ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 9, pp. 1353–1355. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © N.G. Khusainova, D.I. Samigullin, S.A. Koshkin, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 9, pp. 1379–1381.

SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on his 80th anniversary

Reaction of 3-Methylbuta-1,2-dien-1-ylphosphonates with Benzimidazole and 2-Aminobenzimidazole

N. G. Khusainova, D. I. Samigullin, and S. A. Koshkin

Butlerov Institute of Chemistry, Kazan (Volga Region) Federal University, ul. Kremlevskaya 18, Kazan, 420008 Tatarstan, Russia
e-mail: narkis.khusainova@ksu.ru

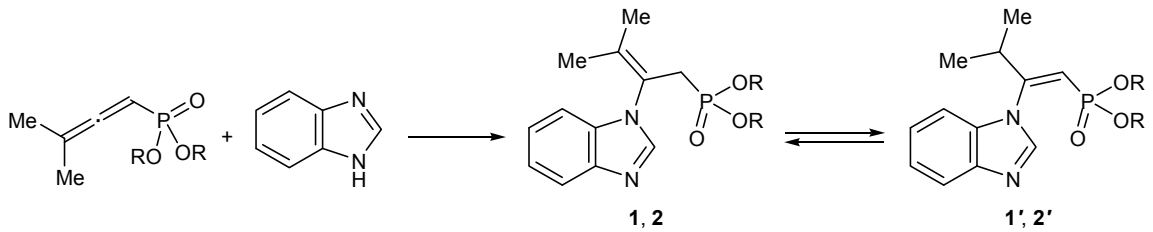
Received April 17, 2015

DOI: 10.1134/S1070428015090262

We previously showed that reactions of allenyl- and vinylphosphonates with imidazole involve addition of the imidazole nitrogen atom to the β-carbon atom of the unsaturated substrate with formation of alkenyl- and alkylphosphonates functionalized with nitrogen-containing pharmacophoric fragment [1]. The addition products were found to exhibit a strong bactericidal activity against such pathogenic microorganisms as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.

While continuing studies in this line we examined the reaction of diethyl and diisopropyl 3-methylbuta-1,2-dien-1-ylphosphonates with benzimidazole and 2-aminobenzimidazole with a view to obtaining new biologically active compounds. An equimolar mixture of diethyl 3-methylbuta-1,2-dien-1-ylphosphonate and benzimidazole was heated for 15 h at 70–75°C, and the upper oily layer was separated and repeatedly washed with hexane until constant n_D^{20} value. We thus isolated compound **1** as a yellow thick oily material. The minor bottom layer was washed in succession with hexane and diethyl ether to isolate unreacted benzimidazole as colorless crystals with mp 169–170°C (published data [2]: mp 171–173°C). The ^{31}P NMR spectrum of **1** contained only one signal at δ_P 24.6 ppm, indicating formation of a single addition product. The following signals were observed in the ^{1}H NMR spectrum of **1**, δ, ppm: 1.07 t (3H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 6.9 Hz), 1.31 t (3H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 7.0 Hz), 1.49 d (3H, CH$_3$C=, $^5J_{PH}$ = 6.0 Hz), 2.00 d (3H, CH$_3$C=, $^5J_{PH}$ = 4.5 Hz), 2.98 d.d (1H, PCH$_2$, $^2J_{PH}$ = 20.7, $^2J_{HH}$ = 15.7 Hz), 3.18 d.d (1H, PCH$_2$, $^2J_{PH}$ = 20.7, $^2J_{HH}$ = 15.7 Hz), 3.98 m (4H, OCH$_2$), 7.30–7.98 m (4H, H$_{arom}$). The presence in the ^{1}H NMR spectrum of doublets of doublets at δ 2.98 and 3.18 ppm with a ^{1}H–^{31}P coupling constant $^2J_{PH}$ of 20.7 Hz, which are typical of methylene group attached to phosphorus, indicated that the benzimidazole nitrogen atom added to the β-carbon atom of 3-methylbuta-1,2-dienylphosphonate with formation of diethyl 2-(1*H*-benzimidazol-1-yl)-3-methylbut-2-en-1-ylphosphonate (**1**). Yield 67%, n_D^{20} = 1.5292. Found, %: C 60.01; H 6.97. $C_{16}H_{23}N_2O_3P$. Calculated, %: C 59.62; H 7.14. Theoretically possible isomerization of adduct **1** into diethyl 2-(1*H*-benz-

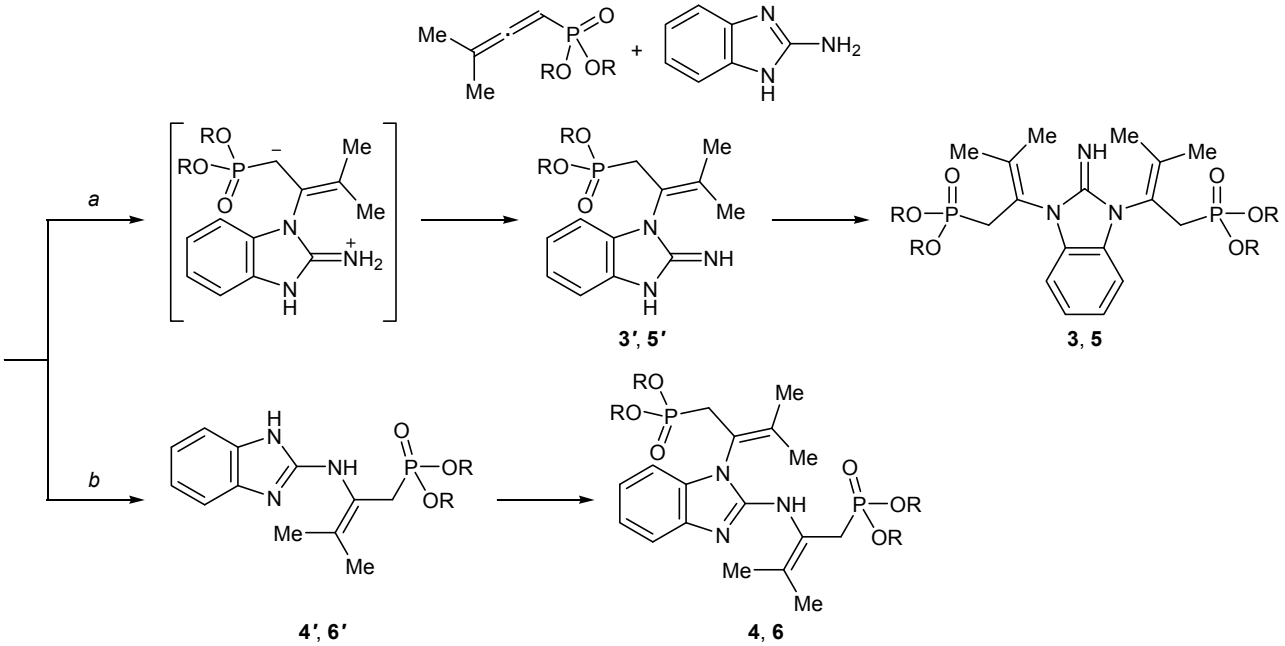
Scheme 1.



1, **2** **1′**, **2′**

1, R = Et; **2**, R = *i*-Pr.

Scheme 2.



3, **4**, R = Et; **5**, **6**, R = *i*-Pr.

imidazol-1-yl)-3-methylbut-1-en-1-ylphosphonate (**1′**) (Scheme 1) can be ruled out taking into account the absence of signals assignable to PCH= and $(CH_3)_2C\mathbf{H}$ protons and nonequivalence of methyl groups at the double C=C bond.

Likewise, benzimidazole reacted with diisopropyl 3-methylbuta-1,2-dien-1-ylphosphonate to produce diisopropyl 2-(1*H*-benzimidazol-1-yl)-3-methylbut-2-en-1-ylphosphonate (**2**). Yield 68%, n_D^{20} = 1.5321. ^{1}H NMR spectrum, δ, ppm: 1.15 d and 1.17 d [3H each, $(C\mathbf{H}_3)_2CHO$, $^3J_{HH}$ = 6.1 Hz), 1.49 d (3H, CH_3C=, $^5J_{PH}$ = 6.0 Hz), 2.02 d (3H, CH_3C=, $^5J_{PH}$ = 4.6 Hz), 2.80 d.d (1H, PCH_2, $^2J_{PH}$ = 20.9, $^2J_{HH}$ = 15.5 Hz), 3.10 d.d (1H, PCH_2, $^2J_{PH}$ = 21.0, $^2J_{HH}$ = 15.5 Hz), 4.58 m [2H, $(CH_3)_2C\mathbf{H}O$], 7.20–7.90 m (4H, H_{arom}). ^{31}P NMR spectrum: δ_P 22.5 ppm. Found, %: C 62.03; H 7.62. $C_{18}H_{27}N_2O_3P$. Calculated, %: C 61.71; H 7.71.

The presence of an amino group in the 2-position enables 2-aminobenzimidazole to react with 3-methylbuta-1,2-dien-1-ylphosphonates along two pathways (Scheme 2) involving addition by the endo- (pathway *a*) or exocyclic nitrogen atom (pathway *b*). By heating an equimolar mixture of diethyl 3-methylbuta-1,2-dien-1-ylphosphonate with 2-aminobenzimidazole until disappearance of the allene stretching vibration band (1955 cm^{-1}) from the IR spectrum of the reaction mixture we obtained a thick oily material whose ^{31}P NMR spectrum contained only one signal at δ_P 26.1 ppm. In the ^{1}H NMR spectrum of the product we observed two doublets at δ 1.53 ($^5J_{PH}$ = 5.0 Hz) and 1.61 ppm ($^5J_{PH}$ = 6.1 Hz) which are typical of protons in two nonequivalent methyl groups linked to an sp^2-carbon atom; also, a signal at δ 2.98 ppm (d.d, $^2J_{PH}$ = 20.3, $^2J_{HH}$ = 15.9 Hz) was present due to methylene protons in the α-position with respect to the phosphorus atom. These findings indicated that the nitrogen atom of benzimidazole added to the central carbon atom of the cumulene system with saturation of the C^1=C^2 bond.

The addition product displayed in the mass spectrum a strong ion peak with *m*/*z* 542.2543, corresponding to the formula $C_{25}H_{41}N_3O_6P_2$ (calculated for $[M + H]^+$: *m*/*z* 542.2543), i.e., it was formed by addition of two phosphonate molecules to one 2-aminobenzimidazole molecule. The mass spectrum of the reaction mixture also contained a low-intensity ion peak with *m*/*z* 338.1628; the calculated elemental composition of that ion, $C_{16}H_{24}N_3O_3P$, matches the 1:1 adduct (calculated for $[M + H]^+$: *m*/*z* 338.1628). We previously showed that 3-methylbuta-1,2-dien-1-ylphosphonate reacts with 2-aminobenzothiazole at the endocyclic nitrogen atom of the latter, and the imine structure of the addition product was unambiguously determined by X-ray analysis [3]. According to the X-ray diffraction data [4], 2-aminobenzimidazole adds to dimethyl propadiene-1,3-dicarboxylate via attack by

the endocyclic nitrogen atom on the central carbon atom of the cumulene system. On the basis of the data of [2, 3] and ^{1}H and ^{31}P NMR and mass spectra, we presumed that diethyl 3-methylbuta-1,2-dien-1-ylphosphonate reacts with 2-aminobenzimidazole at a ratio of 2:1 following pathway *a*, i.e., via addition of two phosphonate molecules to the endocyclic nitrogen atoms of 2-aminobenzimidazole with formation of tetraethyl 2,2′-(2-imino-2,3-dihydro-1*H*-benzimidazole-1,3-diyl)bis(3-methylbut-2-en-1-ylphosphonate) (**3**). Yield 69%, n_D^{20} = 1.5318. ^{1}H NMR spectrum, δ, ppm: 1.09 t (6H, C**H**$_3$CH$_2$O, $^{3}J_{HH}$ = 7.1 Hz), 1.53 d and 1.61 d [3H each, (CH$_3$)$_2$C=, $^{5}J_{pH}$ = 6.1 Hz], 2.98 d.d (2H, PCH$_2$, $^{2}J_{pH}$ = 20.3, $^{2}J_{HH}$ = 15.9 Hz), 3.88 m (4H, CH$_3$C**H**$_2$O), 5.89 br.s (NH), 6.70–7.30 m (4H, H$_{arom}$). ^{31}P NMR spectrum: δ_P 26.1 ppm. The bottom layer of the reaction mixture was a white crystalline solid identified as unreacted 2-aminobenzimidazole, mp 227°C (published data [2]: mp 226–231°C).

Likewise, the reaction of 2-aminobenzimidazole with diisopropyl 3-methylbuta-1,2-dien-1-ylphosphonate afforded tetraisopropyl 2,2′-(2-imino-2,3-dihydro-1*H*-benzimidazole-1,3-diyl)bis(3-methylbut-2-en-1-ylphosphonate) (**5**). Yield 63%, n_D^{20} = 1.5288. ^{1}H NMR spectrum, δ, ppm: 1.14 t [6H, (C**H**$_3$)$_2$CHO, $^{3}J_{HH}$ = 8.1 Hz], 1.51 d (3H, CH$_3$C=, $^{5}J_{PH}$ = 6.0 Hz), 1.60 d (3H, CH$_3$C=, $^{5}J_{PH}$ = 5.9 Hz), 3.0 d.d (2H, PCH$_2$, $^{2}J_{PH}$ = 21.1, $^{2}J_{HH}$ = 6.2 Hz), 4.49 m [2H, (CH$_3$)$_2$C**H**O], 6.70–7.20 m (4H, H$_{arom}$). ^{31}P NMR spectrum: δ_P 25.6 ppm. Found, %: C 57.88; H 8.04. $C_{29}H_{49}N_3O_6P_2$. Calculated, %: C 58.29; H 8.21.

The IR spectra were recorded on a UR-20 spectrometer. The ^{1}H and ^{31}P NMR spectra were measured on a Varian Unity-300 spectrometer at 300 and 121.4 MHz, respectively, using $CDCl_3$ as solvent and reference (for ^{1}H); the ^{31}P chemical shifts were measured relative to 85% H_3PO_4 (external standard). The mass spectra were obtained on an AB Sciex 5600 high-resolution mass spectrometer (electrospray ionization, positive ion detection; voltage 5500 V; nebulizer gas pressure 25 psi; solvent methanol–water, 1:1; TOF MS mode, declustering potential 100 eV, collision energy 10 eV).

This study was funded by the subsidy granted to the Kazan Federal University for the project part of a state assignment in the field of scientific activity.

REFERENCES

1. Khusainova, N.G., Berdnikov, E.A., Mostovaya, O.A., Rybakov, S.M., and Cherkasov, R.A., *Russ. J. Org. Chem*., 2007, vol. 43, p. 1703.
2. *Catalogue of fine Chemicals. Acros Organics*, 2004/2005, p. 1756.
3. Khusainova, N.G., Mostovaya, O.A., Litvinov, I.A., Krivolapov, D.B., Berdnikov, E.A., and Cherkasov, R.A., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, p. 2695.
4. Doad, G.J.S., Okor, D.I., and Scheinmann, F., *J. Chem. Soc., Perkin Trans. 1*, 1988, p. 2993.