ACCEPTED MANUSCRIPT

One-pot synthesis of *N*-Cbz-α-aminophosphonic acids

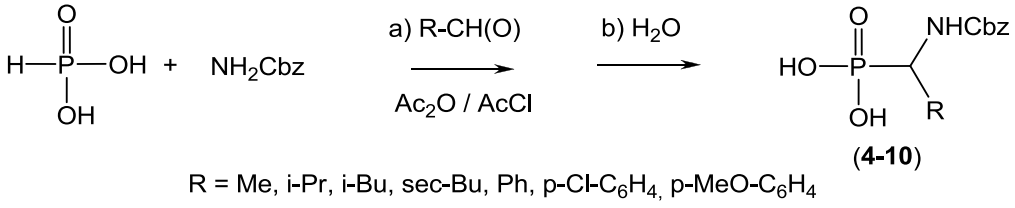
Alexei V.Vinyukov, Maxim E.Dmitriev, and Valery V.Ragulin*

Institute of Physiologically Active Compounds, Russian Academy of Sciences,

Severny pr.,1, Chernogolovka, Moscow Region, 142432, Russia

*Corresponding author. Fax: +7 496 524 95 08.

E-mail address:rvalery@dio.ru



(**4-10**)

Abstract

The paper describes the synthesis of *N*-protected-α-aminoalkylphosphonic acids, phosphoisosteres of amino acids, from phosphorous acid. A simple, milder and effective one-pot procedure for the amidoalkylation of phosphorous acid in a mixture of acetic anhydride and acetyl chloride at room temperature allows the formation of amino phosphorylic function with the protection on the nitrogen atom.

Keywords

amidoalkylation / phosphoisosteres of amino acids / triacetylphosphite / acylimine cation / Arbuzov-type reaction / aminoalkylphosphonic acids

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

INTRODUCTION

One of the most promising approaches to finding physiologically active compounds is the incorporation of an aminophosphonic acid molecule into the corresponding peptide chain of oligomeric structure.[1,2] In this connection, *N*-protected α-aminophosphonic acids can be successfully used as convenient building blocks for the synthesis of phosphorus-containing short peptides.

Usually, the synthesis of *N*-protected α-aminophosphonic acids represents a two-stage process: the construction of aminophosphorylic function and the protection of the nitrogen atom. The creation of the aminophosphorylic fragment is realized by using the well-known procedures of the three-component Kabachnik-Fields reaction[3] or Michael-Pudovik-type addition of hydrophosphorylic compounds to the corresponding Schiff bases.[4] Although the acylation of aminophosphonic acids seems to be a trivial reaction, the literature data on the preparation of N-acylated aminophosphonic acids are contradictory, and in many cases the yields of the reaction in aqueous media are moderate or even low.[5,6] In this connection, the total pre-silylation of the aminoalkylphosphonic acids was proposed for the preparation of N-acylated acids with good yields.[7]

We propose to combine the construction of an α-aminophosphorylic function with the protection on the nitrogen atom with the use of phosphorous acid, one of the simplest hydrophosphorylic compounds. In this connection, the low popular and even maybe, undeservedly forgotten, nonclassic amide version of Kabachnik-Fields reaction[8,9] can be effective approach for one-pot synthesis of N-protected α-aminophosphonic acids.

 ACCEPTED MANUSCRIPT

The procedure for the Kabachnik–Fields-type reaction with amides as the amino component and trivalent phosphorus chlorides, aldehydes or ketones in acetic acid was proposed the first by Oleksyszyn (Oleksyszyn reaction)[8] and then was modified by Yuan and Chen[10] for dialkyl phosphites with carbonyl compounds and amides or carbamates in acetyl chloride. The amidoalkylation of dialkyl phosphites in acetyl chloride is often accompanied by a partial dealkylation of the alkyloxyphosphorylic fragment. For that reason, as a rule, the reaction mixture, containing *N*-acylated α-aminoalkylphosphorylic compounds, is subjected to acidic hydrolysis followed by isolation of the free α-aminoalkylphosphonic acids.[8-10] Milder amidoalkylation of phosphorous acid in acetic anhydride in contrast to the more rigid conditions proposed by Oleksyszyn[11] can be more perspective approach for the synthesis of *N*-protected α-aminophosphonic acids.

Recently, we proposed a milder procedure for the synthesis of *N*-protected α-aminophosphorylic compounds in acetic anhydride at room temperature and the mechanism for amidoalkylation of hydrophosphorylic compounds which includes an Arbuzov-type step of phosphorus–carbon bond formation.[12] We propose that the unique role of acetic anhydride in this reaction consist in the generation *in situ* of intermediated P^{III}–OAc derivatives (**1**), as nucleophilic component of reaction. Also we have isolated the *N,N´*-alkylidenebiscarbamates (**2**) under the reaction conditions as the stable intermediates of this reaction.[12a,b] We proposed the acid catalyzed generation *in situ* of *N*-alkyloxycarbonylimine cation, (positively charged Schiff base) (**3**) as electrophilic reaction component from *N,N´*-alkylidenebiscarbamate (**2**).[12a,d] Nucleophilic attack of the trivalent phosphorus atom of the generated *in situ* intermediated P^{III}–OAc compound (**1**) (Scheme 2) on the positively charged carbon atom of the generated *in situ N*-

alkoxycarbonylimine cation (salt) (**3**) occurs followed by the formation of the phosphorus–carbon bond.

Our approach to the generation *in situ* of imine cations (**3**) from biscarbamates (**2**) was recently successfully used for the formation of C-C bonds according to a Mannich-type reaction.[13] Moreover, we have studied the interaction of acetyldiethylphosphite (prepared beforehand as well as generated *in situ* from tetraethylpyrophosphite) with the *in situ* generated acyliminium cation and successfully confirmed the proposed reaction mechanism.[12e]

Thus, the earlier obtained results allow to search the convenient procedures for one-pot synthesis of N-protected α-aminophosphonic acids.

RESULTS AND DISCUSSION

In this article we report good results on the direct amidoalkylation of the simplest hydrophosphorylic compound - phosphorous acid.

We have found that milder conditions for the three-component condensation reaction of phosphorous acid, benzylcarbamate and corresponding aldehydes in the mixture of acetic anhydride and acetyl chloride (1:1) at room temperature allow *N*-benzyloxycarbonyl-α-aminoalkylphosphonic acids (**4-10**) to be obtained with good yields (Scheme 3). This simple synthetic procedure permit to combine the creation of aminophosphonic function with protection of the nitrogen atom.

This results are in accordance with earlier obtained data confirming our version of the mechanism for this reaction, described above.[12]

As expected, the first attempts to get N-Cbz-α-aminoalkylphosphonic acids (**4-10**) via the direct amidoalkylation of phosphorous acid in acetic anhydride in the presence of catalytic quantities of trifluoroacetic (TFA) or p-toluenesulfonic (TSA) acids were minimally effective. We have assumed that the reason for this is the difficulty of generation in situ of the P^{III}-OAc nucleophilic component with trivalent phosphorus atom from the phosphorous acid, containing three P-OH functions. TFA and TSA can catalyze only the generation of imine cation (**3**) and cannot catalyze the generation of P^{III}-OAc intermediate with trivalent phosphorus atom.

We proposed the generation *in situ* of triacetylphosphite (**11**) as P^{III}-component which must take part in the formation of desired phosphorus-carbon bond and phosphonium salt (**12**) in accordance with the Arbuzov-step reaction. Acetic anhydride is a relatively weak acetylating agent for the generation *in situ* of triacetylphosphite (**11**) from phosphorous acid. Therefore acetyl chloride, as stronger acetylating agent, was added in the reaction mixture for improvement of the conditions for generation *in situ* of triacetylphosphite (**11**) (Scheme 4).

Moreover, the hydrogen chloride generated *in situ* (three equivalents) is a more powerful catalyst for the generation *in situ* of iminium salts (**3**) from biscarbamates (**2**). An additional favorable factor is that the starting phosphorous acid do not have the acid-sensitive ester bonds, and the *N*-benzyloxycarbonylic ester fragment is relatively resistant to the acid reaction conditions at room temperature.

We have investigated the interaction of phosphorous acid, benzylcarbamate and corresponding aldehydes in the mixture of acetic anhydride and acetyl chloride at room

temperature at different relationship of Ac_2O and AcCl (Table 1). We have found that the optimal reaction mixture is Ac_2O / AcCl = 1:1.

Thus, the interaction of phosphorous acid, benzylcarbamate and corresponding aldehydes in the mixture of acetic anhydride and acetyl chloride (1:1 as optimal relationship) at room temperature followed by the water hydrolysis of Arbuzov` type reaction product, diacetylphosphonate (**13**), gave N-benzyloxycarbonyl-α-aminoalkylphosphonic acids (**4-10**) with good yields (Table 1).

Moreover, we have found that the treatment of reaction mixture by alcohol can permit to obtain the esters of aminophosphonic acid. In this case the mixture of aminophosphonic acid and its monoalkyl ester was detected by NMR spectroscopy (see Supplemental Materials). Dialkyl esters of the aminophosphonic acids were not found. We have been able isolate the monoethyl ester of α-(N-benzyloxycarbonyl)amino-benzylphosphonic acid (**8a**) (Table 1). However, careful investigation of conditions for esterification and isolation of esters of α-aminophosphonic acids were no aim of this investigation.

CONCLUSIONS

A one-pot method for the synthesis of *N*-benzyloxycarbonyl-α-aminoalkylphosphonic acids (**4-10**) in good yields by amidoalkylation of phosphorous acid with benzylcarbamate and corresponding aldehyde in the mixture of acetic anhydride and acetyl chloride (1:1) at room temperature was proposed in this paper.

EXPERIMENTAL

General and Reagents: All reagents (benzylcarbamate, phosphorous acid and aldehydes) used in the reactions described in this manuscript are commercial, was purchased from Alfa Aesar and

were used without purification. The reaction described in this paper were controlled using ^{31}P NMR spectroscopy and (or) TLC. All of the compounds, for which spectral and analytical data are given, were gomogenous by TLC. TLC analyses were performed using 0.2 mm silica gel F 254 (Merck) glass plates and Alufol plates (aluminium oxide neutral on aluminium foil as base) (Kavalier), eluent systems: n-buthyl alcohol:acetic acid:water (4:1:1) or chloroform:i-propanol: acetic acid (100:5:1-3) as an eluents. The chromatograms were visualized under ultraviolet light or iodine vapor. All reactions were performed under an atmosphere of argon with magnetic stirring. Melting points were determined on a Boetius PHMK apparatus or in open glass capillaries and are uncorrected. The ^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer. ^{31}P and ^{13}C NMR spectra are fully proton decoupled. ^{31}P NMR chemical shifts are reported on a δ scale (in ppm) downfield from 85% H_3PO_4.

Negative mode mass spectra were acquired using Thermo LXQ mass spectrometer with electrospray ion source. Positive mode mass spectra were acquired using custom design home built high resolution (15000 FWHM) Ortho-TOF mass spectrometer[15a]. The custom built micro-electrospray ion source[15b] was used. The samples were dissolved in MeOH at concentration 3 mg/mL, and then they were diluted 300 times for the analysis. In negative mode 5 µL of the resulting diluted solution was injected in the loop connected to the injection line via the valve. Injection flow rate by syringe pump was 3 µL/min. In positive mode the sample flow rate was 0.2 µL/min. The Supplemental Materials contains sample ^{1}H, ^{13}C, ^{31}P NMR spectra and mass spectra for the products 4-10 (Figures S 1 – S 36)

ACCEPTED MANUSCRIPT

General procedure for the synthesis of N-benzyloxycarbonyl-α-aminoalkylphosphonic acids (4-10)

Dried phosphorous acid (5 mmol) and benzylcarbamate (5 mmol) were dissolved in the of the mixture of acetic anhydride : acetyl chloride (1 : 1) (10-15 mL). The corresponding aldehyde (5-6 mmol) was slowly added dropwise to the formed solution and the reaction mixture was stirred for 17-20 h at room temperature (the reaction progress was controlled by NMR ^{31}P spectroscopy and TLC). Then reaction mixture was added to 30-40 mL of water/ice and obtained solution was stirred 5-10 h and was evaporated in vacuo. The residue was dissolved in ethyl acetate or chloroform (30-40 mL) and washed with water (2×7-10 mL) and the organic phase was evaporated in vacuo. The residue was partitioned between hydrocarbonate solution (50 mL) and ether or hexane (10 mL). Aqueous solution was separated and acidified to pH 2-3 with 6N HCl and then was extracted by ethyl acetate or chloroform (3×15 mL). The organic extracts were combined and dried over sodium sulphate and evaporated in vacuo.

Usually the residue was crystallized from ether or hexane and recrystallized from ether : alcohol (10:1÷3) and N-protected acids was isolated as solid (Table 1).

Reaction mixture for the synthesis of α-(*N*-benzyloxycarbonyl)amino-benzylphosphonic acid (8) in the acetic anhydride : acetyl chloride (1:1) was treated by excess of EtOH or MeOH (~50 ml) under cooling and then was evaporated *in vacuo*. The residue represented the mixture of acid (8) and monoethyl (8a) or monomethyl (8b) ester of acid (8) (see NMR spectra in Supplemental Materials) and was treated by ether or hexane. We have not a success in the isolation of methyl ester (8b), but monoethyl ester of α-(N-benzyloxycarbonyl)amino-benzylphosphonic acid (8a) was isolated (Table 1) and described with using ^{1}H, ^{13}C and ^{31}P NMR spectroscopy.

 ACCEPTED MANUSCRIPT

Data of ^{1}H, ^{31}P, and ^{13}C **NMR** and analytical data of N-benzyloxycarbonyl-α-aminoalkylphosphonic acids (**4-10**) and monoethyl ester **8a**) and yields of acids (**4-10**) at the conditions of different relationship Ac_2O:AcCl in the reaction mixture.

1-(*N*-Benzyloxycarbonyl)amino-ethylphosphonic acid (4)

Yield 63.7% (Ac_2O:AcCl=1:1), yield 66.8% (Ac_2O:AcCl=1:4), yield 34.4% (Ac_2O:AcCl=5:1). White solid. M.p. 105-106ºC. [14]Lit. m.p. 110ºC. ^{1}H NMR (DMSO-d_6, ppm): 1.18 (dd, 3H, CH_3, $^{3}J_{PH}$ = 15.7 Hz, $^{3}J_{HH}$ = 6.9 Hz), 3.71 (m, 1H, PCHN), 5.01 (br. s., 2H, CH_2O), 7.10-7.45 (m, 6H: 5H, Ph + 1H, NH). ^{1}H NMR ($CDCl_3$+drops of TFA, ppm): 1.43 (dd, 3H, CH_3, $^{3}J_{PH}$ = 17.6 Hz, $^{3}J_{HH}$ = 6.4 Hz), 4.17 (m, 1H, PCHN), 5.14 (m, 2H, CH_2O), 7.34 (m, 5H, Ph), 10.9 (br. s., OH). ^{13}C NMR (DMSO-d_6, ppm): 15.9, 44.3 (d, $^{1}J_{PC}$ = 154.8 Hz), 65.4, 127.7, 128.4, 137.2, 155.7 (C=O) (d, $^{3}J_{PC}$ = 5.9 Hz). ^{31}P NMR ($CDCl_3$, ppm): 24.8. ^{31}P NMR ($CDCl_3$+ drops of TFA, ppm): 26.8. ^{31}P NMR (DMSO-d_6, ppm): 22.5. Found: C 46.23, 46.07; H 5.51, 5.57; N 5.56, 5.51; P 12.03, 12.13. Calc. for $C_{10}H_{14}NO_5P$: C 46.34; H 5.44; N 5.40; P 11.95.

1-(*N*-Benzyloxycarbonyl)amino-2-methyl-propylphosphonic acid (5)

Yield 64.5% (Ac_2O:AcCl=1:1), yield 67.7% (Ac_2O:AcCl=1:2), yield 54.3% (Ac_2O:AcCl=2:1). White solid. M.p. 67-68ºC. ^{1}H NMR (DMSO-d_6, ppm): 0.91 (d, 3H, CH_3, $^{3}J_{HH}$ 6.7 = Hz), 2.04 (m, 1H, CH), 3.60 (ddd, 1H, CHN, $^{2}J_{PH}$ 18.3 = Hz, $^{3}J_{HH}$ 10.3 = Hz, $^{3}J_{HH}$ = 4.9 Hz), 5.04 (m, 2H, CH_2O), 7.01 (d, 1H, NH, $^{3}J_{HH}$ = 10.3 Hz), 7.25-7.45 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6, ppm): 18.3 (d, $^{3}J_{PC}$ = 5.5 Hz), 20.7 (d, $^{3}J_{PC}$ = 10.7 Hz), 28.6 (d, $^{2}J_{PC}$ = 4.8 Hz), 54.1 (d, $^{1}J_{PC}$ = 151.1 Hz), 65.4, 127.4, 127.7, 128.3, 137.3, 156.5 (C=O) (d, $^{3}J_{PC}$ = 7.0 Hz). ^{31}P NMR (DMSO-d_6, ppm): 22.1. Found: C 49.83, 49.85; H 6.43, 6.47; N 5.11, 5.20. Calc. for $C_{12}H_{18}NO_5P$: C 50.18; H 6.32; N 4.88.

1-(*N*-Benzyloxycarbonyl)amino-3-methyl-butylphosphonic acid (6)

Yields 75.3% (Ac_2O:AcCl=1:1), 74.7% (Ac_2O:AcCl=1:4), 54.1% (Ac_2O:AcCl = 2:1). White solid. M.p. 131-132ºC. ^{1}H NMR (DMSO-d_6 + drops of TFA, ppm): 0.78 (d, 3H, CH_3, $^3J_{HH}$ = 6.7 Hz), 0.82 (d, 3H, CH_3, $^3J_{HH}$ = 7.3 Hz), 1.25-1.72 (m, 3H, CH + CH_2), 3.66-3.97 (m, 1H, CHN), 5.00 (s. br., 2H, CH_2O), 7.15 (d, 1H, NH, $^3J_{HH}$ = 9.8 Hz), 7.20-7.40 m (5H, Ph), 15.10 (s. br., 2H, 2POH). ^{13}C NMR (DMSO-d_6, ppm): 21.0, 23.4, 24.0 (d, $^3J_{PC}$ = 13.3 Hz), 47.0 (d, $^1J_{PC}$ = 155.2 Hz), 65.3, 127.5, 127.7, 128.3, 137.3, 156.1 (C=O) (d, $^3J_{PC}$ = 5.2 Hz). ^{31}P NMR (DMSO-d_6+ drops of TFA, ppm): 23.6. Found: C 51.65, 51.57; H 6.87, 6.90; N 4.82, 4.77. Calc. for $C_{13}H_{20}NO_5P$: C 51.83; H 6.69; N 4.65.

1-(*N*-Benzyloxycarbonyl)amino-2-methyl-butylphosphonic acid (7)

Yield 56.0% (Ac_2O:AcCl=1:1), yield 41.5% (Ac_2O:AcCl=2:1). White solid. M.p. 96-97ºC. ^{1}H NMR (DMSO-d_6, ppm): 0.78-0.92 (m, 6H, $\underline{CH_3}CH_2$ + $\underline{CH_3}CH$), 1.00-1.15 (m, 1H*, $\underline{CH}CH_3$), 1.15-1.40 (m, 1H, $\underline{CH}CH_3$), 1.50-1.80 (m, 2H, $\underline{CH_2}CH_3$), 3.60 (m, 1H*, PCHN), 3.81 (m, 1H, PCHN), 5.03 (br. s., 2H, CH_2O), 6.82-6.97 (m, 1H, NH), 7.34 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6, ppm): 11.3, 11.7*, 15.2, 16.5* (d, $^3J_{PC}$ 7.0 Hz), 24.4, 26.9*(d, $^3J_{PC}$ 11.3 Hz), 35.1*, 35.5, 51.6* (d, $^1J_{PC}$ = 150.8 Hz), 53.6 (d, $^1J_{PC}$ = 152.2 Hz), 65.3, 127.4, 127.6, 128.3, 137.3, 156.4 (d, $^3J_{PC}$ 8.0 Hz). ^{31}P NMR (DMSO-d_6, ppm): 21.4, 21.6* (* minor diastereomer). Found: C 51.58, 51.47; H 6.87, 6.77; N 4.53, 4.47; P 9.95, 9.91. Calc. for $C_{13}H_{20}NO_5P$: C 51.83; H 6.69; N 4.65; P 10.28.

***α*-(*N*-Benzyloxycarbonyl)amino-benzylphosphonic acid (8)**

Yield 75.5% (Ac_2O:AcCl=1:1), yield 72.5% (Ac_2O:AcCl=1:4), yield 65.6% (Ac_2O:AcCl=1:2), yield 54.5% (Ac_2O:AcCl=3:1). M.p. 156-157ºC. Lit. m.p. 159ºC[17]. ^{1}H NMR ($CDCl_3$, ppm): 4.75-5.10 {m, 1H, PCHN + c (br.) 2H, CH_2O}, 6.96 (m, 1H, NH), 7.05-7.45 (m, 10H, 2Ph). ^{13}C

NMR (DMSO-d_6, ppm): 53.6 (d, $^1J_{PC}$ = 143.4 Hz), 66.0, 126.4, 127.5, 127.9, 136.1, 137.4, 155.7 (C=O) (d, $^3J_{PC}$ = 9.2 Hz). ^{31}P NMR ($CDCl_3$, ppm): 19.0. Found: C 55.84, 55.87; H 5.17, 5.23; N 4.46, 4.54; P 9.45, 9.40. Calc. for $C_{15}H_{16}NO_5P$: C 56.08; H 5.02; N 4.36; P 9.64.

Monoethyl ester of α-(*N*-benzyloxycarbonyl)amino-benzylphosphonic acid (8a)

Yield 31.3% (Ac_2O:AcCl=1:1, and then treatment by EtOH). M.p. 189-190ºC. ^{1}H NMR (DMSO-d_6 + drop of TFA, ppm): 1.13 (t, 3H, CH_3, $^3J_{HH}$ = 6.9 Hz), 3.86 (dk, 2H, $^3J_{HH}$ = 6.9 Hz, $^3J_{PH}$ = 14.2 Hz), 4.95 (dd, 1H, PCHN, $^2J_{PH}$ = 22.0 Hz, $^3J_{HH}$ = 9.7 Hz), 5.03 (AB, 2H, Ph$\underline{CH_2}$O), 7.13-7.51 (m, 10H, 2Ph), 8.07 (d, 1H, NH, $^3J_{HH}$ = 9.7 Hz). ^{13}C NMR (DMSO-d_6 + drop of TFA, ppm): 16.3 (d, CH_3, $^3J_{PC}$ = 5.5 Hz), 52.8 (d, PCN, $^1J_{PC}$ = 150.4 Hz), 61.6 (d, POC, $^2J_{PC}$ = 6.3 Hz), 65.7 (c, $\underline{C}H_2$Ph), 127.2, 127.3, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 136.9, 137.0, 156.1 (d, C=O, $^3J_{PC}$ = 8.9 Hz). ^{31}P NMR (DMSO-d_6 + drop of TFA, ppm): 19.8, 17.9 (2% of acid **8**). Found: C 58.26, 58.18; H 5.82, 5.90; N 3.94, 3.90. Calc. for $C_{17}H_{20}NO_5P$: C 58.45; H 5.77; N 4.01.

α-(N-Benzyloxycarbonyl)amino-p-chloro-benzylphosphonic acid (9)

Yield 77.0% (Ac_2O:AcCl=1:1), yield 58.5% (Ac_2O:AcCl=3:1). M.p. 121-122ºC. ^{1}H NMR (DMSO-d_6, ppm): 4.75 (m, 1H, PCHN), 5.02 (br. s., 2H, CH_2O), 7.18-7.55 (m, 9H, C_6H_4+Ph), 8.00 (d. br., 1H, NH). ^{1}H NMR ($CDCl_3$+TFA, ppm): 5.14 (br. s., 2H, CH_2O), 5.25 (m, 1H, PCHN), 6.14 (m, 1H, NH), 7.10-7.45 (m, 9H, C_6H_4), 10.80-11.15 (m, OH). ^{13}C NMR (DMSO-d_6, ppm): 53.4 (d, PCN, $^1J_{PC}$ = 148.6 Hz), 65.7 (CH_2O), 127.8, 128.4, 129.9, 130.0, 131.7, 137.0, 156.0 (C=O) (d, $^3J_{PC}$ = 9.5 Hz). ^{31}P NMR ($CDCl_3$+TFA, ppm): 26.6. Found: C 50.36, 50.28; H 4.45, 4.33; N 4.08, 4.14; P 9.03, 8.94. Calc. for $C_{15}H_{15}ClNO_5P$: C 50.65; H 4.25; N 3.94; P 8.71.

α-(*N*-Benzyloxycarbonyl)amino-p-methyloxy-benzylphosphonic acid (10)

Yield 81.0% (Ac_2O:AcCl=1:1), yield 58.0% (Ac_2O:AcCl=3:1). M.p. 109-110ºC. ^{1}H NMR (DMSO-d_6, ppm): 3.71 (s, 3H, CH_3O), 4.79 (dd, 1H, $^2J_{PH}$ = 21.5 Hz, $^3J_{HH}$ = 9.8 Hz, PCHN), 5.01 (br. s., 2H, CH_2O), 6.82 (s, 1H, Ar), 6.87 (s, 1H, Ar), 7.25-7.45 (m, 7H, Ar), 7.88 (br. d, 1H, NH, $^3J_{HH}$~8.9 Hz). ^{1}H NMR ($CDCl_3$, ppm): 3.51 (s, 3H, CH_3O), 4.81 (m, 2H, CH_2O), 6.19 (m, 1H, PCHN), 6.60 (m, 1H, NH), 6.80-7.30 (m, 9H, Ar), 10.9-11.6 (m, 2H, 2POH). ^{13}C NMR (DMSO-d_6, ppm): 53.2 (d, $^1J_{PC}$ = 150.1 Hz), 55.1 (CH_3O), 65.6 (CH_2O), 113.3, 127.7, 127.8, 128.3, 129.2, 129.3, 129.9, 137.0, 155.9 (C=O) (d, $^3J_{PC}$ = 9.6 Hz), 158.3 (C_{arom} - O). ^{31}P NMR ($CDCl_3$, ppm): 23.4. ^{31}P NMR (DMSO-d_6, ppm): 18.3. ^{31}P NMR (DMSO-d_6 + drops of TFA, ppm): 21.8. Found: C 54.44, 54.47; H 5.25, 5.31; N 4.15, 4.11; P 8.95, 9.03. Calc. for $C_{16}H_{18}NO_6P$: C 54.71; H 5.16; N 3.99; P 8.82.

Acknowledgments

This study was supported by the Russian Foundation for Basic Research (Grant No. 15-03-06062). Authors would like to thank V. I. Kozlovski for MS spectra and analyses.

ACCEPTED MANUSCRIPT

References

1. a) Kafarski P., Lejczak B.. Synthesis of Phosphono- and Phosphinopeptides, in book edited by Kukhar V. P., Hudson H. R., *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*, Wiley, Chichester, 2000. P.173; b) Mucha A., Kafarski P., Berlicki L., *J. Med. Chem.* **2011**, *54*, 5955-5980.

2. Skorenski M., Oleksyszyn J., Sienczyk M., *Tetrahedron Lett*. **2013**, *54*, 4975-4977.

3. a) Kabachnik M. I., Medved T. Y., *Dokl. Akad. Nauk SSSR* **1952**, *83,* 689-692; b) Fields E., *J. Am. Chem. Soc.* **1952**, *74*, 1528-1531.

4. a) Pudovik A. N., *Dokl. Akad. Nauk SSSR* **1952**, *83,* 865-868; b) Enders D., Saint-Dizier A., Lannou M.-I., Lenzen A., *Eur. J. Org. Chem.* **2006**, *1,* 29-49.

5. Gilmore W. F., Mc Bride M. A., *J. Pharm. Sci.* **1974**, *63,* 1087-1090.

6. Huber III W., Gilmore W. F., Robertson L.W., *J. Med. Chem.* **1975**, *18*, 106-108.

7. Solodenko V. A., Kasheva N. A. and Kukhar V. P., *Synth. Commun.* **1992**, *21*, 1631-1641.

8. a) Oleksyszyn J., Tyka R., Mastalerz P., *Synthesis* **1978**, *6*, 479-480; b) Oleksyszyn J., Subotkowska L., Mastalerz P., *Synthesis* **1979**, *12*, 985-986; c) Oleksyszyn J., *Synthesis* **1980**, *9*, 722-724; d) Oleksyszyn J., Gruszecka E., Kafarski P., Mastalerz P., *Monatsh. Chem.* **1982**, *113*, 59-71.

9. Oleksyszyn J., *J. Prakt. Chem.* **1987**, *329*, 19-28.

10. a) Yuan C., Wang G., Chen S., *Synthesis* **1990**, *6*, 522-524; b) Yuan C., Chen S., Wang G., *Synthesis* **1991**, *6*, 490-493.; c) Yuan C., Wang G., Chen S., *Synthesis* **1992**, *11*, 1124-1128; d) Chung S.-K., Kang D.-H., *Tetrahedron Asymmetry* **1996**, *7*, 21-23; e) Chen S., Coward J.

 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

K., *Tetrahedron Lett*. **1996**, *37*, 4335-4338; f) Chen S., Coward J. K., *J. Org. Chem*. **1998**, *63*, 502-509.

11. Oleksyszyn J., Gruszecka E., *Tetrahedron Lett*. **1981**, *22*, 3537-3540.

12. a) Dmitriev M. E., Ragulin V. V., *Tetrahedron Lett*. **2010**, *19*, 2613-2616; b) Dmitriev M. E., Rossinets E. A., Ragulin V. V., *Russ. J. Gen. Chem.* **2011**, *81*, 1092-1104; c) Dmitriev M. E., Ragulin V. V., *Russ. J. Gen. Chem.* **2012**, *82*, 1882-1885; d) Dmitriev M. E., Ragulin V. V., *Tetrahedron Lett*. **2012**, *53*, 1634-1636; e) Dmitriev M. E., Ragulin V. V. *Russ. J. Gen. Chem.* **2013**, *83*, 1888-1894.

13. Kano T., Yurino T., Asakawa D., Maruoka K., *Angew. Chem. Int. Ed.* **2013**, *52*, 5532-5535.

14. Mucha A., Kafarski P., Plenat F., Cristau H.-J. *Phosphorus, Sulfur, Silicon Relat. Elem.*, **1995**, *105*, 187-193.

15. a) Dodonov A.F., Loboda A.V., Kozlovski V.I., Soulimenkov I.V., Raznikov V.V., Zhen Z., Horwath T., Wollnik H., *Eur. J. Mass Spectrom.* **2000,** *6*, 481-490;

b) Kozlovski V.I., Brusov V., Sulimenkov I., Pikhtelev A. and Dodonov A.F., *Rapid Commun. Mass Spectrom*. **2004**, *18*, 780-786.

 ACCEPTED MANUSCRIPT

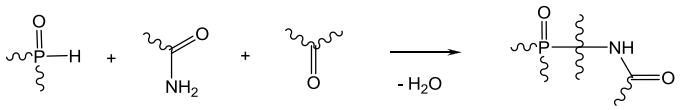
Table 1. *N*-Benzyloxycarbonyl-α-aminoalkylphosphonic acids **(4-10)**

Entry	Compound	R	M.p., ºC	Yields, %		
1	4	Me	105-106, [14]110	[a]64	[b]67	[d]34
2	5	i-Pr	67-68	[a]65	[c]68	[e]54
3	6	i-Bu	131-132	[a]75	[b]75	[e]54
4	7	sec-Bu	96-97	[a]56	-	[e]42
5	8	Ph	156-157,[14]159	[a]76	[b]72, [c]66	[f]54
6	[g]8a	Ph	189-190	[a,g]31	-	-
7	9	p-Cl-C_6H_5	121-122	[a]77	-	[f]58
8	10	p-MeO-C_6H_5	109-110	[a]81	-	[f]58

$Ac_2O \leq AcCl$: [a]Ac_2O / AcCl = 1:1; [b]Ac_2O / AcCl = 1:4; [c]Ac_2O / AcCl = 1:2;

$Ac_2O > AcCl$: [d]Ac_2O / AcCl = 5:1, [e]Ac_2O / AcCl = 2:1; [f]Ac_2O / AcCl = 3:1; [a,g]yield of monoethyl ester

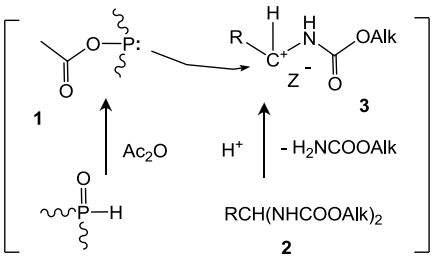
ACCEPTED MANUSCRIPT



Scheme 1. Amide version of Kabachnik-Fields reaction

ACCEPTED MANUSCRIPT

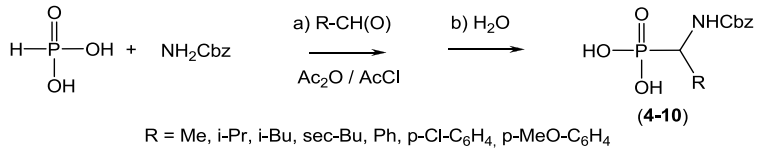
ACCEPTED MANUSCRIPT



Scheme 2. The generation in situ of P^{III}–OAc compound (**1**) and imine cations (**3**) on the formation of P-C bond

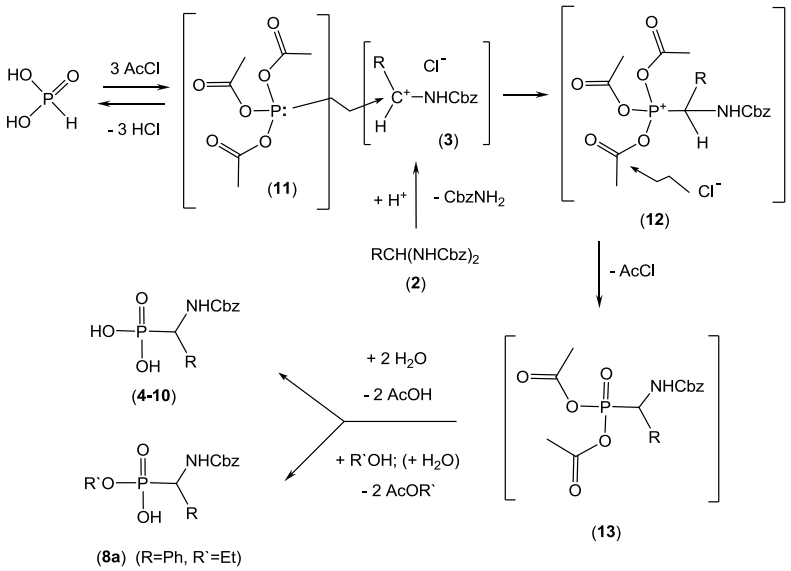
 ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT



Scheme 3. Synthesis of N-Cbz-a-aminoalkylphosphonic acids **4-10**

 ACCEPTED MANUSCRIPT


3 AcCl
- 3 HCl
(11)
(3)
(12)
+ H+
- CbzNH2
RCH(NHCbz)2
(2)
- AcCl
(4-10)
+ 2 H2O
- 2 AcOH
+ R`OH; (+ H2O)
- 2 AcOR`
(13)
(8a) (R=Ph, R`=Et)

Scheme 4