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FACTORS AFFECTING THE DIRECTION AND YIELD OF ALKYLATION REACTIONS OF A-PHOSPHORYLCARBONYL COMPOUNDS WITH HALOCARBONYL DERIVATIVES

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ABSTRACT
The article presents the results of studies on the alkylation of α-phosphorylated carbonyl compounds with halide carbonyl derivatives. The influence of the nature of the reagents and solvents is established. The results of an in-depth study of the alkylation reaction of the more reactive phosphonoacetic aldehyde and the less reactive phosphonoacetates are presented. It is noted that the reaction direction depends on the reaction conditions, and the low yield of the target products is due to the self-condensation of the reagents under the reaction conditions. It was revealed that alkylation of the above reactions in the presence of Na in toluene forms only C-alkylation products. Differences in the direction of the alkylation reaction depending on the choice of reaction conditions are also noted. It is noted that hydrolysis of diethyl acetal with 3% HCl leads to the formation of dialdehyde, which is converted into the corresponding furan under the reaction conditions. It was also established that diacetal at temperatures above 200°C undergoes alcohol elimination, which occurs selectively from the acetal fragment located closer to phosphorus in the compound.

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1. INTRODUCTION

Among the numerous classes of organic compounds, carbonyl compounds occupy a special place. They are widespread both in nature and in industry and play an important role in the biochemical processes of living organisms.

The chemical properties of carbonyl compounds are largely determined by the structure of the carbonyl group, which determines their high reactivity and ability to enter into a variety of chemical reactions [1-9].

The presence of a phosphorus fragment gives specific features to the chemical behavior and physicochemical properties of carbonyl compounds.

In [10-13], it was shown that phosphorylated compounds with an active methylene group undergo alkylation reactions characteristic of 1,3-dicarbonyl compounds. However, the replacement of the carbonyl group with a phosphorylated functional unit leads to the appearance of various features in the chemical properties of these compounds [14-17].

Systematic studies of the reaction of α-phosphorylated carbonyl compounds with halogenated alkanes have shown that the alkylation reaction involves both the active methylene group and the oxygen atoms of the carbonyl and phosphorylated groups, forming oxygen-containing heterocycles with a phosphorus atom in the ring or side chain [18-20].

That's why it is of prime interest to study the alkylation reaction of phosphoryl carbonyl compounds with halogenated carbonyl derivatives.

2. EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer [operating frequencies of 300 (H) and 75 (C) MHz] using TMS as the internal standard. Elemental analysis was performed on a Carlo Erba 1106 instrument. The purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates. Melting points were determined using an SMP 30 instrument.

General method for the alkylation of α-phosphorylcarbonyl compounds with halogenated compounds. A halogenated compound (20 mmol) was added dropwise with vigorous stirring to a mixture of 20 mmol of phosphorylated carbonyl compounds and 20 mmol of K_2CO_3 in 50 ml of DMSO or DMF. The mixture was stirred for 2 h at room temperature, followed by heating at 60-70°C for an additional 2 h. The reaction mixture was cooled with ice water (5-10 °C), treated with water, and extracted with ether. The extract was dried over Na_2SO_4, the ether layer was removed by distillation, and the residue was distilled under vacuum.

3-oxo-5-diethoxyphosphoryl-2,4-tetrahydroxynan (1). Dark yellow precipitate **1** was obtained from 4 g of phosphonoacetaldehyde and 3.2 g of 1,3-dichloroacetone. Yield 3.2 g (29%), mp 123-125 °C. ^{1}H NMR spectrum ($CDCl_3$), δ ppm: 1.1 t (6H, $2CH_3$, ^{3}JHH 7.2 Hs), 2.3 k (2H, =C-CH_2), 3.9-4.0 m (4H, $2OCH_2$), 4.3 s (2H, OCH_2), 7.20 s (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$): δ ppm 16.24, 19.63, 22.54, 29.54, 46.49, 61.65, 63.64, 98.47, 163.08, 196.79. Found, %: C 54.11; H 7.23; P 16.32.

$C_9H_{16}O_3P$ Calculated, %: C 52.98; H 7.58; P 15.43.

Tetraethyl (2-oxoethane-1,1-diyl)bis(phosphonate) (2). 4 g of diethylphosphonoacetic aldehyde, 9 g of K_2CO_3 in 50 ml of DMF were heated for 12 h at 80 °C. The reaction mixture was cooled, treated with water and extracted with ether. The extract was dried with Na_2SO_4, the ether portion was distilled off, the residue was distilled under vacuum, after which product 2 was obtained. Yield 3.4 g (61%), bp 146-148 °C (2 mm Hg), n_D^{20} 1.4310. ^{1}H NMR spectrum ($CDCl_3$) δ ppm: 1.08-1.22 m (12H, $4CH_3$), 3.05 k (1H, CH), 3.75 – 4.0 (8H, $4CH_2$), broadened s (1H, CH). Found, %: C 37.67; H 7.09; R 19.87. $C_{10}H_{22}O_7P_2$ Calculated, %: C 37.97: H 6.69; R 19.62.

Diethyl vinyl phosphate (4). Under similar conditions in the presence of DMSO, **4** is formed. Yield 0.8 g (14%), bp. 132-135 °C. ^{1}H NMR spectrum ($CDCl_3$) δ ppm: 1.25 m (6H, $2CH_3$), 4.46 m (4H, $2OCH_2$), 5.91 m (2H, 2CH=), 6.15 m (1H, CH). Found, %: C 44.23; H 7.06; R 18.67. $C_6H_{13}O_3P$ Calculated, %: C 43.90; H 7.92; R 18.90.

The white powder that precipitated from the solution is dimethyl sulfone. Yield 2.8 g (66%), m.p. 109-111°C.

β-(2,2-Diethoxy-1-ethyloxy)vinylphosphonate (5). 6.5 g of bromoacetaldehyde diethyl acetal was added with stirring to a mixture of 8 g of phosphonoacetaldehyde, 6 g of K_2CO_3 in 50 ml of DMF at room temperature. The mixture was stirred at 60 °C for 5 hours, cooled, treated with water and extracted with ether. The extract was dried over Na_2SO_4. After distilling off the ether

portion, a liquid mass with crystals was formed. The liquid portion was separated and distilled under vacuum, obtaining **5**. Yield 2.2 g (21%), bp 123-125 °C (2 mmHg), n_D^{20} 1.4480. ^{1}H NMR spectrum ($CDCl_3$) δ ppm: 0.9 t (6H, $2CH_3$), 1.1-1.2 t (6H, $2CH_3$), 3.6 d (2H, OCH_2), 3.7-4.1 m (8H, $4CH_2O$), 4.8 t (1H, CH), 6.4 q (1H, CH), 7.2 q (1H, CH). Found, %: C 49.11; H 7.65; P 9.05; $C_{12}H_{25}O_6P$ Calculated, %: C 48.64; H 8.44; P 10.47.

Diethyl(4,4-diethoxybutan-2-yl)phosphonate(6). Crystalline part – product **6.** Yield 0.8 g (10%), m.p. 43-44 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 1.1-1.3 m (12H, $4CH_3$), 1.35 m (2H, CH_2), 3.5 m (1H, CH), 4.1-4.2 m (8H, $4OCH_2$), 4.85 t (1H, CH<), 9.2 hp. (1H, CH=O).[3]

General method for the alkylation of α-phosphorus-α-carbonyl compounds. 2-phosphonoacetate in 50 ml of toluene was stirred at 50-60°C for 3-4 hours until complete dissolution. After complete dissolution of the sodium, bromoacetal (100 mmol) was added, the mixture was stirred for 2 hours, the precipitated salt was filtered off, the toluene was removed, and the residue was distilled under vacuum.

Diethyl (1,1,4,4-tetraethoxybutan-2-yl)phosphonate (7). From 3.5 g of diethyl-

phosphonoacetaldehyde diacetal and 3.0 g of bromoacetaldehyde diethyl acetal, **7** was obtained according to the above procedure. Yield 2.6 g (48%), bp 150-151 °C (2 mmHg). NMR ^{1}H (DMSO-d6) δ ppm: 0.9-1.1 m (18H, $6CH_3$), 1.61 (2H, CH_2), 3.2 m (1H, CH), 3.7-4.08 m (12H, $6CH_2$), 4.86 m (2H, 2CH). Found, %: C 52.34; H 9.12; P 9.23 $C_{16}H_{35}O_7P$ Calculated,%: C 51.89; H 9.45; P 8.37

3-diethoxyphosphoryl furan (9). Product **9** was obtained in high yield by hydrolysis of acetals 6,7,8 with 3% HCl at room temperature. Yield 92%, bp 120 °C (1 mmHg), d_4^{20} 1.1082. ^{1}H NMR spectrum ($CDCl_3$) δ ppm: 1.20 m (6H, $2CH_3$), 4.25 m (4H, $2CH_2$=O), 6.34 q (1H, CH), 7.15 d (2H, 2CHO). Found, %: C 47.78; H 6.98; P 14.65. $C_8H_{13}O_4P$ Calculated, %: C 47.05; H 6.37; P 15.19.

Reaction of triethylphosphonoacetate with ethyl α-bromopropionate. To a mixture of 5 g of triethylphosphonoacetate, 10 g of potash in 50 ml DMSO 4 g of ethyl 2-bromopropionate was added with stirring, followed by heating to 70-80 °C for 6 hours. The mixture was cooled, treated with water and extracted with ether, dried over Na_2SO_4. The ether part was distilled off. After distilling off the ether, the crystalline precipitate of diethyl 2,2-(1,1,3-triethoxy-1,3-dioxo-1,3-diphosphoxane-1,3-diyl)diacetate (**10**) was filtered off. Yield 4.1 g (53%), mp 94-95 °C. ^{1}H NMR spectrum ($CDCl_3$) δ ppm: 1.15 t (6H, $2CH_3$), 1.20 t (6H, $2CH_3$), 2.75 d (4H, $2CH_2$), 3.95-4.1 m (4H, $2CH_2$), 4.2 m (4H, $2CH_2$). ^{13}C NMR spectrum ($CDCl_3$) δ ppm: 14.63, 16.85, 34.39; 36.34, 60.80, 61.42, 167.81. Found,%: C 40.34; H 5.78; P 15.44 $C_{14}H_{29}O_{10}P_2$ Calculated,%: C 40.10; H 6.92; R 14.79.

The filtrate was distilled: the first fraction was diethyl ester of dimethylmaleic acid **(11**), the second fraction was ethyl ester of dimethylfumaric acid **(12)** described in [20].

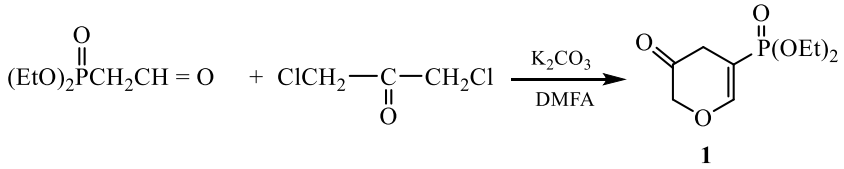
Ethyl 2-diethoxyphosphoryl)-4,4-diethoxybutanoate (13). 4 g of triethylphosphonate and 0.5 g of chopped sodium in 30 ml of toluene were stirred at 60 °C until the metal was completely dissolved, then the mixture was cooled to 10-15 °C and 5 g of bromoacetaldehyde diethyl acetal were added. The mixture was heated to 50-60 °C and stirred for 2-3 hours. It was cooled and filtered; the solvent was distilled off, and the residue was distilled under vacuum. The yield of product **13** was 3.4 g (46%), bp 126-127 °C (2 mmHg), n_D^{20} 1.4390. ^{1}H NMR spectrum (DMSO-d6) δ ppm: 0.9-1.0 m (9H, $3CH_3$), 1.1-1.2 m (6H, $2CH_3$), 1.52 m (2H, CH_2), 3.3 m (1H, CH), 3.7-4.1 m (10H, $5CH_2$), 4.8 t (1H, CH). Found,%: C 48.76; H 7.65; P 9.41 $C_{13}H_{29}O_7P$ Calculated,%; From 49.41; H 8.50; R 9.11.

Diethyl 2-(diethoxyphosphoryl)-3-methylsuccinate (14). Similarly, **14** was obtained from 4 g of triethylphosphonacet and 3 g of ethyl bromopropionate. Yield 5.3 g (48%), bp. 113-115 °C (2 mm

Hg), n_D^{20} 1.4490. ^{1}H NMR spectrum (DMSO-d6) δ ppm: 0.8 d (3H, CH_3), 1.0 t (3H, CH_3), 1.1-1.2 m (6H, $2CH_3$), 2.6 m (1H, CH), 3.1 k (1H, CH), 3.7 m (4H, $2CH_2$), 3.9-4.1 m (4H, $2CH_3$). Found,%: C 48.67; H 7.96; P 9.96 $C_{13}H_{25}O_7P$ Calculated,%: C 48.14; H 7.71; P 9.56

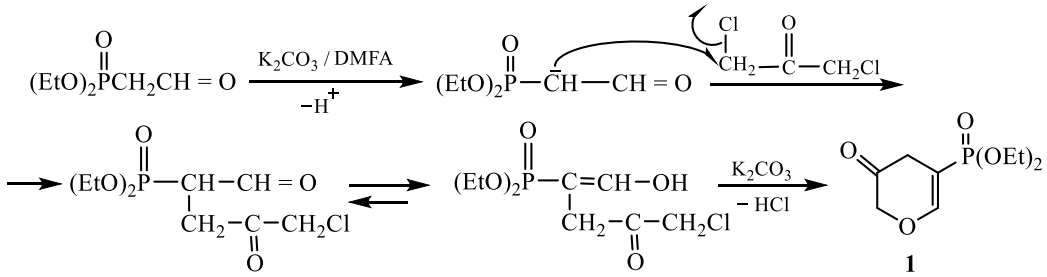
3. RESULT AND DISCUSSION

The condensation reaction of phosphonoacetic aldehyde with 1,3-di-chloroacetone in the presence of potassium carbonate in DMF was studied. An oxinane derivative (1) with a phosphoryl group in the side chain was obtained in 30% yield (Scheme 1)



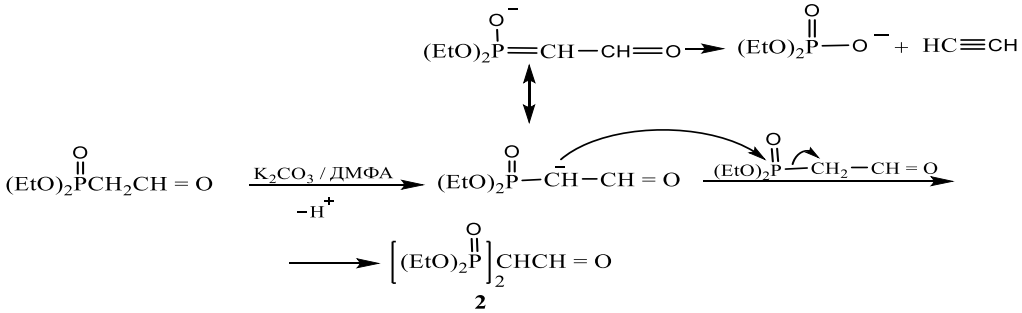
1

The formation of compound 1 should be considered as a product of primary alkylation of the aldehyde at the active methylene group with subsequent prototropic isomerization and O-alkylation to compound **1**



The low yield of product 1 is apparently due to alternative transformations of the substrate and reagent under the action of potash in DMFA.

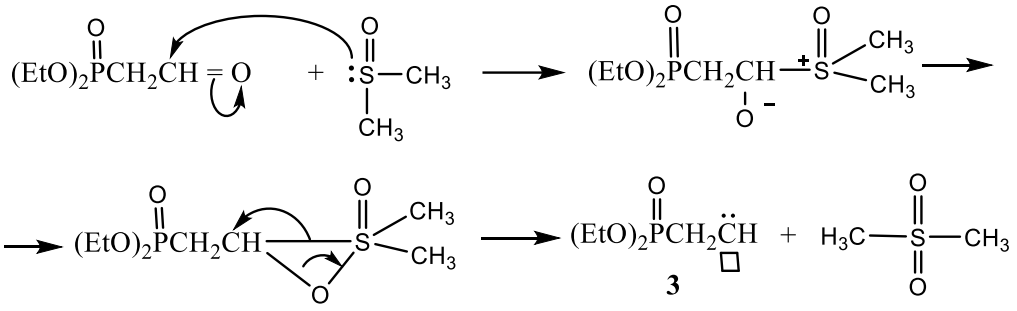
It was shown experimentally that phosphonoacetic aldehyde, under the specified conditions (K2CO3/DMF), undergoes a series of transformations, forming intermolecular condensation products – bis[diethoxyphosphoryl]acetic aldehyde (2) and the product of intramolecular decomposition of phosphonoacetic aldehyde with the formation of acetylene and phosphate ion (Scheme 3)



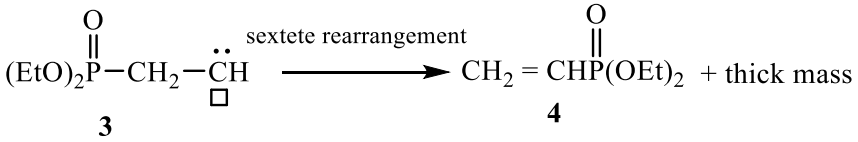
2

When this reaction was carried out in DMSO, dimethyl sulfone, a small amount of vinyl phosphonate (14%), and a thick residue, the structure of which could not be determined, were isolated from the reaction mixture.

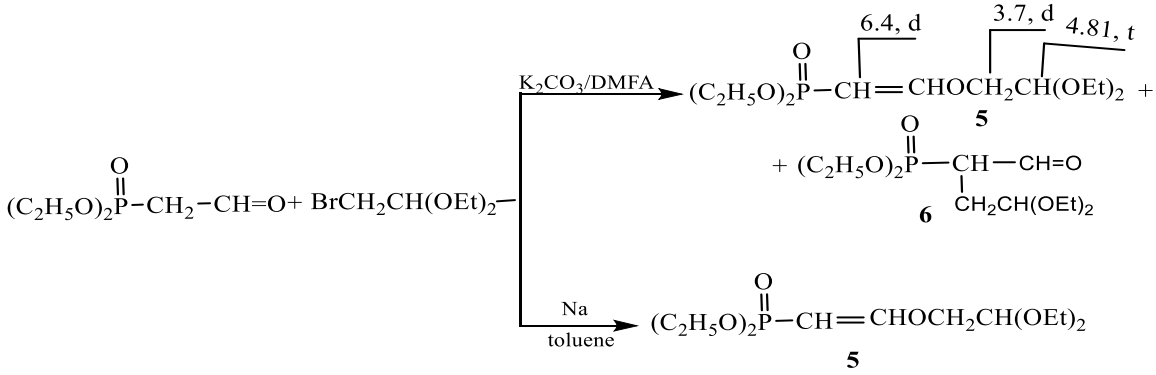
Dimethyl sulfoxide acts as a nucleophilic reagent in this process, attacking the carbonyl carbon to form a bipolar ion, the decomposition of which yields dimethyl sulfone and the corresponding carbene 3



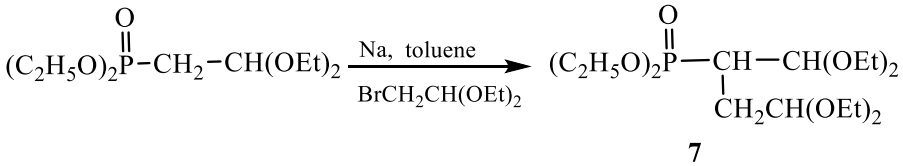
In all likelihood, carbene 3 is partially converted into vinyl phosphonate (4) as a result of a sextet rearrangement (by analogy with the Hoffmann reaction), and partly into a thick mass (Scheme 5)



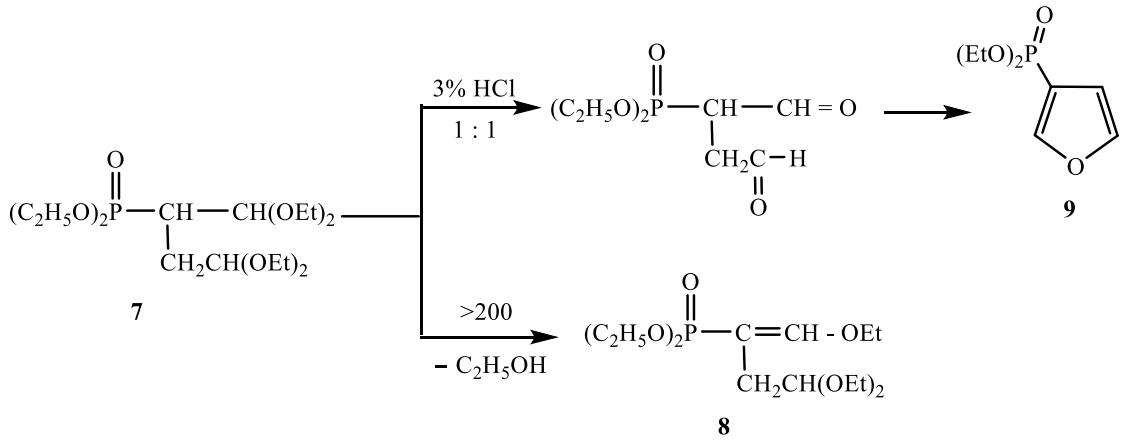
Alkylation of phosphonoacetic aldehyde with bromoacetic aldehyde diethyl acetal in the presence of potassium carbonate in DMF yields a mixture of C- and O-alkylation products (5,6). However, carrying out this reaction in the presence of Na in toluene yields exclusively the O-alkylation product 5



The C-alkylation reaction also takes place during the condensation of phosphonoacetic aldehyde diethyl acetal with acetic aldehyde bromoacetal in the presence of Na in toluene to form 1,1,4,4-tetraethoxy-2-diethoxyphosphorylbutane (7)

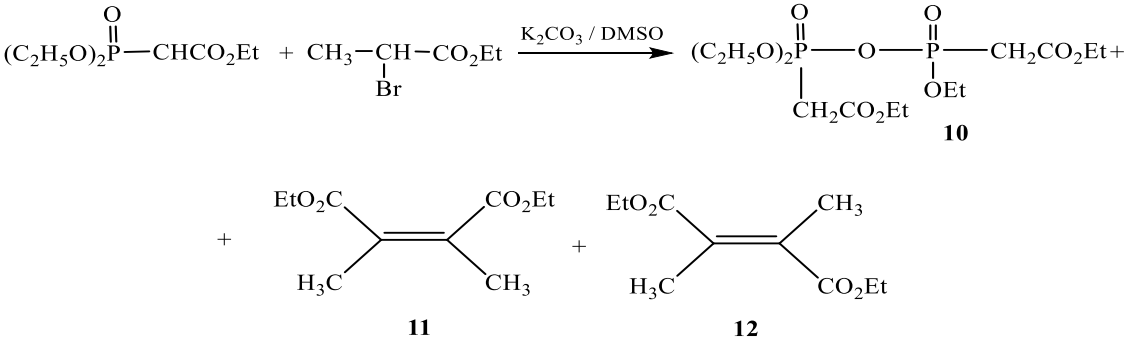


Acetals are known to readily hydrolyze in acidic media to form the corresponding aldehydes. Hydrolysis of product 7 with 3% of HCl has been noted to form a dialdehyde, which, under reaction conditions, is converted to the corresponding furan (9). It has also been established that acetal 7 undergoes alcohol elimination at temperatures above 200°C. Elimination occurs selectively from the acetal fragment located closer to the phosphorus in compound 8



7 **8** **9**

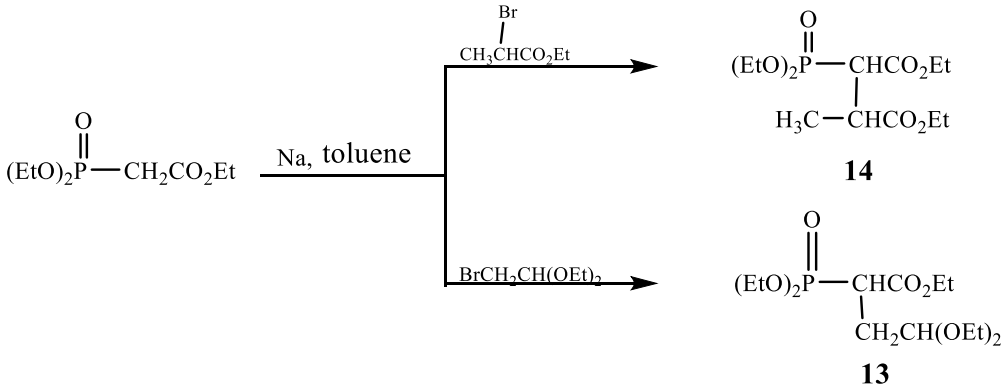
Phosphonacetates, unlike phosphonoacetaldehyde, which exhibit aldo-enol tautomerism, behave differently in condensation reactions with halogenated derivatives. Alkylation of phosphonoacetate under K2CO3/DMSO conditions with halogenated carbonyl derivatives does not yield the desired result. Thus, the reaction of triethyl phosphonoacetate with α-bromopropionate in the presence of potassium carbonate in DMSO forms phosphonate anhydrides (10), as well as esters of maleic (11) and fumaric (12) acids



10 **11** **12**

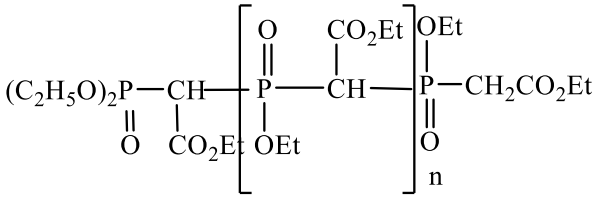
The formation of esters 11 and 12 from ethyl bromoacetate was previously discussed [20].

Phosphonoacetate, using metallic Na in toluene, is easily alkylated with ethyl α-bromopropionate and bromoacetaldehyde acetal, yielding C-alkylation products 13 and 14, respectively, in good yields.



14 **13**

Unlike phosphonoacetic aldehyde, which forms a carbanion in the K2CO3/DMSO system at normal temperature, phosphonoacetate forms a carbanion only at temperatures above 100 °C. Under these conditions, intermolecular condensation of the latter occurs with the formation of oligomers, which can find application in metallurgy.



n = 3, 4 and so on

In summary, it should be noted that the direction and yields of the alkylation reaction of α-phosphorylated carbonyl compounds with α-halocarbonyl derivatives are influenced by both the nature of the reactants and the nature of the solvent. It was found that in DMSO, the alkylation reactions of α-phosphorylcarbonyl compounds with halogenated carbonyl derivatives proceed predominantly with the formation of an O-alkylation product, whereas these reactions in DMF yield a mixture of C- and O-alkylation products. Low yields of the target products are due to self-condensation of the starting materials (both substrates and reactants) under the specified conditions.

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