Polish J. Chem., **76**, 1619–1623 (2002)

Synthesis of New Imidazole Aminophosphonic and Aminophosphinic Acids

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(Received June 6th, 2002; revised manuscript August 5th, 2002)

Imidazole aminophosphonic and imidazole aminophosphinic acids were synthesized by treatment of imidazole aldimines with silylated phosphorus acid esters. The aldimines were obtained from corresponding imidazolecarboxaldehydes and primary amines.

Key words: 4(5)-imidazolecarboxaldehyde, aldimines, aminophosphonic acids, aminophosphinic acids, bromotrimethylsilane, trimethyl phosphite, ethyl phenylphosphinate

Imidazole derivatives of aminophosphonic acids are interesting compounds because of their potential biological activity. Some imidazole phosphonates (as *e.g.* phosphonic analogue of histidine), or related imidazole compounds are considered as enzyme inhibitors [1,2]. Imidazole phosphonic acids are also efficient agents for complexation of heavy metal ions. Recently, it was found, that phosphonic analogue of imidazole-4(5)-glycine was a strong binding agent for Cu(II) ions, more powerful than histidine itself [3]. Literature data concerning imidazole aminophosphonic acids are very scarce. For example, the phosphonic analogue of histidine was synthesized in 1988 [2], and the simplest representative of this class of compounds; the imidazole-4(5)-yl-aminomethylphosphonic acid was obtained a few years ago [4].

In order to have some new imidazole derivatives for biological studies and inspection of their binding abilities toward metal ions, we have synthesized some new aminophosphonic and aminophosphinic acids in the imidazole series. In this work, we report a convenient method of synthesis of these derivatives. It was found, that partially silylated phosphorus acid esters are effective reagents for preparation of aminophosphonates from aldimines [5]. Also, the completely silylated phosphorus esters were efficient in synthesis of a variety of aromatic and heterocyclic aminophosphonic acids [6,7]. We found, that application of this method allowed to obtain the imidazole aminophosphonic acids in high yields.

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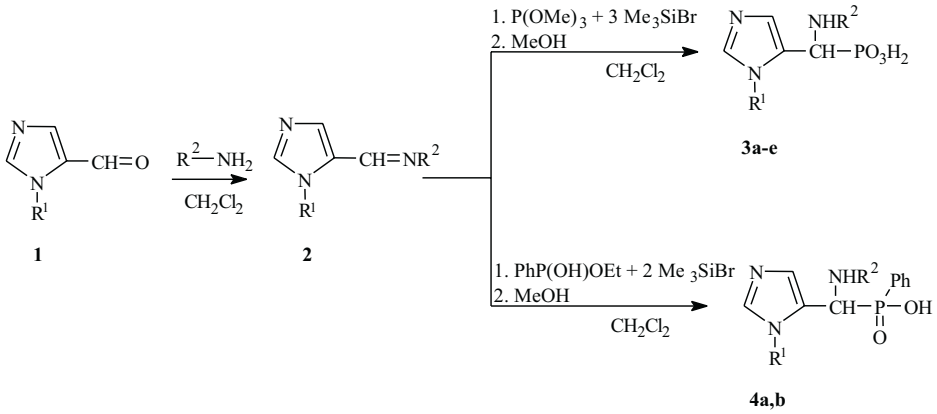
RESULTS AND DISCUSSION

Synthesis of imidazole phosphonic and phosphinic acids is illustrated in Scheme 1. Imidazole aldehydes **1** reacted with primary amines to form corresponding aldimines **2**. The aldimines were not isolated, but reacted further with a mixture of trimethyl phosphite (or ethyl phenylphosphinate) and bromotrimethylsilane. It caused formation of the phosphonic (or phosphinic) silylated intermediates, which after work-up with methanol gave the final aminophosphonic (**3**) or aminophosphinic acids (**4**), respectively (Scheme 1).

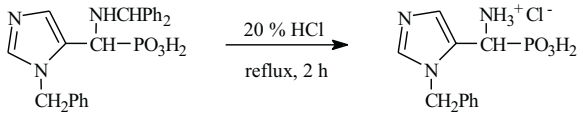
Scheme 1



3a: R^1 = H, R^2 = CH_2Ph; 3b: R^1 = CH_2Ph, R^2 = CH_2Ph; 3c: R^1 = H, R^2 = Bu; 3d: R^1 = CH_2Ph, R^2 = Bu; 3e: R^1 = CH_2Ph, R^2 = $CHPh_2$; 4a: R^1 = H, R^2 = CH_2Ph; 4b: R^1 = CH_2Ph, R^2 = CH_2Ph

Addition of the partially silylated phosphorus esters to a double bond of imines has been studied [5–7]. The silylated esters are good nucleophiles and they easily react with imines [5]. In this case, a nucleophilic reagent taking part in phosphorylation of imidazole imines **2** was: tris(trimethylsilyl ester [$P(OSiMe_3)_3$] [6,7], or di(trimethylsilyl) ester [$PhP(OSiMe_3)_2$], respectively. The silyl esters were formed from corresponding trimethyl phosphite and ethyl phenylphosphinate, by action of bromotrimethylsilane. Use of bromotrimethylsilane made easier the silylation process, in comparison with chlorotrimethylsilane, which was used in the most reactions of silylation [5]. Also, it allowed to obtain the aminophosphonic and phosphinic acids on the direct, straight way. Aminophosphonic acids **3** and **4** were obtained in high yield and purity. 1-Benzylimidazole-5-(amino)methylphosphonic acid (**3f**) was obtained by heating of the *N*-benzhydryl derivative **3e** with aqueous hydrochloric acid. During hydrolysis, the benzhydryl group was removed, leaving the aminophosphonic acid **3f**, as hydrochloride (Scheme 2).

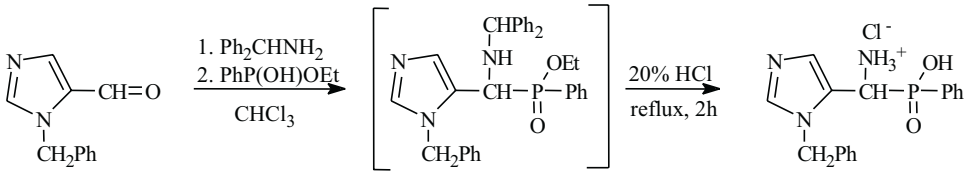
Scheme 2



3e **3f**

The phosphinic derivative **4c**: 1-benzylimidazole-5-(amino)methylphosphinic acid was obtained in a one-pot synthesis, as it is shown in Scheme 3.

Scheme 3



1 **4c**

The synthesized phosphonic and phosphinic acids are investigated as new ligands for metal complexes. Research is in progress and the results will be submitted in a separate publication.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in D_2O or in DMSO-d_6, using 300.13 MHz for ^{1}H NMR, and 121.51 MHz for ^{31}P NMR spectra. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200. Elemental analyses were done in the Laboratory of Instrumental Analysis, in the Institute. All commercially available reagents were used as received from the Aldrich Company.

1-Benzylimidazole-5-carboxaldehyde was prepared according to the procedure [8,9]. Imidazole-4(5)-carboxaldehyde was obtained as described in [10,11].

Aldimines **2** were prepared *in situ* from the imidazole aldehydes and primary amines, following the procedure: Aldehyde **1** (5.0 mmol) was dissolved in dry methylene chloride (50 mL) and the amine was added (5.0 mmol). Obtained mixture was stirred for 24 hrs at room temperature. Then about 3 g anhydrous potassium carbonate was added, and the mixture was filtered to give a solution of the aldimine **2**, which was used directly in the next step.

***Procedure for preparation of imidazole aminophosphonic acids* 3a–e *and imidazole aminophosphinic acids* 4a,b**: Syntheses of the all acids were carried out in the equipment, protected against moisture. In order to obtain the acids **3**, to a 50 mL of methylene chloride solution of imidazole imine **2** (5.0 mmol), trimethyl phosphite (0.63 g, 5.0 mmol) was added. Then bromotrimethylsilane (3.1 g, 20 mmol) was added dropwise and the mixture was stirred for 24 hrs at room temp. and evaporated. The resulting oil was treated with methanol (15 mL) and refrigerated. The product **3** separated out as a white crystalline solid, collected by filtration, washed with diethyl ether and dried. Phosphinic acids **4** were obtained by the following way: Ethyl phenylphosphinate (0.85 g, 5.0 mmol) was added to 50 mL methylene chloride solution of imine **2** (5.0 mmol), followed by bromotrimethylsilane (2.3 g, 15 mmol). The mixture was stirred for 24 hrs, evaporated and treated with methanol (15 mL), diethyl ether (15 mL) and refrigerated. Separated aminophosphinic acids **4** were filtered, and dried.

***Imidazole-4(5)-methyl(N-benzylamino)phosphonic acid* (3a)**: Yield: 0.69 g (52%), m.p. 242–245°C. ^{1}H NMR (D_2O): 8.58 (s, 1H, imid-2), 7.53 (s, 1H, imid.-5), 7.34–7.26 (m, 5H, Ph), 4.48 (d, 1H, **CH**-P, J = 16.7 Hz), 4.23 (s, 2H, Ph**CH$_2$**NH). ^{31}P NMR: 7.18 (s). Anal. for **3a**; $C_{11}H_{14}N_3O_3P$ (267.217): Calc. N, 15.73; P, 11.59; found: 15.70; P, 11.54.

***1-Benzylimidazole-5-methyl(N-benzylamino)phosphonic acid* (3b)**: Yield: 0.96 g (54%), m.p. 229–231°C. ^{1}H NMR (D_2O): 8.70 (s, 1H, imid.-2), 7.80 (s, 1H, imid.-4), 7.4–7.1 (m, 10 H, 2 × Ph), 5.09 (s, 2H, PhC**H$_2$**N), 4.45 (d, 1H, **CH**-P, J = 17.3 Hz), 3.36 (dd, 2H, NHC**H$_2$**Ph, J = 13.3 Hz) ^{31}P NMR: 6.69 (s). Anal. for **3b**; $C_{18}H_{20}N_3O_3P$ (357.335): Calc. N, 11.76; P, 8.67; found: N, 11.64; P, 8.68.

***Imidazole-4(5)-methyl(N-butylamino)phosphonic acid* (3c)**: Yield: 0.75 g (64%), m.p. 238–240°C. ^{1}H NMR (D_2O/D_2SO_4): 8.77 (s, 1H, imid-2), 7.71 (s, 1H, imid-5), 4.72 (d, 1H, **CH**-P, J = 17.1 Hz), 3.03 (m, 2H, NHC**H$_2$**), 1.60 (m, 2H, **CH$_2$**), 1.26 (m, 2H, C**H$_2$**), 0.80 (t, 3H, C**H$_3$**). ^{31}P NMR: 7.29 (s). Anal. for **3c**; $C_8H_{16}N_3O_3P$ (233.203): Calc. N, 18.02; P, 13.28; found: N, 17.91; P, 13.25.

***1-Benzylimidazole-5-methyl(N-butylamino)phosphonic acid* (3d)**: Yield: 1.42 g (88%), m.p. 192–195°C. ^{1}H NMR (D_2O): 8.97 (s, 1H, imid.-2), 7.76(s, 1H, imid.-4), 7.46–7.36 (m, 5H, Ph), 5.65 and 5.36 (dd, 2H, PhC**H$_2$**N, J = 15.5 Hz), 4.37 (d, 1H, C**H**-P, J = 16.6 Hz), 2.65–2.35 (m, 2H, NHC**H$_2$**), 1.28–1.04 (m, 4H, C**H$_2$**C**H$_2$**), 0.72 (t, 3H, C**H$_3$**, J = 7.2 Hz). ^{31}P NMR: 6.70 (s). Anal. for **3d**; $C_{15}H_{22}N_3O_3P$ (323.321): Calc. N, 13.00; P, 9.58; found: N, 12.88; P, 9.59.

***1-Benzylimidazole-5-methyl(N-benzhydrylamino)phosphonic acid* (3e)**: Yield: 1.41 g (65%), m.p. 169–172°C. ^{1}H NMR (DMSO): 9.18 (s, 1H, imid.-2), 7.80 (s, 1H, imid.-4), 7.28–6.95 (m, 15H, 3 × Ph), 5.34 (s, 2H, PhC**H$_2$**N), 4.77 (s, 1H, **CH**Ph$_2$), 3.82 (d, 1H, C**H**-P, J = 20.9 Hz). ^{31}P NMR: 16.44 (s). Anal. for **3e**; $C_{24}H_{24}N_3O_3P$ (433.427): Calc. N, 9.70; P, 7.15; found: N, 9.59; P, 7.12.

***Imidazole-4(5)-methyl(N-benzylamino)phosphinic acid* (4a)**: Yield: 0.90 g (55%), m.p. 235–237°C. ^{1}H NMR (D_2O): 8.51 (s, 1H, imid-2), 7.47–7.16 (m., 11H, Ph, arom.,), 4.63 (d, 1H, C**H-P**, J = 11.8 Hz), 4.20 (q, 2H, Ph**CH$_2$**N, J = 13.5 Hz) ^{31}P NMR: 20.56 (s). Anal. for **4a**; $C_{17}H_{18}N_3O_2P$ (327.309): Calc. N, 12.84; P, 9.46; found: N, 12.77; P, 9.44.

***1-Benzylimidazole-5-methyl(N-benzylamino)phosphinic acid* (4b)**: Yield: 1.56 g (75%), m.p. 258–260°C. ^{1}H NMR (DMSO): 9.02 (s, 1H, imid-2), 7.96 (s, 1H, imid-4), 7.55–6.94 (m., 15 H, Ph's), 5.18 (d, 2H, C**H$_2$**N, J = 2.7 Hz), 4.14 (d, 1H, C**H**-P, J = 12.5 Hz), 4.01–3.70 (q, 2H, C**H$_2$**N, J = 13.5 Hz). ^{31}P NMR: 21.19 (s). Anal. for **4b**; $C_{24}H_{24}N_3O_2P$ (417.427): Calc. N, 10.07; P, 7.42; found: N, 9.98; P, 7.44.

***Preparation of 1-benzylimidazole-5-methyl(amino)phosphonic acid* (3f)**: Aminophosphonic acid **3e** (1.3 g, 3.0 mmol) was refluxed with 20 mL 6M aq. HCl for 2 hrs. The formed benzhydryl alcohol was removed by extraction with toluene (25 mL). The aqueous layer was evaporated to dryness. The remaining residue was dissolved in abs. ethanol (20 mL) and refrigerated. Separated crystals of the product (**3f**) were collected by filtration and dried. Yield: 0.58 g (64%). m.p. 242–245°C. ^{1}H NMR (D_2O): 8.67 (s, 1H, imid-2), 7.73 (s, 1H, imid-4), 7.43–7.33 (m, 5H, Ph), 5.46 (m, 2H, PhC**H$_2$**N), 4.56 (d, 1H, **CH**-P, J = 16.6 Hz) ^{31}P NMR: 7.79 (s). Anal. for **3f**; $C_{11}H_{15}N_3O_3PCl$ (303.68): Calc. N, 13.84; P, 10.20; found: N, 13.65; P, 10.04.

***Preparation of 1-benzylimidazole-5-methyl(amino)phenylphosphinic acid* (4c)**: 1-Benzylimidazole-5-carboxaldehyde (0.93 g, 5.0 mmol) and benzhydrylamine (0.92 g, 5.0 mmol) were dissolved in chloroform (25 mL). The solution was left for 24 h, dried (anh. Na_2SO_4), filtered and ethyl phenylphosphinate (0.85 g, 5.0 mmol) was added. The obtained solution was refluxed for 3 hr and evaporated. The resulted semi-solid was dissolved in 20% aq. HCl (20 mL) and toluene (20 mL). The mixture was refluxed for 2 hrs, cooled, then the organic layer was separated and discarded. The remaining aqueous layer was evaporated to give the **4c** as a whitish solid (1.02 g, 56%). Product was purified by crystallization from abs. ethanol (white crystals). M.p. 240–241°C. ^{1}H NMR (10% D_2SO_4): 8.42 (s, 1H, imid-2), 7.55 (s, 1H, imid-4), 7.39–6.83 (m., 10H, 2 × Ph), 5.12–4.90 (dd, 2H, PhC**H$_2$**N, J = 15.3 Hz), 4.44 (d, 1H, C**H**-P, J = 11.3 Hz). ^{31}P NMR: 22.39 (s). Anal. for **4c**; $C_{17}H_{19}N_3O_2PCl$ (363.77): Calc. N, 11.55; P, 8.51; found: N, 11.46; P, 8.54.

Acknowledgment

This work was supported by the Faculty of Chemistry, Wrocław University of Technology.

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