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Synthesis of alkyl hydrogen (1-aminoalkyl)phosphonates

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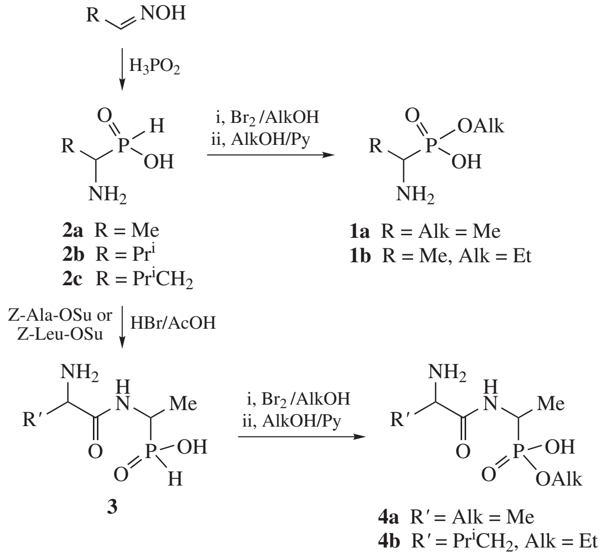
Addition of hypophosphorous acid to aldoximes affords (1-aminoalkyl)phosphinic acids which on treatment with bromine in alkanols are transformed into alkyl hydrogen (1-aminoalkyl)phosphonates.

Alkyl hydrogen (1-aminoalkyl)phosphonates **1** are important organophosphorus analogues of amino acids and can inhibit enzymes of amino acid metabolism. Usually they are prepared from the corresponding phosphonic acids by their conversion into chlorides or activated esters, or by using dicyclohexylcarbodiimide (DCC).[1] Reported synthesis of alkyl hydrogen phosphonates from phosphinic acids in case of amino derivatives **2** involves amino group protection, esterification with DCC, oxidation with sodium periodate and removal of protection.[2]

Here we report a convenient method for the preparation of (1-aminoalkyl)phosphinic acids **2** from oximes, their monoesterification as well as synthesis of a dipeptide phosphorus analogues **3**, **4** (Scheme 1, *cf.* refs. 2–4).



Scheme 1

Acids of type **2** are usually accessed through addition of H_3PO_2[5,6] or bis(trimethylsilyl)phosphonite[7] to N-substituted imines. The use of benzhydryl protection was reported in a three-stage preparation of phosphinic analogues of protein amino acids.[8] Recently we have invented one-step synthesis of acids **2** by a reaction of oximes with anhydrous H_3PO_2[9] that involved the addition of this acid to the C=N bond and reduction of the N–O bond. This approach is further investigated in the present study. The possible intermediate, [1-(*N*-hydroxyamino)ethyl]phosphinic acid, on the pathway to acid **2a** was independently obtained by reduction of acetophosphinic acid oxime. However, this compound was not converted to acid **2** on treatment with H_3PO_2. Similarly, reduction of the N–O bond and formation of an addition product were not observed in the case of *O*-alkylaldoxime. These observations suggested that the addition of H_3PO_2 at the C=N bond is preceded by the reduction of the N–O bond. It is known that *O*-dialkylphosphite esters of ketoxime and ethyl ester of acetohydroxamic acid can undergo a phosphite-phosphate rearrangement by a radical mechanism to give N-phosphorylated imines.[10,11] This mechanism of N–O bond reduction followed by H_3PO_2 addition to the imine double bond is likely to occur in the formation of acids **2**. We have found the conditions providing to control the reaction between oximes and H_3PO_2. Phosphinic analogues of alanine **2a**, valine **2b** and leucine **2c** were obtained in yields of about 50% upon regulated addition of oximes to H_3PO_2 and HCl solutions to heated lower alcohols.[†]

In our one-step procedure for the preparation of monoesters, the amino group protection, activation and esterification of the phosphorus acid moiety were achieved by the action of bromine on solutions of hydrochlorides of amino phosphinic acids **2** in appropriate alcohols.[‡] Here, (1-aminoalkyl)phosphonic acid bromide is initially formed, whose alcoholysis in the presence of pyridine as an HBr scavenger results in monoesters **1**. Previously,[8] oxidation of

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[†] A solution of acetaldoxime (29.5 g, 0.5 mol) in MeOH (40 ml) was added with stirring over 1 h under N_2 to a boiling solution of 95% H_3PO_2 (70 g, 1 mol) in 125 ml of 3% HCl in MeOH. The mixture was refluxed for 4 h, kept for 12 h at 20 °C and evaporated *in vacuo* at <45 °C; the residue was dissolved in a minimum amount of water, neutralized with 25% NH_4OH with stirring and cooling, and chromatographed on a Dowex 50x8 resin (H^+ form, elution with 0.5 N NH_4OH). Ninhydrin positive fractions were evaporated *in vacuo*; the residue was dried *in vacuo* over P_2O_5 and KOH to give 30 g (55%) of acid **2a**.[6] A TLC-homogeneous product was obtained by chromatography on a Dowex 50x8 resin (H^+ form, elution with 15% aqueous Pr^{i}OH), followed by evaporation of the appropriate fractions *in vacuo* and drying of the residue *in vacuo* over P_4O_{10} and KOH. Ascending TLC was performed on Silufol UV$_{254}$ plates (Kavalier, Czechoslovakia), system: Pr^{i}OH–25% NH_4OH–H_2O, 7:1:2 (A); the compounds were detected by colour reactions with ninhydrin and ammonium molybdate. Known acids **2b**,[6] yield 53%, and **2c**,[6] yield 49%, were obtained by a similar manner.

[‡] A solution of Br_2 (650 mg, 4.06 mmol) in $CHCl_3$ (1 ml) was added at 4 °C with stirring to a solution of acid **2a** (436 mg, 4 mmol) in 5 ml of dry MeOH containing 1 equiv. of HCl. After discoloration, the mixture was gradually added at 4 °C with stirring to dry MeOH (10 ml) containing pyridine (1.2 g, 14 mmol). The mixture was kept for 12 h at 20 °C and evaporated *in vacuo*; the residue was dissolved in H_2O (3 ml) and the product was isolated on a Dowex 50x8 resin (H^+ form, elution with 15% aqueous Pr^{i}OH). The fractions containing monoester **1a** according to TLC (system A) were evaporated *in vacuo*; the residue was dried *in vacuo* over P_4O_{10} and KOH to give 450 mg (80%) of monoester **1a**, mp 232–234 °C (decomp.), R_f 0.53 (A). ^{1}H NMR (400 MHz, D_2O) δ: 1.34 (dd, 3H, $^3J_{HH}$ 7.3 Hz, $^3J_{HP}$ 14.9 Hz), 3.34 (dq, 1H, $^3J_{HH}$ 7.3 Hz, $^2J_{HP}$ 12.5 Hz), 3.53 (d, 3H, $^3J_{HP}$ 10.4 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 17.7 (dqq, 1P, $^3J_{1,PH}$ 14.9 Hz, $^3J_{2,PH}$ 10.4 Hz, $^2J_{PH}$ 12.5 Hz).

(1-aminoalkyl)phosphinic acids with bromine in water was used to access the corresponding phosphonic acids. In a similar way, esters **4** were obtained from the known compounds **3**, which were prepared by acylation of racemic acids **2** with activated esters of N-protected L-amino acids, followed by deprotection of the dipeptide analogue.[3,4] The reaction was accompanied by the formation of minor amounts of the corresponding phosphonic acids which were easily separated by ion exchange chromatography.

The products prepared are promising biologically active compounds. Preliminary *in vitro* experiments with *Magnaporthe grisea* (Hebert) Barr fungi, the originator of rice blast, under various growing conditions on solid media, showed that monoesters **1** and **4** inhibited the pigmentation and growth of mycelium (especially ester **4b** at concentrations < 10 μg cm^{-3}), whereas the corresponding phosphonic acids were inactive.

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The following compounds were obtained by the analogous technique.

1b, yield 73%, mp 235–238 °C (decomp.). R_f 0.51 (A). ^{1}H NMR (400 MHz, D_2O) δ: 1.17 (t, 3H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 1.34 (dd, 3H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{3}J_\mathrm{HP}$ 14.9 Hz), 3.34 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{2}J_\mathrm{HP}$ 12.6 Hz), 3.90 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{2}J_\mathrm{HP}$ 12.5 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 16.4 (dtq, 1P, $^{3}J_\mathrm{1,PH}$ 14.9 Hz, $^{3}J_\mathrm{2,PH}$ 7.8 Hz, $^{2}J_\mathrm{PH}$ 12.6 Hz).

4a, yield 79%, decomp. at 223–226 °C. R_f 0.55 (A); a 1:1 mixture of two diastereomers. Diastereomer **4′a**: ^{1}H NMR (400 MHz, D_2O) δ: 1.21 (dd, 3H, $^{3}J_\mathrm{HH}$ 7.4 Hz, $^{3}J_\mathrm{HP}$ 15.2 Hz), 1.43 (d, 3H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 3.46 (d, 3H, $^{3}J_\mathrm{HP}$ 10.2 Hz), 3.96 (q, 1H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 4.06 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.4 Hz, $^{2}J_\mathrm{HP}$ 14.0 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 22.3 (dqq, 1P, $^{3}J_\mathrm{1,PH}$ 15.2 Hz, $^{3}J_\mathrm{2,PH}$ 10.2 Hz, $^{2}J_\mathrm{PH}$ 14.0 Hz); diastereomer **4″a**: ^{1}H NMR (400 MHz, D_2O) δ: 1.21 (dd, 3H, $^{3}J_\mathrm{HH}$ 7.4 Hz, $^{3}J_\mathrm{HP}$ 15.2 Hz), 1.41 (d, 3H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 3.49 (d, 3H, $^{3}J_\mathrm{HP}$ 10.2 Hz), 3.94 (q, 1H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 4.07 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.4 Hz, $^{2}J_\mathrm{HP}$ 14.0 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 22.2 (dqq, 1P, $^{3}J_\mathrm{1,PH}$ 15.2 Hz, $^{3}J_\mathrm{2,PH}$ 10.2 Hz, $^{2}J_\mathrm{PH}$ 14.0 Hz).

4b, yield 64%, decomp. at 220–227 °C, R_f 0,68 (A); a 2:1 mixture of two diastereomers. Diastereomer **4′b**: ^{1}H NMR (400 MHz, D_2O) δ: 0.84 (d, 3H, $^{3}J_\mathrm{HH}$ 6.3 Hz), 0.86 (d, 3H, $^{3}J_\mathrm{HH}$ 6.3 Hz), 1.14 (t, 3H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 1.20 (dd, 3H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{3}J_\mathrm{HP}$ 15.2 Hz), 1.49–1.72 (m, 3H), 3.79 (dd, 1H, $^{3}J_\mathrm{1,HH}$ 7.1 Hz, $^{3}J_\mathrm{1,HH}$ 5.2 Hz), 3.85 (dq, 2H, $^{3}J_\mathrm{HH}$ 7.1 Hz, $^{3}J_\mathrm{HP}$ 7.1 Hz), 4.06 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{2}J_\mathrm{HP}$ 14.7 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 20.9 (dtq, 1P, $^{3}J_\mathrm{1,PH}$ 15.2 Hz, $^{3}J_\mathrm{2,PH}$ 7.1 Hz, $^{2}J_\mathrm{PH}$ 14.7 Hz); diastereomer **4″b**: ^{1}H NMR (400 MHz, D_2O) δ: 0.85 (d, 3H, $^{3}J_\mathrm{HH}$ 6.3 Hz), 0.87 (d, 3H, $^{3}J_\mathrm{HH}$ 6.3 Hz), 1.11 (t, 3H, $^{3}J_\mathrm{HH}$ 7.1 Hz), 1.22 (dd, 3H, $^{3}J_\mathrm{HH}$ 7.3 Hz, $^{3}J_\mathrm{HP}$ 15.2 Hz), 1.49–1.72 (m, 3H), 3.80 (dd, 1H, $^{3}J_\mathrm{1,HH}$ 7.1 Hz, $^{3}J_\mathrm{1,HH}$ 5.2 Hz), 3.87 (dq, 2H, $^{3}J_\mathrm{HH}$ 7.1 Hz, $^{3}J_\mathrm{HP}$ 7.1 Hz), 4.04 (dq, 1H, $^{3}J_\mathrm{HH}$ 7.3 Hz , $^{2}J_\mathrm{HP}$ 14.7 Hz). ^{31}P NMR (162 MHz, D_2O) δ: 20.9 (dtq, 1P, $^{3}J_\mathrm{1,PH}$ 15.2 Hz, $^{3}J_\mathrm{2,PH}$ 7.1 Hz, $^{2}J_\mathrm{PH}$ 14.7 Hz).