholane-3-oxide **17** (Table 1, Method A)

Yield: 55%. mp > 300 °C; ¹H NMR (D₂O, 300 MHz) δ 7.18 (d, $J = 8$ Hz, 2H), 6.87 (d, $J = 8$ Hz, 2H), 4.04 (d, $J_{\text{PCH}} = 11$ Hz, 1H), 3.65 (s, 3H), 3.45–3.70 (m, 1H), 3.25–3.45 (m, 1H), 1.80–2.10 (m, 2H); ¹³C NMR (D₂O, 75.45 MHz) δ 159.4, 129.8 (d, $J_{\text{PCCC}} = 4$ Hz, 2C), 122.7,

114.7 (2C), 57.5 (d, J_{PC} = 93 Hz), 55.5, 41.9, 23.8 (d, J_{PC} = 86 Hz); ^{31}P NMR (D_2O , 121.47 MHz) δ 42.3 (s); HRMS (EI^+) calc for $\text{C}_{10}\text{H}_{14}\text{NO}_3\text{P}$ 228.0789, found 228.0792.

2-(4-Fluoro-phenyl)-3-hydroxy-1,3-azaphosphorinane-3-oxide **23** (Table 2, Method D)

Yield: 49%. mp > 300 °C; ^1H NMR (D_2O , 300 MHz) δ 7.28 (dd, J = 7 Hz, J = 5 Hz, 2H), 7.03 (dd, J = 9 Hz, 2H), 4.19 (d, J_{POCH} = 7 Hz, 1H), 3.37 (dm, J_{gem} = 13 Hz, 1H), 2.95–3.10 (m, 1H), 1.95–2.20 (m, 2H), 1.60–1.85 (m, 2H); ^{13}C NMR (D_2O , 75.45 MHz) δ 163.0 (d, J_{FC} = 244 Hz), 130.4 (d, J_{FCC} = 4 Hz, 2C), 126.0 (d, J_{PCC} = 6 Hz), 115.9 (d, J_{PCCC} = 22 Hz, 2C), 60.8 (d, J_{PC} = 85 Hz), 46.6 (d, J_{PCCC} = 5 Hz), 27.3 (d, J_{PC} = 90 Hz), 21.7 (d, J_{PCC} = 6 Hz); ^{31}P NMR (D_2O , 121.47 MHz) δ 24.9 (s); ^{19}F NMR (D_2O , 282.306 MHz) δ -115.1 (s); HRMS (EI^+) calc for $\text{C}_{10}\text{FH}_{13}\text{NO}_2\text{P}$ 230.0476, found 230.0749.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Some examples of known 1,3-azaphospho-heterocycles

Figure 2.
The three precursors used in this study

Scheme 1.
Synthesis of 2-aminoethyl-*H*-phosphinic acid **9**

Scheme 2.
Synthesis of 3-aminopropyl-*H*-phosphinic acid **10**

Method ^b	Product	Compound	Isolated yield % ^c
<p> $\text{HCl}\cdot\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{P}(=\text{O})(\text{OH})_2$ (1 equiv) + $\text{R}^1-\text{C}(=\text{O})-\text{R}^2$ (1 equiv) $\xrightarrow[\text{heat}]{\text{method}}$ $\text{Cyclic phosphoramidate}$ (R = H, Bu) </p>		15	55
	16	44
	17	55

Method ^b	Product	Compound	Isolated yield % ^c
A		18	42

A *J Org Chem.* Author manuscript; available in PMC 2009 November 21.

Method ^b	Product	Compound	Isolated yield % ^c
$ \begin{array}{c} \text{HCl} \cdot \text{H}_2\text{N} \\ \text{9 (1 equiv)} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{P} - \text{OH} \\ \\ \text{H} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{P} - \text{OR} \\ \quad \\ \text{R}^1 \quad \text{R}^2 \end{array} \xrightarrow[\text{heat}]{\text{method}} \begin{array}{c} \text{O} \\ \parallel \\ \text{P} - \text{OR} \\ \quad \\ \text{R}^1 \quad \text{R}^2 \end{array} \begin{array}{l} \text{(1 equiv)} \\ \text{R = H, Bu} \end{array} $		19	24 ^d
	20	48

Method^b

B

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Compound

21

Isolated yield %^c

48

Product

IEA (1 equiv), microwave heating, 200 °C, 3–6 min.

Method ^b	Product	Compound	Isolated yield % ^c
C		22	^d
D			43
E			76
F			33

Method ^b	Product	Compound	Isolated yield % ^c
D		23	49
D		24	55
D		25	38

+

Isolated yield %^c

Compound

Product

Method^b

31

26

D

+

Isolated yield %^c

Compound

Product

Method^b

34

27

D

Method ^b	Product	Compound	Isolated yield % ^c
E		28	20