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Reviews

Thioethynyl esters of phosphorus acids

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The results of searching for the methods of synthesis of substituted thioethynyl monothio- and dithiophosphates, which are of interest as physiologically active compounds, are summarized. The preparative method for the synthesis of thioesters of *O*,*O*-dialkylmonothiophosphoric acids of a specific type was developed: the reaction of substituted ethynyl bromides with potassium salts of the corresponding monothiophosphoric acids in the presence of an equimolar amount of CuCl. These reactions occur through the stage of formation of Cu^I salts of the corresponding monothiophosphoric acids and are accompanied by redox processes leading to the formation of free radicals. The modified method for the synthesis of substituted thioethynyl monothio- and dithiophosphates is the reaction of Cu^I salts of these acids with the corresponding ethynyl bromides.

Key words: salts of monothiophosphoric and dithiophosphoric acids, thioethynyl and thiopropargyl esters of phosphorus acids.

Thioesters of monothio- and dithiophosphorus acids containing the acetylene bond in the thioester group are of interest as biologically active substances.[1—4] Thioesters in which the acetylene bond is in the β- or γ-position can easily be prepared by the reaction of sodium or potassium monothio- and dithiophosphinates with the corresponding alkynyl halides.[1—3,5—7]

$$\mathrm{RR'P(X)SM + Hal(CH_2)_{\mathit{n}}C{\equiv}CR'' \longrightarrow RR'P(X)S(CH_2)_{\mathit{n}}C{\equiv}CR'' + MHal}$$

R, R′ = Alk, R″ is substituent, X = O, S; $n = 1, 2$

To the beginning of our studies, thioesters of monothiophosphoric acids containing the acetylene bond in the α-position have not virtually been studied. The only publication on the synthesis of similar thioesters of dithiophosphoric acids is available and describes the reaction of dialkoxythiophosphoryl disulfides with lithium acetylenides.[2]

$$\mathrm{(RO)_2P(S)S{-}S(S)P(RO)_2 + LiC{\equiv}CR' \longrightarrow (RO)_2P(S)SC{\equiv}CR'}$$

R = Me, Et; R′ = Me, Ph

Thus, the development of simple and convenient methods for the synthesis of substituted thioethynyl esters of monothio- and dithiophosphoric acids is of doubtless interest.

Substituted thioethynyl esters of *O*,*O*-dialkylthiophosphoric acids have been first obtained in 1980 by the reaction of dialkoxyphosphorylsulfene chlorides with ethynylmagnesium bromides.[8]

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$$(RO)_2P(O)SCl + BrMgC\equiv CR' \longrightarrow (RO)_2P(O)SC\equiv CR'$$

$R = Et, Pr; R' = H, Bu, CH_2SEt, CH_2SBu$

This method has a substantial disadvantage: an inaccessibility of starting dialkoxyphosphorylsulfene chlorides and low yields of thioethynyl esters (<20%).

Attempts to synthesized thioethynyl esters of monothiophosphoric acids by the reaction of potassium *O*,*O*-diethylthiophosphate with ethynyl bromides failed owing to immobility of the Br atom, which is partially "positive" in such compounds.[9]

$$(EtO)_2PSOK + BrC\equiv CR' \nrightarrow (EtO)_2P(O)SC\equiv CR$$

The transformation resembling the Chodkiewicz—Cadiot oxidative dimerization was successfully used for the synthesis of these compounds: ethynylation of acetylenes with ethynyl bromides in the presence of catalytic amounts of CuCl.[10]

$$RC\equiv CH + BrC\equiv CR' \xrightarrow{CuCl,\ Py} RC\equiv C—C\equiv CR'$$

It has been shown[11] that the reaction of alkali metal *O*,*O*-dialkylthiophosphates with substituted ethynyl bromides in the presence of equimolar amounts of CuCl affords the corresponding thioethynyl esters in 60—80% yields. The reaction was carried out in EtOH, Me_2CO, MeCN, THF or without a solvent.

$$(RO)_2PSOM + BrC\equiv CR \xrightarrow{CuCl} (RO)_2P(O)SC\equiv CR'$$

$R = Me, Et, Pr; R' = Bu, Ph, CH_2SEt, CH_2OEt, CH_2OC(O)Me,$ cyclohexyl, cyclohex-1-enyl; M = K, Na

The reaction occurs similarly with *O*,*O*-dialkylthiophosphoric acids in the presence of pyridine.[11]

$$(RO)_2PSOH + BrC\equiv CR' + Py \xrightarrow{CuCl}$$
$$\longrightarrow (RO)_2P(O)SC\equiv CR' + Py\cdot HBr$$

Therefore, it was significant to reveal the role of CuCl in these processes. A possible mechanism is the formation of a π-complex of CuCl at the acetylene bond of ethynyl bromide. However, the fact that the reaction occurs only in the presence of equimolar amounts of CuCl suggests a different mechanism.

It was shown by special experiments that the first stage produces the Cu^I salt of *O*,*O*-dialkylthiophosphoric acid, which further reacts with ethynyl bromide to form the corresponding thioethynyl ester.[7,12]

$$(RO)_2PSOK + CuCl \longrightarrow (RO)_2PSOCu + KCl$$

$$(RO)_2PSOCu + BrC\equiv CR' \longrightarrow$$
$$\longrightarrow (RO)_2P(O)SC\equiv CR' + CuBr$$

The obtained data served as grounds for the modified method for the synthesis of substituted thioethynyl esters of monothiophosphoric acid: the reaction of Cu^I salts of the corresponding acids with substituted ethynyl bromides.[7,12,13] The Cu^I salts of *O*,*O*-dialkyldithiophosphoric acids $(RO)_2PSOCu$ were synthesized by the anion exchange between the K salts of monothiophosphoric acids and CuCl at ~20 °C in alcohol[12]:

R	Yield (%)	M.p./°C
Et	71	100—102
Pr	75	94—96
Bu	69	Viscous oil

The Cu^I salts of monothiophosphoric acids react readily with ethynyl bromides to form the corresponding thioethynyl esters.[13]

$$(RO)_2PSOCu + BrC\equiv CR' \longrightarrow (RO)_2P(O)SC\equiv CR' + CuBr$$

A series of substituted thioethynyl esters of *O*,*O*-dialkylthiophosphoric acids, including those with sterically hindered substituents such as 1-hydroxycyclohexyl and 1-acetoxycyclohexyl groups, was thus synthesized. At the same time, the Cu salts of *O*,*O*-dialkylthiophosphoric acids do not react with alkyl halides.[13]

The distinction in reactivity of the K and Cu^I salts of these acids is clearly manifested by their reaction with 1,4-dibromobut-1-yne. In this reaction, the Cu salt reacts at the ethynyl fragment of dibromobutyne, and the K salt reacts at the alkyl fragment.[13]

$$(EtO)_2PSOM + BrC\equiv CCH_2CH_2Br \longrightarrow$$
$$\xrightarrow{M = Cu} (RO)_2P(O)SC\equiv CCH_2CH_2Br$$
$$\xrightarrow{M = K} (RO)_2P(O)SCH_2CH_2C\equiv CBr$$

1-Bromobut-3-yne reacts only with the K salt and does not react with the copper salt.[13]

$$(EtO)_2PSOM + HC\equiv CCH_2CH_2Br \longrightarrow$$
$$\xrightarrow{M = K} (EtO)_2P(O)SCH_2CH_2C\equiv CH$$
$$\overset{M = Cu}{\nrightarrow}$$

Using the K and Cu^I salts of *O*,*O*-diethylthiophosphoric acid as examples, we showed that unsubstituted propargyl halides react with both salts to form the corresponding thiopropargyl ester.[14]

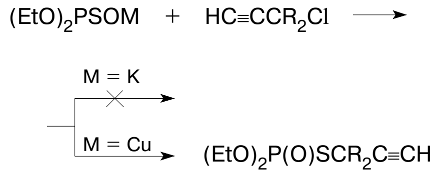
$$(EtO)_2PSOM + HC\equiv CCH_2Hal \xrightarrow{M = K,\ Cu}$$
$$\longrightarrow (EtO)_2P(O)SCH_2C\equiv CH$$

Hal = Cl, Br

In the case of 1,3-dibromopropyne, the reaction also occurs with both salts, however, only the propargyl Br atom reacts.

$$(EtO)_2PSOM + BrC\equiv CCH_2Br \xrightarrow{M = K,\ Cu}$$
$$\longrightarrow (EtO)_2P(O)SCH_2C\equiv CBr$$

It is of interest that sterically hindered propargyl halides, such as 1-chloro-1,1-dimethylpropyne-2 and 1-chloro-1-ethynylcyclohexane, react only with the Cu salt to form thioesters with the tertiary carbon atom at the S atom.[14]



$$(EtO)_2PSOM + HC{\equiv}CCR_2Cl \longrightarrow \begin{cases} \xrightarrow[\times]{M = K} \\ \xrightarrow{M = Cu} (EtO)_2P(O)SCR_2C{\equiv}CH \end{cases}$$

R = Me or R_2 = —$(CH_2)_5$—

Thus, we found a substantial difference in reactivity of the K and Cu^I salts of *O,O*-dialkylthiophosphoric acids with respect to acetylene-containing halides with different structures. Based on the obtained results, we can assume that the reactions of the Cu salts occur *via* the mechanism different from the S_N2 mechanism of nucleophilic substitution, whereas the reactions with the K salts occur, as known, *via* precisely this mechanism. To confirm this assumption, the structure of the Cu^I salt of *O,O*-diethylthiophosphoric acid was studied by the X-ray diffraction (XRD) method,[15] and its reactivity was examined by NMR and ESR.

Note that the K salts of monothiophosphoric acids have the anionic structure and contain the mesomeric $[(RO)_2POS]^-$ anion.[16] According to XRD data,[15] the crystal of this Cu salt consists of tetrameric $Cu_4[(EtO)_2POS]_4$ molecules (Fig. 1) and represents a tetrahedral cluster of Cu atoms coordinated by chelate-bridged diethylthiophosphorus ligands. The S atom of each ligand is bridging toward two Cu atoms of one of the tetrahedral faces, and the O atom is coordinated to the third Cu atom of the same face, the Cu—O and Cu—S bonds being covalent to a great extent, unlike alkali metal salts of monothiophosphoric acids with the ionic character.

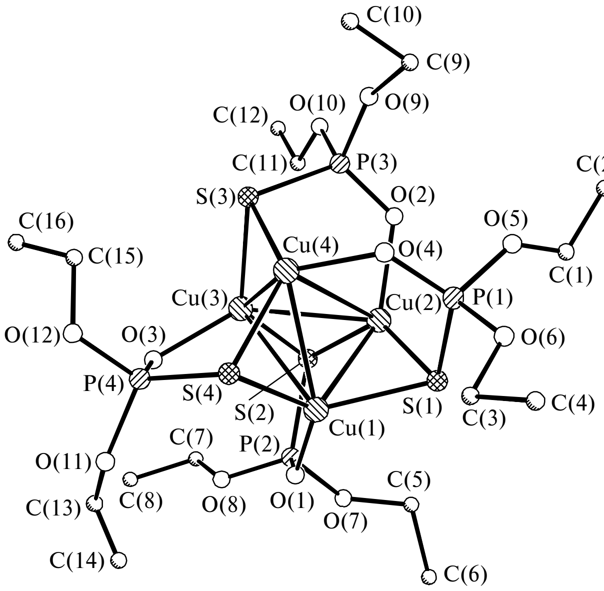


Fig. 1. General view of tetrameric $(EtO)_2PSOCu$.

Using the reaction of the Cu^I salt of *O,O*-diethylthiophosphoric acid (**1**) with phenylbromoacetylene (**2**) as an example, the mechanism of the reaction of the Cu^I salts of monothiophosphoric acids with ethynyl bromides was studied by ^{31}P NMR and ESR methods.[17]

$$\underset{\mathbf{1}}{(EtO)_2PSOCu} + \underset{\mathbf{2}}{BrC{\equiv}CPh} \longrightarrow \underset{\mathbf{3}}{(EtO)_2P(O)SC{\equiv}CPh}$$

A singlet signal with the chemical shift δ_P 38.26 (H_3PO_4 as a standard) is observed in the ^{31}P NMR spectrum of the Cu salt. When an excess of **2** is added to the salt, the signal in the NMR spectrum disappears, and a new signal appeared several days after has δ_P 16.6, which corresponds to the ^{31}P NMR spectrum of authentic *O,O*-diethyl-*S*-phenylethynyl ester of thiophosphoric acid (**3**). Therefore, intermediate paramagnetic species are formed in the reaction mixture. This was confirmed by the ESR spectrum of the reaction mixture recorded at 77 K (Fig. 2). Pronounced anisotropy of this spectrum is characterized by two values of *g* factor (g_1 = 2.083 and g_2 = 2.460), which are very close to those for several Cu^{II} complexes with the structure of a distorted octahedron.[18,19] Evidently, when the Cu salt (**1**) reacts with compound **2**, Cu^I is oxidized to the bivalent state to form paramagnetic complexes stable at a low temperature. Based on this, we assumed that the one-electron reduction of the ≡C—Br bond results in the dissociative capture of electrons with the formation of the Br^- anion and $^{\bullet}C{\equiv}CPh$ radical, which is transferred to the second molecule of salt **1**. As a result, intermediate complexes **4** and **5** are formed.

$$(EtO)_2PSOCu + BrC{\equiv}CPh \longrightarrow$$
$$\longrightarrow \underset{\mathbf{4}}{(EtO)_2PSOCuBr} + {}^{\bullet}C{\equiv}CPh$$

$$(EtO)_2PSOCu + {}^{\bullet}C{\equiv}CPh \longrightarrow \underset{\mathbf{5}}{(EtO)_2PSOCuC{\equiv}CPh}$$

The isolation of diphenyldiacetylene PhC≡C—C≡CPh from the reaction mixture confirms the formation of the $^{\bullet}C{\equiv}CPh$ radical. The possibility of formation of a complex of the type **4** was shown for the reaction of potassium *O,O*-diethylthiophosphate and $CuCl_2$.[20] In this case, at the 1 : 1 ratio of reactants only one Cl atom is replaced by the diethoxylphosphorylthio group to

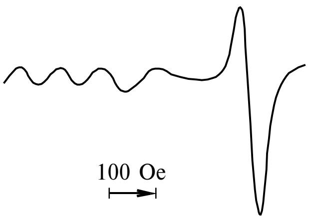


Fig. 2. ESR spectrum of the reaction mixture Et_2POSCu + BrC≡CPh.

form unstable diethoxyphosphoryl thiocuprichloride (**6**) as an intermediate.

$$2\ (EtO)_2PSOK + 2\ CuCl_2 \longrightarrow$$
$$\longrightarrow 2\ \underset{\mathbf{6}}{(EtO)_2PSOCuCl} \longrightarrow [(EtO)_2P(O)S]_2 \cdot 2CuCl$$

Complexes **4** and **5** are unstable, most likely, and reduced to thermodynamically stable Cu^I compounds. These processes can be presented by the following scheme[17]:

$$(EtO)_2PSOCuC{\equiv}CPh \longrightarrow (EtO)_2PSOCu + {}^{\bullet}C{\equiv}CPh$$
$$(EtO)_2PSOCuBr + {}^{\bullet}C{\equiv}CPh \longrightarrow$$
$$\longrightarrow (EtO)_2P(O)SC{\equiv}CPh + CuBr$$

Thus, the differences in reactivity of the Cu^I and K salts of *O,O*-dialkylthiophosphoric acids can be explained as follows. The Cu^I salts represent a tetrahedral cluster in which the dialkylthiophosphorus ligands are bound to the metal atom by the covalent (to a great extent) Cu—S and Cu—O bonds. Naturally, unlike the isolated *O,O*-dialkylthiophosphorus anion of the similar K salt, the strongly coordinated *O,O*-dialkylthiophosphorus ligand in the copper complex does not possess nucleophilic properties and does not react with alkyl halides. At the same time, the covalently bound Cu^I atom is capable of participating in redox processes, due to which the reaction with ethynyl bromides occurs because their Br atom is partially "positive" as in hypohalides.[9] However, from this point of view it remains unclear why particular propargyl halides react with both K and Cu^I salts of *O,O*-dialkylthiophosphoric acids and other halides react with the Cu^I salts only.[14] To answer this question, we studied the ESR spectra of reaction mixtures of various halides of the propargyl type with the Cu^I salt of *O,O*-diethylthiophosphoric acid in a toluene solution.[20]

$$(EtO)_2PSOCu + HalCR_2C{\equiv}C{-}R' \longrightarrow [?] \longrightarrow$$
$$\longrightarrow (EtO)_2P(O)SCR_2C{\equiv}C{-}R' + CuHal$$

In all cases, the paramagnetic Cu^{II} complexes are formed, which is confirmed by the ESR spectra of these mixtures recorded in vitrified toluene solutions at 77 K. Thus, we may conclude that in the reaction of the Cu^I salts of *O,O*-dialkylthiophosphoric acids with propargyl halides, as well as in the reaction with ethynyl bromides, they are oxidized to the bivalent state to form intermediate paramagnetic Cu^{II} complexes stable at low temperatures. Under the reaction conditions where the temperature of the reaction mixture is 20—60 °C, these complexes are, most likely, unstable and readily reduced to thermally stable Cu^I compounds to form thiopropargyl *O,O*-dialkylthiophosphates.

$$(EtO)_2PSOCu + HalCR_2C{\equiv}C{-}R' \longrightarrow$$
$$\longrightarrow (EtO)_2PSOCuHal + {}^{\bullet}CR_2C{\equiv}C{-}R' \longrightarrow$$
$$\longrightarrow (EtO)_2P(O){-}S{-}CR_2{-}C{\equiv}C{-}R' + CuHal$$

The found methods for the synthesis of thioethynyl esters of monothiophosphoric acids were extended to the synthesis of similar thioesters of dialkyldithiophosphoric acids. It was shown that ethynyl bromides react with the K salts of *O,O*-dialkyldithiophosphoric acids in the presence of equimolar amounts of CuCl or with the Cu^I salts of these acids to form the corresponding thioethynyl esters.[7,11]

$$R'C{\equiv}CBr \xrightarrow[\boxed{(RO)_2PSSCu}]{(RO)_2PSSK\ +\ CuCl} (RO)_2P(S)SC{\equiv}CR'$$

R = Me, Et; R′ = Bu, Bu^t

The reaction of the K salt of *O,O*-diethyldithiophosphoric acid with 1-bromohex-1-yne in the presence of equimolar amounts of CuCl in EtOH or Me_2CO was studied in detail. Under these conditions, the corresponding thiohexynyl ester was obtained in a yield of at most 20%.[7,11] The special experiments showed that, as in the case of the K salts of monothiophosphoric acids, the reaction of similar salts of dithiophosphoric acids with substituted ethynyl bromides in the presence of CuCl occurs through the formation of the corresponding Cu^I salts.[7,11]

$$(RO)_2PSSK + CuCl \longrightarrow (RO)_2PSSCu + KCl$$

R = Me, Et, Pr, Bu

Several Cu^I salts of dialkyldithiophosphoric acids were isolated in the individual state by the exchange of anions between the K salts of dialkyldithiophosphoric acids and CuCl. The reaction was performed in EtOH and Me_2CO; the yields of the Cu salts were 20—75% of the theoretical values. The prepared Cu salts were, as a rule, poorly soluble in organic solvents. The modifications soluble in ether and benzene were isolated for the Cu salts of *O,O*-dimethyl and *O,O*-diethyldithiophosphoric acids (60 and 20% yields, respectively[7]):

R	Yield (%)	M.p./°C
Me	60	135—140*
Me	25	Decomp.
Et	20	192—194*
Et	70	Decomp.
Pr	75	>200 decomp.
Bu	75	131—133

* Insoluble in Et_2O and PhH.

It was assumed that in the reaction of the Cu salts of dialkyldithiophosphoric acids with ethynyl bromides the yields of the corresponding thioethynyl esters are determined by the amount of soluble modifications of these salts. This was indirectly confirmed by similar reactions in the absence of solvents, due to which thioethynyl esters of dialkyldithiophosphoric acids were obtained in 80—85% yields of the theoretical values.[7,12]

Thus, we developed the synthesis of substituted thioethynyl esters of dialkylmonothiophosphoric and dialkyldithiophosphoric acids and sterically hindered thiopropargyl esters of dialkylmonothiophosphoric acids, which are of interest as biologically active compounds.

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