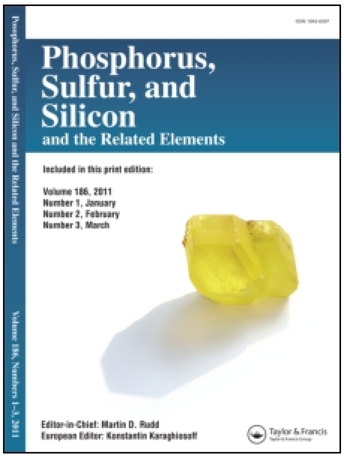

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AMINOPHOSPHONIC ACIDS BEARING HETEROCYCLIC MOIETY. PART 4.[1] SYNTHESIS OF 2-PYRIDYL AND 4-PYRIDYLMETHYL-(AMINO)PHOSPHONIC ACIDS

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2-Pyridyl and 4-pyridylmethyl(amino)phosphonic acids are not available by hydrolysis of corresponding phosphonic esters by means of aq. hydrochoric acid. During hydrolysis of these esters a cleavage of C-P bond occurrs, which leads to a repulsion of phosphorus moiety and formation of the corresponding amine. It was found, that silylation of pyridylmethyl(amino)phosphonic diethyl esters with bromotrimethylsilane and subsequent solvolysis of the silylated product with methanol led to the expected 2-pyridyl and 4-pyridylmethyl(amino)phosphonic acids in high yield.

Keywords: Diethyl pyridylmethyl(amino)phosphonates; silylation; bromotrimethylsilane; debenzylation

INTRODUCTION

Recently we reported a method of synthesis of various pyridinemethyl(amino)-phosphonates[1,2], starting from imines, which were obtained from the corresponding pyridinecarboxaldehydes and benzylic amines. Hydrolysis of those aminophosphonates by means of aqueous hydrochloric acid gave the desired aminophosphonic acids only in the case of 3-pyridyl derivatives[1,2]. The 2-pyridyl and 4-pyridylmethyl(amino)phosphonates were cleaved in those conditions, to form the corresponding amines and phosphoric acid, as a result of a rearrangement[1]. Those results prompted us to find a method suitable for obtaining 2-pyridyl and 4-pyridylmethyl(amino)phosphonic acids, from their esters.

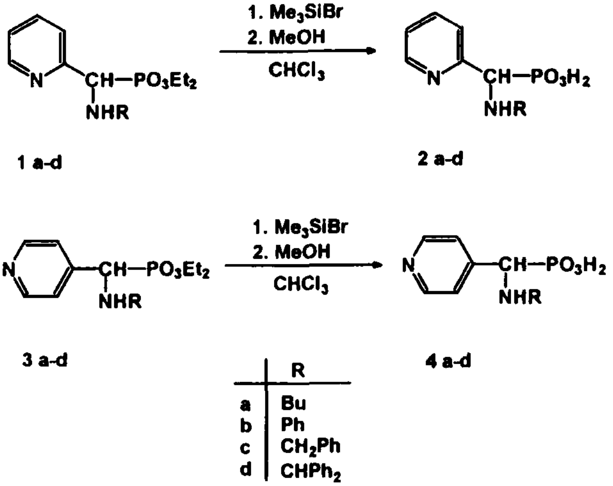
Especially, it was interesting to synthesize the phosphonic analogues of 2-pyridyl and 4-pyridylglycine, the promising agents for enzymatic inhibitory studies[3].

RESULTS AND DISCUSSION

The phosphonic analogue of 3-pyridylglycine has been synthesized by hydrolysis of the corresponding phosphonic ester in a standart procedure[2]. This product was also obtained earlier by Zon and others[3], and used in enzymatic inhibitory studies, but no experimental data concerning the synthesis of this compound were given. The authors asserted also, that the phosphonic analogue of 2-pyridylglycine was synthesized by the same method[3], as it was used for the preparation of the 3-pyridyl analogue, but it seems to be incorrect, because the procedure applied[4] for synthesis of this compound required acidic hydrolysis of the 2-pyridylmethyl-phosphonic derivative, what had to lead to decomposition of the formed phosphonate. The decomposition of such aminophosphonates in acidic medium has been already demonstrated by us[1,2]. Also, no experimental data in this case[3] was given to verify the obtained results.

In searching of methods suitable for safe hydrolysis of pyridylmethyl-(amino)phosphonates to the corresponding phosphonic acids, we turned our attention to a silylation procedure of phosphonic esters[5,6], hoping that the use of a silylation agent allows to obtain the free aminophosphonic acids. We found, that bromotrimethylsilane (Br-TMS) is a effective agent for dealkylation of diethyl esters of pirydylmethyl(amino)phosphonic acids. When diethyl 2-pyridyl and 4-pyridylmethylphosphonates **1** or **3** were treated with bromotrimethylsilane in chloroform solution and kept 24 hrs, the silylated products were formed, which were *in situ* decomposed with methanol to form free aminophosphonic acids **2** and **4**, in high yield.

The presented method of preparation of pyridylmethyl(amino)phosphonic acids is very effective and clean, because the phosphonic acids precipitated from the reaction mixture in a pure state. The acids were identified on the basis of ^{1}H and ^{31}P NMR spectra, elemental analysis and comparison with literature data, if available. It is interesting to mention, that the ^{1}H NMR spectra of N-phenyl derivatives of phosphonic acids **2b** and **4b** performed in D_2O-D_2SO_4 solution, showed the unexpected substitution of ortho protons of the phenyl group by deuterium atoms, during preparation of deuterated solutions of the **2b** and **4b**. The similar exchange was not observed in remaining cases of the obtained aminophosphonic acids. The silylation reaction of the esters was performed only

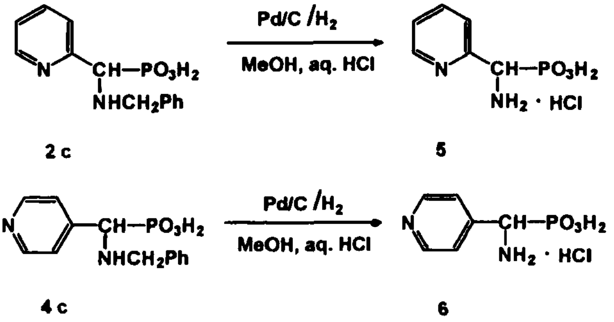


	R
a	Bu
b	Ph
c	CH_2Ph
d	$CHPh_2$

SCHEME 1

on the diethyl esters of pyridylmethyl(amino)phosphonic acids. No attempts of silylation of other alkyl or phenyl esters were made.

The phosphonic analogues of 2-pyridylglycine **5** and 4-pyridylglycine **6** were simply obtained by catalytic debenzylation of N-benzyl derivatives of phosphonic acids **2c** and **4c**, respectively: The products **5** and **6** were isolated as hydrochlorides, because the catalytic hydrogenation was carried out in the presence of two equivalents of hydrochloric acid. Despite of using some hydrochloric acid for hydrogenolysis, the debenzylated phosphonic acids **5** and **6** were obtained safely, in high yield, and no cleavage of the C-P bond was observed. (The cleavage of pyridyl-methyl(amino)phosphonates requires high concentration of HCl and elevated temperature[1]).



SCHEME 2

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz spectrometer in D_2O or in a mixture of D_2O and D_2SO_4, using 300.13 MHz for ^1H NMR spectra and 121.51 MHz for ^{31}P NMR spectra, respectively. Melting points were measured on Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected. Elemental analyses were performed in the Laboratory of Instrumental Analysis in the Institute.

All commercially available reagents were used as received from the suppliers. The diethyl esters of pyridylmethyl(amino)phosphonic acids were prepared according to the described procedure[1].

Silylation of Diethyl Esters 1a–d and 3a–d; Preparation of Phosphonic Acids 2a–d and 4a–d

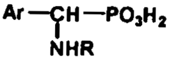
A sample of pyridyl phosphonic ester **1** or **3** (5 mmol) was dissolved in dry chloroform (15 mL) and bromotrimethylsilane (3.8 g, 25 mmol) was added. The mixture was kept for 24 hrs at room temp., protected against moisture, and then evaporated *in vacuo*. The oily residue was dissolved in a mixture of methanol-diethyl ether (1 : 1) (20 mL) and refrigerated. The pyridyl aminophosphonic acid **2** or **4** usually separated out from the mixture after several hours, in a pure state. The separated products were collected by filtration and dried. Data of the obtained phosphonic acids are given in the table.

Elemental Anal. for **2a**: Calc. N: 11.47, P: 12.68; Found: N: 11.23, P: 12.67. Elemental Anal. for **2b**: Calc. N: 10.60, P: 11.72; Found: N: 10.38, P: 11.68. Elemental Anal. for **2c**: Calc. N: 10.07, P; 11.13; Found: N: 9.88, P: 11.14. Elemental Anal. for **2d**: Calc. N: 7.91, P: 8.74; Found: N: 7.81, P: 8.82. Elemental Anal. for **4a** $2H_2O$: Calc. N: 10.00, P: 11.05; Found: N: 9.52, P: 11.20. Elemental Anal. for **4b**: Calc. N: 10.60, P: 11.72; Found: N: 10.14, P: 11.98. Elemental Anal. for **4c** H_2O: Calc. N: 9.45, P: 10.46; Found: N: 8.80, P: 10.72. Elemental Anal. for **4d**: Calc. N: 7.91, P: 8.74; Found: N: 7.63, P: 9.01.

Preparation of Phosphonic Analogues of 2-Pyridylglycine 5 and 4-Pyridylglycine 6:

A solution of the N-benzyl derivative **2c** or **4c** (2.5 mmol, 0.7 g) in a mixture of methanol and water (2 : 1) (60 mL), containing 5 mmol HCl was prepared. Then the catalyst was added (10% Pd/C, 0.5 g), and the mixture was hydrogenated with gaseous H_2, until the consumption of H_2 ceased. Then the catalyst was

TABLE I Physical properties of 2- and 4-pyridylmethyl(amino)phosphonic acids



$$\underset{\displaystyle NHR}{Ar-\underset{|}{C}H-PO_3H_2}$$

No. of compd.	*Ar*	*R*	*Yield %*	*mp °C*	*^1H NMR(D_2O) ppm*	*^{31}P NMR ppm*
2a	2-Py	Bu	56	244–246 (dec.) lit.[1] 244–246	8.52(d, 1H, 6-py, J = 4.9Hz), 7.84(m, 1H, 4-py) 7.50–7.36(m, 2H, 3,5-py), 4.53(d, 1H, CH-P, J = 16.3 Hz), 3.00(m, 2H, CH_2N), 1.58(m, 2H, CH_2), 1.26(m, 2H, CH_2), 0.79(t, 3H, CH_3, J = 7.3 Hz).	6.63(s)
2b	2-Py	Ph	84	257–259 (dec.)	8.60(m, 2H, 4-py, 6-py), 8.22(m, 1H), 7.93(bs, 1H), 7.25(m, phenyl protons and D_2SO_4 and D_2O), 5.32(d, 1H, CH-P, J = 25.3 Hz).	8.81(s)
2c	2-Py	CH_2Ph	80	244–247 (dec.)	8.44(m, 1H), 8.29(m, 1H), 7.87(m, 1H), 7.74(m, 1H), 7.11(m, 5H, Ph), 4.57(d, 1H, CH-P, J = 18 Hz), 4.24(dd, 2H, CH_2, J = 15 Hz).	5.17(s)
2d	2-Py	$CHPh_2$	52	224–226 (dec.)	8.70(d, 1H, 6-py), 8.56(m, 1H), 8.20(m, 1H), 8.01(m, 1H), 7.54–7.39(m, 10H, Ph), 5.77(s, 1H, $CHPh_2$), 4.70(d, 1H, CH-P, J = 18 Hz).	6.26(s)
4a	4-Py	Bu	51	182–185 (dec.)	8.67(m, 2H, 2-py, 4-py), 7.87(m, 2H, 3-py, 5-py), 4.70(d, 1H, CH-P, J = 16.5 Hz), 3.03(m, 2H, CH_2N), 1.59(m, 2H, CH_2), 1.23(m, 2H, CH_2), 0.77(t, 3H, CH_3, J = 7.3 Hz).	6.91(s)
4b	4-Py	Ph	66	208–211 (dec.)	8.72(d, 2H, 2-py, 6-py, J = 6.6 Hz), 8.18(d, 2H, 3-py, 5-py, J = 5.3 Hz), 7.32(m, 2H, Ph), 7.03(m, 1H, Ph), 5.50(bs, D_2SO_4 and D_2O), 5.33(d, 1H, CH-P, J = 23 Hz).	12.1(s)
4c	4-Py	CH_2Ph	71	207–209 (dec.)	8.79(d, 2H, 2-py, 6-py, J = 6.7 Hz), 8.06(d, 2H, 3-py, 5-py, J = 5.4 Hz), 7.44(m, 5H, Ph), 4.90(d, 1H, CH-P, J = 17.8 Hz), 4.50(dd, 2H, CH_2, J = 13.3 Hz).	6.25(s)
4d	4-Py	$CHPh_2$	96	199–202 (dec.)	8.94(d, 2H, 2-py, 6-py), 8.76(d, 2H, 3-py, 5-py), 7.38(m, 10H, Ph), 5.74(s, 1H, $CHPh_2$), 5.01(d, 1H, CH-P, J = 18.7 Hz), (in D_2SO_4 + D_2O).	5.12(s)
5[a]	2-Py	H	81	176–185 (dec.)	8.62(d, 1H, 6-py, J = 4.4 Hz), 8.43(t, 1H, 4-py, J = 7.7 Hz), 7.93(m, 2H, 3-py, 5-py), 4.79(d, 1H, CH-P, J = 16.5 Hz).	6.50(s)
6[a]	4-Py	H	83	>205 (dec.)	8.68(d, 2H, 2-py, 6-py, J = 6.1 Hz), 7.95(d, 2H, 3-py, 5-py, J = 5.5 Hz), 4.74(d, 1H, CH-P, J = 18.2 Hz).	7.22(s)

[a] Product isolated as hydrochloride

filtered off, and the filtrate evaporated *in vacuo*, to give crude phosphonic acid **5** or **6**. The obtained products were additionally recrystallized from methanol (20 mL). Data of the acids **5** and **6** are given in the table.

Elemental Anal. for **5**: Calc. N: 12.47, P: 13.79; Cl: 15.78; Found: N: 11.96, P: 13.89, Cl: 15.41. Elemental Anal. for **6**: Calc. N: 12.47, P: 13.79, Cl: 15.78; Found: N: 11.95, P: 14.10, Cl: 15.59.

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