Transformations of electrophilic reagents in a diethyl phosphite—potassium carbonate—ethanol system

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Transformations of alkyl halides, aldehydes, and activated alkenes in a $(EtO)_2PHO$—K_2CO_3—EtOH heterophase system were studied. The reactions are catalyzed by EtOK that formed and follow the known schemes of the interaction of hydrophosphoryl compounds with electrophiles.

Key words: diethyl phosphite, potassium carbonate, ethanol, alkali metal alkoxides, deprotonation.

Deprotonation of tautomers in reactions of hydrophosphoryl compounds, for example, dialkyl phosphites, with electrophiles occurs in the presence of bases, in particular, alkali metal alkoxides, in the reaction mixture. Dialkyl phosphites are close in acidity to aliphatic alcohols[1—3] and, as a rule, readily form anions under the action of these bases. However, the use in synthetic practice of alkoxides prepared from the corresponding alcohol and alkali metal is often complicated by side processes, because the reaction proceeds too vigorously.[4]

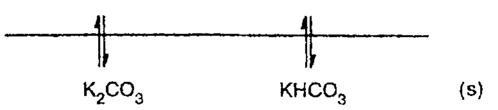
Many works are known in which reactions of dialkyl phosphites with various electrophilic reagents were studied under conditions of phase-transfer catalysis (PTC), including a liquid—solid base system.[5] Special attention was given to the effect of phase-transfer catalysts, and the transformations in the system were considered from the viewpoint of classical concepts of PTC. For example, anhydrous K_2CO_3 in the presence of tetrabutylammonium bromide or 18-crown-6 was used[6,7] for the Michaelis—Becker alkylation of dialkyl phosphites and the addition to electrophilic alkenes according to Pudovik. The reactions were carried out without a solvent at 80—100 °C for 2—8 h with a considerable excess of K_2CO_3. For the alkylation of dialkyl phosphites and diarylphosphine oxides, a mixture of KOH and K_2CO_3 was used[8] as the solid phase, a solution of an alkylating reagent in benzene, THF, or methoxyethane was used as the liquid phases, and 18-crown-6 was the catalyst. It has been shown, in particular, that the alkylation in benzene does not proceed in the presence of potash only, and the addition of phosphine oxide and phosphites to ethyl cinnamate occurs in the presence of catalytic quantities of KOH and K_2CO_3. The phase-transfer version of the Michaelis—Becker reaction has previously been described,[9] according to which dimethyl and diethyl phosphites are methylated with methyl iodide in the presence of potash without catalysts and solvents. The reaction occurs under mild conditions with high yields of alkylation products.

The effect of K_2CO_3 as a deprotonating reagent depends, in many aspects, not only on the substrate structure, but also on the reaction conditions. For the difluoromethylation of phenols with chlorodifluoromethane, we observed[10] that chlorodifluoromethane reacts rather readily with phenol in the presence of K_2CO_3 in ethanol, and the reaction rate decreases sharply when ethanol is replaced by dioxane. Such strong bases as alkali metal alkoxides or 30—50% solutions of NaOH are usually used for the dehydrochlorination of $CHClF_2$.[11]

In this work, we estimated the efficiency of the action of K_2CO_3 in an ethanolic medium in reactions of diethyl phosphites with various electrophiles, considered the mechanism of interaction of all components of the $(EtO)_2PHO$—K_2CO_3—EtOH system, and extended the series of electrophiles reacting with dialkyl phosphites under these conditions.

It has been shown that mixing of K_2CO_3 with EtOH results in the formation of EtOK and $KHCO_3$ and the establishment of the chemical and phase equilibrium between the components of the system (Scheme 1).

Scheme 1



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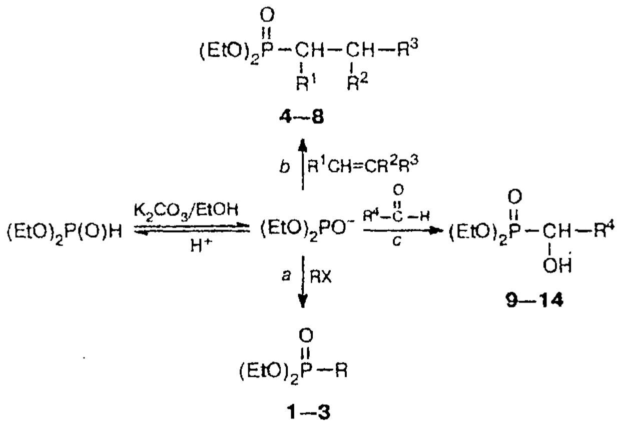
The concentration of EtOK in the solution remains almost constant when the amount of K_2CO_3 added is no less than 25—30 g per liter EtOH (Fig. 1), and the concentration of the K_2CO_3 dissolved is almost three times lower than that of EtOK.

The transition of potassium hydrogencarbonate that formed from the solution (sol) to the solid (s) phase is most likely the driving force of the shift of equilibrium to the right. This is confirmed by the introduction of $KHCO_3$ into the system, which results in a decrease in the concentration of potassium ethoxide to the level determined by the solubility of potassium hydrogencarbonate in ethanol (Fig. 2). Thus, the alkali metal carbonate—alcohol system can be considered as a phase-transfer reaction system for the generation of alkoxide ions.

In the heterophase system described, diethyl phosphite should be transformed into the diethyl phosphite anion, the reaction form active with respect to electrophilic reagents. For this purpose, various electrophiles were added to the diethyl phosphite—K_2CO_3—ethanol system: alkyl halides, alkenes with electron-withdrawing substituents at the double bond, and aromatic aldehydes. It has been established that the interaction occurs in accordance with the classical schemes of the Michaelis—Becker (*a*), Pudovik (*b*), and Abramov (*c*) reactions (Scheme 2).

Scheme 2



RX = $CH_2=CH—CH_2Br$ (**1**), $PhCH_2Cl$ (**2**), $ClCH_2COOEt$ (**3**);
R^1 = Ph, R^2 = R^3 = CN (**4**); R^1 = R^2 = CN, R^3 = COOEt (**7**);
R^1 = Pr^i, R^2 = R^3 = COOEt (**5**); R^1 = R^3 = COOEt, R^2 = H (**6**);
R^1 = R^2 = H, R^3 = CN (**8**);
R^4 = Ph (**9**); 4-FC_6H_4 (**10**); 4-$MeOC_6H_4$ (**11**);
3,4-$(MeO)_2C_6H_3$ (**12**); 4-ClC_6H_4 (**13**); 4-BrC_6H_4 (**14**)

The reactions along directions *b* and *c* occur most readily and in high yields (Table 1). The reaction along route (*a*) requires higher temperatures and a greater amount of K_2CO_3. Under these conditions, the reactions with allyl bromide and benzyl chlorides are accompanied by the formation of minor quantities of by-products, most likely, esters of carbonic acid, which is confirmed by the absorption band at 1740 cm^{-1} in the IR spectra of the nonpurified products.

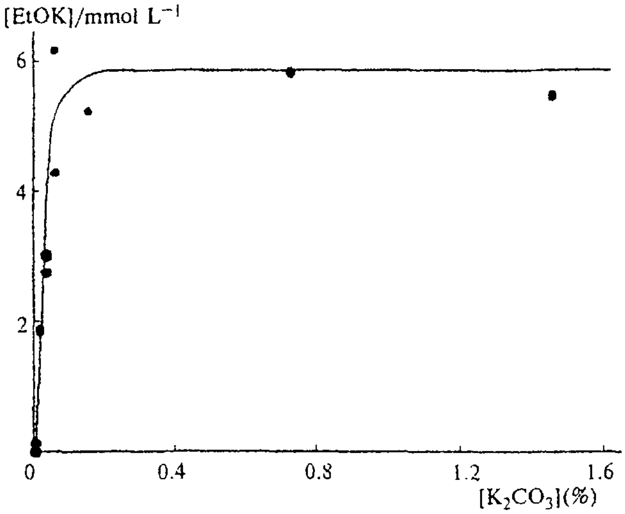


Fig. 1. Dependence of the concentration of EtOK in the K_2CO_3—EtOH system on the amount of K_2CO_3 at 20 °C.

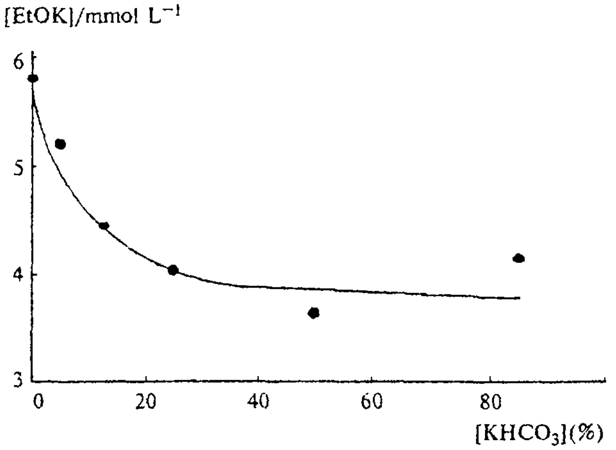


Fig. 2. Dependence of the concentration of EtOK on the content of $KHCO_3$ in the solid phase of the $KHCO_3$—K_2CO_3—EtOH system at 20 °C.

The structures of the known compounds **1**, **3**—**9** are confirmed by the coincidence of the physicochemical constants with the published data[12,17]; the reaction products were characterized by ^{31}P NMR and IR spectroscopy. In addition, phosphonates **4** and **9** were synthesized by traditional procedures using EtONa. Compounds obtained by different methods were identical, which was confirmed by the absence of depression of melting temperatures of the specimens after mixing and identical IR spectra.

The use of the K_2CO_3—ethanol system has several synthetic advantages over the generation of alkoxide from an alkali metal and alcohol: milder reaction condi-

Table 1. Reaction conditions and yields of reaction products in the reactions of electrophiles with $(EtO)_2PHO$ in the K_2CO_3—EtOH system

Compound	K_2CO_3—$(EtO)_2PHO$ /g mol^{-1}	T /°C	t/h	Yield (%)
1	5.0	60	2	92
2	5.0	78	2	8*
3	5.0	78	2	33
4	0.5	25	1	80
5	0.5	25	2	77
6	0.5	28	1	90
7	0.5	25	1	84
8	0.5	40	2	66
9	0.5	25	1	80
10	0.5	20	1	82
11	0.5	20	1	71
12	0.5	40	1.5	82
13	0.5	20	1	66
14	0.5	20	1	73

* Determined from the GLC data.

tions, low concentrations of strong bases in the reaction medium, simplicity of performing syntheses, high yields of products of the addition of diethyl phosphite to electrophilic multiple bonds, and a possibility to exclude phase-transfer catalysts.

Thus, the heterophase diethyl phosphite—K_2CO_3—ethanol system is efficient for the preparation of diethyl phosphonates with different structures.

Experimental

IR spectra were recorded on an IKS-29 instrument (in Nujol or thin films). ^{31}P NMR spectra were recorded on an RYa-2306 spectrometer (16.2 MHz) with 85% H_3PO_4 as the external standard. The reaction course was monitored by TLC (Silufol UV-254, CH_2Cl_2, visualization by 1% $KMnO_4$) and GLC on a Chrom 4 chromatograph (a column 2500×3mm with 5% OV-225 on Chromaton N-Super (0.16—0.20 mm), a katharometer, helium as the carrier gas with a rate flow of 30 mL min^{-1}) at 120 °C. The degree of conversion of diethyl phosphonate was determined by the absolute calibration method.

The distribution of components in the K_2CO_3—EtOH heterophase system was determined by titrimetry. A weighed sample of anhydrous potassium carbonate ($d \le 160$ mesh) was stirred with anhydrous ethanol (10 mL) at 20±0.2 °C for 30 min. In the study of the influence of potassium bicarbonate on the distribution of components in the K_2CO_3—EtOH system, the weight of the solid sample was calculated from the condition that the overall amount of carbonates was equal to 20 mmol. The suspension obtained was filtered through a POR-16 glass filter. The filtrate was weighed, and the alcohol removed. The residue was diluted with water and titrated with 0.1 *N* HCl using acid-base indicators.

Reaction of diethyl phosphite with electrophiles (general procedure). A mixture of diethyl phosphite (30.15 mmol), a substrate (30.15 mmol) (alkyl halide, aldehyde, or activated alkene), and anhydrous K_2CO_3 (36.18 mmol for reaction (*a*) or 3.6 mmol for reactions (*b*) and (*c*)) in 10 mL of anhydrous ethanol was stirred vigorously at the corresponding temperature (see Table 1) in a flask equipped with a reflux condenser and a $CaCl_2$ tube. The reaction course was monitored by GLC and TLC.

The reaction mixture was filtered through a glass filter, and the precipitate was washed with an appropriate solvent. Then the filtrate was neutralized with acetic acid, the solvents were removed, and the residue was separated from potassium acetate. The products were purified by distillation *in vacuo* or by recrystallization. The yields of the reaction products are presented in Table 1.

Diethyl allylphosphonate (1), b.p. 98—99 °C (12 Torr). ^{31}P NMR, δ: 26.1. IR, ν/cm^{-1}: 3070 (H—C=); 1650 (C=C); 1245 (P=O).

Diethyl (ethoxycarbonylmethyl)phosphonate (3), b.p. 101 °C (0.4 Torr). ^{31}P NMR, δ: 19.4. IR, ν/cm^{-1}: 1715 (C=O); 1260 (P=O). The IR spectrum of **3** is identical with that of diethyl (ethoxycarbonylmethyl)phosphonate cited in Ref. 12.

Diethyl (1-phenyl-2,2-dicyanoethyl)phosphonate (4), b.p. 170—172 °C (0.4 Torr). ^{31}P NMR, δ: 18.6. IR, ν/cm^{-1}: 2200 (CN); 1240 (P=O).

Diethyl (2-methyl-1-diethoxycarbonylmethyl)propylphosphonate (5), b.p. 150—152 °C (1 Torr). ^{31}P NMR, δ: 27.9. IR, ν/cm^{-1}: 1710 (C=O); 1240 (P=O).

Diethyl (1,2-diethoxycarbonylethyl)phosphonate (6), b.p. 140—144 °C (1 Torr). ^{31}P NMR, δ: 20.6. IR, ν/cm^{-1}: 1740 (C=O); 1260 (P=O).

Diethyl (2-cyano-2-ethoxycarbonyl-1-phenylethyl)phosphonate (7), b.p. 165—168 °C (0.4 Torr). ^{31}P NMR, δ: 22.1. IR, ν/cm^{-1}: 2200 (CN); 1750 (C=O); 1250 (P=O).

Diethyl 2-cyanoethylphosphonate (8), b.p. 121—123 °C (1 Torr). ^{31}P NMR, δ: 26.9. IR, ν/cm^{-1}: 2230 (CN); 1235 (P=O).

Diethyl α-hydroxybenzylphosphonate (9), m.p. 83—84 °C (from CCl_4). ^{31}P NMR, δ: 20.5. IR, ν/cm^{-1}: 3250 (OH); 1240 (P=O).

Diethyl α-hydroxy-4-fluorobenzylphosphonate (10), m.p. 49—54 °C (from benzene—heptane). ^{31}P NMR, δ: 21.2. IR, ν/cm^{-1}: 3250 (OH); 1250 (P=O). Found (%): C, 49.86; H, 6.64; P, 11.76. $C_{11}H_{16}FO_4P$. Calculated (%): C, 50.39; H, 16.15; P, 11.81.

Diethyl α-hydroxy-4-methoxybenzylphosphonate (11), m.p. 123—125 °C (from CCl_4). Found (%): C, 52.20; H, 6.53; P, 11.47. $C_{12}H_{19}O_5P$. Calculated (%): C, 52.55; H, 6.98; P, 11.29. ^{31}P NMR, δ: 21.4. IR, ν/cm^{-1}: 3250 (OH); 1250 (P=O).

Diethyl α-hydroxy-3,4-dimethoxybenzylphosphonate (12), m.p. 95—97 °C (from benzene—heptane). Found (%): C, 51.56; H, 7.45; P, 9.79. $C_{13}H_{21}O_6P$. Calculated (%): C, 51.31; H, 6.96; P, 10.18. ^{31}P NMR, δ: 21.2. IR, ν/cm^{-1}: 3240 (OH); 1260 (P=O).

Diethyl α-hydroxy-4-chlorobenzylphosphonate (13), m.p. 63—66 °C (from benzene—heptane). Found (%): C, 46.77; H, 5.86; P, 10.57. $C_{11}H_{16}ClO_4P$. Calculated (%): C, 47.41; H, 5.79; P, 11.11. ^{31}P NMR, δ: 20.4. IR, ν/cm^{-1}: 3230 (OH); 1230 (P=O).

Diethyl α-hydroxy-4-bromobenzylphosphonate (14), m.p. 62—72 °C (from heptane—CCl_4). Found (%): C, 40.54; H, 5.47; P, 8.90. $C_{11}H_{16}BrO_4P$. Calculated (%): C, 40.89; H, 4.99; P, 9.59. ^{31}P NMR, δ: 20.1. IR, ν/cm^{-1}: 3250 (OH); 1260 (P=O).

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