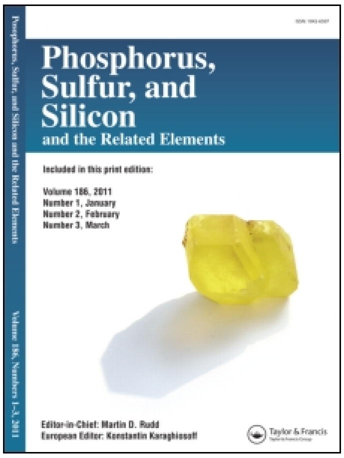

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ONE-POT SYNTHESIS OF 1-(2-AMINOETHYL)- PYRIDYL-1-ARYL METHYL PHOSPHONIC ACID MONOMETHYL ESTERS

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ONE-POT SYNTHESIS OF 1-(2-AMINOETHYL)-PYRIDYL-1-ARYL METHYL PHOSPHONIC ACID MONOMETHYL ESTERS

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New phosphonate mono-methyl esters which are designed to have properties intermediate between the acid and the diesters and thus able to form discrete metal complexes with enhanced solubility in water, were synthesized using 2-(2-aminoethyl) pyridine as starting reagent, considering that the presence of the pyridyl moiety in such aminophosphonates could be of great relevance for preparation of discrete metal complexes. The procedure used allowed to obtain in rather good yields the phosphonic acid mono-methyl esters directly in a one-pot synthesis starting from the corresponding Schiff bases (not isolated) and dimethyl phosphite.

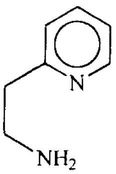
Key words: Ligands for transition metals, NMR and MS-FAB characterizations, amino phosphonates bearing the pyridyl moiety.

INTRODUCTION

α-Aminophosphonic acids are bioisoesters of natural aminoacids serving as important surrogates in order to modify biological processes inhibiting enzyme activity[1] and bacterial growth.[2] Furthermore these compounds, as well as their alkyl di- and mono-esters, show interesting properties in agrochemistry as antifungal agents,[3] herbicides[4] and as plant regulators. Self condensation of α-aminophosphonic acids produces phosphono di- and tri-peptides clinically studied as antibiotics[5] and condensation of racemic phosphonate esters with vinblastine gave epimers showing antitumor activity.[6]

In addition, α-aminophosphonic acids and their mono-alkyl esters are of interest also in hydrometallurgy in order to extract metals[7] and in diagnostic medicine as screening agents, once complexed with lanthanides and actinides.[8,9]

Therefore, the increased interest in the synthesis of specific phosphorus ligands able to complex biologically important metals for use in physiological media, has prompted us to use a variety of structural variation on the heteroaryl nucleus in order to enhance their potential complexing properties. With the aim of synthesizing new phosphonate monoesters which are designed to have properties intermediate between the acids and the diesters and thus are able to form discrete metal complexes with enhanced solubility in water, we devoted our interest on the use of 2-(2-aminoethyl) pyridine (**1**) as starting reagent for the preparation of α-amino phosphonates, of general formula **II**, considering that the presence of the pyridyl moiety in such compounds was found of great relevance for the preparation of discrete copper complexes.[10]



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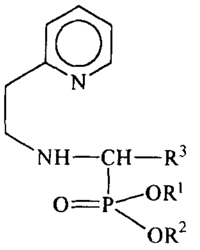
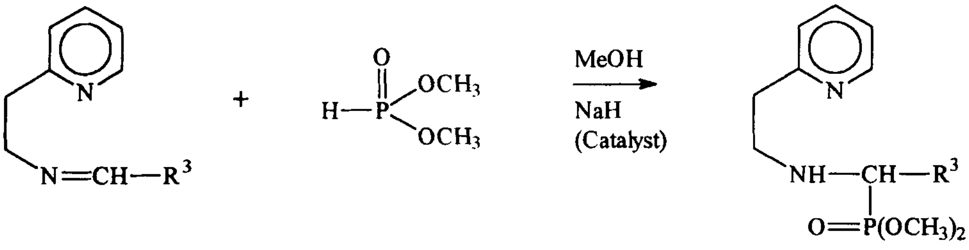


II

RESULTS AND DISCUSSION

One of the best synthetic procedure for the preparation of the mono-alkyl esters of α-amino phosphonic acids consists in the alkaline hydrolysis, in alcohols as solvents, of the diesters[7,11,12] alternatively, they can also be obtained in good yields by refluxing the parent dimethyl esters in acetone with a twice molar amount of KI or NaI,[13] or warming the dimethyl esters with an excess of a primary sterically congested amine, generally used as solvent.[14]

Therefore, according to these published synthetic strategies we had in mind of synthesizing, first the dimethyl esters (**IV**) by adding dimethyl phosphite to the parent Schiff bases according to reaction 1 (this reaction was already used successfully by us for the preparation of similar derivatives),[15,16] and then perform subsequently the hydrolytic cleavage of the corresponding mono-esters.



(1)

III IV

We were almost surprised that reaction 1 gave directly in good yields the mono-esters, (**II**, $R_1 = H$, $R_2 = CH_3$), when 2-(2-aminoethyl) pyridine (**I**) was used as primary amine. In fact, when the oily Schiff bases **III** (not isolated) were allowed to react in neat, or in methanol as solvent, with an equimolar amount of dimethyl phosphite and a catalytic quantity of NaH, usual work-up gave high melting white solids in good yield, but with poor solubility in apolar organic solvents (see experimental part).

NMR, as well as FAB-MS analyses, revealed that in all cases the monoesters (**II**, $R_1 = H$, $R_2 = CH_3$) where the major products formed; in fact, for the characterization of these derivatives is very diagnostic the appearance in the ^1H-NMR spectra of a single sharp doublet for the $P(OCH_3)$ group and a doublet (or quartet) for the CH—P signal possessing a $^2J_{PH}$ of ca. 14–15 Hz, i.e. much lower to that one found for the corresponding diesters[17] (see also Tables I and II).

The FAB-MS technique reveals that, for all compounds investigated, the pseudomolecular ion is observed in high intensity. Furthermore, in all MS spectra, peaks due to cluster ions are also observed, together with the fragmentation pattern characteristic for such family of compounds, as we already reported in the literature.[12,15]

Therefore, considering the interest and the wide potential application of α-aminophosphonic acid mono-alkylesters bearing the pyridine moiety, we were very glad that our reaction, by one-pot synthesis, gave directly the desired mono-methyl esters listed in Table I, because, some times, these compounds are not straightforward obtainable by hydrolytic processes, or they are difficult to isolate in the pure form from the reaction media.[12]

After the removal and the isolation of the mono-esters from the reaction batch, it was possible to obtain from the mother liquors small quantity of some products which by NMR analyses revealed the presence of the parent α-aminophosphonic acids dimethyl esters, in almost pure form.

The ^1H-NMR characteristics of such dimethyl esters are listed in Table II. By comparing the CH—P and —P(OMe) chemical shifts of the mono- and of the diesters, it can be recognized that in the mono esters the methyne resonances are downfield shifted when compared with those of the corresponding di-esters, whereas the opposite trend is observed for the methoxy resonances.

Therefore, both chemical shifts and coupling constants can be used in order to differentiate the signals of the mono- from those of the di-esters even when these compounds are mixed together in solution, allowing a reasonable quantitative determination of the two different molecules.

Coming now to the possible way of formation of our mono-esters we believe that they originate from the parent dimethyl esters via hydrolytic cleavage by the primary amine (**I**) used in the synthesis of the Schiff bases[14] (Scheme I).

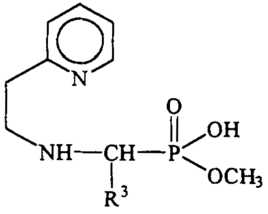
In fact, in previous work we reported on the syntheses of a great variety of α-amino phosphonic acid dimethyl esters from Schiff bases without the formation of the corresponding mono-esters[18]; only when amine (**I**) was used or when a free primary amine was present in the media, mono-methyl esters were obtained in good yield.[17]

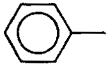
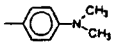
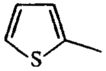
It is worthwhile to note that when cyclohexylcarboxyaldehyde was used in the synthetic routes depicted in Scheme I, no evidence of the formation of the dimethyl ester was observed, whereas the opposite trend, i.e. no mono-ester derivative was isolated, when benzaldehyde was employed as synthon.

Use of 2-(aminomethyl) pyridine for preparing Schiff bases, and then the corresponding phosphonates according to reaction (1), resulted in the formation of the α-aminophosphonic acid dimethyl esters only and in very low yield. Evidences concerning the formation of compound **V** arise from the ^1H-NMR spectra of the oily

TABLE I

Physical characteristics of mono-esters with general formula:



N.	R^3	Yield %	m.p.	^{1}H-NMR δ ($CDCl_3$ or DMSO, TMS) CH	NH	O=P(OMe)$_2$	CH_2	R^3	Py-H
1^a		53	>230	2.90 (dd) $^2J_{PH}$ = -14 Hz	3.86 (m)	3.57 (d) $^3J_{PH}$ = 9.1 Hz	3.20, 3.44 (m)	1.24, 2.15 (m)	7.22 (m), 7.66 (m), 8.43 (m)
2		-^{b}							
3		45	192-194	4.28 (d) $^2J_{PH}$ = -15.6 Hz	3.46 (m)	3.23 (d) $^3J_{PH}$ = 9.8Hz	3.11, 3.46 (m)	2.94 (s), 6.72 (d), 7.64 (d)	6.98 (m), 7.35 (m), 8.33 (m)
4		48	198-200	4.65 (d) $^2J_{PH}$ = -14.6 Hz	~ 3.30^c	3.30 (d) $^3J_{PH}$ = 9.9 Hz	3.04, 3.18 (m)	7.04, 7.53 (m)	7.15 (m), 7.68 (m), 8.42 (m)

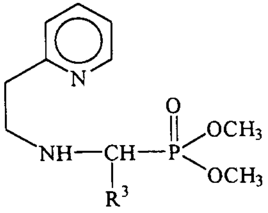
[a] ^{31}P-NMR spectra show a single peak at 11.42 ppm.

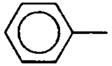
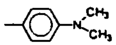
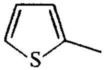
[b] Never observed even in the crude reaction mixture (see text).

[c] Partially masked by OCH_3 and CH_2 resonances

TABLE II

Physical characteristics of dimethyl-esters with general formula:

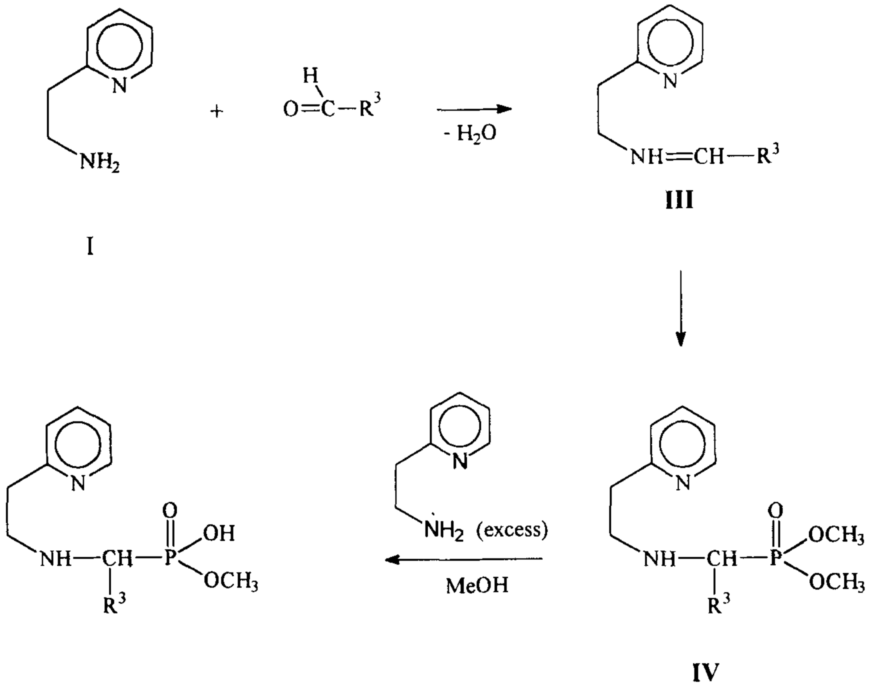


N.	R^3	Yield %	m.p.	^{1}H-NMR δ (CDCl$_3$,TMS) CH	NH	O=P(OMe)$_2$	CH$_2$	R^3	Py-H
1		-[a]							
2		58	48-50	4.10 (d) $^2J_{PH}$ = -20 Hz	-[b]	3.52, 3.67 (d) $^3J_{PH}$ = 10 Hz	2.67-2.97 (m)	7.33 (m)	7.11 (m), 7.52 (m), 8.50 (m)
3		23	oily	4.00 (d) $^2J_{PH}$ = -20 Hz	-[b]	3.52, 3.67 (d) $^3J_{PH}$ = 10 Hz	2.80-3.00 (m)	2.93 (s), 6.68 (d), 7.22 (d)	7.12 (m), 7.55 (m), 8.46 (m)
4		-[c]		4.37 (d) $^2J_{PH}$ = -20 Hz	3.74 (m)	3.62, 3.70 (d) $^3J_{PH}$ = 10 Hz	3.00-3.43 (m)	7.00, 7.57 (m)	7.12 (m), 7.58 (m), 8.48 (m)

[a] No evidences of its formation were observed.

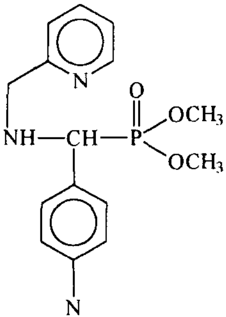
[b] Masked by CH$_2$ resonances

[c] No attempts were made in order to isolate it from the crude reaction mixture.



Scheme I

product isolated from the crude reaction mixture and its chemical shifts are reported in the experimental part.



V

From these preliminary observations it is evident that small variations on the molecular structure of the employed amine and/or aldehyde can drastically influence the nature of the products obtained through reaction (1).

Therefore we can conclude that the use of amine (**I**) is of great utility for obtaining mono-methyl esters of α-amino-phosphonic acids bearing additional complexation sites, i.e. the pyridyl and the —CH—NH— moieties, in excellent spatial positions in order to chelate metals. Preliminary results indicate that the mono-esters here described are excellent complexing agents for transition metals and therefore we shall report on these aspects in the near future.

EXPERIMENTAL

Amines, aldehydes, dimethyl phosphite as well as solvents and all other chemicals used were commercial products from Aldrich, which were purified before use. All syntheses were performed under a dry N_2 atmosphere.

^{1}H-NMR spectra were recorded in $CDCl_3$ and Me_4Si as an internal standard using a Bruker AC-200 instrument operating at 200 MHz. Phosphorus NMR-spectra were recorded at Düsseldorf University with a Bruker AM 200 MHz spectrometer with a resolution >0.003 ppm using 85% H_3PO_4 as external reference.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with standard FAB source and DS 90 data system. 3-Nitro-benzylalcohol was used as matrix.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

The Schiff bases **III** were obtained by warming equimolar amount of aldehyde and 2-(2-amino ethyl) pyridine (**I**) neat, or methanol as solvent, for one hour. Removal of the solvent used yielded oily products which were not isolated or further purified.

General Procedure for the Synthesis of Mono-Esters

To the crude oily Schiff base precursor was added an equimolar amount of dimethyl phosphite with a catalytic amount of NaH and the mixture was stirred for 3 hrs at room temperature. The thick oil obtained was diluted with a mixture of 1:1 diethyl ether/ethyl acetate, and left to stand overnight. The white solid obtained was filtered and purified by crystallization from dioxane. The yields and physical characteristics of the described mono-esters are listed in Table 1.

α-Amino-Phosphonic Acid Dimethyl Esters (See Table II)

Removal at reduced pressure of the solvent mixture used for precipitation of the mono-esters, left ticky oily products which were forced to solidify and crystallize at low temperature by addition of petroleum ether containing a small amount of diethyl ether and/or ethyl acetate. Physical characteristics of the isolated products are listed in Table II.

Synthesis of **V**

To the oily Schiff base obtained by the condensastion at t = 50°C of 2-(aminomethyl) pyridine (5.4 g, 0.05 mol) with 4-dimethylamino benzaldehyde (7.46 g, 0.05 mol) was added at room temperature an equimolecular amount of dimethyl phosphite (5.5 g, 0.05 mol) with a catalytic amount of NaH. The reaction mixture was stirred under N_2 for 4 hours and then the volatile products and reagents were removed at reduce pressure. The ^{1}H-NMR spectrum of the ticky oily compound isolated revealed signals at δ ($CDCl_3$, TMS): 2.95 (s, 6H, CH_3), 3.58 and 3.72 (d, $^3J_{PH} = 9.4$ Hz, 6H, OCH_3), 3.91 (d, $^2J_{PH} = -20$ Hz, 1H, CH), 3.93 (t, 2H, CH_2), 6.72 (d, 2H, ArH), 7.20 (m, 2H, ArH), 7.30 (m, 2H, ArH), 7.61 (m, 1H, ArH) and 8.54 (m, 1H, ArH), FAB-MS: 350 (M+1), 240, 699.

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