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Reactions of *tert*-Butyl Tetraethylphosphorodiamidite with Acetic and Trifluoroacetic Acids

L. K. Sal'keeva, M. T. Nurmagambetova, O. Sh. Kurmanaliev, and T. Kh. Gazizov

Buketov Karaganda State University, Karaganda, Kazakhstan

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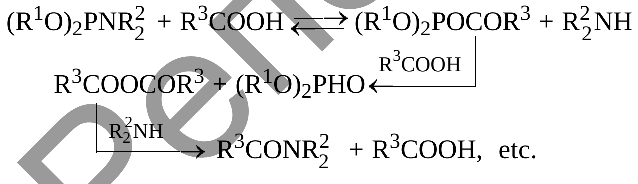
Abstract — Reactions of *tert*-butyl tetraethylphosphorodiamidite with acetic and trifluoroacetic acids involve substitution of the amido group. This process was described by a scheme beginning with protonation of phosphorus and proved by modeling separate reaction stages. A probable scheme of the proposed reactions is described.

Amidoesters of P(III) acids react with carboxylic acids to give hydrophosphoryl compounds and carboxamides [1, 2]. It is proposed that this reaction proceeds through protonation of the nitrogen atom of the phosphoroamidite with the acid proton and results in formation of an acyl phosphite and an amine, followed by nucleophilic attack by the amine nitrogen atom of the carbonyl carbon atom of the acyl phosphite, giving rise to deacylation of the latter and formation of a hydrophosphoryl compound. Nifant'ev *et al.* [3] showed that alcoholysis of P(III) amides in the presence of acetic acid begins with protonation of phosphorus to form a quasiphosphonium compound. However, Evdakov *et al.* [4] showed that alcoholysis of phosphoramidites in the presence of carboxylic acids involves formation of corresponding acyl phosphites. As shown in [5–8], the reactions of P(III) amidoesters with carboxylic acids, leading to acylphosphites, are reversible. In view of this fact, the following step-by-step scheme of the reaction of P(III) amidoesters with carboxylic acids has been proposed and proved by DTA and ^{31}P NMR spectroscopy, as well as by modeling its separate stages [9].

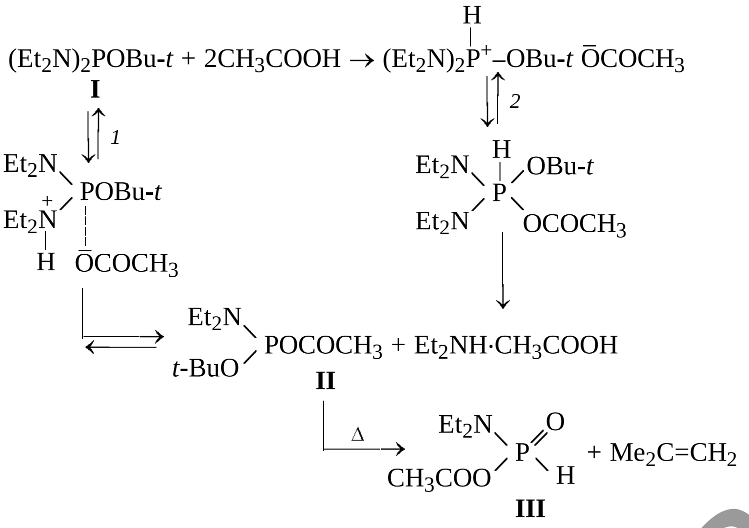


$$\begin{tikzcd}
(R^1O)_2PNR^2_2 + R^3COOH \arrow[r, shift left] & (R^1O)_2POCOR^3 + R^2_2NH \arrow[l, shift left] \arrow[dl, "R^3COOH"'] \\
R^3COOCOR^3 + (R^1O)_2PHO \arrow[d, "R^2_2NH"'] & \\
R^3CONR^2_2 + R^3COOH,\ \text{etc.} &
\end{tikzcd}$$

Hence, according to published data, reactions of P(III) amidoesters with hydrogen halides and carboxylic acids occur by way of substitution of the amido group of the P(III) derivative by halogen or the acyloxy group, respectively. To explain the mechanism of these reactions, two alternative pathways have been proposed. They include N- or P-protonation of the amidoester by the acid. Recently we used the example of the reaction of *tert*-butyl tetraethylphosphorodiamidite with HX (X = Hal) to show for the first time that reactions of P(III) amidoesters with protic acids proceed by the Arbuzov scheme [10, 11]. It was established that the conditions favoring the second stage of the Arbuzov reaction increase the yield of the Arbuzov product, and, vice versa, the conditions favoring formation of a pentacovalent intermediate alter the reaction pathway to the side of substitution of the amido group by the acid residue.

Continuing reseach into reactions of *tert*-butyl phosphoramidites, we reacted $(Et_2N)_2POBu$-*t* (**I**) with CH_3COOH and CF_3COOH. The reaction of compound **I** with CH_3COOH at –50 to –70°C at a 1 : 1 molar ratio without solvent gives a compound with δ_P 139 ppm. The ^{31}P NMR spectrum of the reaction mixture also contains a signal of the starting phosphite **I** (δ_P 124 ppm). The intensity ratio of these two signals is approximately 1 : 1. In the spectrum of the reaction mixture of **I** with 2 mol of CH_3COOH we found only one signal at δ_P 139 ppm. It was assigned the structure of acetyl *tert*-butyl diethylphosphoramidite (**II**). The IR spectrum of compound **II** contains a ν(C=O) band at 1720 cm^{-1} and the ^{1}H NMR spectrum shows a triplet of methyl protons at 1.27 ppm (6H), a multiplet of methylene protons at 3.5 ppm (4H), a singlet of *tert*-butyl protons at 1.8 ppm (9H), and a singlet of acetyl protons at 2.3 ppm (3H). The formation of phosphite **II** can be explained by initial attack of proton on the nitrogen (path *1*) or phosphorus atom (path *2*).

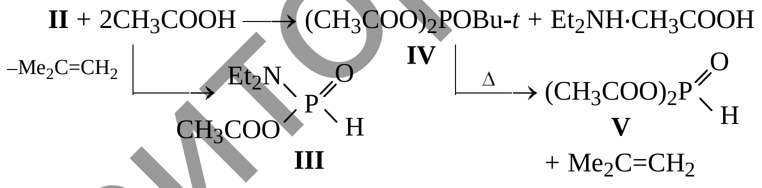
The reaction of phosphite **I** with CH_3COOH at a 1 : 2 molar ratio at room temperature gives phosphite **II**, whereas on heating on a water bath hydrophosphoryl compound **III** (δ_P –4 ppm, J_{PH} 690 Hz) is



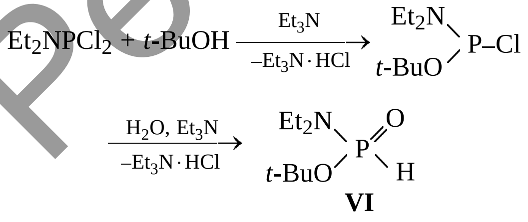
formed as a single product. In the IR spectrum, a P–H absorption band is observed (2430 cm^{-1}).

The reversibility of the reaction of phosphite **I** with acetic acid was modeled on an example of the reaction of phosphite **II** with 2 mol of diethylamine. The ^{31}P NMR spectrum of the reaction mixture contained a single signal of phosphite **I** at δ_P 124 ppm.

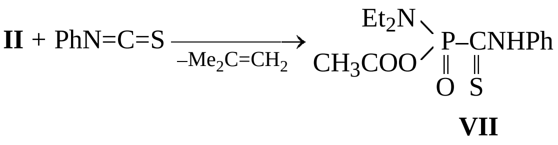
Acidolysis of phosphite **II** with 2 mol of CH_3COOH unexpectedly gave two hydrogen phosphites. One of them was phosphite **III** and the second (δ_P –3 ppm, J_{PH} 620 Hz) was assigned structure **V**. The IR spec-trum contains absorption bands at 1720 and 1740 (C=O) and 2430 cm^{-1} (P–H). On attempted distillation the reaction mixture foams and decomposes.



According to published data, acidolysis of phosphite **II** should lead to *tert*-butyl hydrogen diethylphosphoramidite (**VI**). However, we performed independent synthesis of compound **VI** and found its signal at δ_P –7 ppm (J_{HP} 620 Hz).



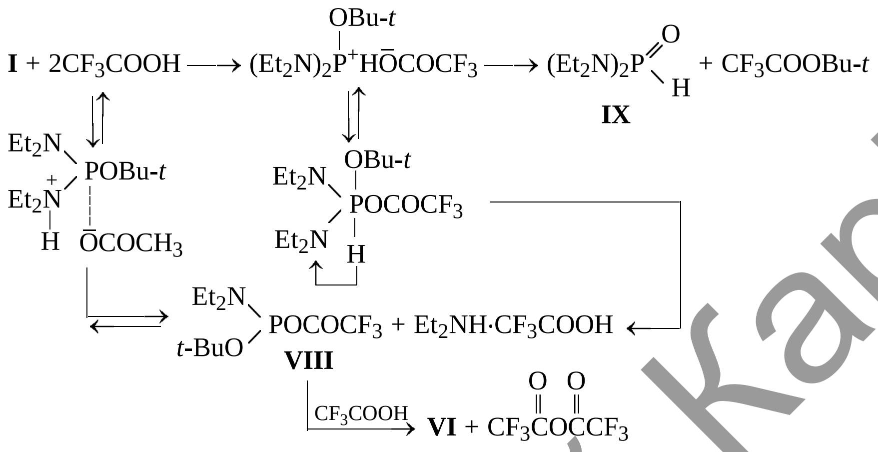
The structure of compound **II** was also proved by its reaction with phenyl isothiocyanate, which gave acetyl *N*,*N*-diethyl(phenylthiocarbamoyl)phosphonamidate (**VII**), δ_P 3 ppm. The IR spectrum of compound **VII** contains absorption bands at 1240 (P=O), 1600 (C=S), 3170 (N–H), and 1500 cm^{-1} (C_6H_5). The ^1H NMR spectrum contains a triplet of methyl protons at δ 1.57 ppm (6H), a multiplet of methylene protons at δ 3.6 ppm (4H), a doublet of aromatic protons at δ 7.6 ppm (5H), and a singlet of acetoxy protons at δ 2.23 ppm (3H).



The reaction of phosphite **I** with CF_3COOH under strong cooling (–50 to –70°C) provides, like with

CH_3COOH, a single product, *tert*-butyl trifluoroacetyl diethylphosphoramidite (**VIII**), δ_P 144 ppm.

The reaction of phosphite **I** with CF_3COOH at room temperature and slow mixing of the reagents proceeds with strong heat release and, according to ^{31}P NMR data, gives two hydrophosphoryl compounds. The first of them, δ_P 19 ppm (J_{PH} 570 Hz), was identified as tetraethylphosphorous diamide (**IX**). The second product, δ_P 7 ppm (J_{HP} 620 Hz), was identified as compound **VI**.



Thus, our study on the reactions of *tert*-butyl tetraethylphosphorodiamidite with CH_3COOH and $CF_3 \cdot COOH$ showed that the formation of the product of substitution of the amido group can also be explained by initial protonation of phosphorus to form a quasi-phosphonium intermediate. An example of a reaction of phosphite **I** with CF_3COOH was found, yielding and Arbuzov product, tetraethylphosphorous diamide.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in the range 400–3700 cm^{-1}. The ^1H NMR spectra were obtained on a Varian T-60 spectrometer (60 MHz) against internal TMS. The ^{31}P NMR spectra were measured on a KGU-4 NMR spectrometer (10.2 MHz) against 85% phosphoric acid.

Reaction of *tert*-butyl tetraethylphosphorodiamidite (I) with CH_3COOH on cooling. Phosphite **I**, 6.2 g, and 3 g of CH_3COOH were mixed at –50 to –70°C. A precipitate formed. After 1 h, the ^{31}P NMR spectrum contained only one signal at δ_P 139 ppm, assigned to acetyl *tert*-butyl diethylphosphoramidite. The reaction mixture was treated with petroleum ether. Two layers formed. The lower layer was treated with 1 g of dry sodium hydroxide. Heat evolution and dissolution of alkali were observed. Distillation gave 1.1 g (62%) of diethylamine, bp 52–53°C, n_D^{20} 1.3820. Published data: bp 51–52°C, n_D^{20} 1.3864. Distillation of the upper layer caused foaming and decomposition.

Reaction of phosphite I with CH_3COOH on heating. A mixture of phosphite **I**, 6.2 g, and 3 g of CH_3COOH was heated for 20 min on a water bath. Isobutylene, 420 ml (75%), liberated. IR spectrum: ν 2340 cm^{-1} (P–H). ^{31}P NMR spectrum: δ_P 4 ppm (J_{PH} 690 Hz); belongs to acetyl diethylphosphoramidite which decomposes on distillation.

Reaction of acetyl *tert*-butyl diethylphosphoramidite with phenyl isothiocyanate. Phosphite **I**, 6.2 g, and 3 g of CH_3COOH were mixed at room temperature. The precipitate of diethylammonium acetate was removed, and the reaction mixture was treated with 3.3 g of phenyl isothiocyanate. The ^{31}P NMR spectrum contained a single signal of acetyl *N*,*N*-diethyl(phenylthiocarbamoyl)phosphonamidate (**VII**), δ_P 3 ppm. Compound **VII** is an oil that decomposes on distillation. Found, %: C 55.32; H 7.38; N 8.28; P 9.81; S 9.98. $C_{15}H_{25}N_2O_2P$. Calculated, %: C 54.88; H 7.62; N 8.53; P 9.45; S 9.75.

Reaction of phosphite I with CF_3COOH on cooling. Phosphite **I**, 6.2 g, was mixed with 5.7 g of CF_3COOH. The precipitate was removed. The ^{31}P NMR spectrum of the crude reaction mixture contained a single signal at δ_P 144 ppm, assigned to *tert*-butyl trifluoroacetyl diethylphosphoramidite. The IR spectrum contains a C=O band at 1690 cm^{-1}.

Reaction of phosphite I with CF_3COOH at room temperature. A mixture of 6.2 g of phosphite **I** and

5.7 g of CF_3COOH was left to stand for 20 min. The ^{31}P NMR spectrum of the reaction mixture contained signals of compounds **IX** and **X** in a 1 : 1 ratio. When distilled, tetraethylphosphorous diamide completely decomposed, and distillation gave 0.8 g (17%) of *tert*-butyl hydrogen diethylphosphoramidite, bp 35–36°C (0.06 mm), d_4^{20} 0.9655, n_D^{20} 1.4340. ^1H NMR spectrum: δ 1.83 ppm $[(CH_3)_3C]$. ^{31}P NMR spectrum: δ_P 7 ppm (J_{PH} 620 Hz). Found, %: C 49.50, H 10.24, N 7.30, P 15.78. $C_8H_{20}NO_2P$. Calculated, %: C 49.74, H 7.25, P 16.06.

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