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Synthesis and Functionalization of Organophosphorus-Substituted Amines with PCH_2NH Fragments

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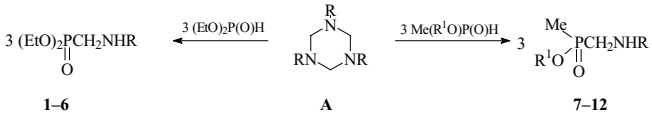
ABSTRACT: *The convenient procedures for the synthesis of new organophosphorus-substituted amines with the PCH_2NH moiety are proposed, starting from the derivatives of organophosphorus PH-acids, as well as 1,3,5-trisubstituted hexahydro-1,3,5-triazines as aminomethylating reagents. Various reactions of functionalization (such as acylation, carboxyethylation, pyridylethylation, and aminoethylation) of the obtained organophosphorus-substituted amines are presented.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:236–241, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20602

INTRODUCTION

Organophosphorus-substituted amines and their derivatives are widely known as interesting biomimetics of amino acids that are also of great interest as biologically active compounds and promising polydentate ligands [1,2]. So organophosphorus-substituted amino acids (*N*-phosphonomethyl glycine, 2-aminoethylphosphonic acids, and phosphinothricin) are well-known plant-growth regulators [1,2], and pyridine-containing organophosphorus-substituted amines are the effective agents for the treatment of bone diseases [3]. In this work, we propose a convenient way for synthesis of new organophosphorus-substituted amines and amino acids with the PCH_2NH moiety using symmetrical 1,3,5-trisubstituted hexahydrotriazines as aminomethylating reagents, which were previously used in the several reactions of aminomethylation (cf. [5–8]). We also found that synthesized amines are the unique organophosphorus synthons to obtain their functionalized derivatives of various structures via acylation, carboxyethylation, pyridylethylation, and aminoethylation of the PCH_2NH fragments.

RESULTS AND DISCUSSION

Thus an excess of diethyl phosphite and *O*-alkyl methylphosphonites easily react with symmetrical 1,3,5-trisubstituted hexahydrotriazines **A** on heating to 120°C with formation of aminomethylphosphonates **1–6** or aminomethylphosphinates **7–12** which may include glycine or β-alanine fragments (Eq. (1)).



1–6 **A** **7–12**

R = Me (**1,7**), Et (**2,8**), CH_2=$CHCH_2$ (**3,9**), Bu (**4,10**), CH_2COOEt (**5,11**), $(CH_2)_2COOEt$ (**6,12**); R^1 = Et (**7-10**), *i*-Pr (**11,12**).

(1)

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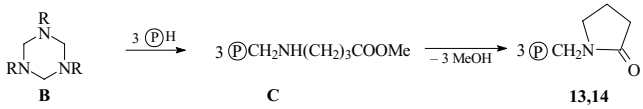
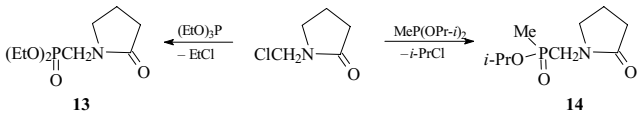
Under the same conditions, the reaction of PH-acids with corresponding triazine **B** results in formation of phosphorus-substituted pyrrolidones **13** and **14**, which are the products of cyclization of intermediate phosphorus-substituted γ-aminobutyric acid esters **C** (Eq. (2)).



R = $(CH_2)_3COOMe$, Ⓟ = $(EtO)_2P(O)$ (**13**), Me(*i*-PrO)P(O) (**14**).

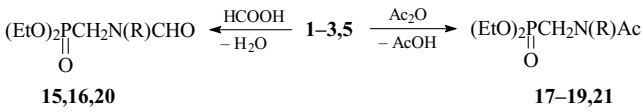
(2)

Phosphorus-substituted pyrrolidones **13,14** were also specially prepared in high yield by reactions of *N*-chloromethylpyrrolidone with triethyl phosphite or *O*,*O*-diisopropyl methylphosphonite in methylene chloride (Eq. (3)).



(3)

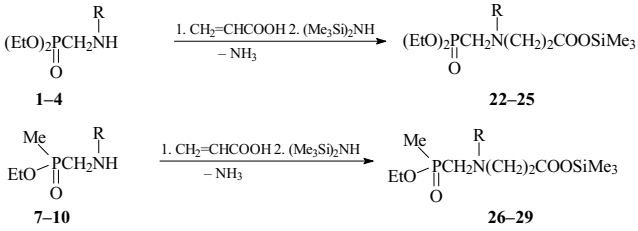
Phosphorus-substituted amines and amino acids involving the NH group are the suitable reagents for the synthesis of various functionalized organophosphorus compounds with PCH_2N moieties, which are interesting as prospective ligands with a chelating structure. So phosphonates **1–3,5** are easily formylated and acylated with formation of phosphorus-substituted amides **15–21** (cf. [9]; Eq. (4)).



R = Me (**16,17**), Et (**18**), $CH_2CH{=}CH_2$ (**16,19**), CH_2COOEt (**20,21**)

(4)

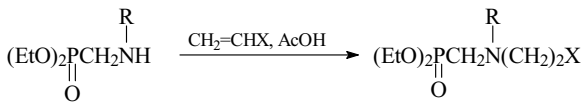
Also we performed successful carboxyethylation and pyridylethylation of phosphorus-substituted methylamines including PCH_2NH groups, aiming to prepare promising polyfunctional compounds. So the reaction of phosphonates **1–4** and phosphinates **7–10** with acrylic acid easily proceeds in methylene chloride and yields after treatment of the reaction mixture with bis(trimethylsilyl)amine phosphonates **22–25** or phosphinates **26–29** with β-alanine fragments (Eq. (5)).



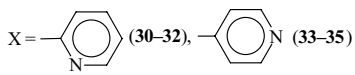
R = Me (**22,26**), Et (**23,27**), $CH_2CH{=}CH_2$ (**24,28**), Bu (**25,29**).

(5)

Here we also showed that phosphorus-substituted methylamines **1–3** containing NH groups smoothly add to 2- and 4-vinylpyridines in the presence of acetic acids to give pyridine-containing aminomethyl phosphonates **30–35** in high yields (Eq. (6)). Note that 6-methyl-3-vinylpyridine does not react with amines **1–3** under these conditions, because of the low activity of 3-vinylpyridine and its derivatives in pyridylethylation of compounds with the labile hydrogen atom [10].

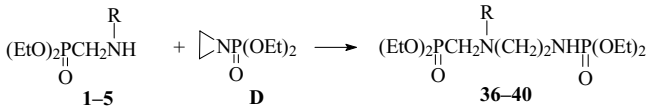


R = Me (**30,33**), Et (**31,34**), $CH_2CH{=}CH_2$ (**32,35**)

X =  (**30–32**), (**33–35**)

(6)

The sufficiently nucleophilic amines **1–5** react with phosphorylated aziridine **D** at 130°C via a three-membered ring opening to form bisphosphorylated ethylenediamines **36–40**, containing P—C and P—N bonds with a good yields (Eq. (7)).



R = Me (**36**), Et (**37**), $CH_2CH{=}CH_2$ (**38**), Bu (**39**), CH_2COOEt (**40**).

(7)

Hence aziridine **D**, which was prepared by a simple procedure developed in [11], can be used as a convenient synthon in various aminoethylation reactions (cf. [12,13]).

The novel organophosphorus amines **1–12, 22–40**, and amides **13–21** present interest as potentially useful compounds (cf. [14,15]). The structures of organophosphorus-substituted amines and

TABLE 1 Yields, Products Constants, and NMR Spectral Data (δ, ppm; J, Hz) for the $PC^1H_2NC^2$ Fragments[a] of Amines **1–12**

No.	*Yield (%)*	*Bp (°C) (p, mmHg)*	n_D^{20}	$\delta(H)\ C^1H_2$ *d*	$^2J_{PH}$	$\delta(C^1)$ *d*	$^1J_{PC}$	$\delta(C^2)$ *d*	$^3J_{PC}$	δ_P *s*[b]
1	79	80 (2)	1.4380	2.79	12.0	47.58	153.4	37.83	15.2	23.08
2	83	92 (1)	1.4374	2.81	12.8	45.72	154.4	45.76	16.0	23.78
3	85	93 (1)	1.4515	2.81	12.4	44.77	157.4	53.46	15.5	23.69
4	87	95 (1)	1.4410	2.82	12.4	45.97	153.8	51.24	16.2	23.70
5	81	133 (2)	1.4469	2.93	12.4	44.78	156.5	51.34	13.6	22.90
6	78	144 (2)	1.4475	2.80	12.0	45.38	153.9	46.74	15.5	23.24
7	74	89 (2)	1.4378	*c*	*c*	49.47	105.7	39.10	15.2	47.09
8	78	98 (2)	1.4410	*c*	*c*	48.83	106.0	46.01	15.7	47.34
9	81	112 (2)	1.4600	*c*	*c*	47.92	107.2	53.89	15.5	47.54
10	80	109 (2)	1.4482	*c*	*c*	48.97	105.9	51.09	15.9	47.52
11	86	128 (1)	1.4555	2.80	11.2	48.48	106.7	51.62	14.2	46.35
12	82	138 (1)	1.4575	2.66	11.2	48.96	106.0	47.00	15.5	46.47

[a]All signals of alkyl and vinyl fragments are in the standard area. In ^1H NMR spectra, fragments NH for all compounds looklike bright signals at 1.6–2.4 ppm. In ^{13}C NMR spectra, fragment C=O for compounds, δ_C, ppm, s: **5**, 171.95; **6**, 172.16; **11**, 171.96; **12**, 172.15. Fragment PCH_3, δ, ppm (J, Hz), for compounds; **7**: δ_H, 1.22 d, $^2J_{PH}$ 13.6, δ_C 12.49 d, $^1J_{PC}$ 91.2; **8**: δ_H, 1.26 d, $^2J_{PH}$ 14.0, δ_C 12.79 d, $^1J_{PC}$ 91.5; **9**: δ_H, 1.25 d, $^2J_{PH}$ 13.8, δ_C 12.87 d, $^1J_{PC}$ 92.0; **10**: δ_H, 1.24 d, $^2J_{PH}$ 14.0, δ_C 12.83 d, $^1J_{PC}$ 91.9; **11**: δ_H, 1.29 d, $^2J_{PH}$ 14.0, δ_C 13.20 d, $^1J_{PC}$ 92.9; **12**: δ_H, 1.24 d, $^2J_{PH}$ 14.0, δ_C 13.20 d, $^1J_{PC}$ 92.7.
[b]Data of $^{31}P\{^1H\}$ spectra.
[c]In ^1H NMR spectra, the signals of the diastereotopic protons of methylene groups C^1H_2 of **7–10** are the characteristic ABX multiplets at 2.6–2.8 ppm.

amides **1–40** were confirmed by the ^1H, ^{13}C, and ^{31}P NMR spectra, which show characteristic signals of the $PC^1H_2NC^2$, $PC^1H_2N(C^2)C^3(O)$, $PC^1H_2N(C^2)C^3H_2$-$C^4H_2C^5$, and $P^1C^1H_2N(C^2)C^3H_2C^4H_2NHP^2$ fragments (see Tables 1–4). The elemental analysis data of synthesized compounds are summarized in Table 5.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were registered on the Varian VXR-400 and Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ against TMS (^1H and ^{13}C) and 85% H_3PO_4 in

TABLE 2 Yields, Products Constants and NMR Spectral Data (δ, ppm; J, Hz) for the $PC^1H_2N(C^2)C^3(O)$ Fragments[a] of Amides **13–21**

No.	*Yield (%)*	*Bp (°C) (p, mmHg)*	n_D^{20}	$\delta(H)\ C^1H_2$ *d*	$^2J_{PH}$	$\delta\ (C^1)$ *d*	$^1J_{PC}$	$\delta(C^2)$ *s*	$\delta(C^3)$ *s*	δ_P^b *s*[c]
13	89	139 (0.5)	1.4706	3.59	10.8	38.50	155.9	47.69	174.05[d]	19.26
14	87	119 (0.5)	1.4846	*e*	*e*	43.04	103.7	48.03	173.92	43.21
15	74	120 (1)	1.4572	3.25	11.2	38.37	155.2	34.38	161.23	18.61 (80)
				3.17	10.0	43.93	158.0	30.12	161.99	18.21 (20)
16	78	140 (3)	1.4595	3.33	11.2	35.74	156.2	49.22	161.62	18.81 (85)
				3.20	10.0	40.99	158.8	44.47	161.70	18.35 (15)
17	80	154 (4)	1.4555	3.45	10.8	41.47	154.9	36.23	169.21	19.76 (85)
				3.31	10.4	45.93	158.2	33.80	169.65	18.47 (15)
18	81	165 (4)	1.4565	3.23	11.2	38.30	156.0	42.34	168.22	19.76 (70)
				3.11	10.0	42.88	158.1	40.13	168.66	18.66 (30)
19	82	132 (1)	1.4662	3.76	10.8	40.18	155.3	51.26	169.75	19.87 (75)
				3.42	9.6	43.59	158.0	48.21	169.65	19.38 (25)
20	74	178 (2)	1.4592	3.46	10.8	37.04	156.2	47.99	162.42[d]	17.89 (55)
				3.37	9.6	42.29	159.0	43.71	162.58[d]	18.39 (45)
21	83	181 (2)	1.4580	3.24	10.4	39.84	156.7	46.69	167.84	19.07 (60)
				3.15	10.0	44.24	159.7	49.45	167.82	18.22 (40)

[a]All signals of alkyl and vinyl fragments are in the standard area. In ^1H NMR spectra, fragment NCHO for compounds, δ_H, ppm, s: **15**, 7.55 and 7.54; **16**, 7.72 and 7.69; **20**, 7.71 and 7.75. Fragment PCH_3 for compound **14**, δ, ppm, d, J, Hz: δ_H 1.25, $^2J_{PH}$ 14.0, δ_C 14.34 d, $^1J_{PC}$ 90.0. In ^{13}C NMR spectra, fragment C(O)O for compounds, δ, ppm, d: **20**, 168.18 and 167.48; **21**, 169.60 and 169.93.
[b]According to the NMR spectra, the amides **15–21** are the mixtures of two stereoisomers, and their ratio was determined from the ^1H and ^{31}P NMR spectra. The spectral parameters of the major isomer are given first.
[c]Data of $^{31}P\{^1H\}$ spectra.
[d]d, $^3J_{PC}$, Hz for compounds: **13**, 3.2; **20**, 3.0 and 3.3.
[e]The overlapping ABX multiplets at the range 3.1–3.6 ppm.

TABLE 3 Yields, Products Constants, and NMR Spectral Data (δ, ppm, J, Hz) for the $PC^1H_2N(C^2)\ C^3H_2C^4H_2C^5$ Fragments[a] of Functionalized Amines **22–35**

No.	Yield (%)	Bp (°C) (p, mmHg)	n_D^{20}	$\delta(H)\ C^1H_2$ d	$^2J_{PH}$	$\delta(C^1)$ d	$^1J_{PC}$	$\delta(C^2)$ d	$^3J_{PC}$	$\delta(C^3)$ d	$^3J_{PC}$	$\delta(C^4)$ s	$\delta(C^5)$ s	δ_P s[b]
22	87	145 (2)	1.4398	2.63	10.8	53.48	161.0	43.79	4.4	54.94	13.3	34.75	172.42	21.99
23	84	141 (1)	1.4374	2.78	10.4	49.79	161.7	49.34	7.1	50.76	9.5	34.59	172.55	24.53
24	86	162(3)	1.4485	2.75	10.4	49.57	159.6	58.62	6.9	51.01	9.0	34.59	172.48	22.16
25	89	168 (3)	1.4445	2.71	10.4	50.43	159.8	55.45	8.8	51.35	8.8	34.61	172.64	22.37
26	83	143 (2)	1.4489	[c]	[c]	50.70	112.9	43.93	3.9	55.61	13.3	34.52	172.41	49.10
27	81	154 (2)	1.4479	[c]	[c]	53.32	113.7	49.41	6.2	54.04	9.6	34.64	172.59	51.20
28	87	164 (2)	1.4545	[c]	[c]	52.86	112.6	58.68	6.3	51.35	9.4	34.57	172.47	47.07
29	90	180 (3)	1.4459	[c]	[c]	53.84	113.1	55.59	6.3	51.53	9.9	34.45	172.61	47.27
30	64	160 (1)	1.4881	2.72	11.2	53.76	162.0	43.96	6.1	59.37	13.3	36.46	160.64	21.52
31	70	162 (1)	1.4920	2.76	10.8	50.06	161.8	49.14	7.9	55.03	8.8	36.14	160.89	22.33
32	72	163 (1)	1.4975	2.82	10.4	49.68	161.7	58.41	7.9	55.30	8.4	36.25	160.78	22.29
33	61	158 (1)	1.4895	2.64	11.1	55.45	162.7	43.87	8.1	59.78	12.1	33.16	149.31	21.87
34	68	160 (1)	1.4935	2.71	10.8	49.79	162.4	49.07	9.8	32.93	7.4	32.93	149.26	22.16
35	71	163 (1)	1.4975	2.75	10.4	49.55	161.2	58.33	9.7	55.56	7.6	32.82	149.10	22.05

[a]All signals of alkyl, vinyl, pyridyl, and trimethylsilyl groups are in the standard area. The ^1H NMR spectra of others fragments show expected signals that look like sometimes as overlapping multiplets. In ^1H NMR spectra, fragments PCH_3 for all compounds **26–29** appear as doublets ($^2J_{PH}$ 14.0 Hz) with the same chemical shift (δ_H 1.25 ppm). In ^{13}C NMR spectra, fragments PCH_3 for compounds δ_C, ppm, d, $^1J_{PC}$, Hz: **26**, 13.03, 92.6; **27**, 13.04, 91.6; **28**, 13.12, 92.2; **26**, 13.08, 91.4.
[b]Data of $^{31}P\ \{^1H\}$ spectra.
[c]The overlapping ABX multiplets.

D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents. The starting derivatives of trivalent organophosphorus acids and symmetrical 1,3,5-trisubstituted hexahydrotriazines were prepared as described in [7,16].

Starting *N-(diethoxyphosphoryl)aziridine* (**D**) was prepared according to [11]. Yield 83%, bp 74°C (1 mm), n_D^{20} 1.4350. $PNCH_2$ group: ^1H NMR spectrum: δ_H 1.83 ppm, d ($^2J_{PH}$ 15.6 Hz); ^{13}C NMR spectrum: δ_C 23.87 ppm, d ($^2J_{PC}$ 7.2 Hz); ^{31}P NMR spectrum: δ_P 13.37 ppm, s.

O,O-Diethyl N-methylaminomethylphosphonate (**1**). A mixture of 21 g of diethyl phosphite and 4.9 g of 1,3,5-trimethylhexahydrotriazine was heated at 110°C for 2 h and then distilled to give 16.3 g of phosphonate **1**.

Phosphonates **2–6**, phosphinates **7–12**, and phosphorylated pyrrolidones **13,14** were prepared similarly. Yields for compounds: **13**, 59%; **14**, 52%.

O,O-Diethyl (2-Oxopyrrolidin-1-yl)methylphosphonate (**13**). To solution of 10 g of triethyl phosphite

TABLE 4 Yields, Products Constants, and NMR Spectral Data (δ, ppm; J, Hz) for the $P^1C^1H_2N(C^2\ H_n)C^3H_2C^4H_2NHP^2$ Fragments[a] of Ethylenediamines **36–40**

No.	Yield (%)	Bp (°C) (p, mmHg)	n_D^{20}	$\delta(H)\ C^1H_2$ d	$^2J_{PH}$	$\delta(H)C^2H_n$	$^3J_{HH}$	$\delta(H)\ C^3H_2$ t	$^3J_{HH}$	$\delta(H)$ NH dt	$^2J_{PH}$	$^3J_{HH}$
36	64	165 (1.5)	1.4510	2.64	10.4	2.26 s	–	2.53	6.4	4.58	11.6	6.4
37	68	172 (1.5)	1.4545	2.69	10.0	2.52 k	7.2	2.61	6.6	4.70	12.0	6.4
38	66	185 (2)	1.4610	2.74	10.0	3.15 d	6.4	2.66	6.4	4.71	12.0	6.4
39	70	165 (0.5)	1.4490	2.70	10.0	2.46 t	7.4	2.63	6.4	4.62	12.1	6.4
40	69	220 (2)	1.4570	3.06	9.6	3.56 s	–	2.82	6.0	4.65	11.6	6.4

No.	$\delta(C^1)$ d	$^1J_{PC}$	$\delta(C^2)$ d	$^3J_{PC}$	$\delta(C^3)$	$^3J(P^1C)$	$^3J(P^2C)$	$\delta(C^4)$ s	$\delta(P^1)$ s[b]	$\delta(P^2)$ s[b]
36	53.10	162.5	44.25	6.2	60.08 dd	6.4	10.8	39.57	22.29	7.47
37	49.79	164.2	49.93	8.1	56.34 t	7.1	7.1	39.85	22.82	7.57
38	49.48	162.9	58.99	7.5	56.44 t	7.0	7.0	39.74	22.67	7.52
39	50.43	163.9	56.12	8.4	56.87 t	6.9	6.9	39.86	22.90	7.55
40	49.67	163.4	55.97	3.7	57.61 dd	6.3	9.6	40.10	22.27	7.47

[a]All signals of alkyl, vinyl, and ethoxy groups are in the standard area. In the ^1H NMR spectrum, the signals of the C^4H_2 fragments appear as multiplets in the range 2.9–3.0 ppm. In the ^{13}C NMR spectrum of compound **40** δ_C (C=O) 171.04 s.
[b]Data of $^{31}P\ \{^1H\}$ spectra.

TABLE 5 Elemental Analyses Data of Compounds

			Calcd (%)		*Found (%)*	
No.	*Empirical Formula*	*Formula Weight*	*C*	*H*	*C*	*H*
1	$C_6H_{16}NO_3P$	181.16	39.78	8.90	39.54	8.82
2	$C_7H_{18}NO_3P$	195.19	43.07	9.29	42.91	9.04
3	$C_8H_{18}NO_3P$	207.20	46.38	8.76	46.12	8.64
4	$C_9H_{22}NO_3P$	223.24	48.42	9.93	48.20	9.86
5	$C_9H_{20}NO_5P$	253.24	42.69	7.96	42.52	7.87
6	$C_{10}H_{22}NO_5P$	267.26	44.94	8.30	44.78	8.09
7	$C_5H_{14}NO_2P$	151.13	39.74	9.34	39.59	9.26
8	$C_6H_{16}NO_2P$	165.16	43.64	9.77	43.48	9.65
9	$C_7H_{16}NO_2P$	177.17	47.46	9.10	47.23	9.03
10	$C_8H_{20}NO_2P$	193.21	49.73	10.43	49.57	10.28
11	$C_9H_{20}NO_4P$	237.24	45.57	8.50	45.43	8.42
12	$C_{10}H_{22}NO_4P$	251.26	47.80	8.82	47.68	8.69
13	$C_9H_{18}NO_4P$	235.22	45.96	7.71	45.81	7.64
14	$C_9H_{18}NO_3P$	219.22	49.31	8.27	49.12	8.14
15	$C_7H_{16}NO_4P$	209.17	40.19	7.71	39.88	7.62
16	$C_9H_{18}NO_4P$	235.22	45.96	7.71	45.72	7.56
17	$C_8H_{18}NO_4P$	223.21	43.05	8.13	42.86	8.02
18	$C_9H_{20}NO_4P$	237.24	45.57	8.50	45.26	8.40
19	$C_{10}H_{20}NO_4P$	249.25	48.19	8.09	47.92	7.96
20	$C_{10}H_{20}NO_6P$	281.25	42.71	7.17	42.64	7.03
21	$C_{11}H_{22}NO_6P$	295.17	44.76	7.48	44.65	7.40
22	$C_{12}H_{28}NO_5PSi$	325.41	44.32	8.68	44.07	8.57
23	$C_{13}H_{30}NO_5PSi$	339.44	46.04	8.92	45.85	8.76
24	$C_{14}H_{30}NO_5PSi$	351.45	47.84	8.61	47.70	8.53
25	$C_{15}H_{34}NO_5PSi$	367.49	49.02	9.33	48.89	9.26
26	$C_{11}H_{26}NO_4PSi$	295.38	44.76	8.88	44.60	8.72
27	$C_{12}H_{28}NO_4PSi$	309.41	46.58	9.13	46.40	9.01
28	$C_{13}H_{28}NO_4PSi$	321.42	48.58	8.71	48.49	8.61
29	$C_{14}H_{32}NO_4PSi$	337.46	49.82	9.56	49.68	9.47
30	$C_{13}H_{23}N_2O_3P$	286.30	54.54	8.10	54.40	8.02
31	$C_{14}H_{25}N_2O_3P$	300.33	55.99	8.39	56.08	8.26
32	$C_{15}H_{25}N_2O_3P$	312.34	57.68	8.07	57.49	7.98
33	$C_{13}H_{23}N_2O_3P$	286.30	54.54	8.10	54.32	7.97
34	$C_{14}H_{25}N_2O_3P$	300.33	55.99	8.39	55.84	8.28
35	$C_{15}H_{25}N_2O_3P$	312.34	57.68	8.07	57.52	7.92
36	$C_{12}H_{30}N_2O_6P_2$	360.33	40.00	8.39	39.78	8.45
37	$C_{13}H_{32}N_2O_6P_2$	374.36	41.71	8.61	41.56	8.53
38	$C_{14}H_{32}N_2O_6P_2$	386.37	43.52	8.35	43.26	8.28
39	$C_{15}H_{36}N_2O_6P_2$	402.41	44.77	9.02	44.58	8.94
40	$C_{15}H_{34}N_2O_8P_2$	432.39	41.67	7.93	41.52	7.74

in 10 mL methylene chloride, a solution of 6 g of *N*-chloromethylpyrrolidone in 5 mL of methylene chloride was added under stirring. The mixture was heated to reflux, solvent was evaporated, and the residue was distilled to give 9.4 g of phosphonate **13**.

Phosphinates **14** was prepared analogously.

*O,O-Diethyl N-Methyl-N-formylaminomethylphosphonate (***15***).* A mixture of 10 g of diethyl *N*-methylaminomethylphosphonate **1**, 3.5 g of 95% formic acid and 30 mL toluene was refluxed with a Dean–Stark trap until the water release was complete. Then the solvent was removed, and the residue was distilled in a vacuum to obtain 8.5 g of phosphonate **15**.

Phosphonates **16,20** were prepared similarly.

*O,O-Diethyl N-Methyl-N-acetylaminomethylphosphonate (***17***).* A mixture of 8.9 g of phosphonate **1**, 7 g of acetic anhydride, and 30 mL toluene was refluxed for 2 h. Then the solvent was evaporated, and the residue was distilled to give 8.8 g of phosphonate **17**.

Amides **18,19,21** were prepared similarly.

*O,O-Diethyl N-Methyl-N-[2-(trimethylsiloxycarbonyl)ethyl]aminomethylphosphonate (***22***).* A solution of 10 g of acrylic acid in 20 mL methylene

chloride was added with stirring a solution of 18.3 g of phosphonate **1** in 20 mL of methylene chloride. After 1 h, the solvent was distilled off, and 30 g of bis(trimethylsilyl)amine was added. The resulting mixture was heated with stirring at 120°C until ammonia ceased to evolve and then distilled in a vacuum to obtain 28.6 g of phosphonate **22**.

Compounds **23–29** were obtained in a similar way.

*O,O-Diethyl N-Methyl-N-[2-(pyridyl)ethyl]aminomethylphosphonate (**30**).* To a mixture of 21.7 g of phosphonate **1** and 10.5 g of 2-vinylpyridine, 7.2 g of glacial acetic acid was added with stirring and cooling to 10°C. After the completion of the exothermic reaction, the mixture was heated on a boiling water bath for 2 h. Then it was cooled, and 100 mL of diethyl ether and a solution of 8 g of potassium hydroxide in 40 mL of water were added with stirring. The organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 80 mL), and the ether extracts were dried over potassium carbonate. The solvent was removed, and the residue was distilled in a vacuum to obtain 18.3 g of phosphonate **30**.

Phosphonates **31–35** were prepared similarly.

*O,O-Diethyl N-Methyl-N-[2-(diethoxyphophoryl)-aminoethyl]aminomethylphosphonate (**36**).* A mixture of 5 g of aziridine **D** and 6 g phosphonate **1** was heated for 2 h at 120–130°C and then distilled in a vacuum to obtain 6.4 g of phosphonate **36**.

Phosphonates **37–40** were obtained analogously.

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