Heteroatom Chemistry
Volume 26, Number 6, 2015

Synthesis of Substituted *N*-Formylaminomethylenediphosphonates and Their Derivatives

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

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

Received 15 April 2015; revised 21 May 2015; accepted 24 May 2015

ABSTRACT: *The convenient methods for the synthesis of new trimethylsilyl esters of aminomethylenediphosphonic acids are elaborated. The new substituted N-formylaminomethylenediphosphonates are obtained via the interaction of trimethylsilyl esters of methylenediphosphonic acids with a mixture of triethyl orthoformate and ethanol. Also boron trifluoride–diethyl etherate as an effective catalyst is used for the interaction of hydrochlorides of ethoxymethylene imines with diethyl trimethylsilyl phosphite. The corresponding aminomethylenediphosphonic acids are presented.* © 2015 Wiley Periodicals, Inc. Heteroatom Chem. 26:405–410, 2015; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21274

INTRODUCTION

The functionalized methylenediphosphonic acids and their derivatives are the perspective organophosphorus biomimetics of natural pyrophosphates and hydroxy or amino acids; also these substances are widely used as effective polydentate ligands and promising bioactive compounds with the multifactor activity [1]. So various derivatives of these diphosphonic acids are good complexones and widely used in medicine [2]; also some of these compounds are used by us as successful antioxidants and cytoprotectors with multifunctional mode of action [3]. Recently, some of the substituted aminomethylenediphosponic acids and their derivatives have been synthesized by us using various formamides and substituted ethoxymethylene imines [4]; also we have obtained some functionalized *N*-formylaminomethylphosphonates as perspective bidentate ligands [5]. In this contribution, we develop a convenient organosilicon-based method for the synthesis of substituted *N*-formylaminomethylenediphosphonates using specially prepared tetra(trimethylsilyl) aminomethylenediphosphonates and their derivatives.

RESULTS AND DISCUSSION

We found that tetra(trimethylsilyl) aminomethylenediphosphonates **1,2** are obtained in high yields directly from the reaction mixtures of phosphorous acid, phosphorus trichloride, and formamide or carboxylic acids nitriles (cf [6]).

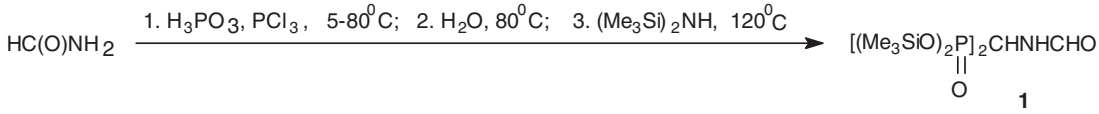
So, *N*-formylaminomethylenediphosphonate **1** was obtained in high yield by subsequent treatment of corresponding mixture with an excess of water and bis(trimethylsilyl)amine (Scheme 1).

The substituted aminomethylenediphosphonates **2** were similarly synthesized in high yields via carboxylic acids nitriles (Scheme 2).

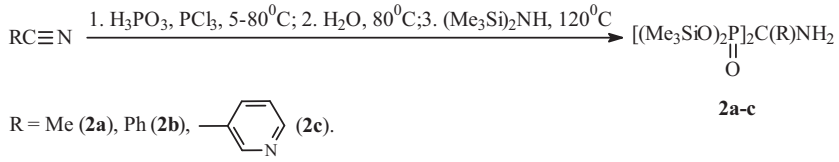
Obviously, the both reactions proceed under mild conditions due to activation of starting

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

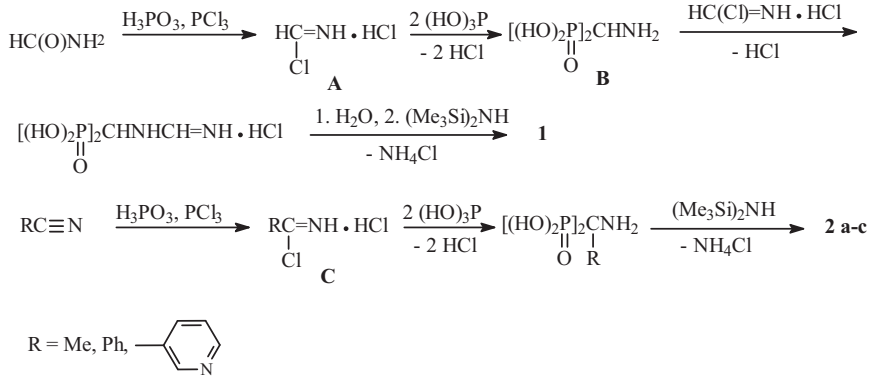
Contract grant sponsor: Russian Foundation for Basic Research.
Contract grant numbers: 14-03-00001 and 15-03-00002.



SCHEME 1 Synthesis of diphosphonate **1**.



SCHEME 2 Synthesis of diphosphonates **2a–c**.



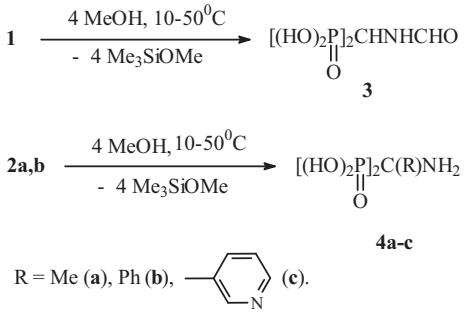
SCHEME 3 The possible routes of the formation of diphosphonates **1,2**.

formamide or nitriles with a mixture of phosphorous acid and phosphorus trichloride via formation of highly reactive immonium salts **A**, **C** (Scheme 3), which was consistent with the known data (cf [4c, 6]).

It should be noted that the formation of *N*-formylaminomethylenediphosphonate **1** was followed by the formylation of intermediate **B** containing the unsubstituted amino group. The treatment of diphosphonate **1**,**2** with methanol excess results in formation of water-soluble corresponding diphosphonic acids **3**,**4** as white hygroscopic crystals in high yields (Scheme 4).

Some similar aminomethylenediphosphonic acids have been described previously as their crystal hydrates; these acids were obtained in poor yields (cf [6a,c]). Also diphosphonates **1,2** were smoothly transformed into *N*-formylaminomethylenediphosphonate **5** in high yields by treatment with an excess of triethyl orthoformate and ethanol (Scheme 5).

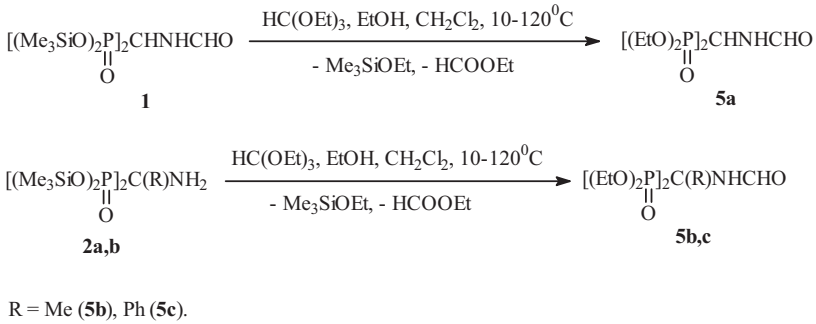
Evidently, the formation of diphosphonates **5** is a result of two or three parallel reactions of ethanolysis, esterification, and formylation of diphosphonates **1,2** (cf [7]). Nevertheless, hardly available aminomethylenediphosphonate **6** with the



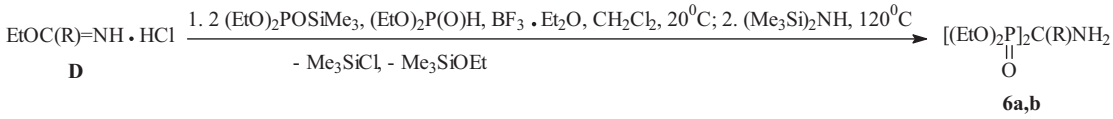
SCHEME 4 Synthesis of acids **3,4**.

unsubstituted amino group is synthesized by us via the interaction of substituted hydrochlorides of ethoxymethylene imines **D** with an excess diethyl trimethylsilyl phosphite and diethyl phosphite in methylene chloride at the presence of boron trifluoride–diethyl etherate as a catalyst (Scheme 6) (cf [4c, 8]).

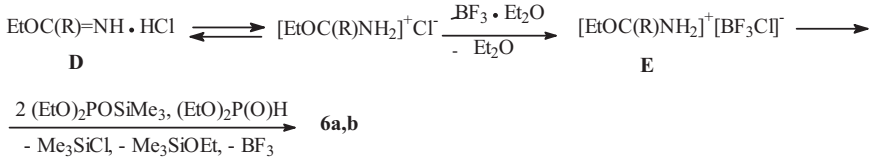
Evidently, the catalytic effect of boron trifluoride–diethyl etherate is based on activation of the C=N groups via generation of electrophilic intermediates **E** in the course of this reaction (Scheme 7) (cf [4c]).



SCHEME 5 Synthesis of N-formyl diphosphonates **5a–c**.



SCHEME 6 Synthesis of diphosphonates **6a,b**.



SCHEME 7 Catalytic activation of imines D.

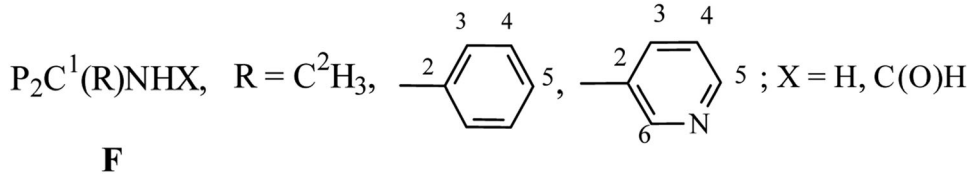


FIGURE 1 The moieties **F** of compounds **1–6**.

The structures of obtained diphosphonates and their derivatives **1–6** are confirmed by ^{1}H, ^{13}C, and ^{31}P NMR spectra. The NMR spectra of compounds **1–6** contain the characteristic signals of the **F** moieties (Fig. 1) whose parameters are listed in the Experimental.

According to NMR data, the compounds **1,3,5** containing *N*-methylformamide moieties were obtained as two stereoisomers mixtures; their compositions were determined by ^{31}P NMR.

CONCLUSIONS

So the convenient synthetic routes to *N*-formyl-substituted or N-unsubstituted aminomethylenediphosphonates and their derivatives starting from available reagents were developed by us. The resulting compounds **1–6** are the promising synthons for the preparation of various functionalized aminomethylenebisphosphorus containing substances. Also, these compounds are perspective polydentate ligands and biologically active substances with versatile properties.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) against TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents. The starting trimethylsilyl esters of trivalent phosphorus acids were prepared as described in [9], and the starting hydrochlorides of ethoxymethylene imines were discussed in [6b].

O,O,O,O-Tetra(trimethylsilyl) N-formylaminomethylenediphosphonate (**1**). Phosphorus trichloride (124.0 g, 903.0 mmol) was added to a mixture of formamide (27.0 g, 600.0 mmol) and phosphorous acid (50.0 g, 609.8 mmol) under stirring at 10°C. The mixture was stirred for 1 h, then the mixture was kept at 20°C during 24 h and was heated at 80°C for 1 h. Water (400 mL) was added to a mixture, which was heated at 80°C for 1 h. Water was removed in a vacuum of 7 mmHg, and bis(trimethylsilyl)amine (320 mL) was added to the residue. The mixture was refluxed to complete sublimation of ammonium chloride and was distilled to give 112.6 g of diphosphonate **1**, yield 74%, bp 142°C (0.5 mmHg). The first isomer, content 55%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: – 0.09 to –0.07 m (4 Me_3Si), 2.71 t (C^1H, $^2J_{PH}$ 22.8 Hz), 7.28 br s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 50.61 t (C^1, $^1J_{PC}$ 154.1 Hz), 156.08 t (CHO, $^3J_{PC}$ 13.5 Hz), 0.78 s (2 Me_3Si), 0.81 s (2 Me_3Si). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 3.37 s. The second isomer, content 45%, ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: to 0.09 to –0.07 m (4 Me_3Si), 2.74 t (C^1H, $^2J_{PH}$ 22.4 Hz), 7.28 br s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 49.64 t (C^1, $^1J_{PC}$ 150.1 Hz), 155.94 br s (CHO), 0.65 s (2 Me_3Si), 0.67 s (2 Me_3Si). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 2.60 s. Anal. calcd for $C_{14}H_{39}NO_7P_2Si_4$ C 33.12; H 7.74. Found: C 32.94; H 7.68.

O,O,O,O-Tetra(trimethylsilyl) 1-aminoethylidenediphosphonate (**2a**). Phosphorus trichloride (42.0 g, 305.8 mmol) was added dropwise to a mixture of acetonitrile (6.2 g, 151.0 mmol) and phosphorous acid (39.0 g, 475.6 mmol), and methylene chloride (5 mL) under stirring at 5°C. The mixture was stirred for 3 h and was kept at 20°C for 24 h, then was heated at 80°C for 2 h. Water (300 mL) was added to a mixture, which was heated at 80°C for 1 h. Water was evaporated in a vacuum of 7 mmHg, and bis(trimethylsilyl)amine (300 mL) was added to the residue. The mixture was refluxed to complete sublimation of ammonium chloride and was distilled to obtain 59.7 g of diphosphonate **2a**, yield 80%, bp 144°C (2 mmHg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: – 0.03 d (2 Me_3Si, $^4J_{PH}$ 2 Hz), – 0.04 d (2 Me_3Si, $^4J_{PH}$ 1.6 Hz), 1.04 t (C^2H_3, $^3J_{PH}$ 16.4 Hz), 1.20 t (NH_2, $^3J_{PH}$ 12.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 51.64 t (C^1, $^1J_{PC}$ 152.4 Hz), 20.10 s (C^2), 0.79 s (2 Me_3Si), 0.84 s (2 Me_3Si). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 6.68 s.

Diphosphonates **2b,c** were prepared similarly. The constants of diphosphonates **2a,b** are consistent with the known data (cf [4c]).

O,O,O,O-Tetra(trimethylsilyl) 1-aminobenzylidenediphosphonate (**2b**). Yield 82%, bp 149°C (1 mmHg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: – 0.21 d (2 Me_3Si, $^4J_{PH}$ 2.8 Hz), – 0.18 d (2 Me_3Si, $^4J_{PH}$ 2.8 Hz), 1.74 t (NH_2, $^3J_{PH}$ 13.2 Hz), 6.8–7.6 m (C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 59.74 t (C^1, $^1J_{PC}$ 147.9 Hz), 135.82 br. s (C^2), 127.21 s and 127.29 s (C^3, C^4), 126.85 s (C^5), 0.49 s (2 Me_3Si), 0.58 s (2 Me_3Si). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 2.26 s.

O,O,O,O-Tetra(trimethylsilyl 1-amino-1-(pyrid-3-yl)methylenediphosphonate (**2c**). Yield 85%, bp 152°C (0.5 mmHg). ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: – 0.17 s (2 Me_3Si), – 0.14 s (2 Me_3Si), 1.83 t (NH_2, $^3J_{PH}$ 14.0 Hz), 6.94 d d (C^4H, $^3J_{HH}$ 4.8 Hz and 8.0 Hz), 7.88 d (C^3H, $^3J_{HH}$ 8 Hz), 8.19 d (C^5H, $^3J_{HH}$ 4.8 Hz), 8.71 s (C^6H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 0.13 s (2 Me_3Si), 0.17 s (2 Me_3Si), 58.04 t (C^1, $^1J_{PC}$ 147.3 Hz), 151.26 s (C^2), 131.94 t (C^3, $^3J_{PC}$ 4.4 Hz), 134.62 s (C^4), 147.52 s (C^5), 148.14 t (C^6, $^3J_{PC}$ 4.8 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 1.62 s. Anal. calcd for $C_{18}H_{42}N_2O_6P_2Si_4$ C 38.83; H 7.60. Found: C 38.68; H 7.52.

N-Formylaminomethylenediphosphonic acid (**3**). A solution of diphosphonate **1** (9.9 g, 19.5 mmol) in ether (15 mL) was added with the stirring to methanol (40 mL) cooled to 10°C. The mixture was heated to boiling. The solvent was removed, and white crystals were kept in a vacuum (1 mmHg) for 1 h to give 4.3 g of acid **3**, yield 97%, mp 159°C (with decomposition). The first isomer, content 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 2.83 t (C^1H, $^2J_{PH}$ 17.4 Hz), 7.14 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 47.40 т (C^1, $^1J_{PC}$ 123.7 Hz), 153.45 s (CHO). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 8.58 s. The second isomer, content 15%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ, ppm: 3.56 t (C^1H, $^2J_{PH}$ 18.8 Hz), 7.17 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 51.04 t (C^1, $^1J_{PC}$ 125.3 Hz), 157.19 s (CHO). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 9.50 s. Anal. calcd for $C_2H_7NO_7P_2$ C 10.97; H 3.22. Found: C 10.85; H 3.26.

Acids **4a–c** were prepared similarly. The constants of acids **4a,b** are consistent with the known data (cf [4c]).

1-Aminoethylidenediphosphonic acid (**4a**). Yield 98%, mp 250°C. ^{1}H NMR (D_2O and C_5D_5N, 400 MHz), δ, ppm: 1.15 t (C^2H_3, $^3J_{PH}$ 13.3 Hz). ^{13}C NMR (D_2O and C_5D_5N, 100 MHz), δ, ppm: 51.74 t (C^1, $^1J_{PC}$ 122.7 Hz), 15.69 s (C^2). ^{31}P NMR (D_2O and C_5D_5N, 162 MHz), δ, ppm: 10.95 s.

1-Aminobenzylidenediphosphonic acid (**4b**). Yield 96%, mp 225°C. ^{1}H NMR (D_2O and C_5D_5N, 400 MHz), δ, ppm: 6.8–7.6 m (C_6H_5). ^{13}C NMR (D_2O and C_5D_5N, 100 MHz), δ, ppm: 60.48 t (C^1, $^1J_{PC}$ 121.2 Hz), 131.26 s (C^2), 125.58 s (C^3), 126.23

s (C^4), 124.30 s (C^5). ^{31}P NMR (D_2O and C_5D_5N, 162 MHz), δ, ppm: 8.59 s.

1-Amino-1-(pyrid-3-yl)methylenediphosphonic acid (**4c**). Yield 95%, mp 191°C (with decomposition). ^1H NMR (D_2O and C_5D_5N, 400 MHz), δ, ppm: 7.0–8.1 m (C_6H_4N). ^{13}C NMR (D_2O and C_5D_5N, 100 MHz), δ, ppm: 60.83 t (C^1, $^1J_{PC}$ 114.2 Hz), 151.31 s (C^2), 133.89 s (C^3), 137.96 s (C^4), 145.19 s (C^5), 147.21 s (C^6). ^{31}P NMR (D_2O and C_5D_5N, 162 MHz), δ, ppm: 10.94 s. Anal. calcd for $C_6H_{10}N_2O_6P_2$ C 26.88; H 3.76. Found: C 26.74; H 3.80.

O,O,O,O-Tetraethyl N-formylaminomethylenediphosphonate (**5a**). Triethyl orthoformate (60.0 g, 404.9 mmol) was added to a solution of diphosphonate **1** (14.0 g, 27.6 mmol) in methylene chloride (20 mL) under stirring at 10°C; then ethanol (20.0 g, 434.1 mmol) was added dropwise to the mixture at the same conditions. The solvent and by-products were removed from a mixture via distillation of mixture until the beginning of triethyl orthoformate distillation. The excess of triethyl orthoformate was removed in vacuum of 7 mmHg, and the residue was distilled to obtain 7.6 g of diphosphonate **5a**, yield 83%, bp 182°C (2 mmHg). The first isomer, content 60%. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.75–0.86 m (4 CH_3), 3.6–3.7 m (4 CH_2), 4.53 t (C^1H, $^2J_{PH}$ 22.0 Hz), 7.79 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.77 s (CH_3), 57.88 t (C^1, $^1J_{PC}$ 150.9 Hz), 62.54 c (CH_2) and 62.84 s (CH_2), 160.31 t (CHO, $^3J_{PC}$ 14.4 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 16.32 s. The second isomer, content 40%, ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.75–0.86 m (4 CH_3), 3.6–3.7 m (4 CH_2), 4.51 t (C^1H, $^2J_{PH}$ 22.0 Hz), 7.26 (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.68 s (CH_3), 41.43 t (C^1, $^1J_{PC}$ 146.1 Hz), 62.45 s (CH_2) and 62.71 s (CH_2), 160.79 br s (CHO). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 15.57 s. Anal. calcd for $C_{10}H_{23}NO_7P_2$ C 36.26. H 7.00. Found: C 36.03; H 6.94.

Diphosphonates **5b,C** *Were Prepared Similarly*

O,O,O,O-Tetraethyl N-formyl-1-aminoethylidenediphosphonate (**5b**). Yield 80%, bp 139°C (0.3 mmHg). The first isomer, content 85%. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.67–0.72 m (4 CH_3), 3.5–3.6 m (4 CH_2), 1.04 t (C^2H_3, $^3J_{PH}$ 15.6 Hz), 7.18 t (CHO, $^4J_{PH}$ 2.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.75 s (CH_3), 17.76 s (C^2), 59.90 t (C^1, $^1J_{PC}$ 149.3 Hz), 62.43 s (CH_2) and 62.63 s (CH_2), 157.31 t (CHO, $^3J_{PC}$ 12.0 Hz). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 19.74 s. The second isomer, content 15%. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.67 – 0.72 m (4 CH_3), 3.5 – 3.6 m (4 CH_2), 1.10 t (C^2H_3, $^3J_{PH}$ 15.6 Hz), 7.03 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.56 s (CH_3), 17.20 s (C^2), 53.46 t (C^1, $^1J_{PC}$ 147.6 Hz), 62.95 s (CH_2) and 63.19 s (CH_2), 163.98 br. s (CHO). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 18.86 s. Anal. calcd for $C_{11}H_{25}NO_7P_2$ C 38.26; H 7.30. Found: C 38.12; H 7.23.

O,O,O,O-Tetraethyl N-formyl-1-aminobenzylidenediphosphonate (**5c**). Yield 84%, bp 198 °C (2 mm Hg). The first isomer, content 80%. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.5 – 0.6 m (4 CH_3), 3.3 – 3.6 m (4 CH_2), 6.6 – 7.5 m (C_6H_5), 7.86 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.16 d (CH_3, $^3J_{PC}$ 3.0 Hz) and 15.14 d (CH_3, $^3J_{PC}$ 2.5 Hz), 62.48 s (CH_2) and 62.68 s (CH_2), 65.45 t (C^1, $^1J_{PC}$ 132.2 Hz), 135.00 t (C^2, $^2J_{PC}$ 4.7 Hz), 127.95 t (C^3, $^3J_{PC}$ 4.0 Hz), 126.31 s (C^4), 127.29 s (C^5), 158.80 t (CHO, $^3J_{PC}$ 7.7 Гц). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 15.83 s. The second isomer, content 20%. ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.5–0.6 m (4 CH_3), 3.3–3.6 m (4 CH_2), 6.6–7.5 m (C_6H_5), 7.76 s (CHO). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 14.95 s (CH_3) and 14.99 s (CH_3), 62.40 s (CH_2) and 62.75 s (CH_2), 62.33 t (C^1, $^1J_{PC}$ 131.8 Hz), 135.00 t (C^2, $^2J_{PC}$ 4.7 Hz), 127.95 t (C^3, $^3J_{PC}$ 4.0 Hz), 126.31 s (C^4), 127.29 s (C^5), 164.69 br s (CHO). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 15.23 s. Anal. calcd for $C_{16}H_{27}NO_7P_2$ C 47.18; H 6.68. Found: C 47.03; H 6.59.

O,O,O,O-Tetraethyl 1-aminoethylidenediphosphonate (**6a**). Boron trifluoride–diethyl etherate (1.2 g, 7.9 mmol) was added with the stirring to a mixture of diethyl phosphite (15.0 g, 108.6 mmol), diethyl trimethylsilyl phosphite (25.0 g, 118.9 mmol), and hydrochloride of 1-ethoxyethylidene imine (11.7 g, 94.7 mmol) in methylene chloride (35 mL). The mixture was refluxed for 1 h, the solvent was removed, and bis(trimethylsilyl)amine (40 mL) was added. The mixture was refluxed to complete ammonium chloride sublimation. The excess of bis(trimethylsilyl)amine was removed, and the residue was distilled to obtain 12.7 г diphosphonate **6a**. Yield 42%, bp 128°C (1 mmHg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.75 t (4 CH_3, $^3J_{HH}$ 7.6 Hz), 0.92 t (C^2H_3, $^3J_{PH}$ 16.4 Hz), 1.13 t (NH_2, $^3J_{PH}$ 12.4 Hz), 3.5–3.6 m (4 CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.87 c (CH_3), 19.30 br s (C^2), 52.31 t (C^1, $^1J_{PC}$ 144.5 Hz), 62.38 s (CH_2) and 62.59 s (CH_2). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 22.96 s. Anal. calcd for $C_{10}H_{25}NO_6P_2$ C 37.86; H 7.94. Found: C 37.55; H 7.87.

Diphosphonate 6b Was Prepared Similarly

O,O,O,O-Tetraethyl 1-aminobenzylidenediphosphonate (**6b**). Yield 34%, bp 165°C (1 mmHg). ^1H NMR ($CDCl_3$, 400 MHz), δ, ppm: 0.77 t (2 CH_3, $^3J_{HH}$ 7.2 Hz) and 0.92 t (2 CH_3, $^3J_{HH}$ 7.2 Hz), 1.99 t (NH_2,

$^3J_{PH}$ 12.8 Hz), 3.5–3.7 m (4 CH_2), 6.9–7.6 m (C_6H_5). ^{13}C NMR ($CDCl_3$, 100 MHz), δ, ppm: 15.85 s ($2CH_3$) and 15.99 s ($2CH_3$), 60.05 t (C^1, $^1J_{PC}$ 139.7 Hz), 63.19 s (2 CH_2) and 63.49 s (2 CH_2), 133.80 br s (C^2), 127.18 t (C^3, $^3J_{PC}$ 4.8 Hz), 127.35 s (C^4), 128.15 s (C^5). ^{31}P NMR ($CDCl_3$, 162 MHz), δ, ppm: 18.97 s. Anal. calcd for $C_{15}H_{27}NO_6P_2$ C 47.50; H 7.17. Found: C 47.26; H 7.02.

REFERENCES

[1] (a) Kukhar, V. P.; Hudson, H. R. In Chemistry and Biological Activity: Wiley: New York, 2000 (b) Ebetino, F. H. Phosphorus Sulfur Silicon Relat Elem 1999, 144–146, 9–12; (c) Fields, S. C. Tetrahedron 1999, 55, 12237–12273; (d) Grigoriev, E. V.; Yashina, N. S.; Prishchenko, A. A.; Livantsov, M. V.; Petrosyan, V. S; Pellerito, L.; Schafer, M. J. Appl Organometal Chem 1993, 7, 353–355; (e) Grigoriev, E. V.; Yashina, N. S.; Prischenko, A. A.; Livantsov, M. V.; Petrosyan, V. S.; Massa, W.; Harms, K.; Wocadlo, S.; Pellerito, L. Appl Organometal Chem 1995, 9, 11–22.

[2] (a) Krasovskaya, S. M.; Uzhinova, L. D.; Andrianova, M. Y.; Prishchenko, A. A.; Livantsov, M. V. Biomaterials 1991, 12, 817–820; (b) Takeuchi, M.; Sakamoto, S.; Yoshida, M.; Abe, T.; Isomura, Y. Chem Pharm Bull 1993, 41, 688–693; (c) Ghosh, S.; Chan, J. M. V.; Andrianova, M. Y.; Lea, C. R.; Meints, G. A.; Lewis, J. C.; Tovian, Z. S.; Flessner, R. M.; Loftus, T. C.; Bruchhaus, I.; Kendrick, H.; Croft, S. L.; Kemp, R. G.; Kobayashi, S.; Nozaki, T.; Oldfield, E. J Med Chem 2004, 47, 175–187.

[3] (a) Tyurin, V. Yu.; Gracheva, Yu. A.; Milaeva, E. R.; Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Maryashkin, A. V.; Bubnov, M. P.; Kozhanov, K. A.; Cherkasov, V. K. Russ Chem Bull 2007, 56, 4, 774–780; (b) Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; and Milaeva, E. R. Heteroatom Chem 2008, 19, 490–494; (c) Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2012, 23, 32–40; (d) Berberova, N. T.; Osipova, V. P.; Kolyada, M. N.; Antonova, N. A.; Zefirov, N. S.; Milaeva, E. R.; Filimonova, S. I.; Gracheva, Yu. A.; Prishchenko, A. A.; Livantsov, M. V.; Livantsova L. I.; Novikova, O. P. Patent RU 2405032 C 1, Rus Patent Bull 2010, 33 (in Russian); (e) Berberova, N. T.; Chernushkina, I. M.; Osipova, V. P.; Kolyada, M. N.; Pimenov, Yu. I.; Gracheva, Yu. A.; Prishchenko, A. A.; Livantsov, M. V.; Livantsova, L. I.; Novikova, O. P.; Milaeva, E. R.; Zefirov, N. S. Patent RU 2457240 C 2, Rus Patent Bull 2012, 21 (in Russian).

[4] (a) Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2009, 20, 319–324; (b) Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Ershov, I. S.; Petrosyan, V. S. Heteroatom Chem 2013, 24, 355–360; (c) Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Ershov, I. S.; Petrosyan, V. S. Heteroatom Chem 2015, 26, 101–105.

[5] Prishchenko, A. A.; Livantsov, M. V.; Novikova, O. P.; Livantsova, L. I.; Petrosyan, V. S. Heteroatom Chem 2010, 21, 236–241.

[6] (a) Ploeger, W.; Schindler, N.; Wollmann, K.; Worms, K. H. Z Anorg allg Chem 1972, 389, 119–128 (in German); (b) Li, J. J. Name Reactions; Springer-Verlag: Berlin, 2003; (c) Gross, H.; Costisella, B., Gnauk, T., Brennecke, L. J Prakt Chem 1976, 318, 116–126 (in German).

[7] (a) Kafarski, P.; Lejczak, B. Synthesis 1988, 307–310; (b) Zymanczyk-Duda, E.; Lejczak, B.; Kafarski, P. Phosphorus Sulfur Silicon Relat Elem 1996, 112, 47–56; (c) Maier, L. Phosphorus Sulfur 1981, 11, 311–322.

[8] (a) Orlovskii, V. V.; Vovsi, B. A. Russ J Gen Chem 1976, 46, 294-300 (in Russian); (b) Midrier, C.; Lantsoght, M.; Volle, J.-N.; Pirat, J.-L.; Virieux, D.; Stevens, C. V. Tetrahedron Lett 2011, 52, 6693–6696.

[9] (a) Wozniak, L.; Chojnowski, J. Tetrahedron 1989, 45, 2465–2524; (b) Romanenko, V. D.; Shevchuk, M. V.; Kukhar, V. P. Curr Org Chem 2011, 15, 2774–2801.