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Highly regioselective heterocyclization reactions of 1*H*-1,2,4-triazole-3-thiols with chloroacetylenephosphonates

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ABSTRACT

1-Chloroacetylene-2-phosphonates react with 1*H*-1,2,4-triazole-3-thiols in anhydrous acetonitrile with high regioselectivity to form the fused heterocycles, 6-(dialkoxyphosphoryl)-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ylium chlorides **1**–**5**. A significant difference from the previously known reactions of binucleophiles with haloacetylenes is the involvement of both acetylenic carbon atoms in the heterocycle formation. A reaction mechanism is hypothesized that assumes the formation of a sulfenium cation at the acetylene C-1 atom followed by attack of the C-2 atom by the ring N-2 atom. Compounds **1**–**5** easily lose one alkyl group from the dialkoxyphosphoryl fragment to form zwitterions (e.g., **6**–**8**) which further can be transformed into inner salts **9** and **10** when heated with concentrated hydrochloric acid.

Five-membered heterocycles with two or three heteroatoms, such as imidazoles, thiazoles, triazoles and others, are key structural units in many pharmaceutical preparations.[1] The usual course of the synthesis of such compounds consists of the reaction of binucleophiles (diamines, diols and thioloamines containing nucleophilic sites at the vicinal position) with carbonyl and carboxyl compounds. Such structures have increasingly been created by using 1-haloacetylenes. The reactivity of the latter is sufficiently high when the second acetylenic carbon atom is connected to an electron-withdrawing activating fragment such as a carbonyl, carboxyl or phosphoryl group.[2] Less active 1-haloacetylenes containing an electron-donor group at the 2-position react with binucleophiles in the presence of a catalyst.[3] The haloacetylenes show advantages over carbonyl (carboxyl) containing reagents as they do not release water, which may affect the reaction course.

The reactions of haloacetylenes with binucleophiles usually proceed regioselectively with attack by both nucleophilic sites on the acetylenic carbon atom C-1 connected to the halogen. For example, reactions of 1-chloroacetylene-2-phosphonates with *ortho*-phenylenediamine, *ortho*-aminophenol, 1,2-alkanediols and vicinal hydroxyalkylamines afford 2-(dialkoxyphosphorylmethyl)-substituted benzimidazoles, benzoxazoles, 1,3-oxolanes and 4,5-dihydrooxazoles, respectively.[2] A similar trend in the reactions with binucleophiles is known for a number of other haloacetylenes.[4]

In continuation of our studies on the reactions of chloroacetylenephosphonates with mono- and binucleophiles, we utilized these highly reactive compounds in condensations with heterocyclic binucleophiles with the aim of obtaining phosphorylated five-membered condensed heterocycles. As heterocyclic binucleophiles, we used readily accessible 5-substituted 4-amino-1*H*-1,2,4-triazole-3-thiols produced by the reaction of carboxylic acids and their derivatives with thiocarbazide.[5]

To our best knowledge, there is only one publication[4] concerning the reaction of 4-aminotriazoles with haloacetylenes. The products were fused heterocyclic systems comprising sulfur and NH_2 groups as the nucleophilic sites and one haloacetylene carbon atom C-1 (Scheme 1).

However, we recently encountered an unexpected course of the reaction of dimethyl 1-chloroacetylene-2-phosphonate with 4-amino-5-methyl-1*H*-1,2,4-triazole-3-thiol. The reaction proceeded readily under mild conditions with high selectivity to afford 3-amino-6-(dimethoxyphosphoryl)-2-methyl-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ylium chloride (**1**) as a result of involvement of both carbon atoms of the haloacetylenic compound in formation of a condensed thiazolotriazolium ring[6] (Scheme 2).

The reaction was conducted by stirring equivalent amounts of the reagents for 3–5 h in anhydrous acetonitrile at room temperature. It is noteworthy that the amino group at position 4 was not involved in the reaction, while the condensed thiazole ring was

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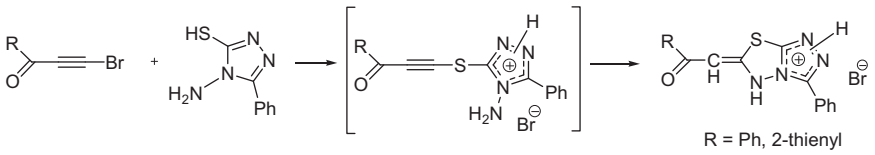
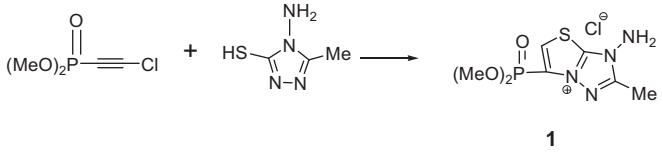
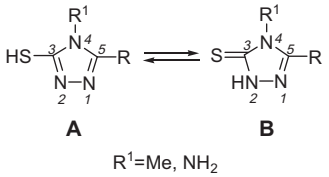


Scheme 1. Reaction of the 4-amino-3-mercapto-5-phenyl-1,2,4-triazole with 1-bromo-2-acyl acetylenes.



Scheme 2. Synthesis of compound **1**.



Scheme 3. Tautomeric forms of 1*H*-1,2,4-triazole-3-thiols.

formed through the nitrogen atom N-2 of the triazole ring resulting in a quaternary salt. The structure of compound **1** was proved by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and an XRD study (Fig. 1).

To identify the causes of the unusual reaction course, we explored in more detail the structure of the parent 3-thiol-1,2,4-triazole, expanded the range of compounds studied and applied a variety of reaction conditions.

The 1*H*-1,2,4-triazole-3-thiols contain several nucleophilic sites and can exist in two tautomeric forms: thiol **A** and thione **B** (Scheme 3).

Using ^{15}N NMR spectroscopy (see Table 1), we found that the original triazoles existed almost exclusively as the thione isomers **B**. The spectra of 4-aminotriazoles contain three signals due to the ^{15}N nuclei of the triazole ring and a signal for the amine nitrogen nucleus. The accuracy of the assignment of the signals was confirmed by recording the spectra with no $^{15}N-^{1}H$ decoupling: the signals of the N-1, N-4 nuclei remained as singlets, whilst the signal for N-2 was split into a doublet, and that of the amine nitrogen was a triplet. These spectral data correspond to the thione structure.

We found that regardless of the substituents at C-5 of the thionotriazole, as well as when the substituent R^1 at C-4 was a methyl instead of an amino group, the reaction in anhydrous acetonitrile,[6] in all cases, resulted in the formation of condensed heterocycles **1–5** (Scheme 4) with the same core structure, that is 2,3-substituted 6-(dialkoxyphosphoryl)-2-methyl-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ylium chlorides.

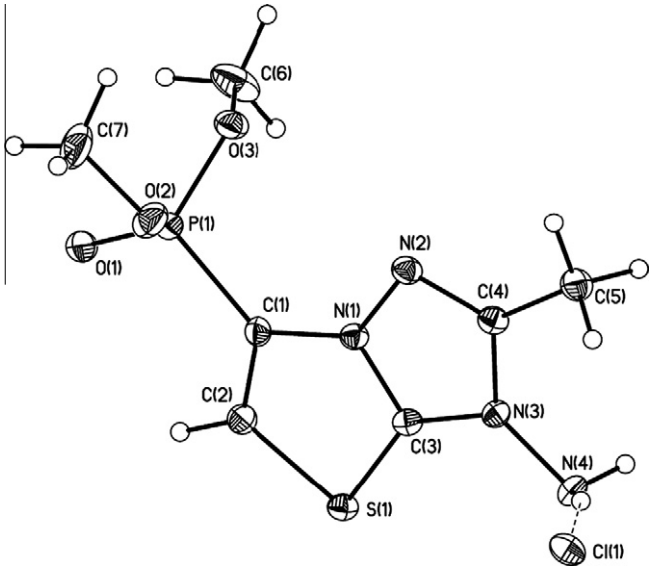


Figure 1. Crystal structure of compound **1** (SHELXTL/ORTEP).

Chlorides **1–5** (see Table 2) were crystalline substances melting at 200–250 °C with decomposition, and were poorly soluble in organic solvents, and readily soluble in water, dimethyl sulfoxide, methanol and ethanol.[7]

The structure of the previously synthesized[6] salt **1** was proved by an X-ray diffraction study[8] (Fig. 1). The structures of compounds **2–5** follow from the similarities of their NMR and mass spectral characteristics to those of compound **1** (see Table 4).

In the ^{1}H NMR spectra of compounds **1–5** the sole proton C-5-H on the thiazolotriazolium ring resonated at a low field at ~8.5 ppm as a doublet due to spin–spin coupling with the phosphorus nucleus, J_{HP} 8.0 Hz. The HCO protons in the R^2 group of the $(R^2O)_2P(O)$ fragment resonated as typical multiplets split by the phosphorus nucleus with the coupling constant $^{3}J_{HP}$ ~12 Hz. The integral intensities of the signals corresponded to the proposed structures. In the ^{13}C NMR spectra the signal of the C-6 carbon atom linked directly to the phosphorus atom was a doublet of low intensity at 125 ppm with a spin–spin coupling constant, $^{1}J_{CP}$ 215–219 Hz, typical of phosphonates with an sp^2-hybridized carbon atom. The signal due to the C-5 carbon of greater intensity was shifted slightly downfield and split into a doublet, 131–132 ppm, $^{2}J_{CP}$ 14–18 Hz. The assignment of this signal was confirmed by recording the ^{13}C NMR spectrum of compound **1** without proton decoupling: the signal was further split into a doublet with a coupling constant, $^{1}J_{CH}$ 204.2 Hz, while the signal at 125 ppm was split with a small constant, $^{2}J_{CH}$ 9.0 Hz.

Prolonged exposure of compounds **1–5** to water, or heating in a polar solvent at a temperature of 50–70 °C, resulted in cleavage of one alkyl group of the dialkoxyphosphoryl fragment with formation of a phosphonate monoanion and release of an alkyl halide, to form the corresponding monophosphonates of zwitterionic structure (see Table 3). Cleavage of the methyl group occurred readily, resulting in a low yield of compound **1** and the failure to isolate diesters corresponding to the zwitterions **7** and **10**. Heating zwitterions **6–8** with hydrochloric acid resulted in removal of the second alkyl group on the phosphoryl fragment to form zwitterions of acid structure (internal salts). The zwitterions **6–8** were crystalline substances melting at temperatures above 200 °C with decomposition.[7] Zwitterions **9** and **10** were crystalline substances melting with decomposition at temperatures above 200 °C, and were readily soluble in water, and poorly soluble in organic solvents including alcohols.[9]

The structures of zwitterions **7**[10] and **9**[11] were proved by X-ray diffraction studies (Figs. 2 and 3, respectively). The structures of