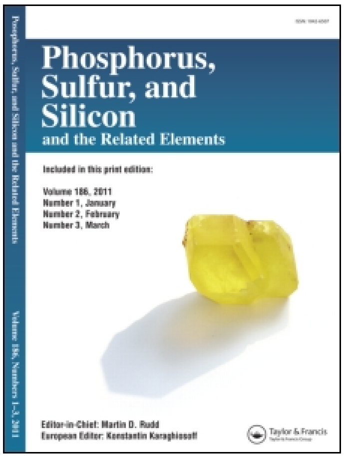

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A SIMPLE ONE-STEP SYNTHESIS OF MONOESTERS OF AMINOPHOSPHONIC

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A SIMPLE ONE-STEP SYNTHESIS OF MONOESTERS OF AMINOPHOSPHONIC ACIDS

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Alkyl monoesters of *N*-substituted aminophosphonic acids have been prepared by heating of the corresponding dialkyl aminophosphonates oxalate salts in water. The formed monoesters were separated as crystalline solids from the aqueous reaction mixture.

Keywords: Dialkyl aminophosphonates; monoalkyl aminophosphonates; oxalates

INTRODUCTION

Aminophosphonic derivatives having a direct P-N bond are considered as analogues of the tetrahedral transition-state involved in peptide hydrolysis[1].

The key intermediates for the synthesis of the products possessing a P-N linkage are monoesters of various 1-aminoalkylphosphonic acids[2]. Contrary to diesters of aminophosphonic acids, the corresponding monoesters are not easily available.

The diesters of aminophosphonic acids are simply obtained by a number of synthetic methods frequently described in chemical literature. The best method seems to be an addition reaction of dialkyl esters of phosphorous acid to imines (Schiff bases). In this case the diesters are mainly formed, and therefore they are generally considered as basic intermediates for the synthesis of the corresponding monoesters.

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In the literature, there are described a few routes leading to alkyl monoesters of aminophosphonic acids. Most of them are depended on a partial hydrolytic cleavage of diester precursors by a strong base[3], or on partial esterification of phosphonic acids[4,5], and also by the dealkylation of diesters at elevated temperature[6,7].

The above methods are rather tedious and not clean. In most cases the cited processes require prolonged heating of a reaction mixture composed with diester and a strong basic or acidic agent, and in consequence it leads to formation of a mixture of various phosphorus products. Therefore, such procedures usually caused an additional purification of the formed monoesters.

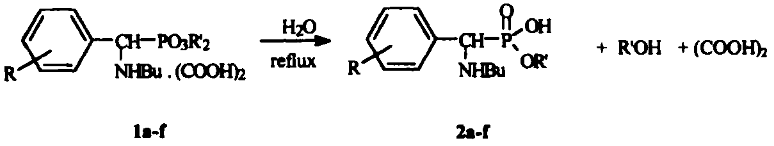
Now, we report a facile, effective method for the preparation of several monoalkyl esters of the aminophosphonic acids.

RESULTS AND DISCUSSION

During our work on the synthesis of diethyl esters of some 1-aminobenzylphosphonic acids[8,9] we found that the best method for isolation and purification of the aminophosphonates is a process of transformation of the crude diesters into oxalate salts. When the crude aminophosphonates (obtained in the reaction of the imine with dialkyl phosphite) were treated with an excess of oxalic acid in acetone solution, the oxalates of the aminophosphonates were separated as crystalline solids. The oxalates are stable compounds and they can be used in a such form for a long storage of the obtained aminophosphonic diesters.

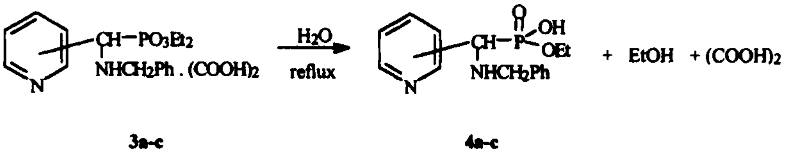
We found, that when the oxalates **1a-f** or **3a-c** were heated in water for several hours, the corresponding monoesters were formed : **2a-f** and **4a-c**, respectively (SCHEME 1 and 2). Isolation of the formed monoesters was simply performed by filtration, because monoesters crystallized in a pure state from the aqueous reaction mixture. The yields of the monoesters were good in most cases.

This way of hydrolysis of oxalates led to the corresponding monoesters only. Phosphonic acids, which could be expected as a final stage of this hydrolysis were not isolated (only traces of phoshonic acids were detected).



a: R = H, R' = Me; **b**: R = H, R' = Et, **c**: R = H, R' = iPr; **d**: R = 4-Me, R' = Et;
e: R = 4-OMe, R' = Et; **f**: R = 2-NO$_2$, R' = Me

SCHEME 1



a: 2-pyridyl; **b**: 3-pyridyl; **c**: 4-pyridyl

SCHEME 2

The monoesters obtained (**2** and **4**) were in most cases new compounds and have been characterized by means of spectroscopic methods (TABLES I and II).

TABLE I Analytical Data of 1-(N-Butylamino)benzylphosphonic Monoesters **2a-f**

No.	*R*	*R'*	*Yield*^{ab} *(%)* *[R.time]*	*M.p* *(°C)*	^{1}*H NMR* ^{31}*P* *(D$_2$O)*	^{31}*P NMR* *(D$_2$O)*
2a	H	Me	95 [3h]	226–228	7.55(bs, 5H, Ph), 4.61(d, 1H, **CH**-P, J=16.4 Hz,), 3.65(d, 3H, OCH$_3$, J=10.8 Hz), 3.02(m, 2H, CH$_2$N), 1.65(m, 2H, CH$_2$), 1.28(m, 2H, CH$_2$), 0.85(t, 3H, CH$_3$, J=7.1 Hz).	14.65(s)
2b	H	Et	65 [10h]	225–226	7.54(bs, 5H, Ph), 4.63(d, 1H, **CH**-P, J= 16.5 Hz,), 4.01(m, 2H, OCH$_2$), 3.00(m, 2H, CH$_2$), 1.65(m, 2H, CH$_2$), 1,25(m, 5H, CH$_2$, CH$_3$), 0.84(t, 3H, CH$_3$, J=7.1 Hz).	13.68(s)
2c	H	iPr	74 [5h]	219–221	7.51(s, 5H, Ph), 4.56(m, 2H, **CH**-P, OCH), 3.01(m, 2H, CH$_2$N), 1.63(m, 2H, CH$_2$), 1.25(m, 8H, CH$_2$, 2xCH$_3$), 0.85(t, 3H, CH$_3$, J=7.1 Hz).	13.14(s)

No.	*R*	*R'*	*Yield*^{ab} *(%)* *[R.time]*	*M.p* *(°C)*	^{1}*H NMR* ^{31}*P* *(D$_2$O)*	^{31}*P NMR* *(D$_2$O)*
2d	4-Me	Et	51 [3h]	219–222	7.40(m, 4H, arom.), 4.55(d, 1H, CH-P, J=16.6 Hz), 3.99(m, 2H, OCH_2), 2.98(m, 2H, CH_2N), 2.37(s, 3H, CH_3), 1.62(m, 2H, CH_2), 1.24(m, 5H, CH_2, CH_3), 0.86(t, 3H, CH_3, J=7.2 Hz).	14.02(s)
2e	4-OMe	Et	59 [10h]	124–126	7.92(d, 2H, arom., J=6.9 Hz), 7.51(d, 2H, arom., J=8.4 Hz), 4.66(d, 1H, CH-P, J=17.1 Hz), 4.09(m, 2H, OCH_2), 3.87(s, 3H, OCH_3), 3.01(m, 2H, NCH_2), 1.67(m, 2H, CH_2), 1.32(m, 5H, CH_2, CH_3), 0.86(t, 3H, CH_3, J=7.1 Hz).	13.87(s)
2f	2-NO_2	Me	85 [3h]	211–213	8.19(m, 1H, arom.), 7.78(m, 3H, arom.), 5.52(d, 1H, CH-P, J=13.8 Hz), 3.69(d, 3H. $POCH_3$, J=12.1 Hz), 3.13(m, 2H, NCH_2), 1.70(m, 2H, CH_2), 1.32(m, 2H, CH_2), 0.84(t, 3H, CH_3, J=7.1Hz).	11.92(s)

a. Yields are calculated on the basis of NMR data.

b. The microanalyses for all compounds were in satisfactory agreement with the calculated values (C ± 0.12, H ± 0.20, N ± 0.15, P ± 0.19).

TABLE II Analytical Data of 1-(N-Benzylamino)pyridylmethylphosphonic Monoesters **4a-c**

No.	*Yield*^{a} *(%)* *[R.time]*	*M.p* *(°C)*	^{1}*H NMR (D$_2$O)*	^{31}*P NMR* *(D$_2$O)*
4a	64 [5h]	202–204	8.44(d, 1H, arom., J=4.05 Hz), 7.72(t, 1H, arom., J=7.8 Hz), 7.25(m, 7H, arom.), 4.33(d, 1H, CH-P, J=16.6 Hz,), 4.06(dd, 2H, $PhCH_2N$, J=13.3 Hz, J=13.2 Hz), 3.55(m, 2H, OCH_2), 0.95(t, 3H, CH_3, J=7.1 Hz).	10.51(s)
4b	92 [5h]	211	8.50(d, 1H, arom., J=5.0 Hz), 8.42(s, 1H, arom.), 7.95(d, 1H, arom., J=8.07 Hz), 7.50(t, 1H, arom., J=5.0 Hz), 7.35(m, 3H, arom.), 7.26(m, 2H, arom.), 4.28(d, 1H, CH-P, J=16.3 Hz), 4.12(dd, 2H, $PhCH_2N$, J=13.3 Hz, J=13.2 Hz), 3.74(m, 2H, OCH_2), 1.09(t, 3H, J=7.1 Hz)	11.65(s)
4c	98 [5h]	198–200	8.72(d, 2H, arom., J=5.9 Hz), 7.96(d, 2H, arom., J= 5.8 Hz), 7.35(m, 5H, Ph), 4.72(d, 1H, CH-P, J=16.3 Hz,), 4.37(d, 2H, $PhCH_2N$, J=13.3 Hz,), 3.86(q, 2H, OCH_2, J=8.2 Hz), 1.13(t, 3H, CH_3, J=7.1 Hz).	8.11(s)

a. Yields are calculated on the basis of NMR data

In order to obtain more exact data concerning the dealkylation of these aminophosphonates, we have carried out some kinetic measurements and determined the rates for the hydrolysis of the oxalates **1a-f** and **3a-c**.

Kinetic measurements were performed in D_2O solution, by means of ^{31}P NMR spectroscopy. On the basis of integration data obtained for individual phosphorus compounds, we were able to calculate the respective concentrations of the formed products, which were used in determining of the pseudo-first-order rates.

The results are given in TABLE III.

TABLE III Pseudo-first-order Rate Constants (k_{obs}) for Hydrolysis of Oxalates **1a-f** and **3a-c** in D_2O at 95°C

Oxalate, Compd. No.	*Oxalate, Conc.* ($M{\cdot}L^{-1}$)	$10^5.k_{obs}{}^{a}$ (s^{-1})
1a	0.20	29.7
1b	0.20	3.1
1c	0.20	9.4
1d	0.20	6.5
1e	0.20	2.7
1f	0.20	22.2
3a	0.24	8.2
3b	0.26	12.0
3c	0.25	21.0

a. Rates reproducible to ± 5%.

According to the kinetic results obtained, dimethyl ester oxalates (**1a, 1f**) are the easiest hydrolysing compounds to the monoesters in this case. The hydrolysis was practically complete in 3–4 hours, according to the rates obtained (TABLE III). Diethyl esters (**1b, 1d, 1e**) were hydrolysed considerably slower (TABLE III) and the complete hydrolysis to corresponding monoesters was achieved in 15–20 hours.

On the basis of obtained results, one can recognize, that the rates of hydrolysis for a series of diethyl esters are of some dependence on a basicity factor of the diesters. As seen from TABLE III the rate of hydrolysis increases, when a substituent in the aromatic ring is less negative. For example, the rate constants are decreasing in the following order of the substituents attached on benzene ring: Me > H > OMe (**1d** > **1b** > **1e**). Likewise, such a dependence is observed in the case of hydrolysis in a series of pyridylmethane-(amino)phosphonates **3a-c**, where the rate is the highest for 4-pyridyl derivative (**3c**), which is the most basic compound (TABLE III).

Procedure for synthesis of the monoesters, presented here, is very simple and convenient : The diester oxalate is mixed with a minimal amount of water (the quantity of water should be sufficient to dissolve the oxalate completely at ~ 95°C) and the aqueous solution is refluxed for appropriate time (TABLE II and III). After cooling, the monoester separates as a crystalline solid from the reaction mixture.

We also found, that a reaction leading to monoesters can be simplified by the following way : An equimolar mixture of aminophosphonic diester and oxalic acid in aqueous solution was refluxed for 5–10 hours and cooled. The formed monoesters were separated as crystalline solids from the mixture.

It is worthly to mention that diesters of hydroxyphosphonic acids (for example : diethyl 1-hydroxy-2′(3′ or 4′)-nitrobenzylphosphonates) do not hydrolyse to monoesters by this way (during heating of the hydroxyester with equimolar amount of oxalic acid in water for 5 hr, the expected monoesters were not formed and instead of this, the starting materials were isolated).

This observation leads to the conclusion that the existence of basic amino groups in aminophosphonates plays a crucial role in this hydrolytic dealkylation.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in D_2O solutions, using 300.13 MHz for ^1H NMR and 121.51 MHz for ^{31}P NMR spectra, respectively. Melting points were determined on a Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected.

Elemental analyses were done in the laboratory of Instrumental Analysis, in the Institute. All commercially available reagents were used as received from the supplier (the Aldrich Company).

Preparation of 1a-f and 3a-c oxalates

The **1e** oxalate[11] and the **3a-c** oxalates[10] are known compounds and were obtained according to the procedures published[10].

The oxalates of **1a, 1b, 1c, 1d** and **1f** were prepared by following the procedure applied for the synthesis of nitrobenzyl(amino)phosphonate oxalates[8,9].

Dimethyl 1-(N-butylamino)benzylphosphonate, Oxalate 1a

Yield: 60%. M.p. 116-118°C. ^{1}H NMR(D_2O) : 7.48(bs, 5H, Ph), 4.90(d, 1H, CH-P, J=18.1Hz), 3.76(d, 3H, OCH_3, J=11.3 Hz), 3.63(d, 3H, OCH_3, J=11.3 Hz), 2.92(m, 2H, NCH_2), 1.55(m, 2H, CH_2), 1.20(m, 2H, CH_2), 0.75(t, 3H, CH_3, J=7.1 Hz). ^{31}P NMR(D_2O) : 20.53(s).

Elemental Anal. Calc. N : 3.88, P: 8.57; Found: N: 4.01, P : 8.70.

Diethyl 1-(N-butylamino)benzylphosphonate, Oxalate 1b

Yield: 63%. M.p. 113.5-115.5°C. ^{1}H NMR(D_2O): 7.46(bs, 5H, Ph), 4.82(d, 1H, CH-P, J=17.94 Hz), 4.02(m 4H, 2x OCH_2), 2.94(m, 2H, NCH_2), 1.54(m, 2H, CH_2), 1.21(m, 8H, CH_2, 2xCH_3), 0.75(t, 3H, CH_3, J=7.1 Hz). ^{31}P NMR(D_2O) : 18.145(s).

Elemental Anal. Calc. N : 3.60, P: 7.95; Found : N : 3.74, P : 8.11.

Diisopropyl 1-(N-butylamino)benzylphosphonate, Oxalate 1c

Yield : 80%. M.p. 106-108 °C. ^{1}H NMR(D_2O) : 7.58(bs, 5H, Ph), 4.78(d, 1H, CH-P, J=17.4 Hz), 4.86–4.59(m, 2H, 2xOCH), 3.10(m, 2H, NCH_2), 1.71(m, 2H, CH_2), 1.36–1.13(m, 14H, 4xCH_3, CH_2), 0.88(t, 3H, CH_3, J=7.2 Hz). ^{31}P NMR(D_2O) : 13.74(s).

Elemental Anal. Calc. N : 3.36, P : 7.42; Found : N : 3.50, P : 7.23.

Diethyl 1-(N-butylamino)-4'-methylbenzylphosphonate, Oxalate 1d

Yield : 72%. M.p. 118–120°C. ^{1}H NMR(D_2O) : 7.52(d, 2H, arom., J=7.92 Hz), 7.42(d, 2H, arom., J=7.9 Hz), 4.89(d, 1H, CH-P, J=17.85 Hz), 4.33–4.10(m, 4H, 2xOCH_2), 3.08(m, 2H, NCH_2), 2.40(s, 3H, CH_3), 1.73(m, 2H, CH_2), 1.43–1.26(m, 8H, 2xCH_3, CH_2), 0.90(t, 3H, CH_3, J=7.1 Hz). ^{31}P NMR(D_2O) : 16.72(s).

Elemental Anal. Calc. N : 3.47, P : 7.68; Found : N : 3.68, P : 7.87.

Dimethyl 1-(N-butylamino)-2'-nitrobenzylphosphonate, Oxalate 1f

Yield : 51%. M.p. 97–122 °C (dec.). ^{1}H NMR(D_2O) : 8.20(d, 1H, arom., J=8.2 Hz), 7.87–7.82(m, 1H, arom.), 7.76–7.60(m, 2H, arom.), 5.67(d, 1H, CH-P, J=19.4 Hz), 3.82(d, 3H, $POCH_3$, J=11.1 Hz), 3.74(d, 3H, $POCH_3$, J=11.1 Hz), 3.08(m, 2H, CH_2N), 1.62(m, 2H, CH_2), 1.24(m, 2H, CH_2), 0.78(t, 3H, CH_3, J=7.4 Hz). ^{31}P NMR(D_2O) : 19.1(s).

Procedure for the preparation of monoesters 2a-f and 4a-c

Oxalate (**1a-f**, or **3a-c**) (5 mmol) was mixed with water (4–5 mL) and refluxed for 3 h (**1a, 1d, 1f**), for 5 h (**1c, 3a-c**), or for 10 h (**1b, 1e**), and then cooled. The separated monoester **2a-f** or **4a-c** was collected by filtration, washed with diethyl ether and dried. The physicochemical data of the obtained products are summarized in TABLE I and II.

Further amounts of the monoesters can be obtained by an additional partial evaporation of the remaining filtrate.

Procedure for kinetic runs

The stock solutions of oxalates of **1a-f** or **3a-c** in D_2O ($c = 0.2\ M{\cdot}L^{-1}$) were prepared. The samples (a 0.5 mL aliquot of a solution) in NMR tubes were thermostated at 95°C for a desired period of time (1h → 10h, respectively), cooled, and the ^{31}P NMR spectra were recorded. The pseudo-first-order rate constants (k_{obs}) were determined from ^{31}P NMR spectra by plotting dependence of *log(a-x)* on time (where the "*a-x*" represents an actual concentration of the unreacted diester oxalate). The concentrations were calculated from the integration values of individual phosphorus compounds. In all cases a pseudo-first-order dependence was obeyed very well. The obtained k_{obs} were means of three kinetic runs and were reproducible within ± 5%. The rates are given in TABLE III.

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References

[1] N.E. Jacobson and P.A. Barlett, *J. Am. Chem. Soc.*, **103**, 654 (1981).

[2] P. Kafarski, B. Lejczak and P. Mastalerz, *Beitr. Wirktofforschung*, **25**, pp. 1–77 (1985).

[3] V. Jagodic and L. Tusek, *J. Org. Chem.*, **37**, 1222 (1972).

[4] C. Wasielewski, M. Hoffmann, E. Witkowska and J. Rachoń, *Rocz. Chem.*, **50**, 1613 (1976).
[5] M. Hoffmann, *Synthesis*, **557** (1986).
[6] I.A. Balykova, V.D. Pak and N.S. Kozlov, *Zh. Obsch. Khim.*, **44**, 2432 (1974).
[7] S.W.A. Bligh, C.M. McGrath, S. Failla and P. Finocchiaro, *Phosphorus, Sulfur and Silicon*, **118**, 189 (1996).
[8] B. Boduszek, A. Halama and J. Zoń, *Tetrahedron*, **53**, 11399 (1997).
[9] B. Boduszek and A. Halama, *Phosphorus, Sulfur and Silicon*, **141**, 239 (1998).
[10] B. Boduszek, *Tetrahedron*, **52**, 12483 (1996).
[11] B. Boduszek and A. Halama, *Phosphorus, Sulfur and Silicon*, **143**, 151 (1998).