



A simple, novel and convenient method for the synthesis of 1-aminophosphinic acids: synthesis of a novel C₂-symmetric phosphinic acid pseudodipeptide

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ABSTRACT

A simple, efficient and novel method has been developed for the synthesis of 1-aminophosphinic acids from simple starting materials. Treatment of aromatic aldehydes with ammonia and hypophosphorus acid gives novel C₂-symmetric 1-aminoarylmethylphosphinic acids. The synthesis of novel C₂-symmetric phosphinic acid pseudodipeptides is also discussed.

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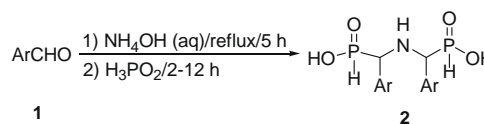
Phosphinic acids are of growing importance in understanding and modulating biological processes.¹ In recent years, the synthesis of α -substituted phosphoryl derivatives (phosphonic and phosphinic acids) has attracted significant attention, due to their biological activities with broad application as enzyme inhibitors, antimetabolites and antibiotics.² Among α -functionalized phosphinic acids, α -aminoalkylphosphinic derivatives have potential biological activities, such as anti-bacterial,² herbicidal³ and fungicidal.⁴ 1-Aminoalkylphosphinic acids, the phosphinic acid analogues of 1-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties. In addition, the structure of the phosphinic functional group mimics the transition state of peptide hydrolysis, and the symmetric nature of the phosphinic acid derivatives is expected to be of benefit in their binding to the homodimer of HIV-protease having C₂-axis symmetry.

A phosphinic moiety (–PO₂–CH₂–) is considered a mimic of the tetrahedral transition state of peptide bond hydrolysis and due to this, phosphinate pseudopeptides have attracted considerable interest providing a wide range of potent inactivators of proteolytic enzymes, particularly metalloproteases.⁵ In contrast to the widely studied 1-aminoalkylphosphonic acid derivatives,^{6–9} relatively few papers have reported the chemistry of 1-aminoalkylphosphinic acids, although there is evidence that α -aminophosphinic acids are pharmaceutically active. Synthetic routes to 1-aminoalkylphosphinic acids involve Mannich-type reaction of amines with aldehydes in the presence of anhydrous hypophosphorus acid and prolonged heating of anhydrous hypophosphorus acid with a Schiff's base.¹⁰ The addition of hypophosphorus acid to structurally diverse imines appears to be a general method for the preparation of N-substituted 1-aminoalkylphosphinic acids.¹¹ However, both of these methods have drawbacks, such as harsh reaction conditions, anaerobic and anhydrous conditions, long reaction times

and also side reactions. On the other hand, the key step in the one-pot synthesis of 1-aminoalkylphosphinic acids is nucleophilic addition of an amine to a carbonyl compound followed by addition of hypophosphorus acid to the resulting imine. Therefore, the formation of 1-hydroxyalkylphosphinic acids frequently accompanies the formation of 1-aminoalkylphosphinic acids.¹² Hydrophosphinylation of *N,N'*-arylidene bisamides has been reported as a new method for the synthesis of 1-aminophosphinic acids.¹³ However, this method also has problems, and includes difficulties in the preparation of starting materials and requires harsh reaction conditions for hydrolysis of the amide intermediate to the amine product.

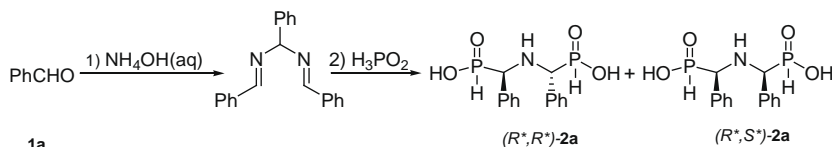
Diimines serve as good precursors for the synthesis of numerous organic compounds, especially heterocyclic compounds.^{14,15} These, easily accessible precursors can be produced by the reaction of aromatic aldehydes with ammonia solution. Recently, we reported the reaction of diimines with diethyl phosphite for the preparation of bis(1-diethoxyphosphorylalkyl)amines.¹⁶ As part of our efforts to introduce novel methods for the synthesis of organophosphorus compounds,¹⁷ herein we report a new method for the synthesis of α -aminophosphinic acids and novel C₂-symmetric phosphinic acid pseudodipeptides. We have found that reaction of aromatic aldehydes with ammonia solution followed by reaction with hypophosphorus acid gives 1-aminophosphinic acids in good yields (Scheme 1).

Thus, the reaction of benzaldehyde, chosen as a model compound, with ammonia followed by treatment with hypophosphorus acid was studied under various reaction conditions. When the reaction was conducted under reflux for 10 h using 5 equiv of



Scheme 1.

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Scheme 2.

H_3PO_2 (anhydrous), the ^{31}P NMR spectrum of the product exhibited two major peaks at δ 17.85 and 17.58 due to the diastereoisomers of **2a**. The ^1H NMR spectrum exhibited two doublets at δ 4.16 and 3.79 indicative of HC–P coupling ($J_{\text{HP}} = 13.5$ Hz). Two doublets at δ 6.88 and 6.83 were indicative of H–P coupling ($J_{\text{HP}} = 552$ Hz). Due to the presence of two stereogenic carbons bonded to a phosphorus atom, and due to the prototopic transfer of the acidic proton between the phosphoryl (P=O) and acidic (P–OH) sites, these compounds exist as two diastereomeric forms: one *meso*-compound (R^*S^* -**2a**) and one racemic pair (S^*S^* or R^*R^* -**2a**), as shown in Scheme 2. When the mixture of diastereoisomers **2a** was washed with a solvent mixture of ethanol/water (9:1) and dried in air at room temperature, a single diastereoisomer was obtained. As we were unable to obtain an X-ray crystal of the two diastereoisomers of **2a**, their unambiguous stereochemical assignments have not been determined. It should be noted that when the reaction was carried out with 50% hypophosphorous acid, 1-hydroxyphenyl methylphosphonic acid was obtained as the major product.

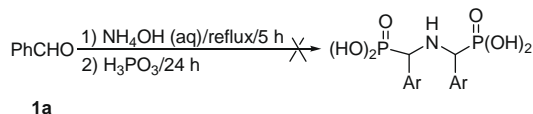
This process was applied successfully to other aromatic aldehydes as summarized in Table 1. Substituted benzaldehydes reacted with ammonia followed by reaction with hypophosphorous acid to afford the desired products **2b–f** in moderate to good yields. 2-Naphthalene carbaldehyde also reacted with hypophosphorous acid in the presence of ammonia to give compound **2g** in 40% yield. Reaction of aliphatic aldehyde **1h** with hypophosphorous acid in the presence of ammonia gave an unidentified mixture of products.

Table 1
Synthesis of 1-aminophosphonic acids **2** from aldehydes

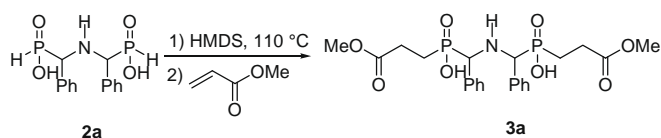
Entry	Ar	Reaction time (h)	Yield ^a (%)
a	C_6H_5 -	10	48
b	<i>p</i> - ClC_6H_4 -	11	71
c	<i>p</i> - FC_6H_4 -	12	61
d	<i>p</i> - MeOC_6H_4 -	12	45
e	<i>p</i> - MeC_6H_4 -	11	64
f	<i>o</i> - FC_6H_4 -	2	42
g	2-Naphthyl	8	40
h	<i>n</i> - C_6H_{13} -	—	— ^b

^a Isolated yields of mixtures of two diastereoisomers.

^b Unknown products obtained.



Scheme 3.



Scheme 4.

These results prompted us to extend this process to phosphorus acid for the synthesis of 1-aminophosphonic acids (Scheme 3). Initially, we carried out the reaction of benzaldehyde **1a** with ammonia in the presence of phosphorus acid under reflux conditions. Unfortunately, the reaction failed, and no product was detected after 24 h at reflux.

Phosphorus–carbon bond formation via Michael addition is a useful method for the synthesis of phosphinic acid dipeptides with application in organic synthesis and bioorganic chemistry. A novel C_2 -symmetric phosphinic acid dipeptide was synthesized by Michael addition of **2a** to methyl acrylate. 1-Aminophosphonic acid **2a** (single diastereoisomer) was activated by silylation with HMDS¹⁸ then reacted with methyl acrylate to afford adduct **3a** in 85% yield (Scheme 4).

In summary, the simple work-up, mild reaction conditions, good yields and clean reactions with no tar formation make this method an attractive and useful contribution to present methodologies.¹⁹ A novel C_2 -symmetric phosphinic acid dipeptide was also synthesized by Michael addition of **2a** to methyl acrylate.²⁰ Further investigations on the stereochemistry of the products and their complexation ability are now in progress.

Acknowledgement

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19. The aldehyde (3 mmol) was added to ammonium hydroxide (30%, 15 mL), and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate was removed by filtration and dried. The solid was dissolved in 5 mL of ethanol, and anhydrous hypophosphorus acid (5 mmol) was added to this mixture and the resulting solution was stirred for 2–12 h at reflux. The solvent was evaporated and the mixture was dissolved in acetone by heating. Dropwise addition of water gave the crude product as a white solid. The crude product was washed with ethanol and dried in air at room temperature to give product **2** in 40–71% yield. The solid product was washed with ethanol/water (50 ml, 9:1) and dried in air at room temperature to give a single diastereoisomer. All products gave satisfactory spectral data in accord with the assigned structures. Analytical and spectral data for compounds **2**: **Compound 2a**: white solid, mixture of two diastereoisomers; ¹H NMR (D₂O/TMS-250 MHz): 3.79, 4.16 (2H, 2d, J = 13.5 Hz, -CHP), 6.83, 6.88 (2H, 2d, J_{HP} = 552 Hz), 6.85–7.40 (10H, m); ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 60.0–62.1 (m, CHP), 127.0, 127.5, 127.7, 128.5, 128.7, 128.9, 134.9, 136.5; ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.58, 17.85 (40:60) ppm; IR (KBr): 3650–2120 (-OH), 1250 (P=O), 1055–710 (P-O) cm⁻¹; Anal. Calcd for C₁₄H₁₇NO₄P₂: C, 51.68; H, 5.27; N, 4.31. Found: C, 51.55; H, 5.20; N, 4.56. **Compound 2b**: white solid, single diastereoisomer, mp: 240–242 °C; ¹H NMR (D₂O/TMS-250 MHz): 3.79 (2H, d, J = 14.0 Hz, -CHP), 6.84 (2H, d, J_{HP} = 552 Hz), 6.91 (4H, d, J = 7.2 Hz), 7.21 (4H, d, J = 7.2 Hz); ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 59.2–61.5 (m, CHP), 128.7, 130.1 (d, J_{CP} = 5.7 Hz), 132.8 (d, J_{CP} = 3.1 Hz), 133.4 (d, J_{CP} = 3.8 Hz); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.37 ppm; IR (KBr): 3650–2120 (-OH), 1250 (P=O), 1080–750 (P-O) cm⁻¹; Anal. Calcd for C₁₄H₁₅Cl₂NO₄P₂: C, 42.75; H, 3.85; N, 3.56. Found: C, 42.56; H, 3.80; N, 3.52. **Compound 2c**: white solid, single diastereoisomer, mp: 230–232 °C; ¹H NMR (D₂O/TMS-250 MHz): 3.98 (2H, d, J = 13.5 Hz, -CHP), 6.99 (2H, d, J_{HP} = 552 Hz), 7.01–7.15 (m, 8H); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.22 ppm; IR (KBr): 3650–2120 (-OH), 1240 (P=O), 1180–580 (P-O) cm⁻¹; ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 60.1 (dd, J_{CP} = 98.5 and 14.1 Hz), 115.4 (d, J_{CP} = 21.4 Hz), 130.1–130.5 (m, Ar), 162.1 (d, J_{CP} = 243.2 Hz), Anal. Calcd for C₁₄H₁₅F₂NO₄P₂: C, 46.53; H, 4.19; N, 3.88. Found: C, 46.56; H, 4.12; N, 3.72. **Compound 2d**: white solid, single diastereoisomer, mp: 212–214 °C; ¹H NMR (D₂O/TMS-250 MHz): 3.63 (s, 6H), 3.73 (2H, d, J = 14.5 Hz, -CHP), 6.86 (2H, d, J_{HP} = 550 Hz), 6.82 (4H, d, J = 8.0 Hz), 6.90 (4H, d, J = 8.0 Hz); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.81 ppm; IR (KBr): 3650–2320 (-OH), 1248 (P=O), 1150–650 (P-O) cm⁻¹; ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 55.3, 59.2–61.5 (m, CHP), 114.8, 120.4, 130.1 (d, J_{CP} = 5.5 Hz), 159.7; Anal. Calcd for C₁₆H₂₁NO₆P₂: C, 49.86; H, 5.50; N, 3.64. Found: C, 49.71; H, 5.43; N, 3.52. **Compound 2e**: white solid, mixture of two diastereoisomers; ¹H NMR (D₂O/TMS-250 MHz): 2.07, 2.10 (s, 6H), 3.72, 4.12 (2H, 2d, J = 14.0 Hz, -CHP), 6.83, 6.88 (2H, 2d, J_{HP} = 551 Hz), 6.75–7.17 (8H, m); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.86, 18.12 ppm; IR (KBr): 3650–2220 (-OH), 1251 (P=O), 1185–610 (P-O) cm⁻¹; ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 20.1, 60.0–62.1 (m, CHP), 128.4 (d, J_{CP} = 5.7 Hz), 128.8 (d, J_{CP} = 5.7 Hz), 129.0, 129.2, 131.6, 133.3, 137.6 (d, J_{CP} = 3.1 Hz), 137.9 (d, J_{CP} = 3.1 Hz). Anal. Calcd for C₁₆H₂₁NO₆P₂: C, 54.38; H, 5.99; N, 3.96. Found: C, 54.30; H, 5.85; N, 4.05. **Compound 2f**: white solid, single diastereoisomer, mp: 226–228 °C; ¹H NMR (D₂O/TMS-250 MHz): 4.15 (2H, d, J = 14.7 Hz, -CHP), 6.90 (2H, d, J_{HP} = 557.5 Hz), 6.75–7.85 (m, 8H); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 15.95 ppm; IR (KBr): 3650–2120 (-OH), 1240 (P=O), 1180–580 (P-O) cm⁻¹; ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 60.1 (dd, J_{CP} = 98.5 and 14.1 Hz), 116.1 (d, J_{CP} = 21.4 Hz), 125.3–130.5 (m, Ar), 161.1 (d, J_{CP} = 242.0 Hz), Anal. Calcd for C₁₄H₁₅F₂NO₄P₂: C, 46.53; H, 4.19; N, 3.88. Found: C, 46.50; H, 4.15; N, 3.75. **Compound 2g**: white solid, single diastereoisomer, mp: 212–214 °C; ¹H NMR (D₂O/TMS-250 MHz): 4.13 (2H, d, J = 13.2 Hz, -CHP), 7.13 (2H, d, J_{HP} = 551 Hz), 6.90–7.80 (m, 12H), 6.90 (2H, d, J = 8.0 Hz); ³¹P NMR (D₂O/H₃PO₄-101.2 MHz): 17.80 ppm; IR (KBr): 3650–2100 (-OH), 1248 (P=O), 1050–750 (P-O) cm⁻¹; ¹³C NMR (D₂O-NaOD/TMS-62.9 MHz): 61.2 (dd, J_{CP} = 97.5 and 13.8 Hz), 126.1–126.5 (m, Ar) 127.6, 128.0 (d, J_{CP} = 7.0 Hz), 128.2, 132.5, 132.6 132.9; Anal. Calcd for C₂₂H₂₁NO₄P₂: C, 62.10; H, 4.98; N, 3.29. Found: C, 61.97; H, 5.03; N, 3.22.
20. A mixture of phosphinic acid **2a** (one diastereoisomer, 1 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (5 mmol, 1 mL) was heated at 110 °C for 2 h under Ar. The mixture was cooled to rt. Methyl acrylate (2 mmol, 0.18 mL) was added dropwise and the resulting mixture was stirred at 60 °C for 12 h. Absolute EtOH (10 mL) was added and the mixture was cooled to rt slowly. The solvent was removed under vacuum. The residue was treated with a solution of sodium bicarbonate (5%, 10 mL) and extracted with ethyl acetate (3 × 10 mL). The aqueous solution was acidified with HCl (5%), and extracted with CHCl₃ (4 × 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure to give **3a** as a white solid in 85% yield. Mp: 95–96 °C; ¹H NMR (DMSO/TMS-250 MHz): 1.55–1.90 (m, 4H), 2.20–2.40 (m, 4H), 3.54 (s, 8H), 5.10–5.75 (br s, NH), 7.10–7.40 (m, 10H); ³¹P NMR (DMSO/H₃PO₄-101.2 MHz): 43.68 ppm; ¹³C NMR (DMSO/TMS-62.9 MHz): 21.8 (d, J_{CP} = 93.7 Hz), 26.6, 52.0, 59.9 (dd, J_{CP} = 99.8 and 13.3 Hz), 127.2–129.5 (m, Ar), 135.6, 172.9 (d, J_{CP} = 16.1 Hz); Anal. Calcd for C₂₂H₂₉NO₈P₂: C, 53.10; H, 5.89; N, 2.82. Found: C, 53.05; H, 5.80; N, 2.65.