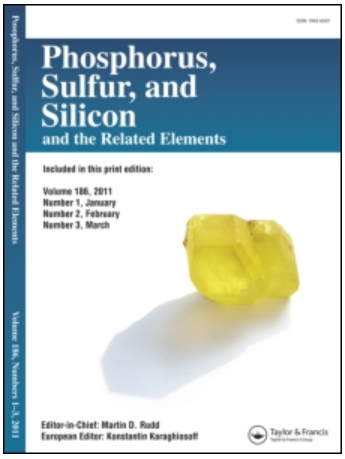

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AN EFFICIENT SYNTHESIS OF 1-AMINOPHOSPHONIC ACIDS AND ESTERS BEARING HETEROCYCLIC MOIETY

Bogdan Boduszek[a]
[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wroclaw, Wroclaw, Poland

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AN EFFICIENT SYNTHESIS OF 1-AMINOPHOSPHONIC ACIDS AND ESTERS BEARING HETEROCYCLIC MOIETY

BOGDAN BODUSZEK

Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wrocław, Wybrzeże Wyspianskiego 27, 50-370 Wrocław, Poland

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New α-aminophosphonic esters and acids derived from furan, thiophene and pyrazole were prepared in high yield, in the reactions of benzylamine, benzhydrylamine or benzyl carbamate with heterocyclic aldehydes and diethyl or diphenyl phosphonates. The protecting groups at amine (benzyl or benzhydryl) were removed by hydrogenolysis or hydrolysis, respectively. The N-benzyloxycarbonyl (Z-group) was removed by treatment with 45% HBr in acetic acid.

Key words: Diphenyl α-aminofurylmethyl phosphonate, α-aminothienylmethylphosphonic acid, α-aminopyrazolylmethylphosphonic acid, imines, benzyl carbamate.

INTRODUCTION

1-Aminophosphonic acids are used in many areas of medicine and agriculture. The importance and utility of 1-aminophosphonic acids are widely demonstrated and discussed in the literature.[1] Especially, α-aminophosphonic acids as phosphorus analogs of α-aminocarboxylic acids have applications in the design of enzyme inhibitors,[2–4] as plant growth regulators,[5] as antibacterial agents,[6] and also as neuroactive compounds.[9] α-Aminophosphonic acids and related compounds find also use as herbicides and antifungal agents.[20–24]

Numerous methods for the synthesis of α-aminophosphonic acids are described in a literature. The first method, discovered by Kabachnik and Medved[11,15] and also by Fields[16] was the reaction between ammonia /or amine/, dialkyl phosphites and aldehydes. Later, some new methods were developed. Fields[16] and Tyka[17] found, that imines can react with dialkyl phosphites, to form α-aminophosphonates. Then Redmore[12] proved that imines at elevated temperatures combined with phosphorous acid to yield α-aminophosphonic acids. Other methods for the synthesis of aminophosphonic acids developed later depended on an application of N-monosubstituted thioureas in the reaction with aldehydes and triphenyl phosphite,[14] or transformation of 1-oxoalkanephosphonates to α-aminoalkanephosphonates.[13] For reviews concerning synthesis of aminophosphonic acids see References 18 and 19. α-Aminophosphonic acids bearing heterocyclic, aromatic rings such as furan, thiophene and pyrazole are unknown or very little known. Only two α-aminophosphonic acids possessing furan and thiophene rings are reported in the literature.[7] Lately, some N-alkylaminophosphonic acids derived from thiophene and pyrrole were described.[8] The authors used special techniques (sonochemical activation) in order to prepare those acids. The described method was limited to the synthesis

only of esters and acids with N-alkylamino groups; no acids with unsubstituted amino group were available.

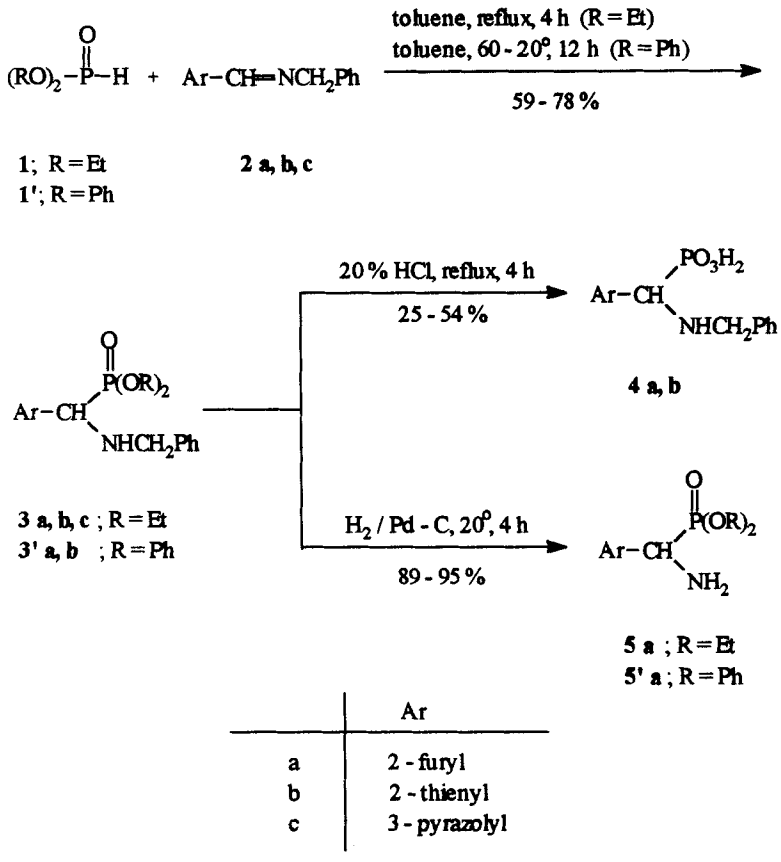
RESULTS AND DISCUSSION

We wish to report an efficient method of synthesis of various α-aminophosphonic esters and acids derived from furan, thiophene and pyrazole. To the best of our knowledge all of the synthesized esters **3**, **5**, **8** and **9**, and acids **4** and **7** are new, not described in the literature (one exception: the acid **7b** was reported in Reference 7). The advantage of the method presented here, is its simplicity (the ultrasonic activation is not required[8]), short time and high yields of products. In addition, the method presented allows to prepare α-aminophosphonic acids and esters with an unsubstituted (free) amino group, which was impossible in the work described in Reference 8. The accessibility of phosphonic esters with a free amino group is very important in peptide synthesis; therefore such obtained products can be used for the preparation of phosphonopeptides.

Our method is based on the application of some amines such as benzylamine, benzhydrylamine or benzyl carbamate in the reaction with heterocyclic aldehydes **6**, followed by addition of diethyl or diphenyl phosphonate **1** or **1'**, respectively. The reaction of benzylamine with aldehydes **6** in toluene underwent smoothly giving Schiff bases **2** in high yields. The formed Schiff bases /imines/ **2** were caused to react *in situ* with diethyl phosphonate **1** at 110°C to give esters **3**. The diethyl esters **3** were isolated and purified as oxalate salts, prepared from crude products. When diphenyl phosphonate **1'** was used in the reaction with imines **2**, the addition reaction took place even at room temperature, giving diphenyl esters **3'**, in high yields. The diphenyl esters **3'** are white, crystalline solids which crystallize out from the reaction mixture. Esters **3** or **3'** were easily hydrolyzed to the corresponding acids **4** with aqueous 20% HCl. The furan derivative **4a** was obtained in low yield, because decomposition of the furan ring took place to a considerable extent in used acidic conditions. The furan esters **3a** and **3'a** were easily hydrogenated using a palladium catalyst to give unblocked α-aminoesters **5**, in standard conditions[17] /10% Pd-C, H_2, H^+/. The thiophene esters **3b** and **3'b** were not affected by hydrogenolysis, because the catalyst was poisoned (Scheme I).

The benzhydrylamine was successfully applied for the preparation of α-aminophosphonic acids in a one-pot synthesis. Benzhydrylamine reacted with aldehyde **6** /in toluene solution/ to give imines, which, in subsequent reaction with diethyl phosphonate gave the corresponding esters, which in turn, were hydrolyzed to the final acids **7**, by means of aqueous 20% HCl. The benzhydryl attached to nitrogen was simultaneously removed during hydrolysis. The reaction failed in the case of furaldehyde probably because of the instability of the furan ring in strong acidic medium used during the reaction.

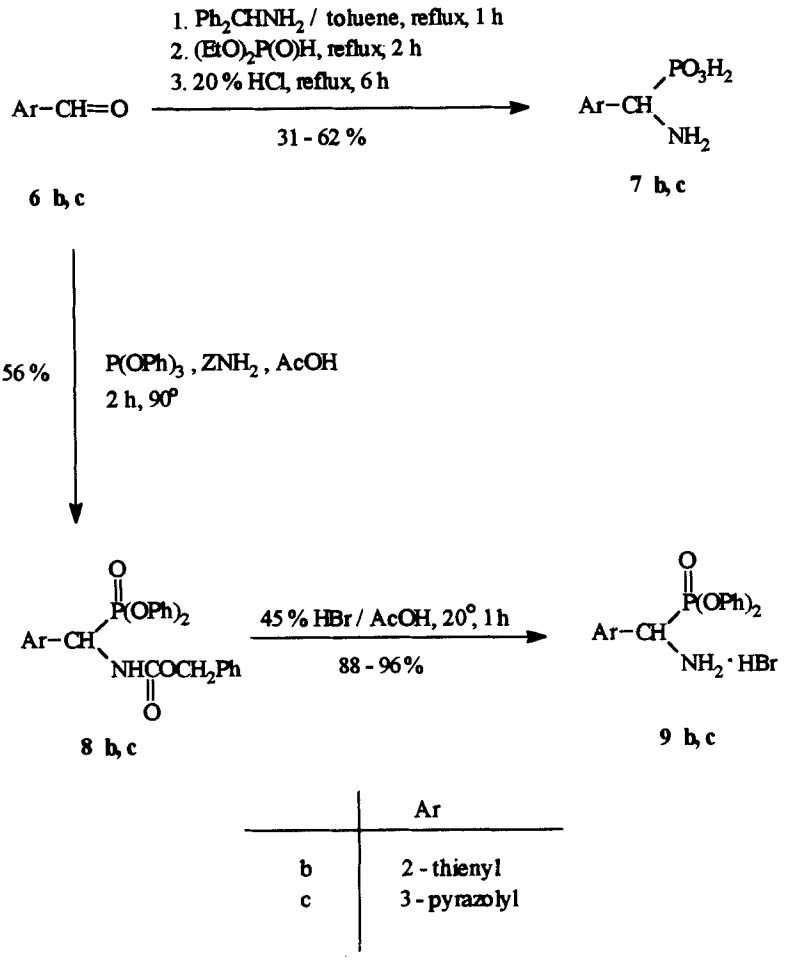
N-protected diphenyl aminophosphonates **8** were synthesized following the literature method,[4,10] with some modifications. In this case, the aldehydes **6** were caused to react in a one-pot synthesis with benzyl carbamate and triphenyl phosphite in acetic acid to give α-N-(benzyloxycarbonyl)aminophosphonates **8** in moderate yields. This method allowed to obtain unsubstituted α-aminophosphonates **9**, suit-



SCHEME I

able for peptide synthesis. In order to prepare aminoesters **9**, the benzyloxycarbonyl group /Z-group/ was removed by treatment of ester **8** with anhydrous 45% HBr in acetic acid. The final products were isolated as hydrobromides (Scheme II). When α-furaldehyde was used for the above reaction complete decomposition took place. Nevertheless, the corresponding furan α-aminophosphonates **5a** and **5'a** were easily obtained by hydrogenolysis of N-benzylaminoesters **3a** and **3'a**.

In conclusion, the synthesis of the new heterocyclic α-aminophosphonic esters and acids was achieved in the reaction of imines prepared from benzyl, or benzhydryl amine with heterocyclic aldehydes and subsequent reaction with diethyl or diphenyl phosphite. The last one is preferred, because the addition to the imine underwent smoothly in mild conditions, and crystalline products were formed. The typical methods of synthesis of aminophosphonic acids, i.e. Kabachnik and Medved method,[11,15] or Redmore method,[12] failed completely in this case due to instability of the heterocyclic ring, or side reactions. The benzylic amines used here are complementary; benzylamine is preferred in the reaction with α-furylaldehyde, the benzhydrylamine can be used for a one-pot synthesis of α-aminophosphonic acids



SCHEME II

derived from thiophene and pyrazole, and benzyl carbamate is efficient in the preparation of diphenyl phosphonic esters with unsubstituted amino group.

Further studies on the application of this approach for the preparation of other heterocyclic α-aminophosphonates are in progress.

EXPERIMENTAL

All commercially available reagents were used as received from the suppliers, with exception of α-furaldehyde, which was distilled prior to use. Melting points were determined with Digital Melting Point Apparatus Electrothermal 9200, and are uncorrected. ^{1}H-NMR spectra were recorded on a Tesla BS 587A, 80 MHz spectrometer and also on a Bruker Advance TM DRX 300 MHz spectrometer. Chemical shifts are expressed in parts per million positive values downfield from internal TMS (in $CDCl_3$ solutions) and HMDSO (as external standard) in D_2O solutions. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR spectrometer. Elemental analyses were performed in the Laboratory of Instrumental Analysis in this Department. TLC was performed on silica gel plates Merck (Art. 5548, HP-TLC Alufolien Kieselgel 60F 254). The imines **2a–c** were prepared *in situ* and used directly in a next step without isolation.

N-Benzylaminophosphonate Esters **3** *and* **3'**

A solution of aldehyde **6a–c** (50 mmol) and benzylamine (50 mmol) in toluene (100 mL) was heated at 110°C for 5–10 min and left for several hours at r.t. The separated drops of water were removed by shaking with anh. sodium sulfate. The mixture was filtered, and to such obtained solution of imine **2a–c** neat phosphonate **1** or **1'** (50 mmol) was added respectively. When diethyl phosphonate was added, the mixture was refluxed for 4 h (in the case of 2-furyl derivative the refluxing time was shortened to 30 min). Then toluene was removed *in vacuo* to obtain crude products. The esters **3a–c** were purified as oxalate salts. The crude ester (45–50 mmol) was dissolved in acetone (100 mL), and a solution of oxalic acid (12.6 g, 100 mmol) in acetone (50 mL) was added. The final solution was refrigerated and the precipitated oxalates of esters **3a–c** were filtered and dried.

In the case of **3'** (when diphenyl phosphonate was added) the mixture was heated to 60°C and left for 12 h at r.t. The esters **3'a–b** crystallized directly from the reaction mixture (white crystals) and were collected by filtration.

The free esters were easily liberated from the oxalate salts by treatment with excess of 5% aqueous sodium carbonate and extraction of the separated esters with chloroform. The extract was evaporated to give pure esters **3** as colorless oils.

O,O'-Diethyl-1-(N-benzylamino)-2-furylmethylphosphonate, (**3a**), *Oxalate*: Yield: 59%; mp = 124–5°C.

^{1}H-NMR (D_2O): δ = 7.62 (bs, 1H, furan), 7.35 (s, 5H, phenyl), 6.70 (m, 1H, furan), 6.54 (m, 1H, furan), 5.11–3.95 (m, 7H, HCP, CH_2O, CH_2N), 1.33 (t, 3H, CH_3), 1.15 (t, 3H, CH_3).
IR (KBr): ν = 3180 (NH), 3000 (CH), 1750 (C=O), 1240 (P=O), 1020 (P—O).
Elemental Anal. for **3a**·$(COOH)_2$: Calc.: N: 3.39, P: 7.49%. Found: N: 3.28, P: 7.22%.
M.Wt. = 413.40

O,O'-Diethyl·1-(N-benzylamino)-2-thienylmethylphosphonate, (**3b**), *Oxalate*: Yield: 78%; mp = 129–30°C.

^{1}H-NMR (D_2O): δ = 7.67–7.47 (m, 2H, thiophene), 7.39 (s, 5H, phenyl), 7.17 (d, 1H, thiophene), 5.11 (d, 1H, HCP, J_{CHP} = 19 Hz), 4.37–3.99 (m, 6H, CH_2O and CH_2N), 1.32 (t, 3H, CH_3), 1.14 (t, 3H, CH_3).
IR (KBr): ν = 3450 (OH), 3000 (CH), 1740 (C=O), 1240 (P=O), 1020 (P—O).
Elemental Anal. for **3b**·$(COOH)_2$: Calc. N: 3.26, P: 7.21, S: 7.47%. Found: N: 3.38, P: 7.21, S: 7.32%.
M.Wt. = 429.48

O,O'-Diethyl-1-(N-benzylamino)-3-pyrazolylmethylphosphonate, (**3c**), *Oxalate*: Yield: 66%, mp = 121–4°C.

^{1}H-NMR (D_2O): δ = 8.71 (s, 1H, pyrazole), 7.67 (bs, 1H, pyrazole), 7.35 (s, 5H, phenyl), 4.96 (d, 1H, HCP, J_{CHP} = 20 Hz), 4.26–4.02 (m, 6H, CH_2O and CH_2N), 1.30 (t, 3H, CH_3), 1.12 (t, 3H, CH_3).
IR (KBr): ν = 3400 (OH), 3150 (NH), 3000 (CH), 1740 (C=O), 1210 (P=O), 1030 (P—O).
Elemental Anal. for **3c**·2·$(COOH)_2$·$2H_2O$: Calc. N: 7.79, P: 5.74%. Found N: 7.81, P: 5.64%.
M.Wt. = 539.43

O,O'-Diphenyl-1-(N-benzylamino)-2-furylmethylphosphonate, (**3'a**): Yield: 63%, mp = 119.5–120°C.

^{1}H-NMR ($CDCl_3$): δ = 7.84 (bs, 1H, furan), 7.42–7.18 (m, 15H, phenyls), 7.03 (m, 1H, furan), 6.38 (m, 1H, furan), 4.30 (d, 1H, HCP, J_{CHP} = 22 Hz), 3.78 (q, 2H, CH_2N), 2.33 (bs, 1H, NH).
IR (KBr): ν = 3310 (NH), 3050 (CH), 1220 (P=O), 960 (P—O).
Elemental Anal. for **3'a**: Calc. N: 3.34, P: 7.38%. Found: N: 3.72. P: 7.71%.
M.Wt. = 419.42

O,O'-Diphenyl-1-(N-benzylamino)-2-thienylmethylphosphonate, (**3'b**): Yield: 62%, mp = 117.0–117.5°C.

^{1}H-NMR ($CDCl_3$): δ = 7.62–7.06 (m, 18H, thienyl, phenyl), 4.70 (d, 1H, HCP, J_{CHP} = 20 Hz), 4.00 (q, 2H, CH_2N), 2.64 (bs, 1H, NH).
IR (KBr): ν = 3320 (NH), 1215 (P=O), 970 (P—O).
Elemental Anal. for **3'b**: Calc. N: 3.22, P: 7.11, S: 7.36%. Found: N: 3.49, P: 7.35, S: 7.62%.
M.Wt. = 435.46

N-Benzylaminophosphonic Acids **4a–b**

A solution of ester **3a–b** (20 mmol) in aqueous 20% HCl was refluxed for 4 h. The volatile materials were evaporated *in vacuo* and the residue was dissolved in water (100 mL), charcoal (1 g) added and

the mixture refluxed for 15 min, filtered, and filtrate evaporated *in vacuo* to give crude acids **4**, which were recrystallized from absolute ethanol (**4a**), or from water (**4b**).

1-(N-Benzylamino)-2-furylmethylphosphonic Acid, (**4a**): Yield: 25%, mp = 235–240°C. /dec/.

^{1}H-NMR (D_2O): δ = 7.43 bs, 1H, furan), 7.25 (bs, 5H, phenyl), 6.45 (d, 1H, furan), 6.35 (m, 1H, furan), 4.30 (d, 1H, HCP, J_{CHP} = 17 Hz), 4.02 (d, 2H, CH_2N).
IR (KBr): ν = 3110 (NH), 1220 (P=O).
Elemental Anal. for **4a**: Calc. N: 5.24, P: 11.59%. Found: N: 5.13, P: 11.67%.
M.Wt. = 267.213

1-(N-Benzylamino)-2-thienylmethylphosphonic Acid, (**4b**): Yield: 54%, mp = 170–2°C. /dec/.

^{1}H-NMR (D_2O + D_2SO_4): δ = 7.72 (d, 1H, thiophene), 7.47 (m, 5H, phenyl), 7.29–6.76 (m, 2H, thiophene), 4.92 (d, 1H, HCP, J_{CHP} = 19 Hz), 4.22 (d, 2H, CH_2N).
IR (KBr): ν = 3600 (OH), 3160 (NH), 1180 (P=O).
Elemental Anal. for **4b**: Calc. N: 4.94, P: 10.93, S: 11.32%. Found: N: 5.08, P: 10.88, S: 11.32%.
M.Wt. = 283.28

α-Aminophosphonate Esters, (**5a**) *and* (**5'a**): *Hydrogenolysis*

A solution of oxalate **3a** (10 mmol) in methanol (100 mL) was prepared. In the case of ester **3'a**, in order to make the solution in methanol, chloroform (40 mL) and 6 M HCl (4 mL) were added additionally. Then the catalyst (10% Pd-C) (0.5 g) was added and hydrogen was bubbled through the stirred solution for 4 h at r.t. Then the mixture was filtered, the filtrate evaporated *in vacuo*, the residue was made alkaline with excess aqueous 5% sodium carbonate and extracted with chloroform (50 mL). The extract was dried (anh. $MgSO_4$), filtered and evaporated to give product **5**, as pale yellow oil. Oxalates of obtained esters **5** were prepared as described above, using the same proportions of acetone /solvent/ and oxalic acid, in relation to the crude esters.

O,O'-Diethyl-1-amino-2-furylmethylphosphonate, (**5a**), *Oxalate*: Yield: 88%, mp = 120–121°C.

^{1}H-NMR (D_2O): δ = 7.51 (bs, 1H, furan), 6.58 (m, 1H, furan), 6.50 (m, 1H, furan), 5.04 (d, 1H, HCP, J_{CHP} = 18 Hz), 4.10 (m, 4H, CH_2O), 1.25 (t, 3H, CH_3), 1.10 (t, 3H, CH_3).
IR (KBr): ν = 3400 (OH, NH), 1610 (C=O), 1250 (P=O).
Elemental Anal. for **5a**·$(COOH)_2$: Calc. N: 4.33, P: 9.58%. Found: N: 4.48, P: 9.35%.
M.Wt. = 323.24

O,O'-Diphenyl-1-amino-2-furylmethylphosphonate, (**5'a**), *Oxalate*: Yield: 95%, mp = 119.5–120.5°C. /dec/.

^{1}H-NMR (D_2O + DMSO): δ = 7.82 (bs, 1H, furan), 7.50–7.00 (m, 10H, phenyl), 6.80 (m, 1H, furan), 6.62 (m, 1H, furan), 5.40 (d, 1H, HCP, J_{CHP} = 19 Hz).
IR (KBr): ν = 3400 (OH, NH), 1600 (C=O), 1260 (P=O).
Elemental Anal. for **5'a**·$(COOH)_2$·$2H_2O$: Calc. N: 3.08, P: 6.80%. Found: N: 3.12, P: 6.70%.
M.Wt. = 455.35

α-Aminophosphonic Acids **7b–c**

A solution of aldehyde **6b–c** (10 mmol) and benzhydrylamine (1.83 g, 10 mmol) in toluene (100 mL) was refluxed for 1 h and then neat diethyl phosphonate **1** (1.4 g, 10 mmol) was added. The solution was refluxed for an additional 2 h and evaporated *in vacuo*. The residue was treated with aqueous 20% HCl (50 mL), and refluxed for 6 h, then cooled. The separated oil was extracted with toluene (50 mL) and discarded. The aqueous layer was evaporated *in vacuo*, the residue dissolved in water (100 mL), charcoal (1 g) added, and boiled for 15 min. After cooling the mixture was filtered and filtrate evaporated to give crude product **7**, which was recrystallized from ethanol (**7b**), or aqueous ethanol (**7c**).

1-Amino-2-thienylmethylphosphonic Acid, (**7b**): Yield: 31%, mp = 239–42°C. /dec./ Lit.[7] mp = 248–50°C. /dec/.

^{1}H-NMR (D_2O): δ = 7.45 (m, 1H, thiophene), 7.21 (m, 1H, thiophene), 7.05 (m, 1H, thiophene), 4.70 (d, 1H, HCP, J_{CHP} = 18 Hz).
IR (Br): ν = 3200 (NH), 1210 (P=O), 940 (P—O).
Elemental Anal. for **7b**: Calc.: N: 7.25, P: 16.04, S: 16.60%. Found: N: 7.01, P: 15.84, S: 16.45%.
M.Wt. = 193.16

1-Amino-3-pyrazolylmethylphosphonic Acid, (**7c**): Yield: 62%, mp = 265–70°C. /dec./

^{1}H-NMR (D_2O + D_2SO_4): δ = 8.26 (bs, 1H, pyrazole), 7.00 (bs, 1H, pyrazole), 4.99 (d, 1H, HCP, J_{CHP} = 17 Hz)
IR (KBr): ν = 3180 (NH), 1210 (P=O).
Elemental Anal. for **7c**: Calc.: N: 23.73, P: 17.49%. Found: N: 23.75, P: 17.53%.
M.Wt. = 177.10.

N-(Benzyloxycarbonyl)-aminophosphonates, (**8b–c**)

A solution of benzyl carbamate /Z-NH_2/ (2.26 g, 15 mmol) and aldehyde **6** (15 mmol) in toluene (50 mL) was refluxed for 1 h. Then toluene was evaporated *in vacuo* and to the remaining residue glacial acetic acid (6.0 g, 100 mmol) and triphenyl phosphite (4.75 g, 15 mmol) were added. The mixture was heated at 90°C for 2 h with stirring. Then the volatile materials were removed by evaporation *in vacuo* and the resulting oil was dissolved in methanol (25 mL, in the case of **8b**), or in aqueous 85% methanol (30 mL, in the case of **8c**), and refrigerated overnight. The precipitated product was filtered, dried, and recrystallized from hot methanol (25 mL): The undissolved material was filtered off and discarded. The filtrate was cooled and the separated white crystals were collected by filtration.

O,O'-Diphenyl-1-[N-(benzyloxycarbonyl)amino]-2-thienylmethylphosphonate, (**8b**): Yield: 56%, mp = 122–3°C.

^{1}H-NMR ($CDCl_3$): δ = 7.66 (m, 1H, thiophene), 7.32 (s, 5H, phenyl), 7.24–6.92 (m, 12H, phenyls, thiophene), 5.85 (d, 1H, NHC=O), 5.80 (d, 1H, HCP, J_{CHP} = 16 Hz), 5.12 (m, 2H, CH_2O).
IR (KBr): ν = 3300 (NH), 1720 (C=O), 1260 (P=O), 970 (P—O).
Elemental Anal. for **8b**: Calc. N: 2.92, P: 6.46, S: 6.69%. Found: N: 2.81, P: 6.42, S: 6.94%.
M.Wt. = 479.47

O,O'-Diphenyl-1-[N-(benzyloxycarbonyl)amino]-3-pyrazolylmethylphosphonate, (**8c**): Yield: 25%, mp = 140–2°C.

^{1}H-NMR ($CDCl_3$): δ = 8.33 (bs, 1H, NH, pyrazole), 7.45 (m, 1H, pyrazole), 7.25 (s, 5H, phenyl), 7.40–7.00 (m, 10H, phenyls), 6.38 (m, 1H, pyrazole), 6.08 (d, 1H, NHC=O), 5.81 (d, 1H, HCP, J_{CHP} = 20 Hz), 5.08 (m, 2H, CH_2O).
IR (KBr): ν = 3320 (NH), 1720 (C=O), 1240 (P=O), 970 (P—O).
Elemental Anal. for **8c**: Calc. N: 9.07, P: 6.68%. Found: N: 8.78, P: 6.76%.
M.Wt. = 463.41

Diphenyl α-Aminophosphonates, Hydrobromides, **9b–c**

The ester **8** (4 mmol) and a solution of 45% HBr in acetic acid (6 mL) were placed together in a flask, protected against moisture. The mixture was stirred occasionally and kept for 1 h at r.t. Then dry diethyl ether (100 mL) was added and the mixture stirred for 15 min, and the ethereal layer decanted. Fresh diethyl ether (100 mL) was added and stirred again. After decantation of ether, the remained precipitate was collected by filtration, washed with dry ether and dried.

O,O'-Diphenyl-1-amino-2-thienylmethylphosphonate, Hydrobromide (**9b**): Yield: 88%, mp = 178–9°C /dec./

^{1}H-NMR (DMSO + D_2O): δ = 7.72–6.92 (m, 13H, thiophene + phenyls), 6.10 (d, 1H, HCP, J_{CHP} = 19 Hz).
IR (KBr): ν = 3100–2800 (NH_2, CH), 1215 (P=O), 980 (P—O).
Elemental Anal. for **9c**: Calc. N: 3.29, P: 7.27, S: 7.52, Br: 18.75%. Found: N: 3.37, P: 7.43, S: 7.72, Br: 18.90%.
M.Wt. = 426.26

O,O'-Diphenyl-1-amino-3-pyrazolylmethylphosphonate, Dihydrobromide, (**9c**): Yield: 96%, mp = 168–70°C. /dec./

^{1}H-NMR (D_2O): δ = 7.80 (m, 1H, pyrazole), 7.30–6.60 (m, 11H, pyrazole + phenyls), 5.54 (d, 1H, HCP, J_{CHP} = 18 Hz).
IR (KBr): ν = 3400 (NH), 3100–2900 (NH_2, CH), 1230 (P=O).
Elemental Anal. for **9c**: $3H_2O$: Calc. N: 7.71, P: 5.68, Br: 29.31%. Found: N: 7.72, P: 5.33, Br: 29.48%.
M.Wt. = 545.155

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REFERENCES

1. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur, and Silicon*, **63,** 193 (1991).
2. E. W. Logusch, D. M. Walker, J. F. McDonald, J. E. Franz, J. J. Villafranca, C. L. DiJanni, J. A. Colanduoni, B. Li and J. B. Shinellar, *Biochemistry*, **29,** 366 (1990).
3. T. D. Meek and J. J. Villafranca, *Biochemistry*, **19,** 5513 (1980).
4. J. Oleksyszyn, B. Boduszek, Ch. M. Kam and J. C. Powers, *J. Med. Chem.*, **37,** 226 (1994).
5. J. W. Goding, "Monoclonal Antibodies. Principles and Practice," Academic Press, N.Y., 1986.
6. C. Rapp, G. Jung, M. Kugler and W. Loeffler, *Liebigs Ann. Chem.*, 655 (1988); M. Okuhara and T. Goto, *Drugs Expl. Res.*, **7,** 559 (1981).
7. J. Lukszo, J. Kowalik and P. Mastalerz, *Chem. Lett.*, 1103 (1978).
8. C. Hubert, B. Oussaid, G. Etemad-Moghadam, M. Koenig and B. Garrigues, *Synthesis*, 51 (1994).
9. C. F. Bigge, G. Johnson, D. F. Ortwine, J. T. Drummond, D. M. Retz, L. J. Brahce, L. L. Coughenour, F. W. Marcoux and A. W. Probert, *J. Med. Chem.*, **35,** 1371 (1992).
10. J. Oleksyszyn, L. Subotkowska and P. Mastalerz, *Synthesis*, 985 (1979).
11. M. J. Kabachnik and T. Y. Medved, *Doklady Akad. Nauk SSSR*, **84,** 689 (1952).
12. D. Redmore, *J. Org. Chem.*, **43,** 992 (1978).
13. Z. H. Kudzin and A. Kotynski, *Synthesis*, 1028 (1980).
14. Z. H. Kudzin and W. J. Stec, *Synthesis*, 469 (1978).
15. M. J. Kabachnik and T. Y. Medved, *Izv. Akad. Nauk SSSR Ser. Chim.*, 1024 (1954).
16. E. K. Fields, *J. Am. Chem. Soc.*, **74,** 1528 (1952).
17. R. Tyka, *Tetrahedron Letters*, 677 (1970).
18. D. Redmore, "Topics in Phosphorus Chemistry," E. J. Griffith, M. Grayson, Eds., Vol. 8, John Wiley & Sons Inc., New York, 1976.
19. K. Prajer and J. Rachon, *Zeitschrift f. Chemie.*, **6,** 209 (1975).
20. L. Maier, *Phosphorus, Sulfur, and Silicon*, **53,** 43 (1990).
21. L. Maier, *Phosphorus, Sulfur, and Silicon*, **56,** 5 (1991).
22. L. Maier and P. J. Diel, *Phosphorus, Sulfur, and Silicon*, **57,** 57 (1991).
23. L. Maier and P. J. Diel, *Phosphorus, Sulfur, and Silicon*, **62,** 15 (1991).
24. D. G. Cameron, H. R. Hudson and M. Pianka, *Phosphorus, Sulfur, and Silicon*, **83,** 21 (1993).