ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 9, pp. 2219–2221. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © G.V. Iakobson, E.B. Erkhitueva, N.I. Svintsitskaya, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 9, pp. 1580–1582.

LETTERS TO THE EDITOR

To the 85th Anniversary of birthday of late Yu.G. Gololobov

Phosphorylation of 5-Substituted NH-Tetrazoles with Dimethyl Chloroacetylenephosphonate

G. V. Iakobson[a], E. B. Erkhitueva[b], and N. I. Svintsitskaya[c]

[a] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic*

[b] *St. Petersburg State University, Universitetskaya nab. 7–9, St. Petersburg, 199034 Russia*
e-mail: serlxa@yandex.ru

[c] *St. Petersburg State Institute of Technology (Technical Univerity), St. Petersburg, Russia*

Received July 23, 2015

Keywords: NH-tetrazoles, chloroacetylenephosphonate, tetrazole-containing vinylphosphonates, nucleophilic addition

DOI: 10.1134/S1070363215090327

Nowadays tetrazole compounds received much attention due to their active utilization in pharmacology. Many drugs of the latest generation contain a tetrazole moiety in the structure [1].

Compounds containing phosphonic groups are known to exhibit antibacterial, antibiotic, antineoplastic, antiviral properties and many other types of biological activity [2]. Therefore, the molecules which combine in their structure phosphorus and tetrazol functions may have an unusual biological activity, and hence, be of practical interest.

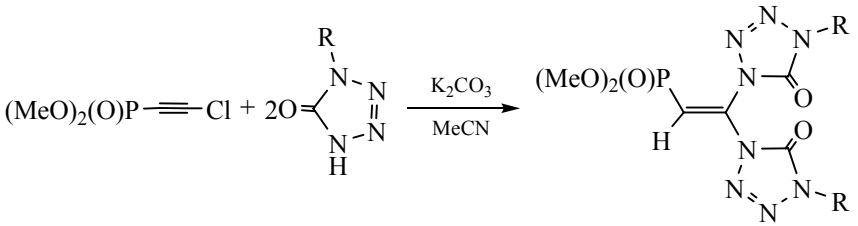
It has been previously shown [3] that the reaction of dimethyl 2-chloroethynylphosphonate with substituted NH-tetrazol-5-ones occurred regioselectively to form the geminally substituted alkenylphosphonates in 65–87% yield (Scheme 1).

Another trend was observed in this reaction when reacting 2-chloroethynylphosphonate with 1-substituted NH-thiotetrazole-5-ones: Under a basic catalysis in a protic solvent the reaction led to the formation of vicinally disubstituted alkenylphosphonates in 80–90% yields [4]. Some of the obtained *Z*-1,2-bis[(1*H*-1,2,3,4-tetrazol-5-yl)sulfanyl]ethenylphosphonates showed high antifungal activity comparable with the activity of fluconazole widely used in medical practice for the treatment of various fungal infections (Scheme 2).

It was of interest to perform the reactions of chloroacetylenephosphonate with 5-substituted NH-tetrazoles like 5-methyl- and 5-phenyltetrazole as well as ethyl tetrazolylacetate.

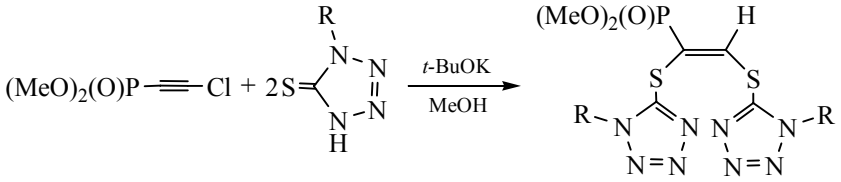
In was found that the reaction of dimethyl chloroacetylenephosphonate with 5-substituted tetrazoles (in

Scheme 1.



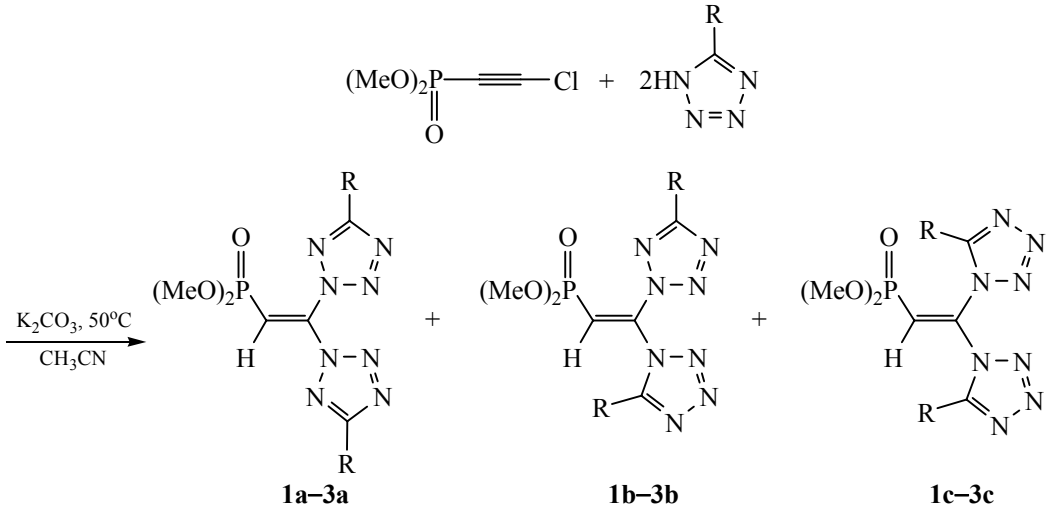
R = Ph, Bn, 2-Cl-C_6H_4, 4-NO_2-C_6H_4, 2,4-NO_2-C_6H_3.

Scheme 2.



R = Me, Ph, NH_2.

Scheme 3.



1a–3a **1b–3b** **1c–3c**

R = Me (**1**), Ph (**2**), CH_2COOEt (**3**).

a ratio of 1 : 2) proceeded in absolute acetonitrile in the presence of anhydrous potassium carbonate to yield new geminally substituted tetrazole-containing vinylphosphonates **1**–**3** (Scheme 3).

The reaction occurred via initial substitution of the chlorine atom to form tetrazolylethynylphosphonate followed by addition of the second molecule of NH-tetrazole to give the appropriate geminally substituted 2,2-bis[5-R-tetrazol-1(2)-yl]ethenylphosphonates. Due to the fact that NH-tetrazoles can exist as 1H- and 2H-tautomers [5], there was the formation of three isomers containing tetrazol-1(2)-yl fragments. In addition, the formation of trace amounts of the corresponding phosphonoacetamides was observed as a result of hydrolysis of the initially formed tetrazolylacetylene-phosphonate.

Attempts to isolate the individual isomers by re-precipitation, extraction or recrystallization failed. Chromatographic separation of the isomers also was unsuccessful, probably due to the ability of phosphonates to be adsorbed on silica gel.

General procedure for the synthesis. A mixture of 0.006 mol of dimethyl chloroacetylenephosphonate, 0.07 mol of calcined potassium carbonate, 0.012 mol of the corresponding 5-substituted tetrazole, and 10 mL of absolute acetonitrile was stirred vigorously at 50°C for 4–8 h. To prevent hydrolysis of the initially formed tetrazolylacetylenephosphonate, the reaction mixture was carefully isolated from air moisture. After the reaction was completed, the precipitate was filtered off and washed with a small amount of absolute acetonitrile. The filtrate was concentrated. The residue was dissolved in benzene and washed with 2% aqueous alkaline solution and then with water. The organic layer was dried with anhydrous sodium sulfate, and decanted from the precipitate. Benzene was distilled off, the oily residue was analyzed.

Dimethyl 2,2-bis[5-phenyltetrazol-1(2)-yl]ethenyl-phosphonate (1) was prepared from 1 g (0.006 mol) of chloroethynylphosphonate and 1.75 g (0.012 mol) of 5-phenyltetrazole; the reaction time 6 h. Yield 1.02 g. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.52 d (3H,

CH_3OP, $^3J_{HP}$ 11.8 Hz), 3.58 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.65 d (3H, CH_3OP, $^3J_{HP}$ 11.8 Hz), 3.70 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.74 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.81 d (3H, CH_3OP, $^3J_{HP}$ 11.8 Hz), 7.17 d (1H, PCH=C, $^2J_{HP}$ 3.0 Hz), 7.24 d (1H, PCH=C, $^2J_{HP}$ 3.7 Hz), 7.30 d (1H, PCH=C, $^2J_{HP}$ 4.4 Hz), 7.37–8.3 m (15H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 52.92 (CH_3OP), 111.12 d (P<u>CH</u>=C, $^1J_{CP}$ 188.6 Hz), 111.90 d (P<u>CH</u>=C, $^1J_{CP}$ 188.6 Hz), 118.56 d (P<u>CH</u>=C, $^1J_{CP}$ 183.5 Hz), 124.43–132.87 m (Ph), 135.95 d (PCH=<u>C</u>, $^2J_{CP}$ 9.5 Hz), 136.29 d (PCH=<u>C</u>, $^2J_{CP}$ 6.7 Hz), 137.53 d (PCH=<u>C</u>, $^2J_{CP}$ 8.1 Hz), 164.99 (C_{Tetr}), 165.56 (C_{Tetr}), 166.04 (C_{Tetr}), 166.87 (C_{Tetr}). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 8.74, 8.52, 8.26.

Dimethyl 2,2-bis[5-methyltetrazol-1(2)-yl]ethenylphosphonate (2) was prepared from 1 g (0.006 mol) of chloroethynylphosphonate and 2 g (0.012 mol) of 5-methyltetrazole; the reaction time 8 h. Yield 1.07 g. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.01–2.94 m (9H, CH_3, tetrazole), 3.53 d (3H, CH_3OP, $^3J_{HP}$ 11.8 Hz), 3.55 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.58 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz) 3.60 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.64 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.70 d (3H, CH_3OP, $^3J_{HP}$ 11.8 Hz), 6.46 d (1H, PCH=, $^2J_{HP}$ 5.2 Hz), 6.57 d (1H, PCH=, $^2J_{HP}$ 3.0 Hz), 6.88 d (1H, PCH=, $^2J_{HP}$ 3.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 8.15 (CH_3, tetrazole), 8.26 (CH_3, tetrazole), 8.56 (CH_3, tetrazole), 51.76 d (CH_3OP, $^2J_{CP}$ 5.4 Hz), 53.01 d (CH_3OP, $^2J_{CP}$ 5.4 Hz), 53.88 d (CH_3OP, $^2J_{CP}$ 4.0 Hz), 110.10 d (P<u>CH</u>=C, $^1J_{CP}$ 189.9 Hz), 111.47 d (P<u>CH</u>=C, $^1J_{CP}$ 188.6 Hz), 117.25 d (P<u>CH</u>=C, $^1J_{CP}$ 184.5 Hz), 133.89 d (PCH=<u>C</u>, $^2J_{CP}$ 6.8 Hz), 134.23 d (PCH=<u>C</u>, $^2J_{CP}$ 8.1 Hz), 135.70 d (PCH=<u>C</u>, $^2J_{CP}$ 5.4 Hz), 162.24 (C_{Tetr}), 163.38 (C_{Tetr}), 163.51 (C_{Tetr}), 164.19 (C_{Tetr}). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 7.57, 8.24, 8.66.

Dimethyl 2,2-bis[5-ethylcarboxymethyltetrazol-1(2)-yl]ethenylphosphonate (3) was prepared from 1 g (0.006 mol) of chloroethynylphosphonate and 1.85 g (0.012 mol) of ethyl tetrazolylacetate; the reaction time 4 h. Yield 1.5 g. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.04–1.37 m (9H, <u>CH_3</u>CH_2O), 3.41 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.49 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.55 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz) 3.63 d (3H, CH_3OP, $^3J_{HP}$ 11.8 Hz), 3.69 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.73 d (3H, CH_3OP, $^3J_{HP}$ 11.0 Hz), 3.92–4.37 m (6H, CH_3<u>CH_2</u>O), 4.01–4.30 m (6H, CH_2C=O), 6.38 d (1H, PCH=C, $^2J_{HP}$ 4.0 Hz), 6.48 d (1H, PCH=C, $^2J_{HP}$ 3.0 Hz), 6.75 d (1H, PCH=C, $^2J_{HP}$ 3.0 Hz). ^{13}C NMR spectrum ($CDCl_3$–DMSO-d_6), δ_C, ppm: 13.65 (<u>CH_3</u>CH_2O), 29.63 (<u>CH_2</u>C=O), 29.96 (<u>CH_2</u>C=O), 31.36 (<u>CH_2</u>C=O), 51.84 (CH_3OP), 53.38 (CH_3OP), 53.76 (CH_3OP), 61.11 (CH_3<u>CH_2</u>O), 61.47 (CH_3<u>CH_2</u>O), 61.82 (CH_3<u>CH_2</u>O), 111.35 d (P<u>CH</u>=C, $^1J_{CP}$ 188.6 Hz), 111.60 d (P<u>CH</u>=C, $^1J_{CP}$ 189.9 Hz), 115.85 d (P<u>CH</u>=C, $^1J_{CP}$ 185.8 Hz), 133.92 d (PCH=<u>C</u>, $^2J_{CP}$ 8.1 Hz), 134.59 d (PCH=<u>C</u>, $^2J_{CP}$ 8.1 Hz), 136.20 d (PCH=<u>C</u>, $^2J_{CP}$ 6.8 Hz), 159.87 (C_{Tetr}), 160.68 (C_{Tetr}), 161.09 (C_{Tetr}), 161.57 (C_{Tetr}), 165.34 (C=O), 165.56 (C=O), 167.07 (C=O), 167.23 (C=O). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm: 8.58, 8.98, 9.57.

NMR spectra were recorded on a Bruker AC-200 [50.328 (^{13}C), 81.014 (^{31}P) MHz] and Bruker AC-400 instruments [400.133 (^1H) MHz].

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grant no. 14-03-31445_mol-a).

REFERENCES

1. Herr, R.J., *Bioorg. Med. Chem*., 2002, vol. 10, no. 11, p. 3379. DOI: 10.1016/S0968-0896(02)00239-0.
2. Issleib, K., Dopfer, K.P., and Balszuweit, A., *Phosphorus, Sulfur, Silicon, Relat. Elem*., 1987, vol. 30, nos. 3–4, p. 633. DOI: 10.1080/03086648708079144.
3. Mel'nikova, Yu.V., Myznikov, L.V., Dogadina, A.V., and Svintsitskaya, N.I., *Russ. J. Gen. Chem*., 2014, vol. 84, no. 11, p. 2160. DOI: 10.1134/S107036321411019X.
4. Erkhitueva, E.B., Dogadina, A.V., Khramchihin, A.V., and Ionin, B.I., *Tetrahedron Lett*., 2013, vol. 54, no. 38, p. 5174. DOI: 10.1016/j.tetlet.2013.07.032.
5. Koldobskii, G.I. and Ostrovskii, V.A., *Russ. Chem. Rev.,* 1994, vol. 63, no. 10, p. 797. DOI: 10.1070/RC1994v063n10ABEH000119.