Synthesis of Dimethylphosphinyl-substituted α-Amino(aryl)methylphosphonic Acids and Their Esters

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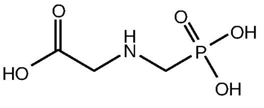
Dimethylphosphinylmethylamine (**1**) and its aldimines **2** were used for the preparation of dimethyl and diethyl α-amino(aryl)methylphosphonates **3a** – **l** *via* imine hydrophosphonylation and Kabachnik-Fields reaction. Their acid hydrolysis gave rise to the corresponding α-aminophosphonic acids **4a** – **e**. Compounds **3** and **4** have two different phosphorus-containing groups – phosphonyl and dimethylphosphinyl – and might have interesting biological activity.

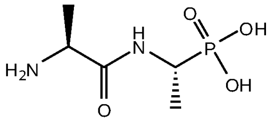
Key words: Dimethylphosphinyl-substituted Phosphonates and α-Aminophosphonic Acids, Kabachnik-Fields Reaction, Imine Hydrophosphonylation

Introduction

Studies on aminophosphonic acids started in the early 1950s, and since then considerable efforts have been devoted to the synthesis and investigation of biological activity of α-aminophosphonic acids, largely because of their structural analogy with α-aminocarboxylic acids [1a – c]. Several α-aminophosphonic acid derivatives such as the herbicide Glyphosate (Roundup) and the antibacterial Alafosfalin are widely used commercially.



Glyphosate



Alafosfalin

The standard synthesis of α-aminophosphonates involves thermal addition of dialkylphosphites to imines, which themselves may be generated *in situ* from the amine and the corresponding aldehyde. These thermal reactions are particularly useful for the large scale preparation of simple α-aminophosphonates. Various modifications have been introduced in recent years with the aim of avoiding solvents and providing mild reaction conditions, especially using Lewis ($Mg(ClO_4)_2$, $SnCl_4$) and Brønsted (CF_3COOH, HBF_4, H_3PO_4, *p*-TsOH) acids as catalysts [2 – 5].

The present work is a continuation of our previous investigations concerning imines of dimethylphosphinylmethylamine as precursors for the preparation of new organophosphorus compounds, containing a dimethylphosphinyl group, with potential biological activity [6, 7]. These imines have been obtained only recently [8], and their potential as polyfunctional reagents is not fully revealed. We wish to report now the synthesis of some new α-aminophosphonates and their hydrolysis to the corresponding α-aminophosphonic acids. The combination of an α-aminophosphonic and a phosphine oxide moiety could result in a series of compounds with potential herbicide and plant growth regulating activities.

Results and Discussion

For the preparation of the desired α-aminophosphonates we chose the Kabachnik-Fields reaction and its parent imine hydrophosphonylation, in order to compare them and find better reaction conditions (Scheme 1).

Phosphonates **3a** – **h** were obtained (as we reported earlier [6] for **3a** – **c** and **3f** – **h**) in good yields and purity (Table 1) by addition of dimethyl or diethyl phosphite to the C=N bond of the aldimines **2a** – **e** (Method A). The reaction mixtures were heated in toluene at 80 °C (70 °C for **3e**) for 8 h. The crude phospho-

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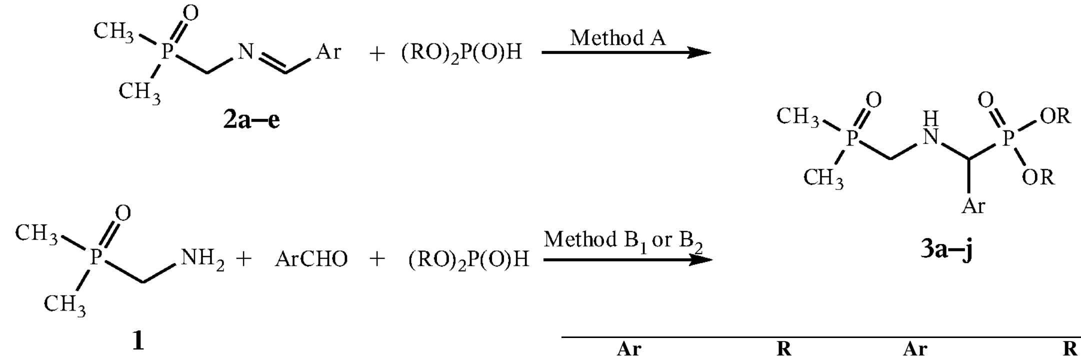


Method A: 80 °C, 8 h, toluene
Method B$_1$: 80 °C, 8 h, toluene
Method B$_2$: r. t., 24 h, TFA (25 mol %)

	Ar	R		Ar	R
3a	C_6H_5	CH_3	**3f**	C_6H_5	CH_2CH_3
3b	C_6H_4-Cl-4	CH_3	**3g**	C_6H_4-Cl-4	CH_2CH_3
3c	C_6H_4-OCH_3-4	CH_3	**3h**	C_6H_4-OCH_3-4	CH_2CH_3
3d	C_6H_4-CH_3-4	CH_3	**3i**	C_6H_4-CH_3-4	CH_2CH_3
3e	C_6H_4-NO_2-4	CH_3	**3j**	C_6H_4-NO_2-4	CH_2CH_3

Scheme 1.

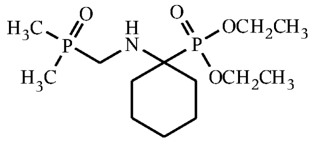
Table 1. Yields of dimethylphosphinyl-substituted α-amino(aryl)methylphosphonates **3a**–**j**, prepared by different methods (see Scheme 1).

			Yield (%)[a]		
	Ar	R	Method A	Method B$_1$	Method B$_2$
3a	C_6H_5	CH_3	72 (53)[b]	–	–
3b	C_6H_4-Cl-4	CH_3	98 (88)[b]	–	–
3c	C_6H_4-OCH_3-4	CH_3	87 (77)[b]	–	–
3d	C_6H_4-CH_3-4	CH_3	94 (84)	–	–
3e	C_6H_4-NO_2-4	CH_3	64 (54)	–	63 (61)
3f	C_6H_5	CH_2CH_3	89 (75)[b]	93 (69)[b]	–
3g	C_6H_4-Cl-4	CH_2CH_3	96 (70)[b]	84 (57)[b]	80 (69)
3h	C_6H_4-OCH_3-4	CH_2CH_3	89 (69)[b]	70 (53)[b]	–
3i	C_6H_4-CH_3-4	CH_2CH_3	–	91 (88)	67 (63)
3j	C_6H_4-NO_2-4	CH_2CH_3	–	52 (50)	86 (78)

[a] Yields of the crude reaction product; yields after purification are given in parentheses; [b] these results have been published in our previous publication [6].

nates **3** are pure enough to be used without further purification (except for the standard work-up by which the starting compounds are removed by extraction of the acidified water solution with CH_2Cl_2). They are low melting crystals or oils that tend to crystallize over time.

At the outset, we performed the Kabachnik-Fields reaction applying its classical thermal conditions (Method B$_1$) by mixing all three components (amine **1**, dialkylphosphite and aromatic aldehyde) in toluene and heating the reaction mixture at 80 °C (70 °C for **3j**) for 8 h. Aminophosphonates **3f**–**j** were obtained also in high yields (70–93 %) and purity. No traces of side products like hydroxyphosphonates or trialkylphosphates were observed in the reaction mixtures by ^{31}P NMR spectroscopy.

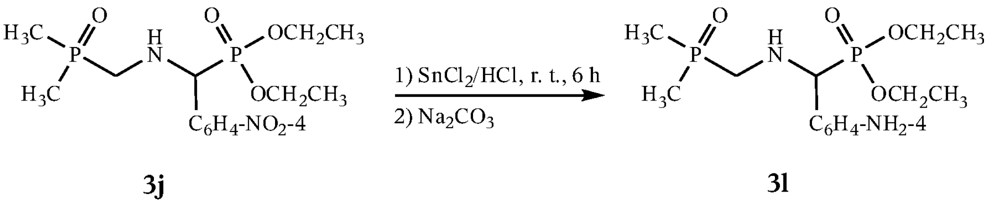


3k

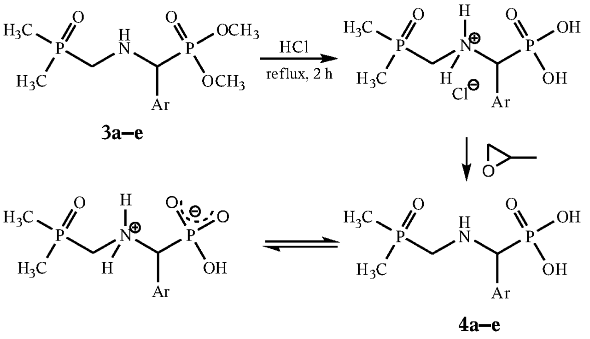
Next, the CF_3COOH-promoted three-component synthesis of α-aminophosphonates **3** starting from aldehydes, amine **1** and dialkylphosphites under solvent-free conditions (Method B$_2$) was examined, and the results are shown in Table 1. The reaction was carried out at r. t. for 24 h, and the aminophosphonates **3e**, **g**, **i**, **j** were obtained in yields comparable with those received by two previous methods (A and B$_1$) and also in high purity (^1H NMR). Method B$_2$ is solvent-free, avoids prolonged heating of the reaction mixture and is more convenient although it requires long reaction times. Acetophenone did not react under the same reaction conditions, but cyclohexanone gave the desired product **3k** in good yield (64 %) and high purity.

The α-aminophosphonate **3l**, containing an amino group in the aromatic ring, could not be prepared by the Kabachnik-Fields reaction, that is why we obtained it with good yield (76 %) and purity by reduction of the ester **3j** (Scheme 2).

The hydrolysis of the phosphonates **3** was carried out with 12 M hydrochloric acid under reflux (Scheme 3). After evaporation of volatiles and treatment with propylene oxide we obtained the crude α-aminophosphonic acids **4a**–**e** with excellent purity



Scheme 2.



	Ar	Yield (%)[a]
4a	C_6H_5	98 (45)
4b	C_6H_4-Cl-4	63 (23)
4c	C_6H_4-OCH_3-4	85 (28)
4d	C_6H_4-CH_3-4	59 (45)
4e	C_6H_4-NO_2-4	85 (59)

[a] Yields of the crude reaction product; yields after purification in parentheses.

Scheme 3.

(^{1}H NMR, ^{31}P{^{1}H} NMR) in 59–98 % yield. For the purpose of their structure analysis they were purified by recrystallization from methanol or water/acetone with high losses.

Structure and purity of all new compounds **3d**, **e**, **i**–**l** and **4a**–**e** were confirmed by IR and ^{1}H and ^{31}P NMR spectral data and elemental analyses.

The solid state IR spectra of compounds **4** are characterized by multiple absorption maxima in the range 3000–2200 cm^{-1} typical for a NH_2^+ and associated OH-group. The intense absorptions at 3450 and 3550 cm^{-1} are assigned to ν(NH) and ν(OH) stretching vibrations and are usually observed for non-hydrogen bonded groups. A low frequency shifting of ν(P=O) (phosphonate) by about 70 cm^{-1} from the typical 1257–1250 cm^{-1} region [9, 10] to 1190–1170 cm^{-1}, is probably due to intermolecular hydrogen bonding (P=O···H–O–P). The ν(P=O) stretching mode of the phosphine oxide group in all acids **4** appears between 1170 and 1140 cm^{-1}, as for the imines **2** [8], where there is no possibility of hydrogen bonding. This value indicates the absence of inter- or intramolecular interactions with participation of the discussed structural fragments. The strong absorption at 1320 cm^{-1}, common to all the IR spectra, corresponds to the $\delta_{as}(CH_3)$ vibration of the phosphine oxide fragment [6–8]. The compounds studied are further characterized by in-plane modes of the aromatic systems at about 1600 and 1500 cm^{-1} and by out-of-plane modes in the range 690–900 cm^{-1} typical for mono- and *p*-disubstituted benzene derivatives.

The ^{1}H NMR spectra of the new phosphonates **3d**, **e**, **i**–**l** are similar to those observed for the previously reported compounds [6] and are in accordance with their structure.

The ^{1}H NMR spectra of the α-aminophosphonic acids **4** also confirm their structure. The resonance signals for the $(CH_3)_2PO$ groups appear as doublets for six protons with $^2J_{PH}$ = −13.7 to −13.9 Hz, except for **4e** which gives two doublets for three protons each with close chemical shifts (δ = 1.71 and 1.72 ppm, $^2J_{PH}$ = −13.8 and −13.5 Hz). The protons of the methylene groups form an ABX system with the phosphine oxide phosphorus atom (X part). The exact signs and values of the chemical shifts and *J* constants ($^2J_{HH}$ = −15.1 to −15.3 Hz and $^2J_{PH}$ = −7.0 to −7.5 Hz) were obtained through calculations. The signals of the methine protons in the phosphonic moiety -C*H*(Ar)–PO_3H_2 are doublets with $^2J_{PH}$ = −15.6 to −16.4 Hz.

The ^{31}P{^{1}H} NMR spectra of the α-aminophosphonic acids **4a**, **b**, **d**, **e** exhibit two resonance signals: at δ = 47.88–48.56 ppm typical for tertiary phosphine oxides [6–8] and at δ = 8.75–9.80 ppm characteristic for α-aminophosphonic acids [11].

All dimethylphosphinyl substituted α-aminophosphonates **3** and α-aminophosphonic acids **4** are under investigation for their potential herbicide and plant growth regulating activity.

Experimental Section

Starting materials

The imines **2** were prepared according to the literature procedure [8]. Dimethyl and diethyl phosphite (purum, Fluka) were purified by distillation prior to use.

Characterization of the compounds

Melting points (uncorrected): micro hot-stage apparatus Boetius PHMK 05. The IR spectra were recorded with a Bomem-Michelson 100 FTIR spectrometer with resolution 2 cm^{-1} and 150 scans, using the solid state KBr pellet technique for acids **4** and $CHCl_3$ as a solvent (0.05 mm KBr cell) for phosphonates **3**. ^1H NMR spectra were recorded on an Avance DRX 250 (250.13 MHz) spectrometer, with $[D_6]$DMSO for **3** and D_2O for **4** as solvents. $^{31}P\{^1H\}$ NMR spectra: Bruker Avance 400 (161.92 MHz). Chemical shifts are measured relative to TMS as internal (^1H) or 85 % H_3PO_4 ($^{31}P\{^1H\}$) as external standard. Column chromatography purifications were carried out on Merck silica gel 60 (0.04 – 0.063 mm) with CH_2Cl_2/CH_3OH (20 : 1) as eluent. TLC: Merck silica gel 60 F_{254} on aluminum sheets, layer thickness 0.2 mm, mobile phase: $CH_2Cl_2 : CH_3OH = 15 : 1$.

*General procedure for the preparation of α-aminophosphonates **3***

Method A: The imine **2** (2 mmol) was dissolved in toluene (5 mL, 15 mL for **2e**), and dimethyl or diethyl phosphite (0.23 mL or 0.32 mL, respectively, 2.5 mmol) was added. The mixture was heated at 80 °C (70 °C for **3e**) for 8 h, and after that the solvent was removed in a vacuum. The residue was dissolved in water (10 mL), and 2 M HCl (2 mL) was added. The solution was washed with diethyl ether (3 × 20 mL), and the aqueous layer was made alkaline with solid Na_2CO_3 and then extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with water (2 × 20 mL), dried and evaporated. The crude products **3a** – **h** (^1H NMR, TLC: one spot) were used in the next step without purification. For the purpose of their structure analysis they were purified by recrystallization from cyclohexane/ethyl acetate (**3a**, **f** – **h**) or column chromatography (**3b** – **e**).

Method B_1: A mixture of amine **1** (0.22 g, 2 mmol), diethyl phosphite (0.40 mL, 3 mmol) and the corresponding aldehyde (2 mmol) in dry toluene (5 mL) was heated at 80 °C (70 °C for **3j**) for 8 h. The solvent was removed in a vacuum, and the residue was worked up as described in Method A.

Method B_2: A mixture of amine **1** (0.22 g, 2 mmol), dimethyl or diethyl phosphite (0.28 mL or 0.40 mL, respectively, 3 mmol), the corresponding carbonyl compound (2 mmol) and trifluoroacetic acid (0.04 mL, 0.5 mmol) was stirred at r. t. for 24 h (48 h for **3k**). The solvent was removed in a vacuum, and the residue was worked up as described in Method A. The crude phosphonates **3e**, **g**, **i** – **k** were purified by column chromatography for the purpose of their spectroscopic analysis.

*Dimethyl [(dimethylphosphinylmethyl)amino]-(4-methylphenyl)methylphosphonate (**3d**)*

Yield of crude α-aminophosphonate: 94 % (Method A). Column chromatography (dichloromethane/methanol = 20 : 1) gave **3d** as a colorless oil. Yield: 84 %. – IR ($CHCl_3$): ν = 3330 (NH), 1600 (Ph), 1460 (Ph), 1290 (CH_3–P), 1230 (P=O), 1160 (P=O), 1050, 1030 (PO–C) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$DMSO): δ = 1.33 (d, 3H, CH_3P, $^2J_{PH} = -12.9$ Hz), 1.38 (d, 3H, CH_3P, $^2J_{PH} = -12.9$ Hz), 2.30 (d, 3H, CH_3–C_6H_4, $^4J_{HH} = 1.6$ Hz), 2.57 – 2.68 (m, 2H, CH_2P; after D_2O exchange 2.60, dd, 1H, $^2J_{HH} = -14.3$ Hz, $^2J_{PH} = -7.9$ Hz and 2.67, dd, 1H, $^2J_{HH} = -14.3$ Hz, $^2J_{PH} = -8.5$ Hz), 3.46 (d, 3H, CH_3O, $^3J_{PH} = 10.6$ Hz), 3.69 (d, 3H, CH_3O, $^3J_{PH} = 10.5$ Hz), 4.26 (dd, 1H, CHAr, $^2J_{PH} = -21.0$ Hz, $^3J_{HH} = 9.0$ Hz; after D_2O exchange 4.22, d, $^2J_{PH} = -21.0$ Hz), 7.17 (d, 2H, $H_{ar.}$, $^3J_{HH} = 7.8$ Hz), 7.28 (dd, 2H, $H_{ar.}$, $^3J_{HH} = 8.2$ Hz, $^4J_{HH} = 2.1$ Hz). – $^{31}P\{^1H\}$ NMR (161.92 MHz, $CDCl_3$): δ = 25.89 ($P(O)(OCH_3)_2$), 44.17 ($P(O)(CH_3)_2$). – $C_{13}H_{23}NO_4P_2$ (319.27): calcd. C 48.90, H 7.26, N 4.39; found C 48.59, H 7.51, N 4.40.

*Dimethyl [(dimethylphosphinylmethyl)amino]-(4-nitrophenyl)methylphosphonate (**3e**)*

Yield of crude α-aminophosphonate: 64 % (Method A) and 63 % (Method B_2). Column chromatography (dichloromethane/methanol = 20 : 1) gave **3e** as a yellowish oil. Yield: 54 % and 61 %, respectively. – IR ($CHCl_3$): ν = 3330 (NH), 1600 (Ph), 1510 (NO_2), 1340 (NO_2), 1300 (P–CH_3), 1240 (P=O), 1160 (P=O), 1050, 1030 (PO–C) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$DMSO): δ = 1.34 (d, 3H, CH_3P, $^2J_{PH} = -13.0$ Hz), 1.41 (d, 3H, CH_3P, $^2J_{PH} = -13.1$ Hz), 2.57 – 2.77 (m, 2H, CH_2P; after D_2O exchange 2.65, dd, 1H, $^2J_{HH} = -14.3$ Hz, $^2J_{PH} = -8.6$ Hz and 2.73, dd, 1H, $^2J_{HH} = -14.3$ Hz, $^2J_{PH} = -7.0$ Hz), 2.92 – 3.07 (m, 1H, NH; disappears after D_2O exchange), 3.54 (d, 3H, CH_3O, $^3J_{PH} = 10.6$ Hz), 3.72 (d, 3H, CH_3O, $^3J_{PH} = 10.6$ Hz), 4.63 (dd, 1H, CHAr, $^2J_{PH} = -22.3$, $^3J_{HH} = 9.2$ Hz; after D_2O exchange 4.56, d, $^2J_{PH} = -22.5$ Hz), 7.70 (dd, 2H, $H_{ar.}$, $^3J_{HH} = 8.8$ Hz, $^4J_{HH} = 2.1$ Hz), 8.25 (d, 2H, $H_{ar.}$, $^3J_{HH} = 8.5$ Hz). – $C_{12}H_{20}N_2O_6P_2$ (350.25): calcd. C 41.15, H 5.76, N 8.00; found C 41.39, H 5.58, N 7.87.

*Diethyl [(dimethylphosphinylmethyl)amino]-(4-methylphenyl)methylphosphonate (**3i**)*

Yield of crude α-aminophosphonate: 91 % (Method B_1) and 67 % (Method B_2). Column chromatography (dichloromethane/methanol = 20 : 1) gave **3i** as a colorless oil. Yield: 88 % and 63 %, respectively. – IR ($CHCl_3$): ν = 3330 (NH), 1600 (Ph), 1290 (CH_3_P), 1230 (P=O), 1160 (P=O), 1050, 1020 (PO–C), 960, 930 (OC–C) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$DMSO): δ = 1.05 (t, 3H, CH_3CH_2, $^3J_{HH} = 7.1$ Hz), 1.22 (t, 3H, CH_3CH_2, $^3J_{HH} = 7.1$ Hz), 1.33 (d, 3H, CH_3P, $^2J_{PH} = -13.0$ Hz), 1.37 (d, 3H, CH_3P, $^2J_{PH} = -13.0$ Hz), 2.29 (s, 3H, CH_3-Ar), 2.55 – 2.70 (m, 3H, NH and CH_2P; after D_2O exchange 2.61, dd, 1H,

$^2J_{HH}$ = −14.3 Hz, $^2J_{PH}$ = −8.5 Hz and 2.68, dd, 1H, $^2J_{HH}$ = −14.3 Hz, $^2J_{PH}$ = −7.4 Hz), 3.69 – 3.91 (m, 2H, POCH_2CH$_3$), 4.04 (dq, 2H, POCH_2CH$_3$, $^3J_{PH}$ = 7.8 Hz, $^3J_{HH}$ = 7.1 Hz), 4.19 (dd, 1H, CHAr, $^2J_{PH}$ = −20.7 Hz, $^3J_{HH}$ = 8.6 Hz, after D_2O exchange 4.13, d, $^2J_{PH}$ = −20.9 Hz), 7.17 (d, 2H, H$_{ar.}$, $^3J_{HH}$ = 7.9 Hz), 7.28 (dd, 2H, H$_{ar.}$, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.8 Hz). – $C_{15}H_{27}NO_4P_2$ (347.33): calcd. C 51.87, H 7.84, N 4.03; found C 51.60, H 7.95, N 3.74.

*Diethyl [(dimethylphosphinylmethyl)amino] (4-nitrophenyl)methylphosphonate (**3j**)*

Yield of crude α-aminophosphonate: 52 % (Method B$_1$) and 86 % (Method B$_2$). Column chromatography (dichloromethane/methanol = 20 : 1) gave **3j** as a yellowish oil. Yield: 50 % and 78 %, respectively. – IR ($CHCl_3$): ν = 3330 (NH), 1600 (Ph), 1500 (NO_2), 1340 (NO_2), 1300 (P–CH$_3$), 1240 (P=O), 1160 (P=O), 1050, 1020 (PO–C), 975, 930 (OC–C) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.09 (t, 3H, CH_3CH$_2$, $^3J_{HH}$ = 7.1 Hz), 1.23 (t, 3H, CH_3CH$_2$, $^3J_{HH}$ = 7.1 Hz), 1.34 (d, 3H, CH$_3$P, $^2J_{PH}$ = −13.1 Hz), 1.40 (d, 3H, CH$_3$P, $^2J_{PH}$ = −13.1 Hz), 2.60 – 2.74 (m, 2H, CH$_2$P; after D_2O exchange 2.65, dd, 1H, $^2J_{HH}$ = −14.3 Hz, $^2J_{PH}$ = −8.4 Hz and 2.71, dd, 1H, $^2J_{HH}$ = −14.3 Hz, $^2J_{PH}$ = −7.3 Hz), 2.84 – 2.98 (m, 1H, NH; disappears after D_2O exchange), 3.79 – 3.98 (m, 2H, POCH_2CH$_3$), 4.07 (dq, 2H, POCH_2CH$_3$, $^3J_{PH}$ = 8.0 Hz, $^3J_{HH}$ = 7.1 Hz), 4.55 (dd, 1H, CHAr, $^2J_{PH}$ = −22.0, $^3J_{HH}$ = 8.4 Hz, after D_2O exchange 4.49, d, $^2J_{PH}$ = −22.1 Hz), 7.69 (dd, 2H, H$_{ar.}$, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.1 Hz), 8.25 (d, 2H, H$_{ar.}$, $^3J_{HH}$ = 8.4 Hz). – ^{31}P{^{1}H} NMR (161.92 MHz, $CDCl_3$): δ = 24.69 (*P*(O)(OCH$_2$CH$_3$)$_2$), 43.02 (*P*(O)(CH$_3$)$_2$). – $C_{14}H_{24}N_2O_6P_2 \cdot H_2O$ (396.31): calcd. C 42.43, H 6.61, N 7.07; found C 42.26, H 6.38, N 6.85.

*Diethyl 1-[(dimethylphosphinylmethyl)amino]-cyclohexylphosphonate (**3k**)*

Yield of crude α-aminophosphonate: 64 % (Method B$_2$). Column chromatography (dichloromethane/methanol = 20 : 1) gave **3k** as a colorless oil. Yield: 61 %. – IR ($CHCl_3$): ν = 3650 – 2800 (OH, H_2O and NH), 1670 (H_2O), 1290 (P−CH$_3$), 1220 (P=O), 1140 (P=O), 1060, 1020 (PO–C), 940 (OC–C) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.23 (t, 6H, CH_3CH$_2$, $^3J_{HH}$ = 7.0 Hz), 1.37 – 1.46 (m, 2H, cyclohexyl), 1.41 (d, 6H, CH$_3$P, $^2J_{PH}$ = −13.1 Hz), 1.48 – 1.62 (m, 6H, cyclohexyl), 1.65 – 1.75 (m, 2H, cyclohexyl), 2.88 – 2.96 (m, 2H, CH$_2$P), 4.02 (dq, 4H, POCH_2CH$_3$, $^3J_{PH}$ = 8.1 Hz, $^3J_{HH}$ = 7.0 Hz). – $C_{13}H_{29}NO_4P_2 \cdot H_2O$ (343.34): calcd. C 45.48, H 9.10, N 4.08; found C 45.66, H 9.11, N 4.09.

*Diethyl (4-aminophenyl)[(dimethylphosphinylmethyl)-amino]methylphosphonate (**3l**)*

*Reduction of nitrophosphonate **3j***: To 0.20 g (0.51 mmol) of the ester **3j** dissolved in ethanol (4 mL) a solution of $SnCl_2 \cdot 2H_2O$ (1.2 g, 5.3 mmol) in 10 M HCl (8 mL) was added dropwise. The reaction mixture was stirred at r. t. for 6 h. It was made alkaline with solid Na_2CO_3 and extracted with dichloromethane (3 × 20 mL). The organic layer was dried and evaporated in a vacuum. Yield of crude α-aminophosphonate: 76 %. Column chromatography (dichloromethane/methanol = 20 : 1) gave **3l** as a colorless oil. Yield: 73 %. – IR ($CHCl_3$): ν = 3470 (NH_2), 3390 (NH), 3330, 3200 (NH_2), 1615 (NH_2), 1605 (Ph), 1290 (P–CH$_3$), 1240 (P=O), 1160 (P=O), 1050, 1030 (PO–C), 965, 940 (OC–C) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D$_6$]DMSO): δ = 1.03 (t, 3H, CH_3CH$_2$, $^3J_{HH}$ = 7.1 Hz), 1.20 (t, 3H, CH_3CH$_2$, $^3J_{HH}$ = 7.1 Hz), 1.34 (d, 3H, CH$_3$P, $^2J_{PH}$ = −13.1 Hz), 1.37 (d, 3H, CH$_3$P, $^2J_{PH}$ = −13.1 Hz), 2.27 – 2.44 (m, 1H, NH, disappears after D_2O exchange), 2.54 – 2.75 (m, 2H, CH$_2$P; after D_2O exchange 2.59, dd, 1H, $^2J_{HH}$ = −14.4 Hz, $^2J_{PH}$ = −8.2 Hz and 2.69, dd, 1H, $^2J_{HH}$ = −14.4 Hz, $^2J_{PH}$ = −7.2 Hz), 3.52 – 3.92 (m, 2H, POCH_2CH$_3$), 3.90 (dd, 1H, CHAr, $^2J_{PH}$ = −19.9, $^3J_{HH}$ = 11.3 Hz), 4.01 (dq, 2H, POCH_2CH$_3$, $^3J_{PH}$ = 7.5 Hz, $^3J_{HH}$ = 7.1 Hz), 5.03 (bs, 2H, NH$_2$), 6.53 (d, 2H, H$_{ar.}$, $^3J_{HH}$ = 8.2 Hz), 7.02 (dd, 2H, H$_{ar.}$, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.0 Hz). – ^{31}P{^{1}H} NMR (161.92 MHz, $CDCl_3$): δ = 24.03 (*P*(O)(OCH$_2$CH$_3$)$_2$), 43.65 (*P*(O)(CH$_3$)$_2$). – $C_{14}H_{26}N_2O_4P_2 \cdot H_2O$ (348.32): calcd. C 48.28, H 7.52, N 8.04; found C 48.61, H 7.82, N 7.85.

*General procedure for the preparation of α-aminophosphonic acids **4a** – **e***

The crude phosphonates **3a** – **e** (without purification) were heated under reflux with 12 M hydrochloric acid (2 mL) for 2 h. The volatiles of the reaction mixture were evaporated at reduced pressure to leave the corresponding α-aminophosphonic acid hydrochloride. It was repeatedly taken up in acetone (3 – 4 mL) and evaporated. Then the residue was dissolved in a small amount of methanol (1 – 1.5 mL) and acetone (4 – 5 mL), and an excess of propylene oxide (2 mL) was added. After stirring for 5 – 10 min a white precipitate of α-aminophosphonic acid **4** was formed. It was filtered off and washed with cold acetone. The α-aminophosphonic acids **4** were recrystallized from the corresponding solvent.

*[(Dimethylphosphinylmethyl)amino](phenyl)-methylphosphonic acid (**4a**)*

Yield of crude α-aminophosphonic acid **4a**: 98 %. Recrystallization from methanol gave **4a** as colorless crystals.

Yield: 45 %. M. p. 215 – 217 °C. – IR (KBr): ν = 2600 – 2000 (OH), 1610 (Ph), 1498 (Ph), 1320 (CH_3), 1170 (P=O), 1140 (P=O), 710 (Ph) cm^{-1}. – ^{1}H NMR (250.13 MHz, D_2O): δ = 1.70 (d, 6H, $(CH_3)_2P$, $^2J_{PH}$ = −13.7 Hz), 3.47 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2, $^2J_{PH}$ = −7.3 Hz), 3.60 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2, $^2J_{PH}$ = −7.5 Hz), 4.59 (d, 1H, CHPh, $^2J_{PH}$ = −15.6 Hz), 7.49 – 7.55 (m, 5$H_{ar.}$). – $^{31}P\{^1H\}$ NMR (D_2O): δ = 9.80 (PO_3H_2), 48.42 (CH_3P=O). – $C_{10}H_{17}NO_4P_2$ (277.194): calcd. C 43.33, H 6.18, N 5.05; found C 43.05, H 5.86, N 5.39.

*(4-Chlorophenyl)[(dimethylphosphinylmethyl)amino]methylphosphonic acid (**4b**)*

Yield of crude α-aminophosphonic acid **4b**: 63 %. Recrystallization from methanol gave **4b** as colorless crystals. Yield: 23 %. M. p. 127 – 130 °C. – IR (KBr): ν = 3200 – 2400 (OH), 1620 (Ph), 1556 (Ph), 1494 (Ph), 1350 (CH_3), 1182 (P=O), 1166 (P=O), 856 (Ph) cm^{-1}. – ^{1}H NMR (250.13 MHz, D_2O): δ = 1.71 (d, 6H, $(CH_3)_2P$, $^2J_{PH}$ = −13.7 Hz), 3.49 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2, $^2J_{PH}$ = −7.3 Hz), 3.62 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2, $^2J_{PH}$ = −7.5 Hz), 4.55 (d, 1H, CHAr, $^2J_{PH}$ = −15.7 Hz), 7.48 – 7.54 (m, 4$H_{ar.}$). – $^{31}P\{^1H\}$ NMR (D_2O): δ = 9.54 (PO_3H_2), 48.56 (CH_3P=O). – $C_{10}H_{16}ClNO_4P_2 \cdot H_2O$ (329.654): calcd. C 36.43, H 5.50, N 4.25; found C 36.57, H 5.37, N 4.52.

*[(Dimethylphosphinylmethyl)amino](4-methoxyphenyl)methylphosphonic acid (**4c**)*

Yield of crude α-aminophosphonic acid **4c**: 85 %. Recrystallization from methanol gave **4c** as colorless crystals. Yield: 28 %. M. p. 143 – 145 °C. – IR (KBr): ν = 3200 – 2400 (OH), 1605 (Ph), 1560 (Ph), 1510 (Ph), 1350 (CH_3), 1255 (CH_3O–C_6H_4), 1175 (P=O), 1165 (P=O), 855 (Ph). – ^{1}H NMR (250.13 MHz, D_2O): δ = 1.69 (d, 6H, $(CH_3)_2P$, $^2J_{PH}$ = −13.7 Hz), 3.44 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2 Hz, $^2J_{PH}$ = −7.2 Hz), 3.56 (dd, 1H, CH_2, $^2J_{HH}$ = −15.2 Hz, $^2J_{PH}$ = −7.6 Hz), 3.86 (s, 3H, CH_3OAr), 4.49 (d, 1H, CHAr, $^2J_{PH}$ = −15.8 Hz), 7.09 (d, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.7 Hz), 7.50 (dd, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.7 Hz). – $C_{11}H_{19}NO_5P_2$ (307.220): calcd. C 43.00, H 6.23, N 4.56; found C 42.80, H 5.95, N 4.33.

*[(Dimethylphosphinylmethyl)amino](4-methylphenyl)methylphosphonic acid (**4d**)*

Yield of crude α-aminophosphonic acid **4d**: 59 %. Recrystallization from water/acetone gave **4d** as colorless crystals. Yield: 45 %. M. p. 196 – 198 °C. – IR (KBr): ν = 3560 (OH), 3446 (NH), 2800 – 2200 (hydrogen bonded OH), 1598 (Ph), 1568 (Ph), 1500 (Ph), 1360 (CH_3), 1190 (P=O), 1170 (P=O), 886 (Ph) cm^{-1}. – ^{1}H NMR (250.13 MHz, D_2O): δ = 1.69 (d, 6H, $(CH_3)_2P$, $^2J_{PH}$ = −13.7 Hz), 2.37 (s, 3H, CH_3Ar), 3.45 (dd, 1H, CH_2, $^2J_{HH}$ = −15.3, $^2J_{PH}$ = −7.4 Hz), 3.58 (dd, 1H, CH_2, $^2J_{HH}$ = −15.3, $^2J_{PH}$ = −7.5 Hz), 4.50 (d, 1H, CHAr, $^2J_{PH}$ = −15.6 Hz), 7.34 (d, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.3 Hz), 7.42 (dd, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.5 Hz). – $^{31}P\{^1H\}$ NMR (D_2O): δ = 9.43 (PO_3H_2), 47.88 (CH_3P=O). – $C_{11}H_{19}NO_4P_2 \cdot H_2O$ (309.235): calcd. C 42.72, H 6.84, N 4.53; found C 42.40, H 6.64, N 4.61.

*[(Dimethylphosphinylmethyl)amino](4-nitrophenyl)methylphosphonic acid (**4e**)*

Yield of crude α-aminophosphonic acid **4e**: 85 %. Recrystallization from water gave **4e** as yellowish crystals. Yield: 59 %. M. p. 222 – 224 °C. – IR (KBr): ν = 3000 – 2200 (OH), 1600 (Ph), 1575 (Ph), 1510 (Ph), 1550 (NO_2), 1350 (NO_2), 1337 (CH_3), 1174 (P=O), 1140 (P=O) cm^{-1}. – ^{1}H NMR (250.13 MHz, D_2O): δ = 1.71 (d, 3H, CH_3P, $^2J_{PH}$ = −13.8 Hz), 1.72 (d, 3H, CH_3P, $^2J_{PH}$ = −13.5 Hz), 3.49 (dd, 1H, CH_2, $^2J_{HH}$ = −15.1, $^2J_{PH}$ = −7.0 Hz), 3.63 (dd, 1H, CH_2, $^2J_{HH}$ = −15.1, $^2J_{PH}$ = −7.1 Hz), 4.65 (d, 1H, CHAr, $^2J_{PH}$ = −16.4 Hz), 7.50 (dd, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 1.7 Hz), 8.33 (d, 2H, $H_{ar.}$, $^3J_{HH}$ = 8.7 Hz). – $^{31}P\{^1H\}$ NMR (D_2O): δ = 8.75 (PO_3H_2), 48.56 (CH_3P=O). – $C_{10}H_{16}N_2O_6P_2$ (322.191): calcd. C 37.28, H 5.01, N 8.69; found C 37.38, H 5.21, N 8.41.

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[1] a) P. Mastalerz, P. Kafarski, in *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*, (Eds.: V. P. Kukhar, H. R. Hudson), John Wiley, Chichester-Toronto, **2000**, chapter 1, pp. 1 – 32; b) J. Oleksyzsyn, in *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*, (Eds.: V. P. Kukhar, H. R. Hudson), John Wiley, Chichester-Toronto, **2000**, chapter 15, pp. 537 – 558; c) H. R. Hudson, in *Aminophosphonic and Aminophosphinic Acids, Chemistry and Biological Activity*, (Eds.: V. P. Kukhar, H. R. Hudson), John Wiley, Chichester-Toronto, **2000**, chapter 13, pp. 443 – 474.

[2] S. Laschat, H. Kunz, *Synthesis* **1992**, 90 – 95.

[3] S. Bhagat, A. Chakraborti, *J. Org. Chem.* **2007**, *72*, 1263 – 1270.

[4] J. Wu, W. Sun, H.-G. Xia, X. Sun, *Org. Biomol. Chem.* **2006**, *4*, 1663 – 1666.

[5] T. Akiyama, M. Sanada, K. Fuchibe, *Synlett* **2003**, 1463 – 1464.

[6] T. Cholakova, Y. Zagraniarsky, G. Hägele, T. Tosheva, B. Ivanova, R. Scopelliti, S. Varbanov, *Z. Naturforsch.* **2005**, *60b*, 215 – 220.

[7] T. Cholakova, Y. Zagraniarsky, S. Simova, S. Varbanov, A. Dobrev, *Phosphorus, Sulfur and Silicon* **2005**, *180*, 1721 – 1728.

[8] S. Varbanov, A. Georgieva, G. Hägele, H. Keck, V. Lachkova, *Phosphorus, Sulfur and Silicon* **2000**, *159*, 109 – 121.

[9] C. Hubert, B. Oussaid, G. Etemad-Moghadam, M. Koenig, B. Garriguea, *Synthesis* **1994**, 51 – 55.

[10] L. Cottier, G. Descotes, G. Gonera, G. Grabowski, J. Lewkowski, R. Skowronski, *Phosphorus, Sulfur and Silicon* **1996**, *118*, 181 – 188.

[11] D. Green, U. Gruss, G. Hägele, H. R. Hudson, L. Lindblom, M. Pianka, *Phosphorus, Sulfur and Silicon* **1996**, *113*, 179 – 207.