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To the 80th Anniversary of B.I. Ionin

New Reactions of Chloroethynylphosphonates

A. V. Dogadina and N. I. Svintsitskaya

St. Petersburg State Technological Institute (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: dog_alla@mail.ru

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Abstract—Studies of chloroethynylphosphonates reactions with heterocyclic *S*,*N*-binucleophiles and conventional CH-acids derivatives are summarized.

Keywords: chloroethynylphosphonate, thiotriazole, thiotetrazole, phosphorylated thiazolo[3,2-*b*][1,2,4]triazol-7-ium chloride, 3-substituted 6-(dialkoxyphosphoryl)thiazolo[3,2-*d*][1,2,3,4]tetrazol-7-ium chloride, CH-acid, phosphorylated triketone

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In 2015 Boris I. Ionin, Honored Scientist of Russian Federation, Professor, Doctor of Sciences (Chemistry), our teacher and friend would celebrate his 80th anniversary. Recently he supervised active research on reactivity of chloroacetylenephosphonate, a compound that he discovered 50 years ago. In this work we summarize our latest results in this field; some of them are presented for the first time.

Chloroacetylenephosphonate was prepared by B.I. Ionin and A.A. Petrov in 1965 via the Arbuzov reaction from triethyl phosphite and dichloroacetylene [1]. The chlorine atom in chloroacetylenephosphonate was found fairly labile due to strong polarization of the push-pull triple bond. The presence of several potential reaction sites in the molecule led to high and versatile reactivity of chloroethynylphosphonates. The pioneering research by B.I. Ionin gave start to many works on the discussed compounds reactivity. For instance, chloroacetylenephosphonates were recognized as highly active mild phosphorylating agents in the reactions with nucleophiles [2]. In 1990s chemistry of chloroacetylenephosphonates was undeservedly forgotten.

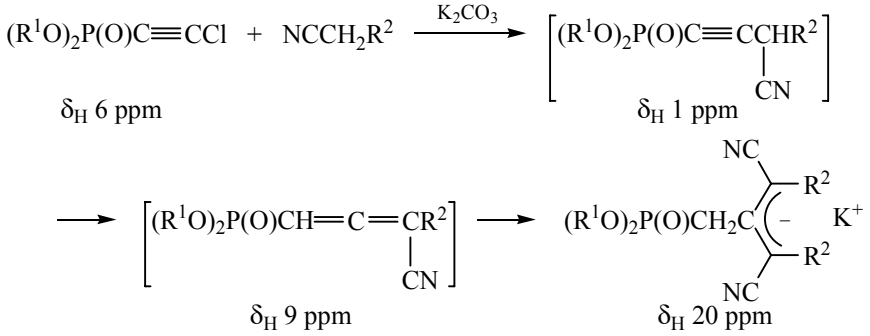
Since the early 2000s B.I. Ionin with co-workers extended the range of chloroacetylenephosphonates reactions with nucleophiles to involve selected conventional CH-acids; under conditions of basic catalysis the latter could act as classic nucleophilic carbanions. It was found that the reaction of chloroacetylenephosphonates with malonic acid dinitrile and ethyl cyanoacetate proceeded in anhydrous acetonitrile in the presence of excess of anhydrous K_2CO_3 (acceptor of the evolving hydrogen chloride) and gave potassium salts of the corresponding substituted phosphonic acids in high yield [3] (Scheme 1).

The reaction progress was monitored with NMR $^1H–\{^{31}P\}$ spectroscopy; chemical shifts of the substrate, intermediates, and the final reaction products are indicated in the scheme. According to the NMR data, the reaction mechanism involved several stages: initial substitution of the chlorine atom of chloroacetylenephosphonate with the residue of the corresponding CH-acid, acetylene–allene rearrangement of the acetylenic intermediate, addition of the second molecule of the CH-acid, and substitution of the labile hydrogen atom of the malonic fragment with potassium to yield the final product.

In the course of the reaction, a strong absorption band at 1920 cm^{-1} assigned to the allene fragment appeared and then vanished in the IR spectra of the mixture.

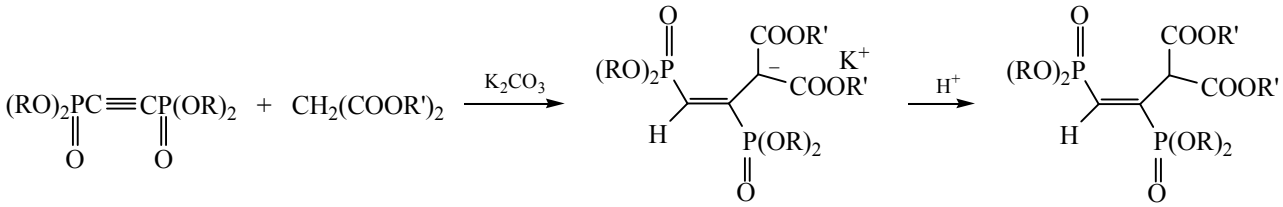
The reaction of chloroacetylenephosphonates with malonic acid esters proceeded similarly but the salt of acetylenic structure was formed (in 30–40% yield) besides the corresponding potassium salt of the product of CH-acid anion double addition [3]. That was evidently due to the low rate of isomerization of dialkoxyphosphoryl ethynylmalonate into the

Scheme 1.

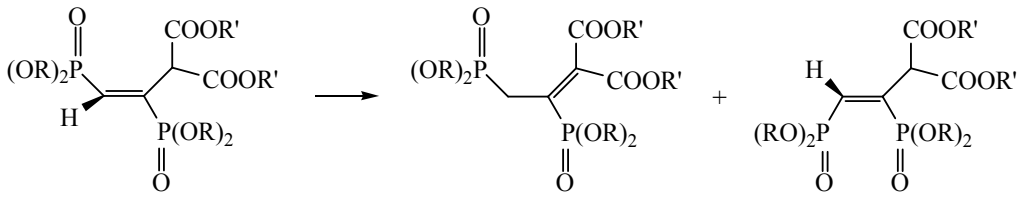


R^1 = OMe, OEt; R^2 = CN, COOEt.

Scheme 2.



Scheme 3.



corresponding allene allowing the competitive substitution reaction leading to dialkoxyphosphoryl ethynylmalonate potassium salt.

The reaction of malonic acid derivatives with acetylenediphosphonates prepared via the Arbuzov reaction from chloroacetylenephosphonate followed a simpler Scheme 2.

Reactions of acetylenediphosphonates with methyl-(ethyl) malonates proceeded as stereospecific addition with formation of *E*-isomers of malonoalkenyl diphosphonates potassium salts. Treatment of the products with equivalent amount of trifluoroacetic acid led to substitution of potassium with hydrogen to give *E*-malonoalkenyl diphosphonates. Chromatographic purification of the prepared salts on silica gel gave the same result due to the presence of adsorbed proton-donor molecules on silica. The protonation was accompanied by isomerization via the double bond shift as well. Interestingly, *E*-2-alkoxycarbonyl-3,4-bis-(dialkoxyphosphoryl)but-3-enoic acid esters underwent gradual isomerization via migration of the double bond to form 2-alkoxycarbonyl-3,4-bis(dialkoxyphosphoryl)but-2-enoic acid esters and *Z*-2-alkoxycarbonyl-3,4-bis(dialkoxyphosphoryl)but-3-enoic acid [4] (Scheme 3).

Stereoselectivity of the reaction was violated in the cases of malonic acid dinitrile and malononitrile interaction with acetylenediphosphonates that led to formation of *E*- and *Z*-isomers of the corresponding (malononitrile)alkenyldiphosphonate potassium salts in the ratio of 2 : 1 and 1 : 1, respectively, in good yield [4]. The structure of the products was confirmed by X-ray diffraction analysis (Fig. 1).

Treatment of the potassium derivatives with trifluoroacetic acid caused formation of the CH-forms accompanied by isomerization [4] (Scheme 4).

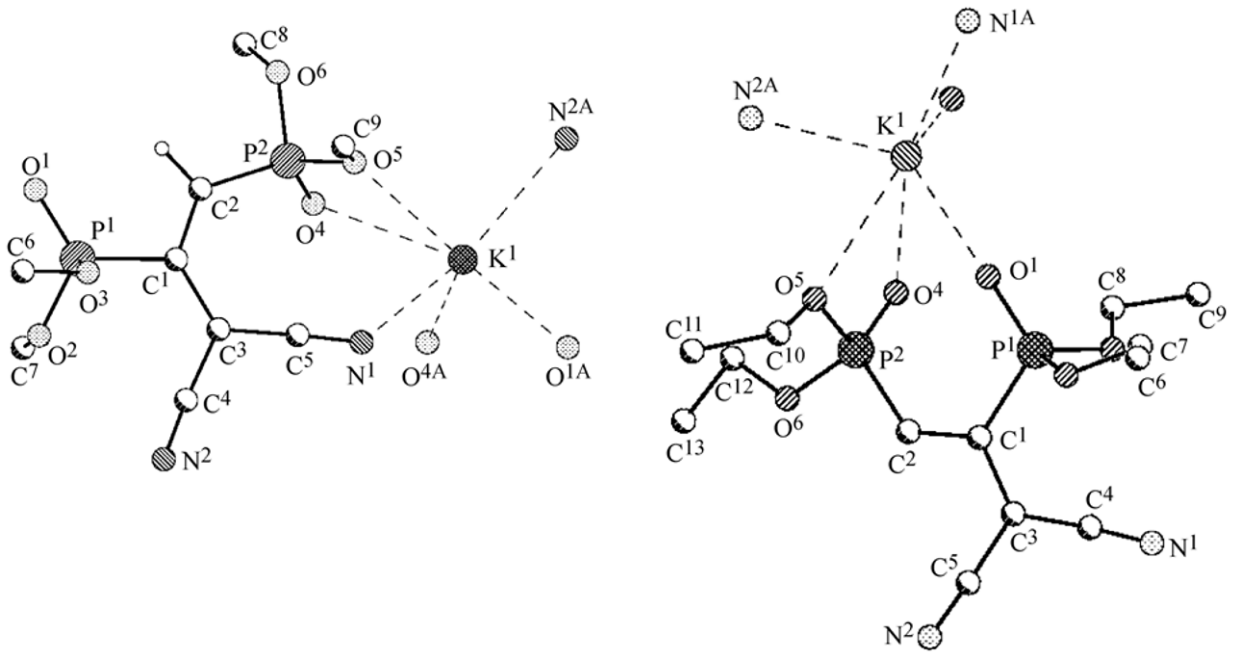


Fig. 1. Crystal structure of potassium salts of nitriles of *E*-2-cyano-3,4-bis(dimethoxyphosphoryl)but-3-enoic and *Z*-2-cyano-3,4-bis-(diethoxyphosphoryl)but-3-enoic acids.

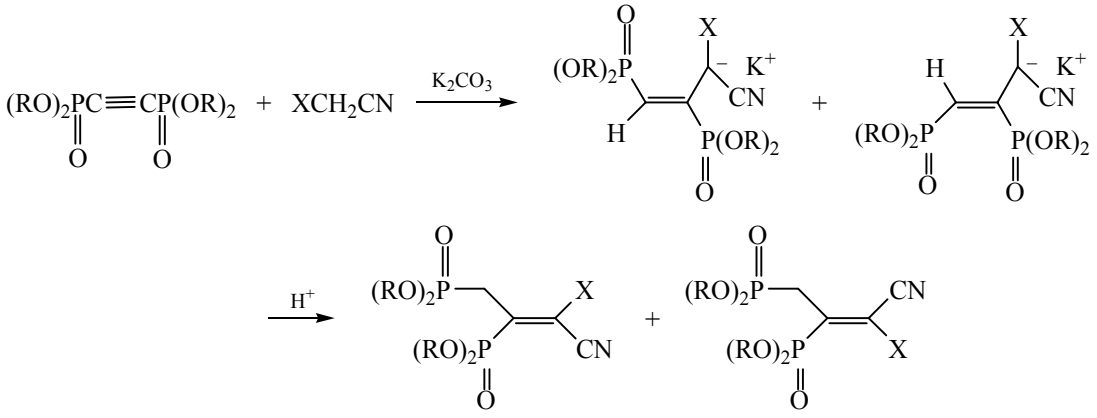
Reaction of chloroacetylenephosphonates with such conventional CH-acids as acetylacetone and its derivatives under the same conditions stopped at the stage of nucleophilic substitution of the chlorine atom in chloroacetylenephosphonates (the acetylenic structure was preserved) followed by substitution of the hydrogen atom in the CH-acidic fragment to form the corresponding potassium salts in good yield [5]. The same reaction scheme was operative in the case of acetylenediphosphonate [6] (Scheme 5).

Reaction of chloroacetylenephosphonate with ethyl acetoacetate and its homologs in the presence of potassium carbonate proceeded similarly, as nucleo-philic substitution of the chlorine atom followed by substitution of the second proton of the CH-acid by potassium cation to form the corresponding potassium salts [7] (Scheme 6).

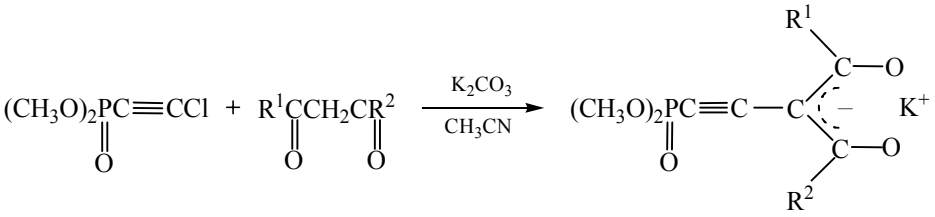
Hydration of the prepared 2-(dialkoxyphosphoryl)-acetylenyl-1,3-diketones potassium salts led to the unique class of organic compounds, phosphorylated triketones of triacylmethane structure [8] (Scheme 7).

According to ^{1}H and ^{13}C NMR spectroscopy data, the structure of the acyl triketones corresponded to complete enolization of dimethylphosphonoacetyl

Scheme 4.

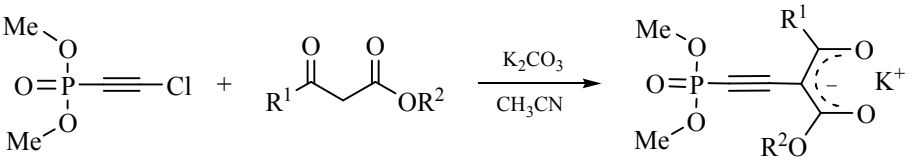


Scheme 5.



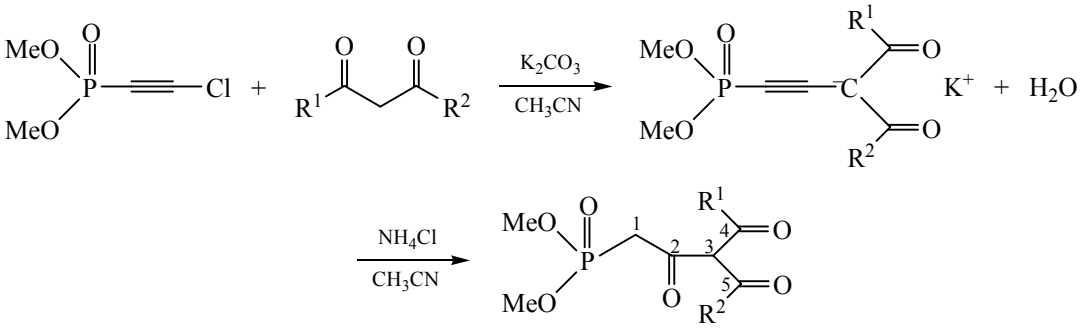
$R^1 = R^2$ = Me, Ph.

Scheme 6.



R^1, R^2 = Me, *t*-Bu, Ph.

Scheme 7.



R^1, R^2 = Me, Ph.

group. The other two acyl substituents were evidently involved in the keto-enol equilibrium but their structures were closer to ketone with one or both oxygen atoms forming hydrogen bond with the hydrogen atom of enol hydroxyl, likely with formation of bifurcating hydrogen bond [8].

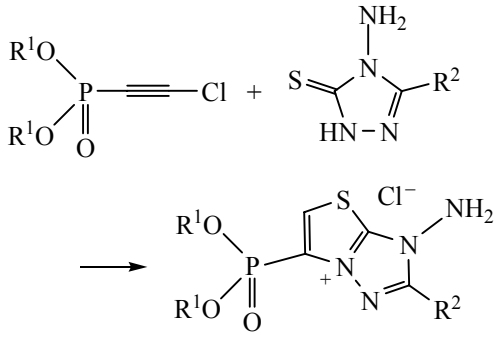
Dimethoxyphosphorylacetyl group in dimethyl-3-benzoyl-2,4-dioxo-4-phenylbutylphosphonate was completely enolized as well, while the two non-equivalent benzoyl groups existed in the form that was closer to ketone structure. The non-equivalence of the benzoyl groups indicated formation of the hydrogen bond between the enol hydroxyl and oxygen of one of the carboxylic groups and pointed at slow exchange in the system at the time scale of NMR experiment [8].

Reaction of dimethyl chloroacetylenephosphonate with amidomalonates in anhydrous acetonitrile in the presence of potassium carbonate proceeded at room temperature and led to a new class of compounds, phosphorylated oxazolines. The reaction proceeded via 2-C-alkylation of amidomalonates followed by heterocyclization involving the triple bond of the suggested intermediate. The intermediate formed via substitution of the chlorine atom in chloro-acetylenephosphonate with acetamidomalonate residue had two nucleophilic sites: carboxylic and amine groups of the amide fragment. Interaction of those two moieties with acetylenic bond could yield oxazoline and aziridine structure, respectively. It was shown that the reaction almost exclusively gave 2-substituted 4,4-bis(ethoxycarbonyl)-5-(dimethoxyphosphorylmethyl-idene)-1,3-oxazolines in 80–90% yield [9] (Scheme 8).

The reaction proceeded stereoselectively with formation of *Z,E*-isomers in the 10 : 1 ratio. The

isomers were isolated and identified. Their configuration (*cis*-arrangement of the dimethoxyphosphoryl group and oxygen atom of the oxazoline ring with respect to the exocyclic double bond) was elucidated from X-ray diffraction data (Fig. 2).

The most interesting and original results were obtained during investigation of the chloroacetylenephosphonates reactions with heterocyclic thiones such as 5-substituted 3-thio-1,2,4-triazoles. New pathway of phosphorylation with chloroacetylenephosphonates was discovered, including attack of the C^2Cl carbon atom of the acetylene bond by the *S*-nucleophilic site of the heterocycle molecule followed by cyclization via C^1 carbon atom of chloroacetylenephosphonate and the nitrogen atom adjacent to the thione group; the overall process yielded the corresponding phosphorylated thiazolo[3,2-*b*][1,2,4]triazol-7-ium chlorides [10].



R^1 = Me, Et, *i*-Pr; R^2 = H, Me, Et, Pr, (*o*-OMe)Ph.

It was shown that reactions of dimethyl chloroacetylenephosphonates with 4-amino(methyl)-3-thio-1,2,4-triazoles further led to elimination of chloromethane from thiazolotriazolium giving the corresponding zwitterion in high yield. Elimination of chloromethane proceeded so readily that attempts to isolate the corresponding chlorides as individual compounds failed, except for 3-amino-6-(dimethoxyphosphoryl)-2-methyl-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ium chloride [11] (Scheme 9).

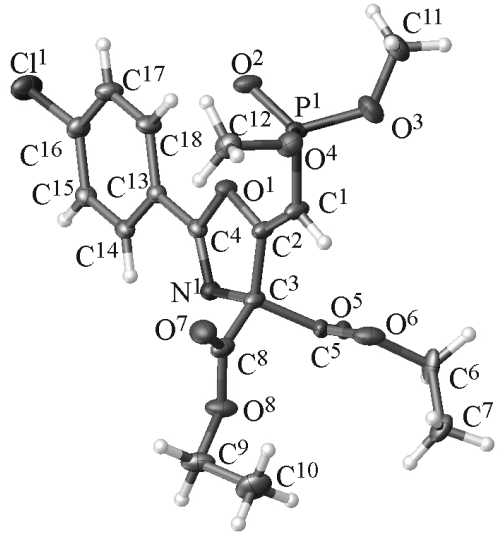
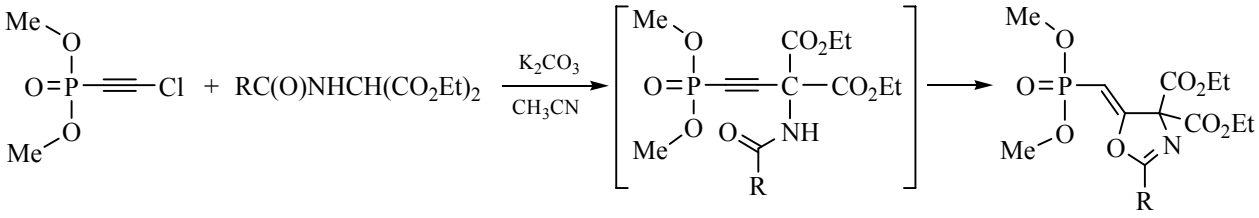


Fig. 2. Crystal structure of *Z*-2-(*p*-chlorophenyl)-4,4-bis-(ethoxycarbonyl)-5-dimethoxyphosphorylmethylidene-1,3-oxazoline.

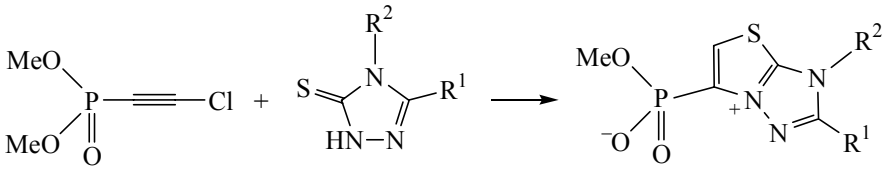
Dealkylation reactions were typical of the other prepared chlorides as well. For example, prolonged interaction of thiazolium chlorides with water at room temperature or upon heating in polar solvent at 60–80°C caused elimination of an alkyl group from the dialkoxyphosphoryl fragment yielding the corresponding alkyl halide and monoalkoxy phosphonates of zwitterionic structure. Hydrolysis under more severe conditions (for example, in concentrated hydrochloric acid) led to complete dealkylation with formation of the corresponding phosphonic acids. Basing on the reactions, a number of 2-substituted 3*H*-thiazolo[3,2-*b*]-[1,2,4]triazol-7-ium 6-alkoxyphosphonates and 3-amino(methyl)-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ium 6-hydroxyphosphonates were prepared [10, 12].

Formation of the heterobicyclic phosphonates of thiazolotriazole structure in the reaction of chloroacetylenephosphonates with 5-substituted 4-amino-(methyl)-3-thio-1,2,4-triazoles was probably due to the thione structure of the latter. Indeed, it is well-known that electron density in the push-pull chloro-

Scheme 8.

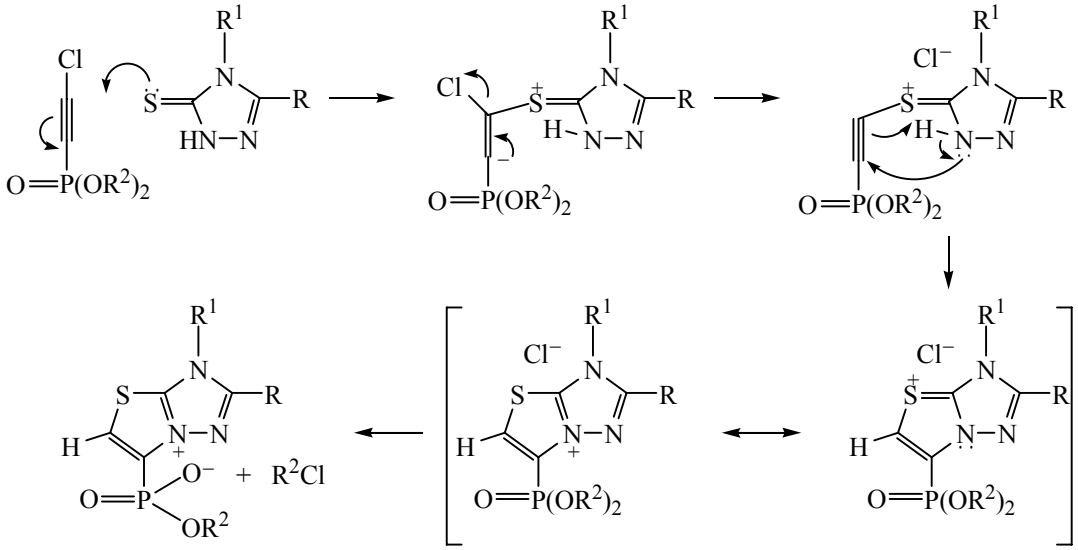


Scheme 9.



R^1 = H, Me, Et, Pr, (*o*-OMe)Ph; R^2 = NH_2, Me.

Scheme 10.



acetylenephosphonates is shifted towards the phosphonate group thus allowing attack of the chloroacetylenic carbon atom with a nucleophile, in particular, thione sulfur atom. It is likely accompanied with the chloride anion eliminating leading to the sulfenium cation. The latter shows strong polarization of the triple bond in the opposite direction compared to the starting chloroacetylenephosphonate. Furthermore, almost synchronized attack of the second nucleophilic site, the nitrogen N^2 atom, at the electron-deficient carbon atom bonded with the phosphorus-containing group may occur. Participation of the thione tautomer in the reaction was confirmed by ^{15}N NMR spectroscopy without proton decoupling observing the doublet signal of N^2. The atarting thiotriazoles existed almost exclusively in the thione form even in such polar solvents as acetonitrile, dimethyl sulfoxide, or HMPA. The proposed mechanism of the reaction of chloroacetylenephosphonates with substituted 3-thio-1,2,4-triazoles is presented in Scheme 10.

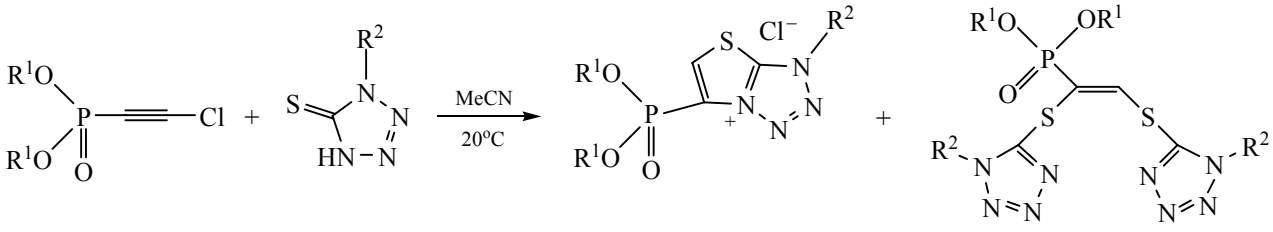
The same reaction scheme was operative during interaction of chloroacetylenephosphonates with equimolar amount of 1-substituted 5-thio-1,2,3,4-tetrazoles in anhydrous acetonitrile at room temperature. The reaction led to preferential formation of the cyclization product—3-substituted 6-(dialkoxyphosphoryl)thiazolo-[3,2-*d*][1,2,3,4]tetrazol-7-ium chlorides—and traces of linear compounds [13] (Scheme 11).

The reaction progress was monitored with ^1H and ^{31}P NMR spectroscopy. After the conversion was complete, ^{31}P NMR spectrum of the reaction mixture contained a signal of the target chloride at 3–8 ppm and weak signals of the alkenylphosphonates (vicinal and geminal) at 7–12 ppm in ratio of about 10 : 1.

Predominant formation of the bicyclic chlorides could be due to the thione structure of the starting thiotetrazoles. However, unambiguous elucidation of the thiotetrazoles structure from ^{15}N NMR data was not possible because of high lability of the hydrogen atom of the tetrazole ring.

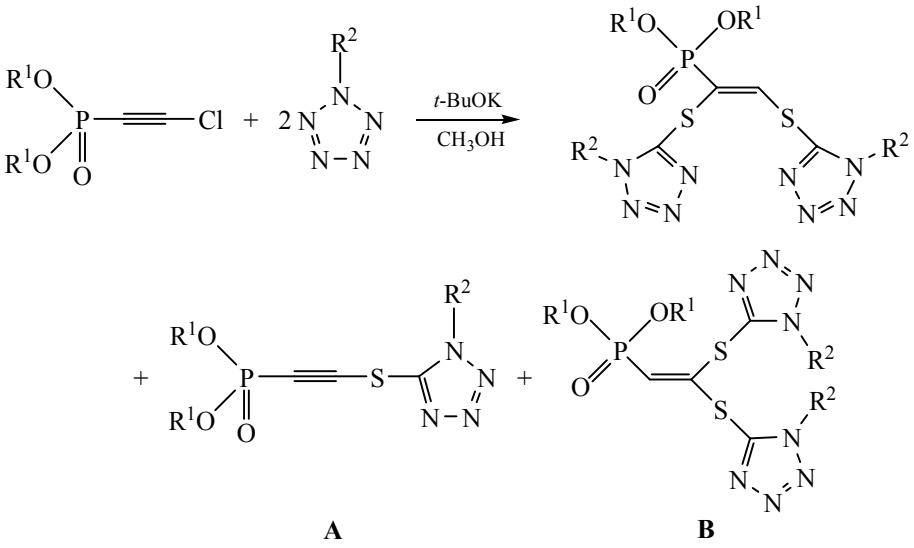
Formation of the alkenylphosphonates was confirmed by independent synthesis performed in methanol using *t*-BuOK as a catalyst at the

Scheme 11.



R = Me, Et, *i*-Pr; R^1 = NH_2, Me, Ph.

Scheme 12.



R = Me, Et, *i*-Pr; R^1 = NH_2, Me, Ph.

chloroacetylenephosphonate : thiotetrazole ratio of 1 : 2. The reaction afforded the alkenylphosphonates with yield of 80–90% [14]. From ^1H, ^{13}C, and ^{31}P NMR spectroscopy data, the reaction mixture additionally contained small amounts of acetylenephosphonate **A**, geminally substituted alkenylphosphonate **B**, and the corresponding chloride (Scheme 12).

To conclude, the main feature of the reaction of chloroacetylenephosphonates with thiotriazoles and thiotetrazoles is formation of phosphorylated bicyclic heteroaromatic compounds due to the thione structure of the starting thioazoles. The reaction proceeds with high chemo- and regioselectivity since the nucleophilic site of the thione always attacks the carbon C^2Cl atom of chloroacetylenephosphonate to form sulfenium cation. The latter reacts with the proton-containing nitrogen atom of triazole (tetrazole) ring exclusively via attack at the phosphorus-substituted carbon atom. Minor formation of dithioazole-substituted alkenylphosphonates is explained by elimination of hydrogen chloride from the sulfenium salt to give intermediate thioazole-substituted acetylenephosphonate, followed by addition of the second thioazole molecule.

In present, study of the synthetic aspects of chloroacetylenephosphonates reactions with various heterocyclic nucleophiles, CH-, and NH-acids are continued by followers of B.I. Ionin and devoted to his memory as creator of such intriguing molecule.

ACKNOWLEDGMENTS

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