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LETTERS TO THE EDITOR

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

Reactions of Chloroethynylphosphonates with 4,5-Substituted 1*H*-Imidazole-2-thiones

D. M. Egorov[a], Yu. L. Piterskaya[a], V. F. Mironov[b], and A. V. Dogadina[a]

[a] *St. Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia*
e-mail: dog_alla@mail.ru

[b] *Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, Kazan, Tatarstan, Russia*

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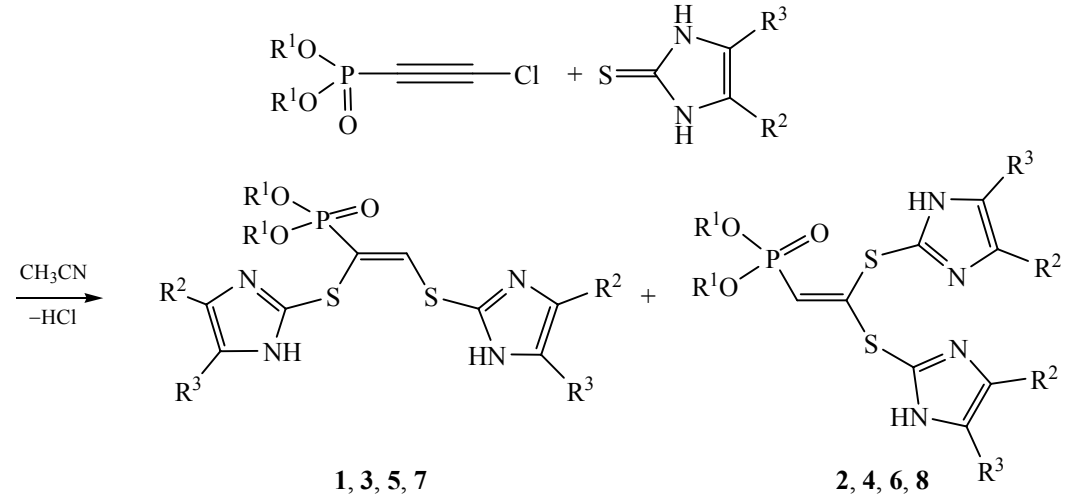
Pharmacological properties of imidazole and thioimidazole derivatives are well known. The introduction of a phosphoryl moiety into imidazole or thioimidazole ring can further modulate the properties of a bioactive molecule due to the changes in solubility, liophilicity, and chemical reactivity as described in [1–4].

We have recently shown that phosphorylation of 1-methyl-1*H*-imidazole-2-thiones with chlorethynylphosphonates proceeded stereo- and regioselectively to form *Z*-isomers of vicinally substituted bis[1-methyl-1*H*-imidazol-2-yl-sulfanyl]ethenylphosphonates [5].

In the present work we found that the reaction of chlorethynylphosphonates with substituted 4,5-1*H*-imidazole-2-thiones took place with high chemoselectivity and low regioselectivity to give the corresponding geminally and vicinally disubstituted dialkyl *Z*-(1*H*-imidazol-2-ylsulfanyl)ethenylphosphonates **1**–**8**

Scheme 1.



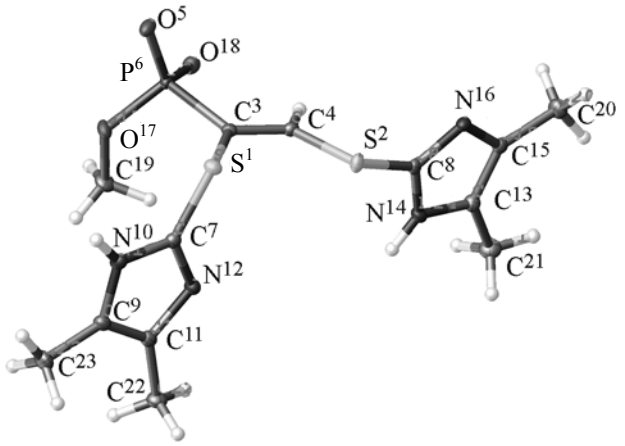
1, **3**, **5**, **7** **2**, **4**, **6**, **8**

$R^1 = R^2 = R^3 = Me$ (**1**, **2**); $R^1 = Et$, $R^2 = R^3 = Me$ (**3**, **4**); $R^1 = Me$, $R^2 = R^3 = Ph$ (**5**, **6**); $R^1 = Et$, $R^2 = Ph$, $R^3 = H$ (**7**, **8**).

in a ratio of ≈1 : 1 in the yields over 80% (Scheme 1). The reactions were performed in anhydrous acetonitrile at room temperature using a reactants ratio of 1 : 2.

The reaction probably proceeded according to the previously suggested scheme [5] via intermediate formation of sulfenium salt which containing a labile imidazole ring proton eliminated a hydrogen chloride molecule to form the corresponding imidazolylsulfanylethynylphosphonate. The latter added the second thioimidazole molecule to give disubstituted ethenylphosphonates **1**–**8**, whose structures were proved by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. ^{31}P NMR spectra of vicinal ethenylphosphonates **1**, **3**, **5**, and **7** contained the signals in the stronger field (δ_P 7.43–14.6 ppm) compared with those for geminally substituted ethenylphosphonates **2**, **4**, **6**, and **8** (δ_P 9.67–16.07 ppm). In ^{1}H NMR spectra of the compounds obtained the olefin proton resonated as a doublet signal in a weak field (7.81–8.48 ppm, $^{3}J_{HP}$ 11.6–14.1 Hz) for vicinal isomers and in a strong field (4.72–5.68 ppm, $^{3}J_{HP}$ 8.8–12.7 Hz) for the geminal isomers. The structure of the vicinal isomers was unambiguously confirmed by X-ray diffraction analysis by an example of single crystal of methyl *Z*-[1,2-bis(4,5-dimethyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate **1a** (see figure) obtained by repeated crystallization of phosphonate **1** accompanied by the cleavage of the methyl group, which we had observed earlier [5].

Dimethyl *Z*-[1,2-bis(4,5-dimethyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate (1). A mixture of 2.5 mmol of dimethyl chloroethynylphosphonate and 5.0 mmol of 4,5-dimethyl-1*H*-imidazole-2-thione in 10 mL of absolute acetonitrile was stirred at room temperature for 6–10 h. The resulting precipitate was filtered off. After removing the solvent, the residue was purified by column chromatography on silica gel, eluting with chloroform–ethyl acetate mixture, 85 : 15. Yield 43%, colorless crystals, mp 210°C (decomp., ethanol). ^{1}H NMR spectrum (CD_3OD, 400.13 MHz), δ, ppm (*J*, Hz): 2.05 s and 2.17 s (12H, $C\underline{H}_3C$=), 3.48 d (6H, OCH_3, $^{3}J_{HP}$ 11.6), 7.81 d (1H, PC=C<u>H</u>, $^{3}J_{HP}$ 11.6). ^{13}C NMR spectrum (CD_3OD, 100.61 MHz), δ_C, ppm (*J*, Hz): 9.01 ($\underline{C}H_3C$=), 52.61 d ($\underline{C}H_3O$, $^{3}J_{CP}$ 5.4), 119.74 d (P<u>C</u>=CH, $^{1}J_{CP}$ 175.1), 126.30 and 126.72 (=<u>C</u>CH_3), 128.07 d (PC=<u>C</u>H, $^{2}J_{CP}$ 23.5), 148.26 and 148.45 (SC=N). ^{31}P NMR spectrum (CD_3OD, 161.98 MHz): δ_P 11.87 ppm. Mass spectrum: *m*/*z* 389.4453 $[M + H]^+$ (calculated for $C_{14}H_{21}N_4O_3PS_2$: *M* 388.0793).



Geometry of *Z*-[1,2-bis(4,5-dimethyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]methoxyphosphonic acid **1a** molecule.

Diethyl *Z*-[1,2-bis(4,5-dimethyl-1*H*-imadazol-2-ylsulfanyl)ethenyl]phosphonate (3) was obtained similarly from diethyl chloroethynylphosphonate and 4,5-dimethyl-1*H*-imidazole-2-thione. Yield 51%, colorless crystals, mp 210°C (decomp., ethanol). ^{1}H NMR spectrum ($CDCl_3$, 400.13 MHz), δ, ppm (*J*, Hz): 1.27 t (6H, $OCH_2C\underline{H}_3$, $^{3}J_{HH}$ 6.2), 2.26 s and 2.27 s (12H, $C\underline{H}_3C$=), 4.73 m (4H, OCH_2, $^{3}J_{HH}$ 6.2, $^{3}J_{HP}$ 13.0), 8.13 d (1H, PC=C<u>H</u>, $^{3}J_{HP}$ 13.3). ^{13}C NMR spectrum ($CDCl_3$, 100.61 MHz), δ_C, ppm (*J*, Hz): 9.23 and 9.93 ($\underline{C}H_3C$=), 23.80 d ($\underline{C}H_3CH_2O$, $^{3}J_{CP}$ 5.4), 72.91 d ($CH_3\underline{C}H_2O$, $^{2}J_{CP}$ 6.7), 119.86 d (P<u>C</u>=CH, $^{1}J_{CP}$ 189.2), 129.71 d (PC=<u>C</u>H, $^{2}J_{CP}$ 20.2), 130.09 and 133.34 (=<u>C</u>CH_3), 158.99 and 159.21 (SC=N). ^{31}P NMR spectrum ($CDCl_3$, 161.98 MHz): δ_P 7.43 ppm. Mass spectrum: *m*/*z* 417.1106 $[M + H]^+$ (calculated for $C_{16}H_{25}N_4O_3PS_2$: *M* 416.4985).

Diethyl [2,2-bis(4,5-dimethyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate (4). Yield 36%, colorless crystals, mp 183°C (ethanol). ^{1}H NMR spectrum ($CDCl_3$, 400.13 MHz), δ, ppm (*J*, Hz): 1.22 t (6H, $OCH_2C\underline{H}_3$, $^{3}J_{HH}$ 6.2), 2.25 s and 2.31 s (12H, $C\underline{H}_3C$=), 4.72 m (4H, $OC\underline{H}_2CH_3$, $^{3}J_{HH}$ 6.2, $^{3}J_{HP}$ 12.3), 5.68 d (1H, PCH=, $^{2}J_{HP}$ 9.0). ^{13}C NMR spectrum ($CDCl_3$, 100.61 MHz), δ_C, ppm (J_{CP}, Hz): 9.76 and 10.34 ($\underline{C}H_3C$=), 23.64 d ($\underline{C}H_3CH_2O$, $^{3}J_{CP}$ 6.0), 72.13 d ($CH_3\underline{C}H_2O$, $^{2}J_{CP}$ 6.1), 112.90 d (PCH=, $^{1}J_{CP}$ 201.9), 125.80 d (PCH=<u>C</u>, $^{2}J_{CP}$ 19.5), 128.41 and 131.29 (=<u>C</u>CH_3), 150.05 (SC=N). ^{31}P NMR spectrum ($CDCl_3$, 161.98 MHz): δ_P 9.67 ppm. Mass spectrum: *m*/*z* 417.1106 $[M + H]^+$ (calculated for $C_{16}H_{25}N_4O_3PS_2$: *M* 416.4985).

Dimethyl *Z*-[1,2-bis(4,5-diphenyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate (5) was obtained similarly from dimethyl chloroethynylphosphonate and 4,5-diphenyl-1*H*-imidazole-2-thione. Yield 43%, colorless crystals, mp 210°C (decomp., ethanol). ^{1}H NMR spectrum (CD_3OD, 400.13 MHz), δ, ppm (*J*, Hz): 3.65 d (6H, OCH_3, $^3J_{HP}$ 12.1), 7.35 m (12H, $H^{o,p}$), 7.46 m (8H, H^m), 8.48 d (1H, PC=C<u>H</u>, $^3J_{HP}$ 12.6). ^{13}C NMR spectrum (CD_3OD, 100.61 MHz), δ_C, ppm (*J*, Hz): 53.44 d (CH_3O, $^3J_{CP}$ 6.0), 114.38 d (P<u>C</u>=CH, $^1J_{CP}$ 192.2), 127.97 (C^p), 128.54 (C^o), 128.85 (C^m), 129.65 and 130.88 (C^{ipso}), 131.29 d (PC=<u>C</u>H, $^2J_{CP}$ 23.7), 135.08 and 136.08 (=<u>C</u>Ph), 154.25 and 154.48 (SC=N). ^{31}P NMR spectrum (CD_3OD, 161.98 MHz): δ_P 14.60 ppm. Mass spectrum: *m*/*z* 637.7230 $[M + H]^+$ (calculated for $C_{34}H_{29}N_4O_3PS_2$: *M* 636.1419).

Dimethyl [2,2-bis(4,5-diphenyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate (6). Yield 39%, colorless crystals, mp 210°C (decom., ethanol). ^{1}H NMR spectrum (CD_3OD, 400.13 MHz), δ, ppm (*J*, Hz): 3.01 d (6H, OCH_3, $^3J_{HP}$ 12.2), 4.72 d (1H, PC=C<u>H</u>, $^3J_{HP}$ 12.7), 6.61 m and 6.62 m (8H, H^o), 6.66 m and 6.72 m (8H, H^m), 6.68 m and 6.74 m (4H, H^p). ^{13}C NMR spectrum (CD_3OD, 100.61 MHz), δ_C, ppm (*J*, Hz): 51.57 d (<u>C</u>H_3O, $^3J_{CP}$ 6.0), 106.48 d (PCH=<u>C</u>, $^1J_{CP}$ 194.2), 127.45 (C^p), 127.71 (C^o), 127.88 (C^m), 128.19 (C^{ipso}), 131.09 and 131.71 (=<u>C</u>Ph), 135.68 d (PCH=<u>C</u>, $^2J_{CP}$ 14.1), 156.76 and 156.83 (SC=N). ^{31}P NMR spectrum (CD_3OD, 161.98 MHz): δ_P 16.07 ppm. Mass spectrum: *m*/*z* 637.7230 $[M + H]^+$ (calculated for $C_{34}H_{29}N_4O_3PS_2$: *M* 636.1419).

Diethyl *Z*-[1,2-bis(4-phenyl-1*H*-imidazol-2-ylsulfanyl)ethenyl]phosphonate (7) was obtained similarly from diethyl chloroethynylphosphonate and 4-phenyl-1*H*-imidazole-2-thione. Yield 47%, colorless crystals, mp 210°C (decomp., ethanol). ^{1}H NMR spectrum (CD_3OD, 400.13 MHz), δ, ppm (*J*, Hz): 1.24 t (6H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 7.0), 4.11 m (4H, $OC\underline{H}_2$, $^3J_{HH}$ 7.0, $^3J_{HP}$ 14.8), 7.45 t (2H, H^p, $^3J_{HH}$ 5.5), 7.54 d (4H, H^o, $^3J_{HH}$ 5.5), 7.78 t (4H, H^m, $^3J_{HH}$ 5.5), 7.93 s and 8.05 s (2H, C<u>H</u>=CPh), 8.35 d (1H, PC=C<u>H</u>, $^3J_{HP}$ 14.1). ^{13}C NMR spectrum (CD_3OD, 100.61 MHz), δ_C, ppm (*J*, Hz): 16.25 d (<u>C</u>H_3CH_2, $^3J_{CP}$ 6.7), 62.85 d ($CH_3\underline{C}H_2$, $^2J_{CP}$ 6.1), 119.34 d (P<u>C</u>=CH, $^1J_{CP}$ 190.5), 122.31 and 122.85 (=<u>C</u>Ph), 124.98 and 125.05 (C^o), 127.17 and 127.64 (C^p), 128.80 and 128.67 (C^m), 129.61 and 130.17 (<u>C</u>H=CPh), 131.63 d (PC=<u>C</u>H, $^2J_{CP}$ 22.3), 134.24 and 135.85 (C^{ipso}), 157.83 and 158.05 (SC=N). ^{31}P NMR spectrum (CD_3OD, 161.98 MHz): δ_P 9.69 ppm. Mass spectrum: *m*/*z* 513.5841 $[M + H]^+$ (calculated for $C_{24}H_{25}N_4O_3PS_2$: *M* 512.1106).

Diethyl [2,2-bis(4-phenyl-1*H*-imidazol-2-ylsulfanyl)-ethenyl]phosphonate (8). Yield 41%, colorless crystals, mp 187°C (ethanol). ^{1}H NMR spectrum ($CDCl_3$, 400.13 MHz), δ, ppm (*J*, Hz): 1.32 t (6H, $OCH_2C\underline{H}_3$, $^3J_{HH}$ 7.0), 4.11 m (4H, $OC\underline{H}_2CH_3$, $^3J_{HH}$ 7.0, $^3J_{HP}$ 15.1), 5.20 d (1H, PC<u>H</u>=C, $^2J_{HP}$ 8.8), 7.28 t (2H, H^p, $^3J_{HH}$ 7.0), 7.38 d (4H, H^o, $^3J_{HH}$ 7.0), 7.49 s and 7.57 s (2H, CH=CPh), 7.70 t and 7.78 t (2H, H^m, $^3J_{HH}$ 7.0). ^{13}C NMR spectrum ($CDCl_3$, 100.61 MHz), δ_C, ppm (*J*, Hz): 15.17 d (<u>C</u>H_3CH_2, $^3J_{CP}$ 6.7), 62.45 d ($CH_3\underline{C}H_2$, $^2J_{CP}$ 6.1), 107.63 d (P<u>C</u>=CH, $^1J_{CP}$ 195.2), 114.66 and 115.29 (CH=<u>C</u>Ph), 124.61 and 124.68 (C^o), 127.32 and 127.38 (C^p), 128.49 (C^m), 132.39 and 132.94 (<u>C</u>H=CPh), 137.37 d (PC=<u>C</u>H, $^2J_{CP}$ 23.1), 138.41 (C^{ipso}), 157.28 (SC=N). ^{31}P NMR spectrum ($CDCl_3$, 161.98 MHz): δ_P 12.93 ppm. Mass spectrum: *m*/*z* 513.5841 $[M + H]^+$ (calculated for $C_{24}H_{25}N_4O_3PS_2$: *M* 512.1106).

^{1}H, ^{13}C, ^{31}P NMR spectra were recorded on a Bruker Avance 400 spectrometer. Mass spectra (HR-ESI) were taken on a Bruker MicrOTOF spectrometer.

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REFERENCES

1. Matevosyan, G.L. and Zavlin, P.M., *Chem. Heterocycl. Compd*., 1990, vol. 26, no. 6, p. 599. DOI: 10.1007/BF00756408.
2. Sauerbrey, S., Malhi, P.K., Schwieger, S., Arduengo III, A.J., and Streubel, R., *Heteroatom Chem*., 2012, p. 1. DOI: 10.1002/hc.21043.
3. Sauerbrey, S., Malhi, P.K., Schnakenburg, S., Arduengo III, A.J., and Streubel, R., *Dalton Trans*., 2012, vol. 41, p. 5368. DOI: 10.1039/2dt12483a.
4. Yurchenko, A.A., Huryeva, A.N., Zarudnitskii, E.V., Marchenko, A.P., Koidan, G.N., and Pinchuk, A.M., *Heteroatom Chem*., 2009, vol. 20, no. 5, p. 289. DOI: 10.1002/hc.20550.
5. Egorov, D.M., Piterskaya, Yu.L., and Dogadina, A.V., *Russ. J. Gen. Chem.*, 2015, vol. 85, no. 2, p. 502. DOI: 10.1134/S1070363215020255.