ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 10, pp. 2049–2051. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © K.S. Titov, M.N. Krivchun, N.I. Svintsitskaya, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 10, pp. 1748–1750.

LETTERS TO THE EDITOR

Synthesis of Phosphorus-Containing 7-Oxabicyclo[2.2.1]hepta-2,5-dienes

K. S. Titov, M. N. Krivchun, and N. I. Svintsitskaya

St. Petersburg State Institute of Technology (Technological University), Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: kstitov@mail.ru

Received September 4, 2014

Keywords: oxanorbornadienes, Diels–Alder reaction, acetylenephosphonates, furan

DOI: 10.1134/S107036321410034X

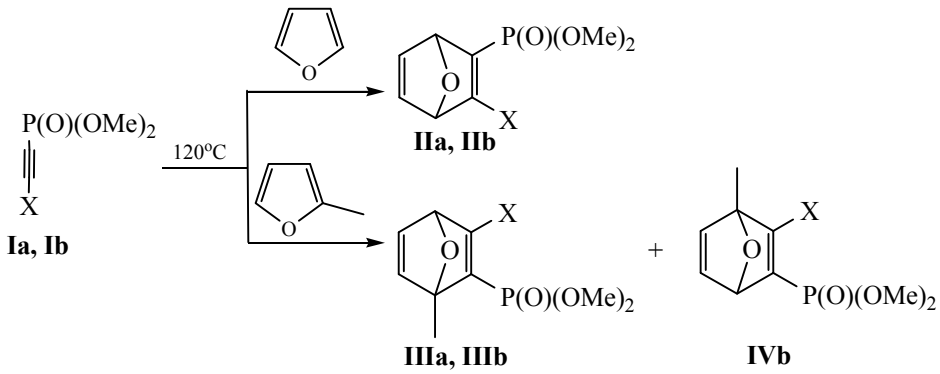
Acetylenediphosphonates and 2-chloroacetylenephosphonates are highly reactive dienophiles, which enter into the cyclocondensation reactions with classical donor 1,3-alkadienes [1, 2].

The Diels–Alder reaction involving furan as a diene component are of particular interest due to the possibility of obtaining oxanorbornenes and oxanorbornadienes. The latter are widely used as intermediates in creating more complex ring structures [3, 4] and analogs of biologically active compounds [5, 6]. Oxanorbornadienedicarboxylates (isosteres of oxanorbornadienediphosphonates) are suitable linkers for binding thiol and amine fragments with serum albumin serving as a macromolecular carrier for the delivery of drugs into organs and target cells [7]. The literature data concerning the synthesis of oxanorbornadienylphosphonates are scarce [8–11].

In order to obtain new phosphorus-substituted oxanorbornadienes we performed the Diels–Alder reaction of tetramehyl acetylenediphosphonate **Ia** and dimethyl 2-chloroacetylenephosphonate **Ib** with furan and 2-methylfuran. The reactions resulted in the formation of the corresponding (7-oxabicyclo[2.2.1]-hepta-2,5-dien-2-yl)phosphonates **II**–**IV** with 75–91% yields (Scheme 1).

The reactions were carried out under rigid conditions by prolonged heating (120°C) of a mixture of the corresponding acetylenephosphonate and 20% excess of furan or 2-methylfuran in a sealed tube under argon atmosphere in the absence of any solvent and in the presence of 1,4-hydroquinone as a polymerization inhibitor. The isolation and purification of the target compounds were carried out by vacuum distillation. The resulting compounds were colorless liquids.

Scheme 1.



X = $PO(OMe)_2$ (**a**), Cl (**b**).

Interaction of dimethyl 2-chloroacetylphosphonate **Ib** with 2-methylfuran proceeded with low regioselectivity, resulting in the corresponding isomeric mixture of (7-oxabicyclo[2.2.1]hepta-2,5-dien-2-yl)phosphonates **IIIb** and **IVb** with a predominance of 1-methyl derivative **IIIb**.

Structure of **II**–**IV** was confirmed by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy, and mass spectrometry. In the ^{1}H NMR spectra of (7-oxabicyclo[2.2.1]hepta-2,5-dien-2-yl)phosphonates **II**–**IV** there were characteristic doublet signals of methine (4.73–6.13 ppm) and vinyl protons (6.34–6.97 ppm). In the ^{13}C NMR spectra of **II**–**IV** the carbon atom C^{1} at the double bond directly attached to the phosphorus atom resonated as a doublet signal at 134–155 ppm with a large spin-spin coupling constant ($^{1}J_{CP}$ 205–211 Hz). The chemical shift of the phosphorus of the synthesized (7-oxabicyclo[2.2.1]-hepta-2,5-dien-2-yl)phosphonates **II**–**IV** was in the range of 12–14 ppm.

General procedure for the synthesis of compounds II–IV. A precooled ampule (–30°C) was charged with 12 mmol of the appropriate acetylenephosphonate, 16 mmol of furan or 2-methylfuran, and 5 mol % of hydroquinone. The ampule was then flushed with argon and sealed. The reaction mixture was heated at 120°C for 8–12 h. The reaction progress was monitored by ^{31}P NMR spectroscopy. After the reaction wascompleted, an excess of furan was removed in a vacuum. The reaction product was isolated by vacuum distillation.

Tetramethyl (7-oxabicyclo[2.2.1]hepta-2,5-dien-2,3-diyl)bisphosphonate (IIa). Yield 87% (3.24 g), mp 134–136°C (0.1 mmHg). ^{1}H NMR spectrum, δ, ppm: 3.65 d (12H, CH_3OP, $^{3}J_{HP}$ 12.0 Hz), 6.13 s (2H, CH), 6.97 d (2H, CH=, $^{3}J_{HH}$ 5.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 52.83 d (CH_3OP, $^{2}J_{CP}$ 5.8 Hz), 85.44 d.d (CH, $^{2}J_{CP}$ 16.2, $^{3}J_{CP}$ 6.5 Hz), 141.28 d (CH=, $^{3}J_{CP}$ 12.7 Hz), 155.38 d.d (CP, $^{1}J_{CP}$ 205.7, $^{2}J_{CP}$ 15.4 Hz). ^{31}P NMR spectrum: δ_P 13.39 ppm. Mass spectrum (HRMS-ESI), *m*/*z*: 333.1695 $[M + Na]^+$ (calculated for $C_{10}H_{16}O_7P_2Na$: 333.1666).

Dimethyl (3-chloro-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-yl)phosphonate (IIb). Yield 91% (2.54 g), mp 80–83°C (0.1 mmHg). ^{1}H NMR spectrum, δ, ppm: 3.34 d (6H, CH_3OP, $^{3}J_{HP}$ 13.6 Hz), 4.90 br.s (1H, CH), 5.32 br.s (1H, CH), 6.84–6.88 m (2H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 52.25 d (CH_3OP, $^{2}J_{CP}$ 4.7 Hz), 85.90 d (CH, $^{2}J_{CP}$ 13.5 Hz), 87.60 d (CH, $^{3}J_{CP}$ 12.9 Hz), 134.70 d (CP, $^{1}J_{CP}$ 211.4 Hz), 140.86 (CH=), 144.65 (CH=), 164.10 d (CCl, $^{2}J_{CP}$ 5.4 Hz). ^{31}P NMR spectrum: δ_P 12.64 ppm. Mass spectrum (HRMS-ESI), *m*/*z*: 259.5738 $[M + Na]^+$ (calculated for $C_8H_{10}ClO_4PNa$: 259.5786).

Tetramethyl (1-methyl-7-oxabicyclo[2.2.1]hept-2,5-dien-2,3-diyl)bisphosphonate (IIIa). Yield 75% (2.26 g), mp 138–140°C (0.1 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.40 br.s (3H, CH_3), 3.57 d (12H, CH_3OP, $^{3}J_{HP}$ 12.7 Hz), 6.24 br.s (2H, CH), 6.71 d (1H, CH=, $^{3}J_{HH}$ 4.8 Hz), 7.05 t (1H, CH=, $^{3}J_{HH}$ 4.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.67 d and 53.86 d (CH_3OP, $^{2}J_{CP}$ 6.0 Hz), 86.13 d.d (CH, $^{2}J_{CP}$ 14.0, $^{3}J_{CP}$ 6.2 Hz), 93.45 d.d (C, $^{2}J_{CP}$ 13.8, $^{3}J_{CP}$ 6.5 Hz), 142.67 d and 145.78 d (CH=, $^{3}J_{CP}$ 12.5 Hz), 147.29 d.d (CP, $^{1}J_{CP}$ 210.7, $^{2}J_{CP}$ 15.8 Hz). ^{31}P NMR spectrum: δ_P 12.76 ppm. Mass spectrum (HRMS-ESI), *m*/*z*: 347.1962 $[M + Na]^+$ (calculated for $C_{11}H_{18}O_7P_2Na$: 347.1932).

Dimethyl (1-methyl-3-chloro-7-oxabicyclo[2.2.1]-hepta-2,5-dien-2-yl)phosphonate (IIIb). Yield 75% (2.26 g) [together with the isomer **IVb**, content 78%], mp 84–87°C (0.1 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.45 br.s (3H, CH_3), 3.28 d (12H, CH_3OP, $^{3}J_{HP}$ 12.0 Hz), 4.73 m (1H, CH), 6.56 d (1H, CH=, $^{3}J_{HH}$ 4.0 Hz), 6.76 t (1H, CH=, $^{3}J_{HH}$ 4.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.36 br.s (CH_3), 52.14 d (CH_3OP, $^{2}J_{CP}$ 6.0 Hz), 86.89 d (CH, $^{3}J_{CP}$ 12.1 Hz), 94.97 d (CCH_3, $^{2}J_{CP}$ 14.1 Hz), 135.80 d (CP, $^{1}J_{CP}$ 207.3), 141.89 (CH=), 147.50 (CH=), 165.86 br.s (CCl). ^{31}P NMR spectrum: δ_P 13.16 ppm. Mass spectrum (HRMS-ESI), *m*/*z*: 273.6039 $[M + Na]^+$ (calculated for $C_9H_{12}ClO_4PNa$: 273.6052).

Dimethyl (4-methyl-3-chloro-7-oxabicyclo[2.2.1]-hepta-2,5-dien-2-yl)phosphonate (IVb). Yield 75% (2.26 g) [together with the isomer **IIIb**, content 22%], mp 84–87°C (0.1 mmHg). ^{1}H NMR spectrum, δ, ppm: 1.28 br.s (3H, CH_3), 3.33 d (12H, CH_3OP, $^{3}J_{HP}$ 12.0 Hz), 5.16 m (1H, CH), 6.34 d (1H, CH=, $^{3}J_{HH}$ 5.1 Hz), 6.78 t (1H, CH=, $^{3}J_{HH}$ 5.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 19.96 (CH_3), 53.14 d (CH_3OP, $^{2}J_{CP}$ 5.6 Hz), 84.27 d (CH, $^{2}J_{CP}$ 14.1 Hz), 93.89 d (CCH_3, $^{3}J_{CP}$ 12.0 Hz), 135.49 d (CP, $^{1}J_{CP}$ 210.3), 143.94 (CH=), 145.65 (CH=), 166.37 br.s (CCl). ^{31}P NMR spectrum: δ_P 12.72 ppm. Mass spectrum (HRMS-ESI), *m*/*z*: 273.6039 $[M + Na]^+$ (calculated for $C_9H_{12}ClO_4PNa$: 273.6052).

^{1}H, ^{13}C and ^{31}P NMR spectra ($CDCl_3$) were recorded on a Bruker Avance 400 spectrometer [400.13 (^{1}H), 100.61 (^{13}C), 161.98 MHz (^{31}P)]. Mass spectra (HRMS-ESI) were registered on a Bruker micrOTOF spectrometer.

ACKNOWLEDGMENTS

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

REFERENCES

1. Tverdomed, S.N., Dogadina, A.V., and Ionin B.I., *Russ. J. Gen. Chem.*, 2006, vol. 76, no. 6, p. 885. DOI: 10.1134/S1070363206060089.
2. Titov, K.S. and Ionin, B.I., *Russ. J. Gen. Chem.*, 2013, vol. 83, no. 11, p. 2122. DOI: 10.1134/S1070363213110315.
3. Rayabarapu, D.K. and Cheng, C.-H., *Acc. Chem. Res.*, 2007, vol. 40, no. 10, p. 971. DOI: 10.1021/ar600021z.
4. Lautens, M., Fagnou, K., and Heibert, S., *Acc. Chem. Res.*, 2003, vol. 36, no. 1, p. 48. DOI: 10.1021/ar010112a.
5. Sera, A., Itoh, J., and Yamaguchi, H., *Tetrahedron Lett.*, 1990, vol. 31, no. 45, p. 6547. DOI: 10.1016/S0040-4039(00)97113-2.
6. Grieco, P., Zelle, R., Liss, R., and Finn, J., *J. Am. Chem. Soc.*, 1983, vol. 105, no. 5, p. 1403. DOI: 10.1021/ja00343a072.
7. Kislukhin, A.A., Higginson, C.J., Hong, V.P., and Finn M.G., *J. Am. Chem. Soc.*, 2012, vol. 134, p. 6491. DOI: 10.1021/ja301491h.
8. Tverdomed, S.N., Roschenthaler, G.-V., Kalinovich, N., Lork, E., Dogadina, A.V., and Ionin, B.I., *J. Fluor. Chem.*, 2008, vol. 129, no. 6, p. 478. DOI: 10.1016/j.jfluchem.2008.02.009.
9. Mahajna, M., Quistad, G.B., and Casida, J.E., *Chem. Res. Toxicol.*, 1996, vol. 9, no. 1, p. 241. DOI: 10.1021/tx950127f.
10. Hall, R.G. and Trippett, Stuart, *Tetrahedron Lett.*, 1982, vol. 23, no. 25, p. 2603. DOI: 10.1016/S0040-4039(00)-87407-9.
11. Acheson, R.M. and Ansell, P.J., *J. Chem. Soc. Perkin Trans. 1*, 1987, p. 1275.