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Synthesis of Phosphorus-Substituted Dialkylamides of Organophosphorus Acids, Containing P–C–N–P Moiety

Andrey A. Prishchenko, Mikhail V. Livantsov, Olga P. Novikova, Ludmila I. Livantsova, and Valery S. Petrosyan

Department of Chemistry, M. V. Lomonosov Moscow State University, Moscow 119991, Russia

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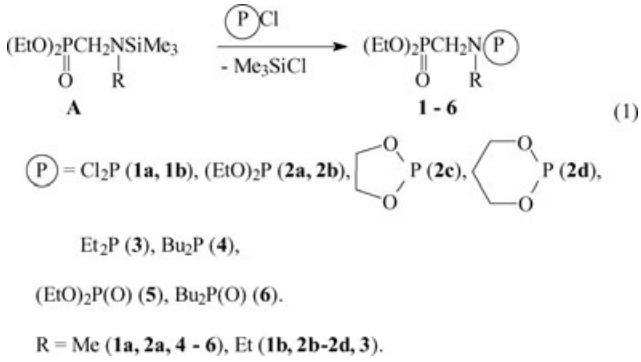
ABSTRACT: *Reactions of N-(trimethylsilyl)aminomethylphosphonates with organophosphorus acid chlorides were studied, which allowed to develop convenient synthetic approaches to novel phosphorus-substituted dialkylamides of organophosphorus acids, including a P–C–N–P moiety. Certain properties of the resulting compounds are presented.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:495–499, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20468

INTRODUCTION

Organophosphorus acid amides of various structures are widely used in organic synthesis as highly reactive synthons [1] and ligands in a series of catalytic systems [2]. They are also of interest as biologically active compounds [3]. In the present work, we have developed convenient methods for preparing novel organophosphorus acid amides containing P—C—N—P moiety. It was previously shown that easily available *N*-(trimethylsilyl)aminomethylphosphonates **A** [4] are convenient synthons for preparing promising phosphorus-containing carboxamides and sulfonamides containing $PCH_2NC(O)$ and PCH_2NSO_2 fragments [5,6].

RESULTS AND DISCUSSION

In the present study, we found that the reaction of phosphonates **A** with chlorides of three- and four-coordinate organophosphorus acids in methylene chloride leads to phosphorus-substituted amides **1–6** in high yields (Eq. (1)).



Bisphosphorus-substituted methylphosphonic diamide **7** was prepared by the reaction of an excess of phosphonate **A** with methylphosphonic dichloride under mild conditions (Eq. (2)).

Dedicated to academician Martin I. Kabachnik (1908–1997).

Correspondence to: Andrey A. Prishchenko; e-mail: aprishchenko@yandex.ru.

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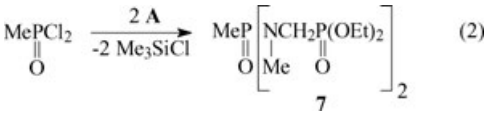
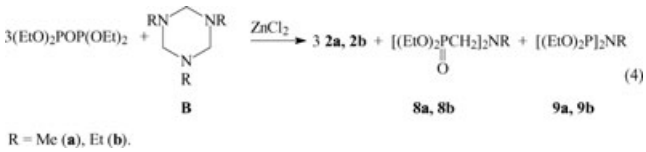
TABLE 1 Yields, Product Constants, and NMR Spectral Data for the $P^1C^1H_mN(C^2H_n)P^2$ Fragments (δ, ppm; J, Hz) of Compounds **1–14**[a]

No.	Yield (%)	bp (°) (p mm Hg)	n_D^{20}	$\delta_H(C^1H_m)$	$^2J_{PH}$	$^3J_{PH}$	$\delta(C^1)$ dd	$^1J_{PC}$	$^2J_{PC}$	$\delta(C^2)$d	$^2J_{PC}$	$\delta(P^1)$, d	$\delta(P^2)$, d	$^3J_{PP}$
1a	98	–	–	3.4–3.5m	–	–	46.54	160.5	28.1	37.43	14.3	18.54	162.49	12.9
1b	98	–	–	3.4–3.5m	–	–	41.92	159.4	22.9	43.81	19.7	18.90	163.13	8.5
2a	84	111 (1)	1.4472	2.98 t	8.0	8.0	42.97	159.3	24.1	32.17	13.7	22.29	142.72	18.3
2b	86	115 (1)	1.4485	3.01 dd	8.4	6.8	37.86	157.9	17.3	38.80	20.5	22.59	143.19	12.2
2c	81	129 (1.5)	1.4742	3.03 t	8.6	8.6	39.09	158.3	22.6	39.35	16.7	21.24	141.25	9.7
2d	74	123 (1)	1.4735	2.9–3.1m	–	–	37.95	158.0	15.7	39.54	23.5	21.85	142.37	8.6
3	85	108 (1)	1.4672	2.90 t	8.0	8.0	44.47	156.0	15.1	43.83	11.3	23.02	67.89	7.0
4	83	128 (1)	1.4680	2.87 t	8.0	8.0	51.28	157.1	28.4	34.88 s	–	22.54	63.71	23.8
5	81	139 (1)	1.4418	3.06 t	9.2	9.2	44.05	159.7	4.8	34.34 s	–	20.97	6.96	19.5
6	81	168 (1)	1.4630	3.02 t	8.0	8.0	41.31 d	160.6	–	33.35 s	–	21.10	48.23	15.3
7	78	202 (1)	1.4705	3.05 t	8.8	8.8	42.29 d	159.9	–	32.83 s	–	21.19	34.41 t	18.5
12a	89	138 (1)	1.4718	3.34 dd	12.0	9.2	40.57	158.6	6.6	40.54 s	–	21.23	73.60	12.9
12b	87	160 (2)	1.5018	3.35 t	9.2	9.2	39.09	157.8	3.1	40.63 s	–	21.83	84.55	8.3
12c	85	169 (1)[b]	–	3.30 t	8.6	8.6	43.75 d	160.8	–	34.87 s	–	21.44	81.16	14.7
13	74	152 (2)	1.4498	2.9–3.1m	–	–	38.26	156.2	4.5	39.11	4.6	21.69	30.79	8.5
14	64	178(1)	1.4981	4.81 dd	23.6	11.2	55.53	158.9	5	29.11[c]	6.2	19.03	7.09	29.2

[a]All signals of the alkyl and ethoxy groups are in the standard area. Fragment C^2H_3. % ^{1}H NMR spectrum, δ, ppm (J, Hz): **2a**: 2.37 dd ($^3J_{PH}$ = 7.6, $^4J_{PH}$ = 1.2); **4**: 2.54 dd ($^3J_{PH}$ = 5.2, $^4J_{PH}$ = 1.6); **5**: 2.40 dd ($^3J_{PH}$ = 9.2, $^4J_{PH}$ = 1.2); **6**: 2.35 dd ($^3J_{PH}$ = 9.2, $^4J_{PH}$ = 1.2); **7**: 2.43 dd ($^3J_{PH}$ = 9.6, $^4J_{PH}$ = 2.8); **12c**: 2.52 d ($^2J_{PH}$ = 10.4); **14**: 2.27 d ($^3J_{PH}$ = 9.6 Hz); the signals of the C^2H_2 fragments of the other compounds appear as multiplets in the range 2.6–3.1 ppm. Fragment PCH_3, δ, ppm (J, Hz): **7**: δ_H 1.25 d ($^2J_{PH}$ = 15.2), δ_C 9.37 d ($^1J_{PC}$ = 116.3); **13**: δ_H 1.32 d ($^2J_{PH}$ = 16.8), δ_C 11.40 d ($^1J_{PC}$ = 134).
[b]mp 43°C.
[c]dd, $^3J_{PC}$ 3 Hz.

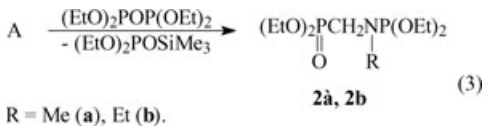


(2)



(4)

Amides **2a** and **2b** were also prepared from tetraethyl pyrophosphite, but the latter proved to be less reactive in analogous transformations. Thus, its reaction with phosphonates **A** could only be effected on heating at 130°C in the presence of a catalyst, zinc chloride. As a result, amides **2a** and **2b** were obtained in high yields (Eq. (3)).

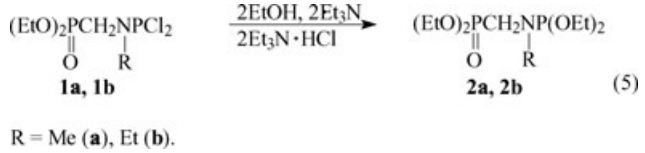


(3)

The reaction of tetraethyl pyrophosphite with symmetrical hexahydrotriazines **B** under similar conditions leads to amides **2a** and **2b** in high yields. Along with these products, bis(phosphonomethyl)amines **8a** and **8b** were isolated in low yields (10%–15%), and the ^{31}P NMR spectra of low-boiling fractions displayed signals of amides **9a** and **9b** (Eq. (4)).

Hence, under conditions of these reactions, ring cleavage in compounds **B** occurs mainly by a symmetric pathway (cf. [4]).

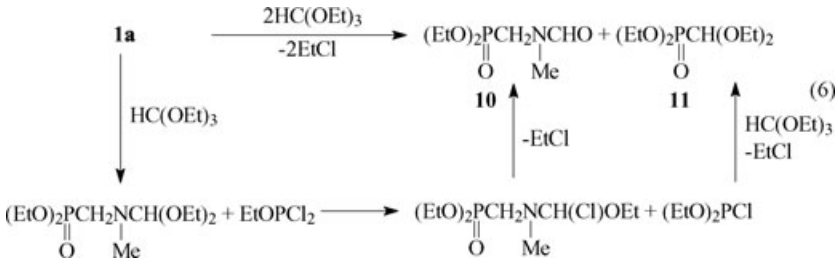
Substituted amidophosphorous dichlorides **1a** and **1b** were prepared in quantitative yields, but, unlike amides **2–7**, they are thermally unstable. They can be stored for a long time at 20°C but polymerize on distillation. Treatment of amidochlorides **1a** and **1b** with a mixture of ethanol and triethylamine gives phosphoroamidites **2a** and **2b** in high yields (Eq. (5)).



(5)

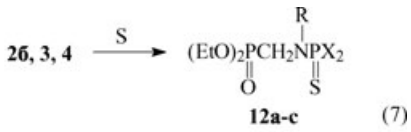
The reaction of amidochloride **1a** with an excess of triethyl orthoformate involves cleavage of the P—N bond. Subsequent reactions of

the intermediates and triethyl orthoformate lead to *N*-formylaminomethylphosphonate **10** and diethoxymethylphosphonate **11** (Eq. (6)). The presented reaction scheme agrees with data in [7–9].



(6)

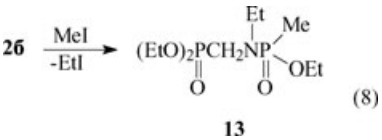
Amides **2–4** containing a three-coordinate phosphorus atom were used by us to prepare novel four-coordinate phosphorus compounds with a PCH_2NP fragment. So amides **2b–4** smoothly take up sulfur in benzene to form thio derivatives **12** (Eq. (7)).



(7)

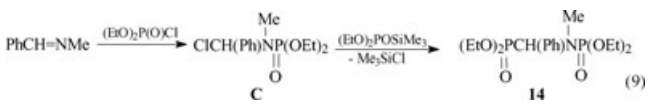
X = EtO (**a**), Et (**b**), Bu (**c**); R = Et (**a**,**b**), Me (**c**).

Amide **2b** reacts with an excess of methyl iodide under mild conditions by an Arbuzov reaction scheme, yielding amidophosphonate **13** (Eq. (8)).



(8)

The unique route to novel four-coordinate phosphorus-substituted amide of diethyl phosphoric acid **14** was found by us. So the adduct of benzal(methyl)amine and diethyl chlorophosphate C, prepared under mild (cf. [10]) conditions, reacts with diethyl trimethylsilyl phosphite to form phosphorus-substituted amidophosphate with PCHNP fragment **14** (Eq. (9)).



(9)

The novel phosphorus-substituted organophosphorus acid amides **1–7** and **12–14** present interest as promising ligands and biologically active compounds. Their structure was confirmed by the NMR spectra containing characteristic signals of the $P^1C^1H_mN(C^2H_n)P^2$ fragments (see Table 1). The ^{31}P NMR signals of the obtained compounds are located in the ranges characteristic of their simplest analogs with the same coordination of the phosphorus atoms. The elemental analyses data of synthesized compounds, confirmatory of their composition, are summarized in Table 2.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were obtained on a Varian VXR-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ against TMS (^1H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents.

*O,O-Diethyl N-(dichlorophosphino)-N-methylaminomethylphosphonate (***1a***)*

To a solution of 10 g of *O,O*-diethyl *N*-methyl-*N*-(trimethylsilyl)aminomethylphosphonate in 40 mL of methylene chloride, a solution of 6.5 g of phosphorus trichloride in 20 mL of methylene chloride was added dropwise with stirring at 0°C. The solvent was removed at 20°C, and the residue was kept in a vacuum (1 mmHg) at 20°C to give 10.9 g of phosphonate **1a**.

Phosphonate **1b** was obtained analogously.

*O,O-Diethyl N-(diethoxyphosphino)-N-methylaminomethylphosphonate (***2a***)*

(a) To a solution of 6.5 g of diethyl *N*-methyl-*N*-(trimethylsilyl)aminomethylphosphonate in 10 mL of methylene chloride, a solution of 4.1 g of diethyl phosphorochloridite in 5 mL of methylene chloride was added dropwise with stirring at 10°C. The solvent was removed, and the residue was distilled in a vacuum to give 6.5 g of phosphonate **2a**.

TABLE 2 Elemental Analyses Data of Synthesized Compounds[a]

No	Empirical Formula	Formula Weight	Calcd. (%)		Found (%)	
			C	H	C	H
2a	$C_{10}H_{25}NO_5P_2$	301.27	39.87	8.36	39.65	8.26
2b	$C_{11}H_{27}NO_5P_2$	315.29	41.90	8.57	41.78	8.52
2c	$C_9H_{21}NO_5P_2$	285.23	37.90	7.42	37.73	7.29
2d	$C_{10}H_{23}NO_5P_2$	299.25	40.14	7.75	40.02	7.64
5	$C_{10}H_{25}NO_6P_2$	317.27	37.86	7.94	37.62	7.87
6	$C_{14}H_{33}NO_4P_2$	341.37	49.26	9.74	48.98	9.66
7	$C_{13}H_{33}N_2O_7P_3$	422.33	36.97	7.88	36.75	7.81
12a	$C_{11}H_{27}NO_5P_2S$	347.36	38.04	7.83	37.89	7.72
12b	$C_{11}H_{27}NO_3P_2S$	315.36	41.89	8.63	41.74	8.57
12c	$C_{14}H_{33}NO_3P_2S$	357.44	47.04	9.31	46.88	9.23
13	$C_{10}H_{25}NO_5P_2$	301.27	39.87	8.36	39.69	8.22
14	$C_{16}H_{29}NO_6P_2$	393.37	48.85	7.43	48.64	7.26

[a]The compounds **1a, 1b, 3, 4** are unstable in the air atmosphere; therefore, these substances were analyzed as their derivatives **2a, 2b, 12b**, and **12c**.

Compounds **2b, 2c**, and **2d–7** were obtained analogously.

(b) To a mixture of 5.1 g of diethyl *N*-methyl-*N*-(trimethylsilyl)aminomethylphosphonate, 5.4 g of tetraethyl pyrophosphite, and 0.2 g of zinc chloride was heated at 130°C for 1 h and then distilled to give 4.9 g of phosphonate **2a**, yield 81%.

Phosphonate **2b** was obtained analogously, yielding 83%.

(c) To a mixture of 6.3 g of tetraethyl pyrophosphite, 1 g of 1,3,5-trimethylhexahydrotriazine, and 0.2 g of zinc chloride was heated at 135°C for 1 h and then distilled to give 5.2 g of phosphonate **2a**, yield 74%. Repeated distillation of the high-boiling fraction gave 0.5 g of *N*,*N*-bis(diethoxyphosphinoylmethyl)-*N*-methylamine (**8a**). Yield 20%, bp 155°C (1 mmHg), nD^{20} 1.4530. $PC^1H_2NC^2H_3$ fragment: ^{1}H NMR spectrum, δ, ppm: 3.01 d (C^1H_2, $^2J_{PH}$ = 9.6 Hz); ^{13}C NMR spectrum, δ_C, ppm: 54.02 dd (C^1, $^1J_{PC}$ = 157.5, $^3J_{PC}$ = 10.4 Hz), 46.22 t (C^2, $^3J_{PC}$ = 7.9 Hz); ^{31}P NMR spectrum, δ_P, ppm: 21.55 s (cf. [11]). The ^{31}P NMR spectrum of the low-boiling fraction [bp 75–85°C (1 mmHg)] contains, together with the signal of the starting tetraethyl pyrophosphite (δ_P 125.5 ppm), a signal of *N*,*N*-bis(diethoxyphosphino)-*N*-methylamine (**9a**), δ_P 143.22 ppm (cf. [12]).

Phosphonate **2b** (yield 72%) and *N*,*N*-bis(diethoxyphosphinoylmethyl)-*N*-ethylamine (**8b**) were obtained analogously, yield 15%, bp 159°C (1 mmHg), n_D^{20} 1.4480. $PC^1H_2NC^2H_2$ fragment: ^{1}H NMR spectrum, δ, ppm: 3.10 d (C^1H_2, $^2J_{PH}$ = 9.2 Hz); ^{13}C NMR spectrum, δ_C, ppm: 49.00 dd (C^1, $^1J_{PC}$ = 156.9, $^3J_{PC}$ = 7.5 Hz), 49.97 t (C^2, $^3J_{PC}$ = 7.8 Hz). ^{31}P NMR spectrum, δ_P, ppm: 22.01 s (cf. [11]). The ^{31}P NMR spectrum of the low-boiling fraction contains a signal of *N*,*N*-bis(diethoxyphosphino)-*N*-ethylamine (**9b**), δ_P 143.72 ppm (cf. [12]).

(d) To a solution of 10.9 g of phosphonate **1a** in 50 mL of diethyl ether, a solution of 3.6 g of ethanol and 8.2 g of triethylamine in 30 mL of ether was added dropwise with stirring at 0°C. The resulting mixture was left for a day at 20°C, the triethylamine hydrochloride was filtered off, the solvent was removed, and the residue was distilled to give 8.9 g of phosphonate **2a**, yielding 76%.

Phosphonate **2b** was obtained analogously, yielding 78%.

Reaction of Phosphonate **1a** *with Triethyl Orthoformate*

To a solution of 10.9 g of phosphonate **1a** in 20 mL of methylene chloride, a solution of 12.6 g of triethyl orthoformate in 20 mL of methylene chloride was added dropwise with stirring at 0°C. The resulting mixture was left for a day at 20°C, the solvent was removed, and the residue was distilled to give 6.3 g (78%) of *O*,*O*-diethyl *N*-formyl-*N*-methylaminomethylphosphonate (**10**), bp 125°C (1 mmHg), n_D^{20} 1.4570. According to NMR data, phosphonate **10** is a 4:1 ratio of two stereoisomers. First isomer: $PC^1H_2N(C^2H_3)C^3(O)H$ fragment: ^{1}H NMR spectrum, δ, ppm: 3.25 d (C^1H_2, $^2J_{PH}$ = 11.3 Hz), 2.65 s (C^2H_3), 7.56 s (C^3H); ^{13}C NMR spectrum, δ_C, ppm: 38.40 d (C^1, $^1J_{PC}$ = 155.2 Hz), 34.35 s (C^2), 161.20 s (C^3); ^{31}P NMR spectrum, δ_P, ppm: 18.61 s. Second isomer: $PC^1H_2N(C^2H_3)C^3(O)H$ fragment: ^{1}H NMR spectrum, δ, ppm: 3.15 d (C^1H_2, $^2J_{PH}$ = 10.0 Hz), 2.45 s (C^2H_3), 7.53 s (C^3H); ^{13}C NMR spectrum, δ_C, ppm: 43.95 d (C^1, J_{PC} = 158.0 Hz), 30.10 s (C^2), 162.00 s

(C^3); ^{31}P NMR spectrum, δ, ppm: 18.20 s (cf. [13]). Repeated distillation of the low-boiling fraction gave 6.7 g of *O,O*-diethyl (diethoxymethyl)phosphonate (**11**), yield 72%, bp 79°C (1 mmHg), n_D^{20}1.4255. PCH fragment: ^1H NMR spectrum, δ, ppm: δ 4.55 d ($^2J_{PH} = 5.0$ Hz); ^{13}C NMR spectrum, δ_C, ppm: 98.19 d ($^1J_{PC} = 207.0$ Hz); δ_P 11.15 ppm (cf. [14]).

*O,O-Diethyl N-(diethoxyphosphinothioyl)-N-ethylaminomethylphosphonate (***12a***)*

A mixture of 3.2 g of phosphonate **2b**, 0.4 g of sulfur, and 10 mL of benzene was heated on a water bath for 1 h and then cooled. The residual sulfur was then filtered off, the solvent was removed, and the residue was distilled to give 2.9 g of phosphonate **12a**.

Compounds **12b** and **12c** were obtained analogously.

*O,O-Diethyl N-[ethoxy(methyl)phosphinoyl]-N-ethylaminomethylphosphonate (***13***)*

To a solution of 4.2 g of phosphonate **2b** in 15 mL of ether, a solution of 6 g of methyl iodide in 5 mL of ether was added dropwise with stirring at 10°C. The resulting mixture was refluxed for 1 h, the solvent was removed, and the residue was distilled to give 3 g of phosphonate **13**.

*O,O-Diethyl N-methyl-N-(diethoxyphosphoryl)-amino(phenyl)methylphosphonate (***14***)*

To a solution of 4.5 g of benzal(methyl)amine in 15 mL of methylene chloride, a solution of 6.4 g of diethyl chlorophosphate in 10 mL of methylene chloride was added dropwise with stirring at 10°C. After 30 min, diethyl trimethylsilyl phosphite, 8.6 g, was added. The resulting mixture was left to stand for 48 h at 20°C. The solvent was removed, and the residue was distilled in a vacuum to give 9.4 g of phosphonate **14**.

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