ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 7, pp. 1394–1397. © Pleiades Publishing, Ltd., 2019.
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Alkylation of Diethylphosphonoacetic Aldehyde and Triethyl Phosphonoacetate with Ethyl α-Bromopropanoate

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Received November 30, 2018; revised November 30, 2018; accepted January 27, 2019

Abstract—The alkylation reactions of phosphonoacetic aldehyde and ethyl phosphonoacetate with ethyl α-bromopropanoate in DMSO in the presence of K_2CO_3 have been studied.

Keywords: phosphonoacetic aldehyde, ethyl α-bromopropanoate, ethyl phosphonoacetate, 1,3-dichloroacetone, phosphite

DOI: 10.1134/S1070363219070077

α-Phosphorylated carbonyl compounds are interesting from fundamental and practic viewpoints, due to the presence of highly reactive carbonyl and active methylene groups. Systematical investigations of alkylation of phosphorous-substituted CH-acids with mono and polyhalogenoalkanes have been performed over the recent decade [1–4]. The obtained data indicate low yield of alkylation products from phosphonoacetic aldehyde and phosphonoacetates [1, 5, 6]. Thus, detailed study of alkylation of more reactive phosphonoacetic aldehyde and less reactive phosphonoacetates with an active alkylating agent (ethyl α-bromopropanoate) is interesting.

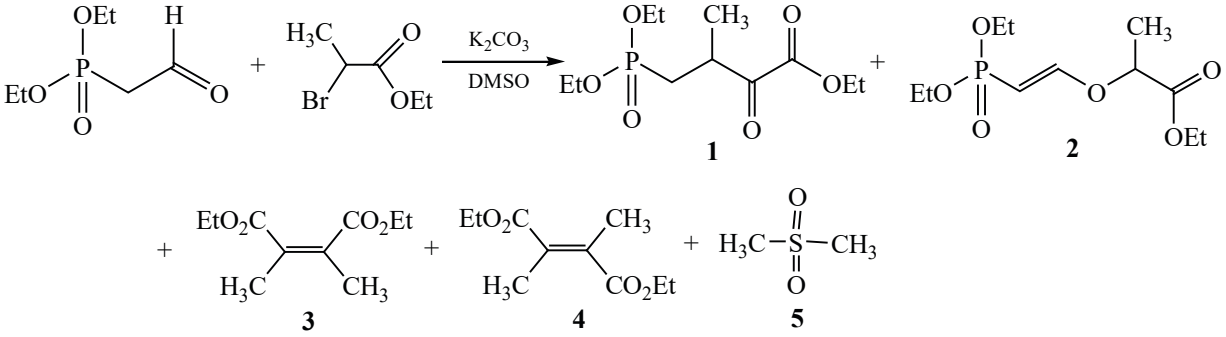
Alkylation of phosphonoacetic aldehyde with ethyl α-bromopropanoate was carried out at relatively low temperature (40–50°C) in dimethylsulfoxide medium in the presence of excess of K_2CO_3. The products of Darzens condensation (**1**), *O*-alkylation (**2**), self-condensation of α-bromopropionate (**3**, **4**), and dimethylsulfone **5** were isolated (Scheme 1).

We suggested that the reaction in alkali medium started with proton elimination from either phosphonoacetic aldehyde (anion **A**) or α-bromopropionate (anion **B**, Scheme 2). The anion **B** condensation with the second α-bromopropionate molecule gave compounds **3** and **4**. The reaction of carbanion **A** with α-bromopropionate led to the formation of insignificant amount of enol ether **2**. The structure of that compound was confirmed by the presence of weak signals at δ 5.0 and 7.1 ppm in ^{1}H NMR spectrum. The formation of compound **1** could be considered a result of the reaction of anion **B** with phosphonoacetic aldehyde via the Darzens reaction (Scheme 3).

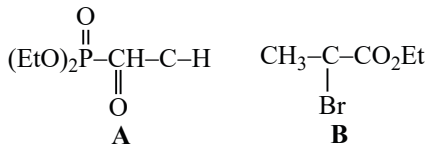
Dimethylsulfone **5** was formed as a result of the reaction of DMSO with phosphonoacetic aldehyde. Spectral, physical, and chemical constants of the obtained sulfone were identical to those described in [7].

Detailed investigation of those reactions led to conclusion that low yield of the alkylation products was caused by self-condensation of phosphonoacetic aldehyde under

Scheme 1.



Scheme 2.



A **B**

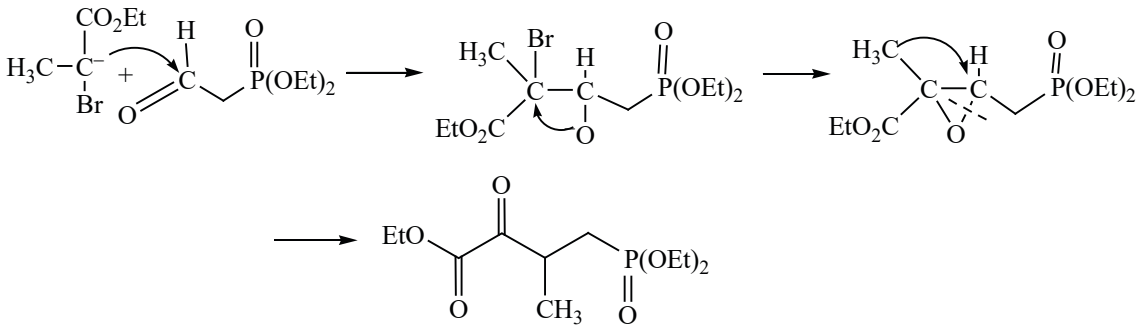
the action of DMSO (the reaction medium). Apparently, nucleophilic attack of carbanion **A** on the phosphorous atom of the second phosphonoacetic aldehyde molecule resulted in the formation of intermediate **C**, decomposition of which led to bis(diethoxyphosphoryl)acetic aldehyde **6** (Scheme 4).

The reaction of triethyl phosphonoacetate with ethyl α-bromopropanoate in the presence of large excess of K_2CO_3 in DMSO was also investigated. The analysis of the reaction products (either raw or purified) did not reveal the formation of an alkylation product. Anhydride of tetraethyl phosphonoacetate **7** and diethyl dimethylmaleinate (**3**) and diethyl dimethylfumarate (**4**) were isolated from the reaction mixture (Scheme 5).

Probably, self-condensation of active α-bromopropionate occurred at low temperature with the formation of compounds **3** and **4**. At higher temperature (70–80°C), unreacted phosphonoacetate was condensed at the phosphorous atom of the second phosphonoacetate molecule, forming product **7** due to nucleophilic properties of the phosphoryl group [8] (Scheme 6).

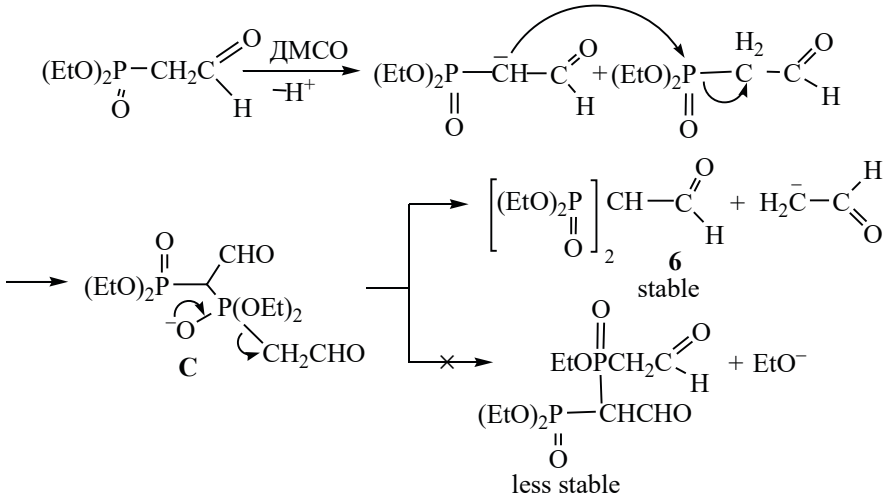
It was also interesting to investigate the reactions of the phosphorylated ketones with α-bromopropanoate in view of preparation of the $(EtO)_2P(O)CH_2C(O)CH_2P(O)(OEt)_2$ phosphorylated ketones via the Arbuzov reaction of 1,3-dichloroacetone with 2 eq. of triethyl phosphite. However, it was shown that the mentioned reaction in toluene occurred as the Perkov reaction with the formation of phosphate. Then, the second chlorine atom in the obtained phosphate was substituted with an ethoxy group

Scheme 3.

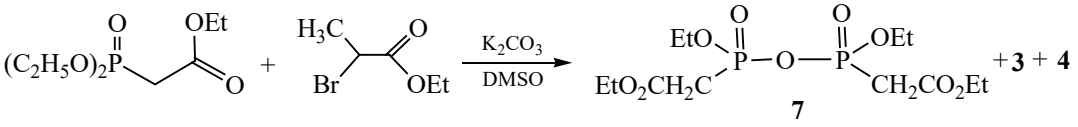


1

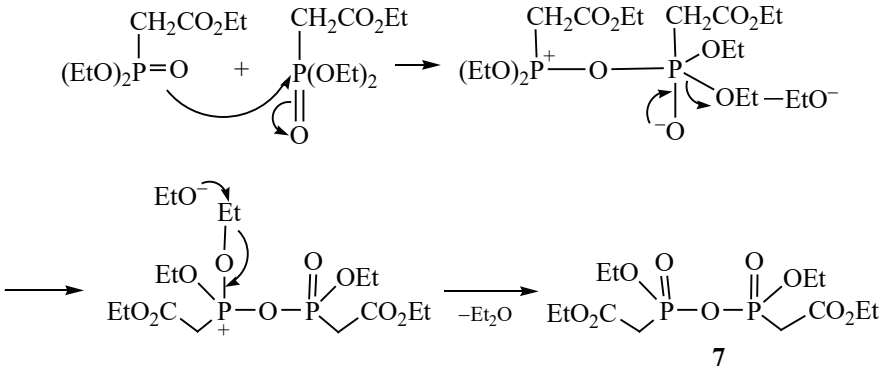
Scheme 4.



Scheme 5.



Scheme 6.



under the action of the second equivalent of phosphite. Finally, compound **8** was formed (Scheme 7).

In summary, we figured out that alkylation of phosphonoacetic aldehyde with ethyl α-bromopropanoate in DMSO in the presence of K_2CO_3 led to the formation of the products of *O*-alkylation, Darzens condensation, and self-condensation of ethyl α-bromopropanoate (diethyl dimethylmaleinate, diethyl dimethylfumarate), as well as dimehylsulfone. Some amount of phosphonoacetic aldehyde was condensed to form bis(diethoxyphosphoryl) acetic aldehyde under the reaction conditions. It was shown that alkylation of ethyl phosphonoacetate with α-bromoprapanoate led also to the product of self-condensation of ethyl α-bromopropanoate and phosphonoacetate. The reaction of 1,3-dichloroacetone with phosphite occurred as the Perkov reaction followed by the substitution of chlorine atom with ethoxy group.

EXPERIMENTAL

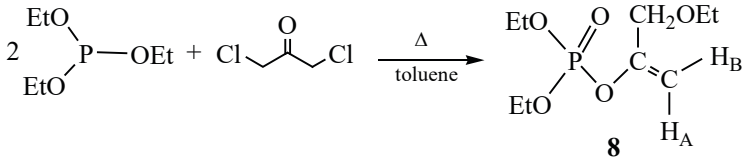
^{1}H and ^{13}C NMR spectra in DMSO-d_6 were registered using a Bruker AV-300 device [300 (^{1}H) and 75 (^{13}C) MHz]; TMS was used as internal reference. Melting points were measured using an SMP 30 device.

Reaction of phosphonoacetic aldehyde with ethyl α-bromopropanoate. A mixture of 5 g (0.03 mol) of phoshomoacetic aldehyde, 4.6 g of K_2CO_3, and 5.3 g (0.03 mol) of ethyl α-bromopropanoate in 30 mL of DMSO was stirred for 4 h at 40–50°C. The mixture was cooled down, treated with water, and extracted with diethyl ether (3×50 mL). Ether was distilled off, the crystalline precipitate was filtered off, and the filtrate was distilled. The first fraction was **diethyl dimethylmaleinate (3)**. Yield 1.72 g (22%), mp 96–98°C (6 mmHg), n_D^{20} 1.4495 [9]. ^{1}H NMR spectrum, δ, ppm: 1.18 t (6H, $\underline{C}H_3CH_2$, J = 7.1 Hz), 2.54 s (6H, CH_3C=), 4.06 q (4H, CH_2O, J = 7.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.56 (CH_3), 20.82 (C=), 60.48 (CH_2O), 171.03 (COO).

The second fraction was **diethyl dimethylfumarate (4).** Yield 2.1 g (24%), bp 105°C, mp 62°C, n_D^{20} 1.4457 [10].

The third fraction was **ethyl 3-methyl-4-diethoxyphosphoryl-2-oxobutanoate (1).** Yield 1.8 g (16.8%), bp 120°C (2 mmHg), n_D^{20} 1.4287. ^{1}H NMR spectrum, δ, ppm: 1.17–1.22 m (9H, CH_3, J = 6.9 Hz), 1.24 d (3H, $C\underline{H}_3CH$, J = 6.9 Hz), 1.75 q (1H, $\underline{C}HCH_3$, J = 6.9 Hz), 2.8 d. d (2H, PCH_2, $^3J_{HH}$ = 7.4, $^2J_{HP}$ = 21.3 Hz), 3.95 q

Scheme 7.



(2H, OCH_2, J = 6.6 Hz), 4.08 m (4H, $POCH_2$). ^{13}C NMR spectrum, δ_C, ppm: 6.40 d ($\underline{C}H_3CH$, $^3J_{CP}$ = 8.9 Hz), 14.42 (CH_3), 16.56 d ($\underline{C}H_3CH_2O$, $^3J_{CP}$ = 6.8 Hz), 21.49 d (PCH_2, $^1J_{CP}$ = 150.6 Hz), 40.77 d (CH, $^2J_{CP}$ = 7.2 Hz) 60.83 (OCH_2), 61.60 d (CH_2OP, $^2J_{CP}$ = 6.0 Hz), 167.22 (COO), 192.06 ($CH\underline{C}OCO$). Found, %: C 51.24; H 8.67; P 11.45. $C_{11}H_{21}PO_6$. Calculated, %: C 49.81; H 8.30; P 11.70.

The colorless crystals were **dimethylsulfone (5).** Yield 2.4 g (27.6%), mp 109°C. ^1H NMR spectrum, δ, ppm: 2.84 s.

Synthesis of diethyl dimethylmaleinate (3) and diethyl dimethylfumarate (4) from ethyl α-bromopropanoate. A mixture of 10 g (0.05 mol) of ethyl α-bromopropanoate, 15.3 g of K_2CO_3, and 40 mL of DMSO was stirred for 10 h at 40–50°C. The mixture was cooled down, treated with water, and extracted with diethyl ether. Ether was distilled off, and the crystals of **diethyl dimethylfumarate (4)** were filtered off. The filtrate was **diethyl dimethylmaleinate (3).**

Bis(diethylphosphoryl)acetic aldehyde (6). A mixture of 5 g (0.03 mol) of phosphonoacetic aldehyde and 5 mL of DMSO was heated at 60°C for 10 h. The mixture was cooled down, treated with water, and extracted with diethyl ether. Ether was distilled off, and the residue was distilled. Yield 3.4 g (68%), bp 150–153°C (2 mmHg), n_D^{20} 1.4300. ^1H NMR spectrum, δ, ppm: 1.15 t (12H, CH_3, J = 6.9 Hz), 2.95 d. d (1H, CH, $^3J_{HH}$ = 3.3, $^2J_{HP}$ = 21.9 Hz), 3.88–4.02 m (8H, CH_2O), 9.46 d. t (1H, CHO, $^3J_{HH}$ = 3.3, $^3J_{HP}$ = 2.7 Hz). Found, %: C 37.67; H 7.09; P 19.87. $C_{10}H_{22}P_2O_7$. Calculated, %: C 37.97; H 6.69; P 19.62.

Anhydride of phosphonoacetic acid (7). 3.4 g (0.02 mol) of ethyl α-bromopropanoate was dropwise added to a mixture of 3 g (0.02 mol) of triethyl phosphonoacetate, 2.4 g of K_2CO_3, and 40 mL of DMSO at room temperature. The obtained mixture was stirred for 2–3 h at 40–50°C, then 12 h at 70–80°C. The mixture was cooled down, treated with water, and extracted with diethyl ether (3×50 mL). Ether was distilled off, and the crystals were filtered off and recrystallized from ethyl acetate. Yield 2.5 g (56%), mp 98°C. ^1H NMR spectrum, δ, ppm: 1.17 t (6H, CH_3, J = 8.4 Hz), 1.22 t (6H, CH_3, J = 8.4 Hz), 2.85 d (4H, CH_2P, $^2J_{HP}$ = 22.0 Hz), 3.95 q (4H, CH2O, J = 7.1 Hz) (4H, CH_2O, J = 7.5 Hz), 4.06 q (4H, CH_2O, J = 6.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.41 (CH_3), 16.65 (CH_3), 36.04 d (PCH_2, $^1J_{CP}$ = 131.0 Hz), 60.83 ($COO\underline{C}H_2$), 61.60 d (OCH_2, $^2J_{CP}$ = 6.0 Hz), 167.31 d (COO, $^2J_{CP}$ = 6.3 Hz). Found, %: C 38.21; H 6.76; P 16.26. $C_{12}H_{24}P_2O_9$ Calculated, %: C 38.50; H 6.42; P 16.04.

3-Ethoxy-2-diethoxyphosphoryloxyprop-1-ene (8). A mixture of 6 g (0.2 mol) of triethyl phosphite and 2 g (0.1 mol) of 1,3-dichloroacetone in 10 mL of toluene was refluxed for 10 h, cooled down, and distilled. Yield 5.3 g (68.7%), bp 128–130°C (2 mm Hg), n_D^{20} 1.4307. ^1H NMR spectrum, δ, ppm: 1.22 t (3H, CH_3, J = 7.2 Hz), 1.27 t (6H, CH_3, J = 7.2 Hz), 3.98 q (2H, CH_2O, J = 7.5 Hz), 4.05 q (4H, CH_2O, J = 6.9 Hz), 4.27 s (2H, OCH_2), 4.97 d. d ($1H_A$, $C{=}CH_A$, $^2J_{HH}$ = 2.4, $^4J_{HP}$ = 2.1 Hz), 5.06 d. d ($1H_B$, $C{=}CH_B$, $^2J_{HH}$ = 2.4, $^4J_{HP}$ = 1.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.14, 16.22, 16.32 ($3CH_3$), 44.63 d (CH_2, $^3J_{CP}$ = 8.3 Hz), 63.40 d ($CH_3\underline{C}H_2OP$, $^2J_{CP}$ = 5.9 Hz), 64.71 (OCH_2), 101.6 d (C=, $^3J_{CP}$ = 3.8 Hz), 150.63 d (=CO, $^2J_{CP}$ = 8.3 Hz). Found, %: C 45.54; H 7.78; P 13.16. $C_9H_{19}O_5P$. Calculated, %: C 45.37; H 7.9; P 13.02.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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