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Synthesis of New Heterocyclic Mono- and Bisorganophosphorus Acids and Their Derivatives with 1,2-Phenylene Fragments

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ABSTRACT: *The interaction of esters of phosphorous acid containing $POSiMe_3$ and PH fragments with anhydrides of phthalic and 2-sulfobenzoic acids is proposed as convenient methods for the synthesis of new heterocyclic mono- and bisorganophosphorus acids and their derivatives with 1,2-phenylene fragments, carboxyl and sulfonyl groups. Also some properties of the obtained compounds are presented.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem 00:1–4, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21098

INTRODUCTION

The functionalized derivatives of mono- and bisorganophosphorus acids containing aromatic and heterocyclic fragments with various hydroxyl groups present great interest as promising polydentate ligands and organophosphorus biomimetics of hydroxylcarboxylic acids and natural pyrophosphates. Various derivatives of substituted hydroxymethylenebisphosphonic acids are good complexones and widely used in medicine [1–3]. Recently, we have proposed the convenient methods of synthesis of a series of mono- and bisorganophosphorus acids, which were interesting as effective antioxidants with the multifunctional mode of action [4–8]. In the present work, we report the results of the interaction of the esters of phosphorous acid containing $POSiMe_3$ and PH fragments with anhydrides of phthalic and 2-sulfobenzoic acids. This interaction results in the formation of new heterocyclic mono- and bisorganophosphorus acids and their derivatives with 1,2-phenylene fragments and carboxyl and sulfonyl groups.

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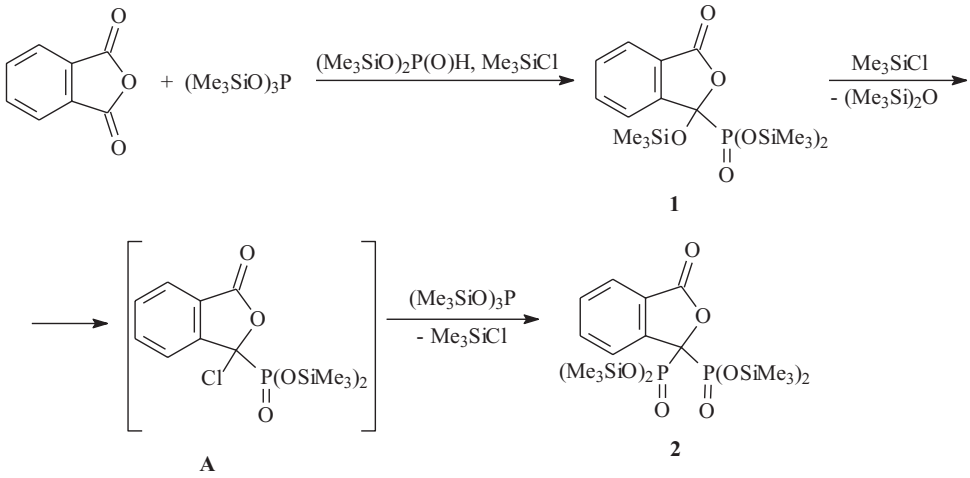
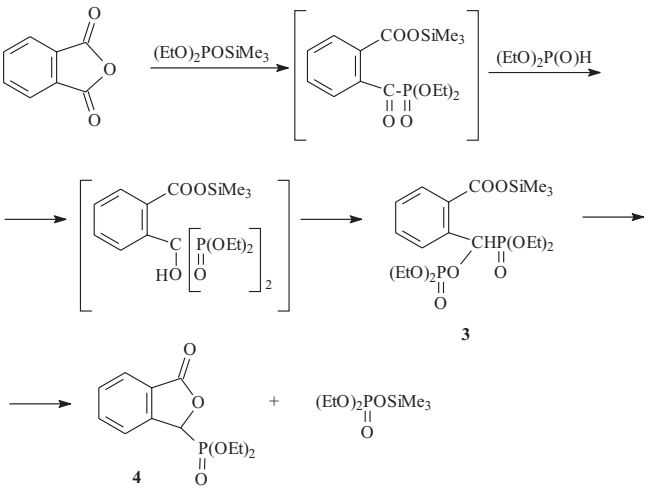
RESULTS AND DISCUSSION

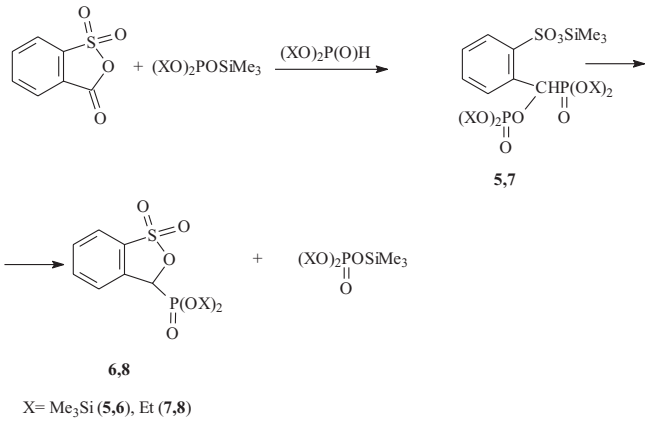
Anhydrides of phthalic and 2-sulfobenzoic acids readily react with various nucleophiles and are widely used in the organic and organometallic synthesis [9–11]. Previously, we had developed the convenient methods for the synthesis of the functionalized organophosphorus amides of iso- and terephthalic acids [12]. In this work, we studied the reactions of trimethylsilyl phosphites with phthalic and 2-sulfobenzoic anhydrides and showed that different results of these reactions were determined by different reactive precursors. Thus, an excess of tris(trimethylsilyl) phosphite reacts slowly with phthalic anhydride in methylene chloride in the presence of bis(trimethylsilyl) phosphite and trimethylchlorosilane already at 20°C. The reaction proceeds via an intermediate formation of cyclic phosphonate **1** detected by the NMR and results in cyclic diphosphonate **2**, which was isolated after distillation in 87% yield (cf. [13,14]) (Scheme 1). Perhaps this interaction easily proceeds due to the



SCHEME 1 Synthesis of diphosphonate **2**.



SCHEME 2 Synthesis of phosphonate **4**.



SCHEME 3 Synthesis of phosphonates **6**,**8**.

possible formation of the highly reactive chloroester **A** as an intermediate in the reaction mixture.

Under the same conditions, the similar reaction of more nucleophilic diethyl trimethylsilyl phosphite and diethyl phosphite with phthalic anhydride proceeds exothermally and results in the product of a phosphonate–phosphate rearrangement **3** in 89% yield. On distilling compound **3**, the formation of cyclic phosphonate **4** and diethyl trimethylsilyl phosphate was registered by the NMR (cf. [15, 16]) (Scheme 2).

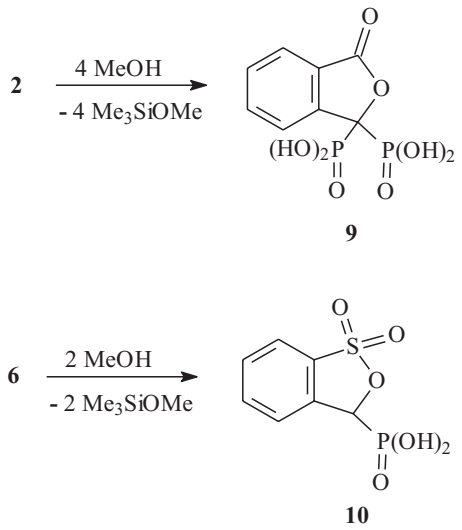
Under similar conditions, more electrophilic 2-sulfobenzoic anhydride reacts with both trimethylsilylphosphites to give only the phosphonate–phosphates **5** and **7**, which are transformed into cyclic phosphonates **6**, **8**, and the corresponding trimethylsilyl phosphates at distillation (Scheme 3).

The reaction of diphosphonate **2** and phosphonate **6** with an excess of methanol results in cyclic mono- and diphosphonic acids **9**, **10**, which are white hygroscopic crystals (Scheme 4).

The resulting compounds, **2**, **3**, **6**, and **8–10**, containing phosphonate, and carboxyl and sulfonyl groups along with the heterocyclic moieties are of interest as potential ligands and biologically active substances. The NMR spectra of compounds **1–10** contain the characteristic signals of the **B–D** fragments (Fig. 1) whose parameters are listed in the Experimental.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on the Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**1–8**) or CD_3OD (**9,10**) against TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry



SCHEME 4 Synthesis of acids **9** and **10**.

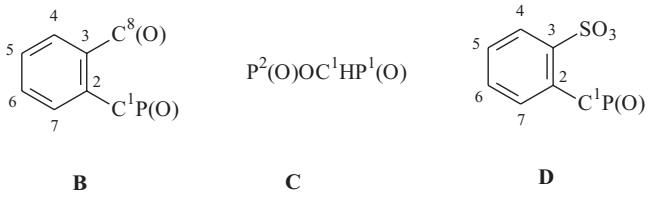


FIGURE 1 Fragments **B–D**.

argon in anhydrous solvents. Starting trimethylsilyl esters of phosphorous acid were prepared according to the procedures described in [17].

*Tetra(trimethylsilyl) (3-oxo-1,3-dihydro-2-benzofuran-1,1-diyl)bisphosphonate (**2**).* A mixture of 16.4 g of tris(trimethylsilyl) phosphite, 5.7 g of bis(trimethylsilyl) phosphite, 3.7 g of phthalic anhydride, and 2 mL of trimethylchlorosilane in 15 mL of methylene chloride was stirred for 1 h. Then the solvent was distilled off. In the NMR spectrum of the mixture, the signals of the phosphonate **1** were observed. ^{1}H NMR, δ, ppm: 7.25–7.50 (m, C_6H_4), –0.05 (s, Me_3SiOC), –0.31 (s, Me_3SiOP), and –0.38 (s, Me_3SiOP). ^{13}C NMR, δ, ppm: 101.86 (d, C^1, $^1J_{PC}$ = 227.5 Hz), 126.32 (s, C^2), 145.98 (d, C^3, $^3J_{PC}$ = 9.5 Hz), 133.66 (s, C^4), 124.26 (s, C^5, C^6), and 124.29 (s, C^5, C^6), 130.35 (s, C^7), 166.60 (s, C^8), 0.85 (s, Me_3SiOC), 0.54 (s, Me_3SiOP), and 0.14 (s, Me_3SiOP). ^{31}P NMR, δ, ppm: –6.45 (s). Then trimethylchlorosilane (2 mL) was added to the reaction mixture. The mixture was kept at 20°C for 2 weeks and then distilled to obtain 12.7 g of bisphosphonate **2**. Yield 87%, boiling point (bp) 172°C (1 mm Hg), melting point (mp) 52°C. ^{1}H NMR, δ, ppm: 7.25–7.55 (m, C_6H_4), –0.23 (s, 2 Me_3Si), and –0.09 (s, 2 Me_3Si). ^{13}C NMR, δ, ppm: 83.14 (t, C^1, $^1J_{PC}$ = 162.5 Hz), 124.8–125.3 (m, C^2, C^5, C^6), 145.20 (t, C^3, $^3J_{PC}$ = 5.6 Hz), 133.63 (s, C^4), 129.40 (s, C^7), 169.04 (s, C^8), –0.23 (s, 2 Me_3Si), and –0.09 (s, 2 Me_3Si). ^{31}P NMR, δ, ppm: –8.91 (s). Found: C 41.03; H 6.84. $C_{20}H_{40}O_8P_2Si_4$. Calcd.: C 41.22; H 6.92.

*Trimethylsilyl 2-{(diethoxyphosphoryl)[(diethoxyphosphoryl)oxy]methyl}benzoate (**3**).* A solution of 12 g of diethyl trimethylsilyl phosphite and 3.8 g of diethyl phosphite in 20 mL of methylene chloride was added to a mixture of 3.7 g of phthalic anhydride and 15 mL of methylene chloride. After the completion of the exothermic reaction, the solvent was distilled off and the residue was distilled. Yield 11 g (89%), bp 187°C (1 mm Hg). ^{1}H NMR, δ, ppm: 6.79 (dd, C^1H, $^2J_{PH}$ = 14.8 Hz, $^3J_{PH}$ = 10.8 Hz), 6.9–7.6 (m, C_6H_4), 3.4–3.7 (m, 4 CH_2OP), 0.7–0.9 (m, 4 CH_3), –0.04 (s, Me_3Si). ^{13}C NMR, δ, ppm: 69.70 (dd, C^1, $^1J_{PC}$ = 166.9 Hz, $^2J_{PC}$ = 5.6 Hz), 129.41 (d, C^2, $^2J_{PC}$ = 5.6 Hz), 135.61(s, C^3), 131.72 (s, C^4), 127.81 (s, C^5, C^6), and 127.97 (s, C^5, C^6), 130.80 (s, C^7), 166.11 (s, C^8), 62.5–63.7 (m, 4 CH_2OP), 15.5–16.1 (m, 4 Me), –0.74 (s, Me_3Si). ^{31}P NMR, δ, ppm: 16.45 (d. P^1, $^3J_{PP}$ = 33.4 Hz), –1.49 (d, P^2, $^3J_{PP}$ = 33.4 Hz). Found: C 45.82; H 6.78. $C_{19}H_{34}O_9P_2Si$. Calcd.: C 45.96; H 6.90. The fraction boiling at 110–130°C (1 mm Hg) contains phosphonate **4**, ^{1}H NMR, δ, ppm: 5.44 (d, C^1H, $^2J_{PH}$ = 8.3 Гц), ^{13}C NMR, δ, ppm: 75.10 (d, C^1, $^1J_{PC}$ = 163.4 Гц), ^{31}P NMR, δ, ppm: 13.48 (s), and diethyl trimethylsilyl phosphate (δ_P –9.32 ppm, (s)).

The phosphonates **6** and **8** were obtained similarly.

*Bis(trimethylsilyl) (1,1-dioxido-3H-2,1-benzoxathiol-3-yl)phosphonate (**6**).* Yield 52%, bp 142°C (1 mm Hg). ^{1}H NMR, δ, ppm: 5.53 (d, C^1H, $^2J_{PH}$ = 8.2 Hz), 7.3–7.5 (m, C_6H_4), –0.01 (m, Me_3Si). ^{13}C NMR, δ, ppm: 77.85 (d, C^1, $^1J_{PC}$ = 171.2 Hz), 130.91 (d, C^2, $^2J_{PC}$ = 5.3 Hz), 135.61 (d, C^3, $^3J_{PC}$ = 4 Hz), 133.56 (s, C^4), 127.30 (s, C^5, C^6), and 125.04 (s, C^5, C^6), 130.34 (s, C^7), 0.23 (s, Me_3Si). ^{31}P NMR, δ, ppm: –6.80 (s). Found: C 39.43; H 5.72. $C_{13}H_{23}O_6PSSi_2$. Calcd.: C 39.58; 5.88. The fraction boiling at 90–110°C (1 mm Hg) contains tris(trimethylsilyl) phosphate (δ_P –26.01 ppm). Before the distillation, the reaction mixture contained compound **5**, ^{1}H NMR, δ, ppm: 6.15 (dd, C^1H, $^2J_{PH}$ = 14.8 Гц, $^3J_{PH}$ = 10 Hz), ^{13}C NMR, δ, ppm: 69.90 (dd, C^1, $^1J_{PC}$ = 179.5 Гц, $^3J_{PC}$ = 6.6 Гц). ^{31}P NMR, δ, ppm: –1.76 (d, P^1, $^3J_{PP}$ = 41.6 Hz), –19.66 (d, P^2, $^3J_{PP}$ = 41.6 Hz).

*Diethyl (1,1-dioxido-3H-2,1-benzoxathiol-3-yl) phosphonate (**8**).* Yield 47%, bp 133°C (1 mm Hg). ^{1}H NMR, δ, ppm: 5.79 (d, C^1H, $^2J_{PH}$ = 8.1 Hz), 7.4–7.9 (m, C_6H_4), 3.7–3.9 (m, 2 CH_2O), 1.1–1.3 (m, 2 CH_3). ^{13}C NMR, δ, ppm: 77.15 (d, C^1, $^1J_{PC}$ = 165.3 Hz), 130.78 (d, C^2, $^2J_{PC}$ = 5.2 Hz), 132.30 (d, C^3, $^3J_{PC}$ = 4.3 Hz), 133.95 (s, C^4), 121.63 (s, C^5, C^6), and 124.79

(s, C^5, C^6), 130.57 (s, C^7), 64.61 (d, 2 CH_2OP, $^2J_{PC}$ = 7Hz), and 64.30 (d, 2 CH_2OP, $^2J_{PC}$ = 7 Hz), 15.92 (d, CH_3, $^3J_{PC}$ = 5.9 Hz). ^{31}P NMR, δ, ppm: 11.11 (s). Found: C 42.94; H 4.87. $C_{11}H_{15}O_6PS$. Calcd.: C 43.14; 4.94.The fraction boiling at 80–100°C (1 mm Hg) contains diethyl trimethylsilyl phosphate (δ_P –9.46 ppm (s)). Before the distillation, the reaction mixture contained compound **7**, ^{1}H NMR, δ, ppm: 6.41 (dd, C^1H, $^2J_{PH}$ = 12 Hz, $^3J_{PH}$ = 11.2 Hz), ^{3}C NMR [1], δ, ppm: 69.20 (dd, C^1, $^1J_{PC}$ = 167.9 Hz, $^3J_{PC}$ = 5.4 Hz). ^{31}P NMR, δ, ppm: 15.73 (d, P^1, $^3J_{PP}$ = 29.8 Hz), –2.42 (d, P^2, $^3J_{PP}$ = 29.8 Hz).

*(3-Oxo-1,3-dihydro-2-benzofuran-1,1-diyl)diphosphonic acid (***9***).* A mixture of 12.7 g of diphosphonate **2** and 50 mL of methanol was heated to boiling. The solvent was distilled off and the residue was kept in a vacuum at 1 mm Hg for 1 h. Yield 6.2 g (97%), mp >250°C. ^{1}H NMR, δ, ppm: 7.60–8.05 (m, C_6H_4). ^{13}C NMR, δ, ppm: 84.25 (t, C^1, $^1J_{PC}$ = 149.3 Hz), 125.15 (t, C^2, $^2J_{PC}$ = 3.9 Hz), 145.71 (s, C^3), 134.07 (s, C^4), 124.78 (s, C^5, C^6), and 125.03 (s, C^5, C^6), 129.41 (s, C^7), 170.83 (s, C^8). ^{31}P NMR, δ, ppm: 9.17 (s). Found: C 32.42; H 2.92. $C_8H_8O_8P_2$. Calcd.: C 32.67; H 2.74.

The acid **10** was obtained similarly.

*(1,1-Dioxido-3H-2,1-benzoxathiol-3-yl)phosphonic acid (***10***).* Yield 96%, mp 70°C. ^{1}H NMR, δ, ppm: 6.07 (d, C^1H, $^2J_{PH}$ = 8 Hz), 7.6–7.9 (m, C_6H_4). ^{13}C NMR, δ, ppm: 78.90 (d, C^1, $^1J_{PC}$ = 162 Hz), 130.73 (d, C^2, $^2J_{PC}$ = 4.2 Hz), 133.69 (d, C^3, $^3J_{PC}$ = 4 Hz), 134.06 (s, C^4), 121.44 (s, C^5, C^6), and 124.71 (s, C^5, C^6), 130.47 (s, C^7). ^{31}P NMR, δ, ppm: 9.81 (s). Found: C 33.37; H 2.74. $C_7H_7O_6PS$. Calcd.: C 33.61; H 2.82.

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