Reactions of 1,2-ethanedithiol and 2-mercaptoethanol with unsaturated derivatives of four-coordinate phosphorus acids

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The reaction of 1,2-ethanedithiol with diethyl vinylphosphonate in the presence of EtONa occurs as the addition of the sulfhydryl group to the β-carbon atom of the substrate to give 1 : 1 and 1 : 2 adducts. The nucleophilic addition of 2-mercaptoethanol at the β position of the multiple bond of diethyl vinyl-, diethyl allenyl-, and diethyl prop-1-ynylphosphonates involves only the sulfhydryl group.

Key words: 1,2-ethanedithiol, 2-mercaptoethanol, diethyl vinylphosphonate, diethyl allenylphosphonate, diethyl prop-1-ynylphosphonate, nucleophilic addition, functionalization.

The enhanced reactivity of unsaturated derivatives of four-coordinate phosphorus acids, *viz.*, phosphorylated alkenes, allenes, and alkynes, makes them suitable for the synthesis of various functionalized acyclic and cyclic compounds possessing pronounced biological activities. In particular, the addition reactions of various nucleophilic reagents to these unsaturated derivatives have been studied in detail.[1,2] However, the addition reactions of bifunctional nucleophilic reagents, such as mercaptoalkanols and dithiols, remain virtually uninvestigated. Recently, we have demonstrated[3] that 3,3-disubstituted allenylphosphonates readily react with 1,2-ethanedithiol in the presence of EtONa to form both the addition products at the $\pi_{1,2}$-bond of the cumulene involving only one sulfhydryl group of the dithiol and products, whose molecules consist of two phosphorylbutene groups symmetrically linked to each other by the ethylenedithio bridge.

In the present study, we examined the addition of 1,2-ethanedithiol (**1**) and 2-mercaptoethanol (**2**) to diethyl vinyl-, 3,3-dimethylallenyl-, and prop-1-ynylphosphonates in the presence of EtONa.

The reaction of dithiol **1** with vinylphosphonate **3** afforded 1 : 1 and 2 : 1 addition products (**4** and **5**, respectively; see Scheme 1). The ^{1}H NMR spectrum of compound **4** shows multiplets for the protons of the methylene groups, including the —PCH$_2$— group. The presence of the free sulfhydryl group in compound **4** is evidenced by a triplet at δ 1.88 (^3J = 7.9 Hz). In the EI mass spectrum of compound **4**, the molecular ion peak has a low intensity. The most abundant peak belongs to the $C_8H_{18}O_3PS$ ion ([M]$^+$ found, *m/z* 225.071; [M]$^+$ calculated, *m/z* 225.0714) formed upon abstraction of the SH group from the molecular ion. The CI mass spectrum contains an intense peak [MH]$^+$ at *m/z* 259; its exact mass (259.059) corresponds to the formula $C_8H_{20}O_3PS_2$. Based on analysis of the data from the mass spectrum and the ^{1}H NMR spectrum, we assigned the structure of diethyl [2-(2-mercaptoethylthio)ethyl]phosphonate to compound **4**.

Scheme 1

$$\underset{\mathbf{3}}{(EtO)_2P(O)CH{=}CH_2} + \underset{\mathbf{1}}{HSCH_2CH_2SH} \longrightarrow$$

$$\longrightarrow \underset{\mathbf{4}}{(EtO)_2P(O)CH_2CH_2SCH_2CH_2SH} +$$

$$+ \underset{\mathbf{5}}{[(EtO)_2P(O)CH_2CH_2SCH_2{-}]_2}$$

The ^{1}H NMR spectrum of compound **5** shows signals for the protons of the methylene groups bound to the P and S atoms, whereas the signal for the proton of the sulfhydryl group is absent. The EI mass spectrum of

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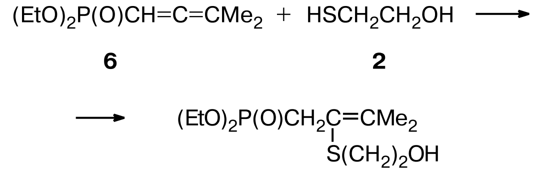
compound **5** has a molecular ion peak ($[M]^+$ found, *m/z* 422.112; $[M]^+$ calculated, *m/z* 422.1116), which corresponds to the molecular formula $C_{14}H_{32}O_6P_2S_2$. The ion at *m/z* 225 with the maximum intensity is apparently formed upon abstraction of the $C_6H_{14}O_3PS$ fragment (*m/z* 197) from the molecular ion. Based on these data, it can be stated that compound **5** has the structure of 2,2´-ethylenedithiodi(diethyl ethylphosphonate).

Earlier, we have prepared analogous mono- and bis-addition products[3] by the reaction of 1,2-ethanedithiol with allenylphosphonate.

Unlike dithiol **1**, 2-mercaptoethanol (**2**) contains two different nucleophilic reaction centers, *i.e.*, the formation of addition products involving each of these centers is theoretically possible. The reaction of diethyl 3-methylbuta-1,2-dienylphosphonate (**6**) with an equimolar amount of 2-mercaptoethanol (**2**) in the presence of EtONa afforded only addition product **7**. In its IR spectrum, a band at 1955 cm^{-1} corresponding to stretching vibrations of the allene triad is absent. The IR spectrum shows a broad intense band at 3400 cm^{-1} characteristic of absorption of the OH group. In the ^1H NMR spectrum of compound **7**, a signal for the sulfhydryl proton is absent; the singlet at δ 3.85 belongs to the proton of the OH group. The doublet for the protons of the methylene group at the P atom (δ 3.07, $^2J_{P,H} = 21.6$ Hz) and the signals for the protons of two Me groups at the sp^2-hybridized C atoms are indicative of the formation of diethyl [2-(2-hydroxyethylthio)-3-methylbut-2-enyl]phosphonate (**7**) (Scheme 2). The ^{31}P NMR spectrum of adduct **7** shows the only signal at δ 27.8.

Scheme 2



$$(EtO)_2P(O)CH{=}C{=}CMe_2 + HSCH_2CH_2OH \longrightarrow (EtO)_2P(O)CH_2\underset{\displaystyle S(CH_2)_2OH}{\underset{|}{C}}{=}CMe_2$$

6 **2** **7**

In the mass spectrum of adduct **7**, the molecular ion peak corresponds to the formula $C_{11}H_{23}O_4PS$ ($[M]^+$ found, *m/z* 282.105; $[M]^+$ calculated, *m/z* 282.1055). The ion at *m/z* 126 corresponding to the formula $C_7H_{10}S$ ($[M]^+$ found, *m/z* 126.051; $[M]^+$ calculated, *m/z* 126.0503) is generated from the ion at *m/z* 264 ($[M]^+ - H_2O$) as a result of the cleavage of the P—C bond located at the β position with respect to the double bond, which is, as a consequence, less strong. The process is accompanied by migration of the H atom to the neutral fragment.

Regioselectivity of the addition of 2-mercaptoethanol (**2**) is retained in the reaction with vinylphosphonate **3**. A triplet of the sulfhydryl group is absent, whereas a broadened signal at δ 3.42 corresponding to the proton of the OH group is present in the ^1H NMR spectrum of adduct **8**, and an intense band at 3400 cm^{-1} (OH) is observed in the IR spectrum. These facts are indicative of the involvement of the SH group of mercaptoethanol **2** in the addition at the double bond of vinylphosphonate **3**. The integral intensity ratio of the signals for the protons in the ^1H NMR spectrum of adduct **8** confirms that the addition occurs with the involvement of the SH group to form diethyl [2-(2-hydroxyethylthio)ethyl]phosphonate (**8**) (Scheme 3). The mass spectrum of compound **8** has a molecular ion peak corresponding to the formula $C_8H_{19}O_4PS$ ($[M]^+$ found, *m/z* 242.077; $[M]^+$ calculated, *m/z* 242.0742). In the EI mass spectrum, the most abundant peak belongs to the ion with the composition $C_8H_{17}O_3PS$ ($[M]^+$ found, *m/z* 224.064; $[M]^+$ calculated, *m/z* 224.0636), which appears as a result of elimination of the water molecule from the molecular ion.

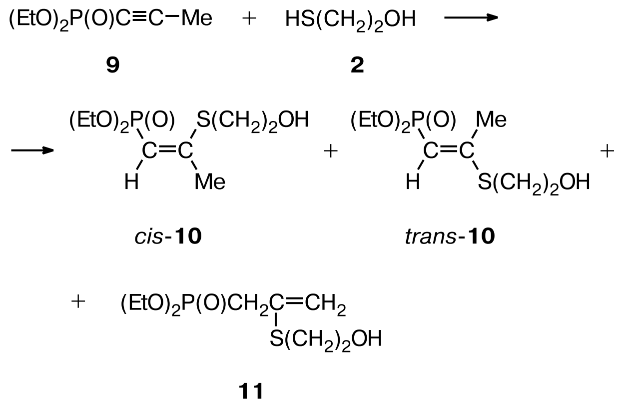
Scheme 3

$$\underset{\mathbf{3}}{(EtO)_2P(O)CH{=}CH_2} + \underset{\mathbf{2}}{HSCH_2CH_2OH} \longrightarrow$$

$$\longrightarrow \underset{\mathbf{8}}{(EtO)_2P(O)CH_2CH_2SCH_2CH_2OH}$$

The reaction of diethyl prop-1-ynylphosphonate (**9**) with an equimolar amount of 2-mercaptoethanol (**2**) afforded several addition products. The ^{31}P NMR spectrum of the reaction mixture shows three signals at δ 16.5, 17.4, and 26.2 in a ratio of 3 : 6.5 : 1. In the IR spectrum of the mixture, an absorption band at 2210 cm^{-1} characteristic of the triple bond is absent. A broad band at 3200 cm^{-1} corresponds to stretching vibrations of the OH group. Based on comparison of the integral intensities of the signals in the ^1H and ^{31}P NMR spectra of the reaction mixture, the signal at δ_P 17.4 was assigned to the P atom in diethyl 2-(2-hydroxyethylthio)prop-1-enylphosphonate (**10**), in which the thioorganyl and phosphoryl groups are in *trans* positions with respect to the double bond. This is evidenced by the coupling constant of the protons of the Me group at the sp^2-hybridized C atom with the P atom (*cis*-$^4J_{P,H} = 3.05$ Hz). It is known[4,5] that, depending on the spatial arrangement of the P atom and the Me group relative to the plane of the C=C bond, the coupling constants of the protons of the Me group with the P atom vary in a range of *cis*-$^4J_{P,H}$ = 2.9—8.3 Hz > *trans*-$^4J_{P,H}$ = 0—2.5 Hz. The signal at δ_P 16.5 belongs to adduct **10** with the *cis*-arranged phosphoryl- and sulfur-containing groups (*trans*-$^4J_{P,H} = 1.1$ Hz). In addition, the ^1H NMR spectrum of the reaction mixture has low-intensity signals belonging to the methylene protons, which are in a geminal position with respect to the P atom, and two doublets for two nonequivalent protons at the sp^2-hybridized C atom (compound **11**). In the ^{31}P NMR spectrum, the signal at δ_P 26.14 corresponds to compound **11**. According to the ^{1}H and ^{31}P NMR spectroscopic data, compound **11** has the structure of diethyl 2-(2-hydroxyethylthio)allylphosphonate. Apparently, the unexpected formation of prop-2-ene **11** is attributable[6] to partial isomerization of prop-1-ene **10** (Scheme 4).

Scheme 4



Hence, the reactions of 1,2-ethanedithiol and 2-mercaptoethanol with unsaturated derivatives of four-coordinate phosphorus acids provide a convenient approach to the synthesis of new organophosphorus compounds functionalized with thioorganyl groups.

Experimental

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 (300 and 121.42 MHz, respectively). The ^{1}H NMR chemical shifts were determined in $CDCl_3$ relative to Me_4Si as the internal standard, and the ^{31}P NMR chemical shifts were measured relative to 85% H_3PO_4 as the external standard. The mass spectra were obtained on a MAT-212 mass spectrometer (ionizing voltage was 60 eV, emission current was 0.1 mA, direct inlet of the sample into the ion source, a gradual increase in the temperature of the evaporator). The exact masses for the ions were determined by peak matching at 10000 resolution. All operations were carried out under argon.

Reaction of vinylphosphonate 3 with 1,2-ethanedithiol (1). A saturated solution of EtONa in EtOH (four—five drops) was added to a mixture of phosphonate **3** [7] (3.41 g, 0.021 mol) and dithiol **1** (1.89 g, 0.020 mol). The reaction mixture warmed up to 107 °C. Then the mixture was kept at 85—95 °C for 2 h until the band in the IR spectrum at 1640 cm^{-1} (C=C) disappeared. Vacuum distillation afforded compounds **4** and **5**.

Compound 4. The yield was 2.28 g (43%), b.p. 105—107 °C (0.06 Torr), n_D^{20} 1.5058. MS, m/z (I_{rel} (%)): 259 $[M + H]^+$ (4), 258 $[M]^+$ (1), 225 $[M - SH]^+$ (100). ^{1}H NMR, δ: 1.48 (t, 6 H, $\underline{H}_3$CH$_2$OP, ^3J = 7.1 Hz); 1.88 (t, 1 H, HS, ^3J = 7.9 Hz); 2.18 (m, 2 H, PCH$_2$); 2.92 (m, 6 H, CC$\underline{H}_2$SC$\underline{H}_2$C$\underline{H}_2$S); 4.26 (m, 4 H, CH$_3$C$\underline{H}_2$OP).

Compound 5. The yield was 1.39 g (31%), b.p. 204—205 °C (0.06 Torr), n_D^{20} 1.4935. MS, m/z (I_{rel} (%)): 422 $[M]^+$ (9), 225 $[M - C_6H_{14}O_3S]^+$ (100). ^{1}H NMR, δ: 1.49 (t, 12 H, C$\underline{H}_3$CH$_2$OP); 2.19 (m, 4 H, PCH$_2$); 2.92 (s, 4 H, SCH$_2$CH$_2$S); 2.95 (m, 4 H, PCCH$_2$S); 4.28 (m, 8 H, CH$_3$C$\underline{H}_2$OP).

Reaction of buta-1,2-dienylphosphonate 6 with 2-mercaptoethanol (2). The reaction of phosphonate **6** [8] (3.74 g, 0.018 mol) with 2-mercaptoethanol (**2**) (1.43 g, 0.018 mol) was carried out under the above-described conditions. The reaction mixture was kept at 85—95 °C until the stretching vibration of the allene triad in the IR spectrum (1955 cm^{-1}) disappeared and then distilled. The yield of compound **7** was 3.21 g (62%), b.p. 127—128 °C (0.07 Torr), n_D^{20} 1.5012. MS, m/z (I_{rel} (%)): 282 $[M]^+$ (9), 126 (100). ^{1}H NMR, δ: 1.44 (t, 6 H, C$\underline{H}_3$CH$_2$OP, $^3J_{H,H}$ = 7.1 Hz); 1.98 (d, 3 H, CH$_3$C=, $^5J_{P,H}$ = 4.1 Hz); 2.14 (d, 3 H, CH$_3$C=, $^5J_{P,H}$ = 6.0 Hz); 2.98 (t, 2 H, CH$_2$S, $^3J_{H,H}$ = 5.9 Hz); 3.07 (d, 2 H, CH$_2$P, $^2J_{P,H}$ = 21.6 Hz); 3.79 (t, 2 H, CH$_2$O, $^3J_{H,H}$ = 6.0 Hz); 3.85 (s, 1 H, OH); 4.24 (m, 4 H, CH$_3$C$\underline{H}_2$OP).

Reaction of vinylphosphonate 3 with 2-mercaptoethanol (2). Analogously, the reaction of phosphonate **3** (3.28 g, 0.02 mol) with 2-mercaptoethanol (**2**) (1.56 g, 0.02 mol) afforded compound **8** in a yield of 3.1 g (64%), b.p. 138 °C (0.2 Torr), n_D^{20} 1.4890. MS, m/z (I_{rel} (%)): 242 $[M]^+$ (1), 224 (100). ^{1}H NMR, δ: 1.45 (t, 6 H, C$\underline{H}_3$CH$_2$OP, $^3J_{H,H}$ = 7.1 Hz); 2.18 (m, 2 H, PCH$_2$, $^2J_{P,H}$ = 17.3 Hz); 2.86 (t, 2 H, SC$\underline{H}_2$CH$_2$OH, $^3J_{H,H}$ = 6.9 Hz); 2.90 (m, 2 H, PCH$_2$C$\underline{H}_2$S); 3.42 (s, 1 H, OH); 3.86 (t, 2 H, SCH$_2$C$\underline{H}_2$O, $^3J_{H,H}$ = 6.9 Hz); 4.23 (m, 4 H, CH$_3$C$\underline{H}_2$OP).

Reaction of propynylphosphonate 9 with 2-mercaptoethanol (2). Analogously, the reaction of phosphonate **9** [9] (3.52 g, 0.020 mol) wih 2-mercaptoethanol (**2**) (1.56 g, 0.020 mol) afforded compound **10** as a mixture of the *trans* and *cis* isomers. The yield was 3.0 g (59%), b.p. 135—138 °C (0.06 Torr), n_D^{20} 1.5099. Found (%): C, 45.09; H, 8.07. $C_9H_{19}O_3PS$. Calculated (%): C, 45.38; H, 7.98.

Isomer *trans*-10. ^{1}H NMR, δ: 1.46 (t, 6 H, C$\underline{H}_3$CH$_2$OP, $^3J_{H,H}$ = 7.0 Hz); 2.44 (dd, 3 H, CH$_3$C=, *cis*-$^4J_{P,H}$ = 3.05 Hz, *trans*-$^4J_{H,H}$ = 0.75 Hz); 3.10 (t, 2 H, SCH$_2$, $^3J_{H,H}$ = 6.6 Hz); 3.94 (t, 2 H, SCH$_2$C$\underline{H}_2$O, $^3J_{H,H}$ = 6.5 Hz); 3.98 (br.s, 1 H, OH); 4.20 (m, 4 H, CH$_3$C$\underline{H}_2$OP, $^3J_{H,H}$ = 7.0 Hz); 5.42 (br.d, 1 H, PCH=, $^2J_{P,H}$ = 12.6 Hz).

Isomer *cis*-10. ^{1}H NMR, δ: 1.48 (t, 6 H, C$\underline{H}_3$CH$_2$OP, $^3J_{H,H}$ = 7.0 Hz); 2.36 (dd, 3 H, CH$_3$C=, *trans*-$^4J_{P,H}$ = *cis*-$^4J_{H,H}$ = 1.05 Hz); 3.09 (t, 2 H, SCH$_2$, $^3J_{H,H}$ = 5.6 Hz); 3.84 (t, 2 H, SCH$_2$C$\underline{H}_2$O, $^3J_{H,H}$ = 5.6 Hz); 3.98 (br.s, 1 H, OH); 4.26 (m, 4 H, CH$_3$C$\underline{H}_2$OP); 5.92 (br.d, 1 H, PCH=, $^2J_{P,H}$ = 17.2 Hz).

The ^{1}H NMR spectrum of the reaction mixture shows also low-intensity signals of **compound 11** (δ): 1.47 (t, 3 H, CH$_3$C$\underline{H}_2$OP, $^3J_{H,H}$ = 7.0 Hz); 2.91 (dd, 2 H, PCH$_2$, $^2J_{P,H}$ = 21.3 Hz); 3.91 (t, 2 H, SCH$_2$C$\underline{H}_2$O, $^3J_{H,H}$ = 6.1 Hz); 5.21 (br.d, 1 H, HC=C, $^4J_{P,H}$ = 4.7 Hz); 5.49 (br.d, 1 H, HC=C, $^4J_{P,H}$ = 5.4 Hz).

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