ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 8, pp. 1728–1730. © Pleiades Publishing, Ltd., 2019. Russian Text © The Author(s), 2019, published in Zhurnal Obshchei Khimii, 2019, Vol. 89, No. 8, pp. 1305–1308.

LETTERS TO THE EDITOR

Double Arbuzov Reaction. Synthesis of Bis(ω-cyanoalkyl)phosphinic Acids

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Received March 7, 2019; revised March 7, 2019; accepted March 21, 2019

Abstract—A general method for the synthesis of symmetric $bis(\omega$ -cyanoalkyl)phosphinic acids from ammonium hypophosphite was proposed. The reaction of bis(trimethylsilyl)hypophosphite generated *in situ* with the ω -bromoalkylnitrile molecule according to the Arbuzov reaction and the subsequent silylation of the hydrophosphoryl intermediate leads to the formation of bis(trimethylsilyl)phosphonite. The latter reacts with the second ω -haloalkylnitrile molecule by the Arbuzov reaction with the formation of the second phosphorus-carbon bond.

Keywords: Double Arbuzov reaction, ammonium hypophosphite, bis(trimethylsilyl)hypophosphite, ω-haloalkylnitriles, bis(ω-cyanoalkyl)phosphinic acids

DOI: 10.1134/S1070363219080292

Recently, we have described the double reaction of trivalent phosphorus silyl esters generated in situ from hypophosphites with two haloalkane molecules according to the Arbuzov reaction scheme, which leads to the sequential formation of two phosphorus-carbon bonds and, as a result, symmetric dialkylphosphinic acids [1]. Introduction of α . ω -dielectrophiles into the reaction made it possible to carry out one-pot synthesis of 5- and 6-membered cyclic phosphinic acids [2]. The use of a wider range of dielectrophiles in boiling mesitylene made it possible to obtain 4-, 7-, and 8-membered cyclic phosphinic acids [3]; this reaction has been called the Double Arbuzov reaction. The efficiency of the reaction is due to the combination of the processes of formation of two phosphorylating agents and two phosphorylation processes in one reaction vessel, which allowed the synthesis of various symmetric dialkylphosphinic acids, including functionally substituted phosphinic acids containing various phosphoryl or aminocarboxylic functions [1, 4–6]. The unknown symmetric phosphinic acids bearing a nitrile function can be of interest for further transformations with the construction of heterocyclic or phosphoryl fragments.

The aim of this work was the synthesis of $bis(\omega$ cyanoalkyl)phosphinic acids **1** from ammonium hypophosphite **2** and the corresponding ω -haloalkyl nitriles **3** (Scheme 1).

As proposed earlier [1, 2], the double Arbuzov reaction is a five-stage process, including in situ generation of bis(trimethylsilyl)hypophosphite 4 (Scheme 1), the first phosphorylating agent, as well as in situ generation of bis(trimethylsilyl)phosphonite 5 as a second phosphorylating agent. The product of the first phosphorylation is hydrophosphoryl intermediate 6, the silvlation of which under the reaction conditions leads to the formation of phosphonite 5. The latter can interact with the second molecule of electrophile 3 according to the Arbuzov reaction [1, 2]. As a result of the second phosphorylation, silylphosphinate 7 is formed, the alcoholysis of which gives rise to symmetric phosphinic acid 1 (Scheme 1). An advantage of the studied reaction is the absence of the products of reaction between silvl esters of trivalent phosphorus 4–6 generated *in situ* with the nitrile function of ω -haloalkyl nitriles 3 and intermediates 5–7 under the reaction conditions.

In summary, the introduction of ω -haloalkyl nitriles as an electrophilic component into the double Arbuzov reaction allows one to obtain new symmetric bis(ω cyanoalkyl)phosphinic acids.





General procedure for the synthesis of symmetric bis(ω-cyanoalkyl)phosphinic acids. A mixture of 0.02 mol of ammonium hypophosphite, 0.04 mol of hexamethyldisilazane and 0.04-0.45 mol of the corresponding ω -haloalkylnitrile was boiled with stirring for $\sim 7-8$ h. After cooling in an argon stream to room temperature, 12 mL of aqueous alcohol (5:1)was slowly added dropwise to the reaction mixture with cooling. The resulting crystalline product was isolated and recrystallized from a concentrated aqueous solution. Thus, phosphinic acids 1c and 1d were isolated. If the crystalline product does not form after alcoholysis, the reaction mixture was evaporated in vacuum, the residue was twice evaporated with water, and acids 1a and 1b were isolated from concentrated aqueous solution. The resulting compounds were white crystalline substances in the form of hydrates melting with decomposition.

Bis(2-cyanoethyl)phosphinic acid (1a). Yield 67%, mp 102–107°C (foaming with subsequent hardening), 244–249°C (dec.). ¹H NMR spectrum (D₂O), δ, ppm: 2.02 d.t(4H, CH₂, ${}^{3}J_{HH}$ =7.3, ${}^{2}J_{PH}$ =12.8 Hz), 2.66 d.t(4H, CH₂, ${}^{3}J_{HH}$ =7.3, ${}^{3}J_{PH}$ =13.4 Hz). ¹³C NMR spectrum (D₂O), δ_C, ppm: 10.76 d (${}^{2}J_{PC}$ = 2.9 Hz), 24.74 d (${}^{1}J_{PC}$ =92.1 Hz), 121.04 d (${}^{3}J_{PC}$ =13.6 Hz). ³¹P NMR spectrum (D₂O): δ_P 43.82 ppm. Mass spectrum, *m/z*: 173.1 [*M* + H⁺] (calcd. C₆H₉N₂O₂P: 172.1). Found, %: C 37.68, 37.54; H 6.08, 6.14; N 15.03, 14.90. C₆H₉N₂O₂P·H₂O. Calculated,%: C 37.90; H 5.83; N 14.73.

Bis(3-cyanopropyl)phosphinic acid (1b). Yield 53%, mp 98–105°C (foaming with subsequent hardening), 254–261°C (dec.). ¹H NMR spectrum (D₂O), δ , ppm: 1.80–2.20 m (8H, CH₂), 2.61 t (4H, CH₂, ${}^{3}J_{HH} = 6.4$ Hz). 13 C NMR spectrum (D₂O), δ_{C} , ppm: 17.58 d (${}^{3}J_{PC} =$ 19.9 Hz), 17.73, 27.10 d (${}^{1}J_{PC} =$ 91.4 Hz), 120.99 (CN). 31 P NMR spectrum (D₂O): δ_{P} 53.15 ppm. Mass spectrum, *m/z*: 201.2 [*M* + H⁺] (calcd. C₈H₁₃N₂O₂P: 200.2). Found, %: C 43.87, 44.10; H 7.05, 7.11; N 14.07, 13.98. C₈H₁₃N₂O₂P·H₂O. Calculated, %: C 44.04; H 6.93; N 14.04.

Bis(4-cyanobutyl)phosphinic acid (1c). Yield 64%, mp 103–109°C (foaming with subsequent hardening), 263–269°C (dec.). ¹H NMR spectrum (D₂O), δ, ppm: 1.47–1.88 m (12H, CH₂), 2.46 t (4H, CH₂, ${}^{3}J_{\rm HH} = 6.4$ Hz). ¹³C NMR spectrum (D₂O), $\delta_{\rm C}$, ppm: 16.43, 20.84 d (${}^{2}J_{\rm PC} = 3.9$ Hz), 25.92 d (${}^{3}J_{\rm PC} = 16.4$ Hz), 27.36 d (${}^{1}J_{\rm PC}$ 90.08 Hz), 122.06 (CN). ³¹P NMR spectrum (D₂O): $\delta_{\rm P}$ 58.62 ppm. Mass spectrum, *m/z*: 229.2 [*M* + H⁺] (calcd. C₁₀H₁₇N₂O₂P: 228.2). Found, %: C 48.60, 48.52; H 8.02, 7.86; N 11.23, 11.10. C₁₀H₁₇N₂O₂P·H₂O. Calculated, %: C 48.78; H 7.78; N 11.38.

Bis(*o***-cyanobenzyl)phosphinic acid (1d).** Yield 92%, mp 188–193°C (foaming with subsequent hardening), 267–274°C (dec.). ¹H NMR spectrum (D₂O), δ, ppm: 3.01 d (4H, CH₂, ${}^{2}J_{PH}$ = 16.1 Hz), 7.18–7.38 m (4H, CH), 7.43–7.65 m (4H, CH). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 2.94 d (4H, CH₂, ${}^{2}J_{PH}$ = 16.1 Hz), 7.23–7.75 m (8H, CH). ¹³C NMR spectrum (DMSO-*d*₆), δ_C, ppm: 38.08 d (${}^{1}J_{PC}$ = 81.5 Hz), 111.93 d (${}^{4}J_{PC}$ = 5.9 Hz), 118.40 d (${}^{4}J_{PC}$ = 1.5 Hz), 125.94 d (${}^{4}J_{PC}$ = 2.2 Hz), 130.56 d (${}^{3}J_{PC}$ = 4.1 Hz), 132.33 (2C), 140.72 d (${}^{3}J_{PC}$ = 7.4 Hz). ³¹P NMR spectrum (D₂O): δ_P 33.14 ppm. ³¹P NMR spectrum (DMSO-*d*₆): δ_P 22.61 ppm. Found, %: C 60.86, 61.01; H 5.12, 5.16; N 9.03, 9.08; P 10.03, 10.11. C₁₆H₁₃N₂O₂P. Calculated, %: C 61.15; H 4.81; N 8.91; P 9.86.

¹H, ³¹P and ¹³C NMR spectra were recorded on a Bruker DPX-200 Fourier spectrometer. Melting points were determined in a block in an open capillary. Chromatographic analysis was performed on an Agilent 1100 series LC/MSD system with DAD, ELSD and a single quadrupole mass-selective detector using electrospray ionization mode.

FUNDING

This work was financially supported by the Presidium of the Russian Academy of Sciences (Program no. 14), the Russian Foundation for Basic Research (grants no. 18-03-00959, 18-03-01123) and the Russian Science Foundation (grant no. 19-13-00294, chromatographic, spectral and elemental analysis) within the frame of governmental task for the Institute of Physiologically Active Substances of the Russian Academy of Sciences for 2019.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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