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Reaction of chloroacetylenephosphonates with 5-thiotetrazoles

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alkenephosphonates

ABSTRACT

1-Chloroacetylene-2-phosphonates react with 1-substituted 5-thio-1*H*-1,2,3,4-tetrazoles in anhydrous acetonitrile to form new fused heterocycles, 6-(dialkoxyphosphoryl)-3*H*-[1,3]thiazolo[3,2-*d*][1,2,3,4]tetrazol-7-ium chlorides, with a small quantity of *Z*-dialkyl (1,2-bis{[1-amino(methyl/phenyl)-1*H*-tetrazol-5-yl]sulfanyl}ethenyl)phosphonates.

Pharmaceutical chemistry has led to many drugs containing a tetrazole ring as a structural fragment. Tetrazoles are not found in nature, and there is scarce data on their biological activity. These compounds are known to be resistant to metabolic processes. They can be considered as isosteric analogs of various functional groups in drugs. Thus, 5-substituted tetrazoles are nonclassical isosteres of the carboxyl group and the thiazolidinedione ring, and 1,5-substituted tetrazoles can be used as isosteres of the *cis*-amide bond of peptides. A class of cephalosporin antibiotics is known, which includes a 1-substituted 5-thiotetrazole fragment.[1]

Our previous work has shown the success of introducing a 5-substituted 3-thio-1,2,4-triazole (in the thione form) in regioselective reactions with chloroacetylenephosphonates to give phosphorylated heterocycles with fused rings of the thiazolotriazolium type.[2]

In this study, we have performed a similar reaction of chloroacetylenephosphonates[3] with 1-substituted 5-thiotetrazoles.[4] Earlier, the thione structure of 5-substituted 3-thio-1,2,4-triazole was clearly proven using ^{15}N NMR spectroscopy: the spectrum showed a doublet splitting for the signal due to the N-2 atom.[2] We have applied the same strategy to reveal tautomeric forms of 5-substituted thiotetrazoles. However, we failed to establish clearly the structures of the thiotetrazoles by ^{15}N NMR spectroscopy, probably because of the high acidity of the N-hydrogen atom. In the ^{15}N NMR spectra of the thiotetrazoles (recorded with and without proton decoupling) we observed only singlet signals. In the ^{1}H NMR spectra of the tetrazole, the ring proton appeared as a broad signal due to proton exchange between two positions. Table 1 shows the ^{13}C and ^{15}N NMR spectral data of thiotetrazoles.

The reaction was carried out in anhydrous acetonitrile using an equimolar ratio of the reactants, with stirring at 20–60 °C. Monitoring of the reaction progress was performed using ^{31}P NMR spectroscopy. The reaction led to the complete disappearance of the signal of the initial chloroacetylenephosphonate and resulted in the preferential formation of the new cyclization products, 3-substituted 6-dialkoxyphosphoryl-3*H*-thiazolo[3,2-*d*]tetrazol-7-ium chlorides **1**–**9**. However, it did not proceed chemoselectively: new alkenephosphonates of linear structure, *Z*-dialkyl-(1,2-bis{[1-amino(methyl/phenyl)-1*H*-tetrazol-5-yl]sulfanyl}ethenyl)phosphonates **10**–**12** were also obtained (see Scheme 1).[5]

The structures of the products were established on the basis of ^{1}H, ^{13}C, and ^{31}P NMR spectra. For example, in the ^{1}H NMR spectrum of compound **3** upfield region there was a characteristic doublet due to the vinyl proton of the thiazole fragment of the fused ring at δ 8.08 ppm ($^{3}J_{HP}$ 11.0 Hz). The ^{13}C NMR spectrum of compound **3** was characterized by the doublet signals of three carbon atoms of the thiazole fragment: C-6 at 120.71 ppm ($^{1}J_{CP}$ 216.3 Hz), C-5 at 137.39 ppm ($^{2}J_{CP}$ 24.1 Hz), and C-8 at 150.07 ppm ($^{3}J_{CP}$ < 1.0 Hz). The chemical shifts of the phosphorus nuclei in chlorides **1**–**9** were in the range of 3.1–8.8 ppm (see Table 2). Recrystallization of

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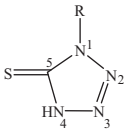
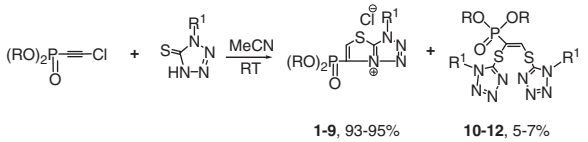
Table 1
NMR spectral data of 5-thiotetrazoles and 1-methyl-5-thiotetrazole sodium salt[a]



R	δ_C, ppm	δ_N, ppm
CH_3	33.44 (CH_3); 166.04 (C-5)	226.02 (N-1); 288.33 (N-4); 363.78 (N-2); 374.04 (N-3)
Ph	124.98 (*m*-CH); 129.81 (*o*-CH); 130.30 (*p*-CH); 134.27 (*ipso*-CH); 162.16 (C-5)	247.20 (N-1); 336.68 (N-4); 375.98 (N-2); 394.65 (N-3)
NH_2	156.08 (C-5)	77.23 (NH_2); 246.27 (N-1); 312 (N-4); 377.03 (N-2); 387.07 (N-3)
CH_3 (Na salt)	32.99 (CH_3); 168.11 (C-5)	224.16 (N-1); 320.92 (N-4); 363.68 (N-2); 385.55 (N-3)

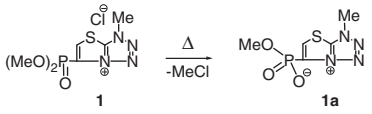
[a] Bruker avance 400, 100.61 MHz (^{13}C), 40.54 MHz (^{15}N), solvent DMSO-d_6.



1-9, 93-95% **10-12**, 5-7%

R=Me, R^1=Me (**1**); R=Me, R^1=Ph (**2**); R=Et, R^1=Me (**3**);
R=Et, R^1=Ph (**4**); R=Me, R^1=NH_2 (**5**); R=Et, R^1=NH_2 (**6**);
R=*i*-Pr, R^1=Me (**7**); R=*i*-Pr, R^1=Ph (**8**); R=*i*-Pr, R^1=NH_2 (**9**);
R=Me, R^1=Me (**10**); R=Et, R^1=Me (**11**); R=Et, R^1=Ph (**12**)

Scheme 1. Synthesis of compounds **1**–**9**.



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

chloride **1** from a mixture of MeOH and *i*-PrOH allowed the product of dealkylation to be isolated, that is, zwitterionic monoester **1a**, that was consistent with published data (see Scheme 2).[2]

The ^{15}N NMR spectrum of compound **1a** contains singlet resonances due to N-1 at δ_N 380.74, N-2 at δ_N 348.88 and N-3 at δ_N 216.65, and a doublet for N-7 at δ_N 268.28 ($^2J_{NP}$ 5.6 Hz). More convincing evidence was obtained from X-ray data. Figure 1 shows a general view of representative zwitterion **1a**.[6]

The formation of the linear products **10**–**12** and their structures were confirmed by an authentic synthesis, which was performed using anhydrous methanol as the solvent, potassium *tert*-butoxide as the catalyst, and the reactants in a ratio of 1:2. The yields of alkenes **10**–**12** in this synthesis were 80–85%.[7]

The structures of trisubstituted alkenes **10**–**12** were confirmed by NMR spectroscopy. In the ^1H NMR spectrum the alkene proton resonated upfield as a doublet in the range 8.50–8.99 ppm, with a spin–spin coupling constant with the phosphorus nuclei ($^3J_{HP}$) of 13.5–16.0 Hz. The ratio of the integral intensities of the signals corresponded with the assumed structures of the compounds. The ^{13}C NMR spectra also confirmed the structures of phosphorylated alkenes **10**–**12**. In the ^{13}C NMR spectrum of compound **11**, signals due to the carbons of the alkene fragment appeared upfield: C-1, δ_C 117.75 ppm ($^1J_{CP}$ 196.1 Hz), C-2, δ_C 151.16 ppm ($^2J_{CP}$ 23.1 Hz).

There were also singlet signals for the two carbon atoms of the tetrazole fragment (C=N) at δ_C 149.11–149.94 ppm. The chemical shifts of the phosphorus nuclei of compounds **10**–**12** were in the range of 7.30–12.00 ppm.

X-ray diffraction data of isolated alkene **12** also confirmed the formation of the phosphonate of a trisubstituted *Z*-alkene (Fig. 2).[8]

The same compound was obtained in high yield by an authentic synthesis involving the reaction in anhydrous methanol catalyzed by potassium *tert*-butoxide in a ratio of 1:2. The ^{31}P NMR spectrum of the reaction mixture indicated the formation of a small amount of the product with a cyclic structure, which points to the occurrence of the thiotetrazole thionyl form, and related thiolotetrazolylacetylenephosphonate.

These results suggest that the thiotetrazole thiol form reacts with chloroacetylenephosphonates to produce compounds **10**–**12** with linear structure. A special feature of the reaction of chloroacetylenephosphonate with thiotetrazoles is the formation of compounds **10**–**12** with thiotetrazole fragments at both carbon atoms of the alkene system, in contrast to the published results,[9] pointing to the formation of substituted geminal alkenephosphonates under similar reactions. The formation of vicinal substituted alkenes in this case may be associated with a high mobility for the proton in the tetrazole moiety, what causes elimination of HCl from the

Table 2
NMR spectral data of compounds **1**–**9** and **1a**

Compound	NMR spectral data: δ, ppm (*J*, Hz)[a]					ESI-MS, *m*/*z* [M–Cl][b]
	C-5-H($^3J_{HP}$)	C-5 ($^2J_{CP}$)	C-6 ($^1J_{CP}$)	C-8 ($^3J_{CP}$)	P	
1	8.09 (11.0)	138.37 (24.9)	119.25 (216.8)	149.78 (<1.0)	8.62	249.2070
2	8.19 (11.2)	136.31 (24.9)	120.64 (215.4)	149.95 (<1.0)	7.99	311.2764
3	8.08 (11.0)	137.39 (24.1)	120.71 (216.3)	150.07 (<1.0)	5.63	277.2561
4	8.30 (11.3)	136.43 (24.9)	121.14 (216.1)	150.23 (<1.0)	5.55	339.3296
5	8.29 (11.5)	137.57 (24.2)	119.11 (218.8)	150.74 (<1.0)	8.81	250.1950
6	8.29 (11.3)	136.69 (25.1)	120.54 (217.3)	150.82 (<1.0)	5.98	278.2479
7	8.08 (11.3)	136.52 (25.6)	121.86 (217.4)	150.27 (<1.0)	3.32	305.3132
8	8.29 (11.0)	135.72 (25.1)	122.44 (216.3)	150.35 (<1.0)	3.14	367.3824
9	8.30 (11.6)	135.93 (24.9)	121.66 (218.8)	150.89 (<1.0)	3.53	306.3010
1a	8.25 (4.8)	132.19 (13.0)	131.15 (179.9)	155.48 (8.0)	−7.09	256.9874[M+Na]

[a] Bruker avance 400, 400.13 MHz (^1H), 100.61 MHz (^{13}C), 161.98 MHz (^{31}P), 40.54 MHz (^{15}N), solvents CD_3OD-d_4 and $CDCl_3$.
[b] Bruker micrOTOF.

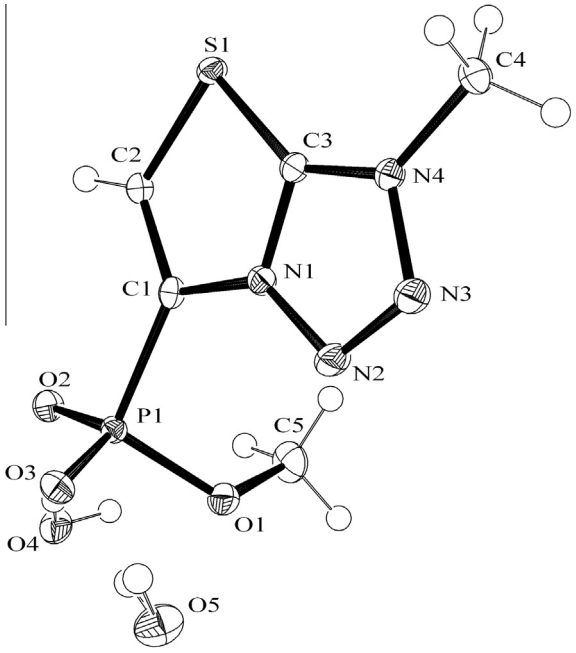


Figure 1. Crystal structure of zwitterion **1a** (SHELXTL/ORTEP).

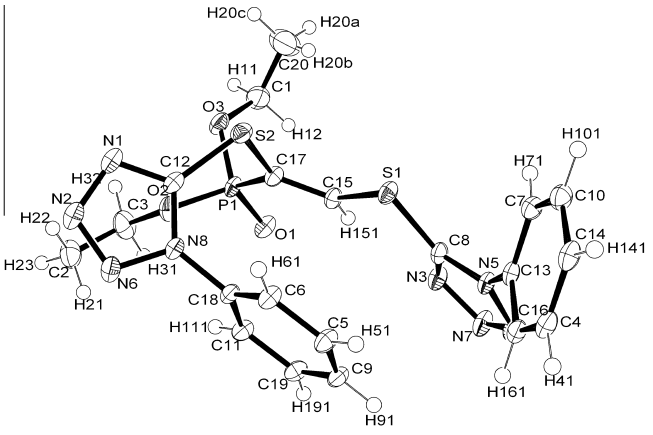
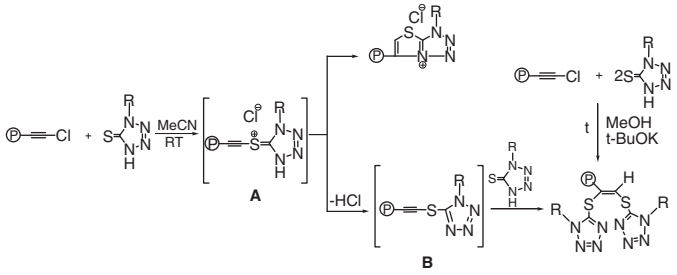


Figure 2. Crystal structure of compound **12** (SHELXTL/ORTEP).

intermediate sulfenic salt **A** to form an acetylenephosphonate-containing thiotetrazole residue. Polarization of the acetylene bond in the thiolotetrazole-acetylenephosphonate is probably almost absent, as seen from the ^{13}C NMR spectral data: both the acetylene carbon atoms have almost the same chemical shifts.

It should be noted that in the ^{1}H, ^{13}C, and ^{31}P NMR spectra of the reaction mixture, in addition to the signals of compounds **1**–**9** and **10**–**12**, we detected signals related to the acetylenic structure **B**. Product **B** was identified from the ^{13}C NMR spectra, which contained doublet signals due to C-1 at δ 85.1–89.6 ppm ($^{1}J_{CP}$ 288.8–292.2 Hz), and C-2 at δ 82.1–84.2 ppm ($^{2}J_{CP}$ 49.3–51.3 Hz). The value of $^{1}J_{CP}$ coupling constant clearly shows the bonding between the phosphorus atom and the sp^3-hybridized carbon atom. For comparison, the related data in the ^{13}C NMR spectrum of the original chloroacetylenephosphonates are as follows: C-1, δ 58.3–59.7 ppm ($^{1}J_{CP}$ 306.8–308.3 Hz), C-2, δ 79.7–80.6 ppm ($^{2}J_{CP}$ 57.3–58.6 Hz).

According to the obtained results, we assume the following mechanism for the reaction of chloroacetylenephosphonates with 1-substituted 5-thiotetrazoles (see Scheme 3).



Scheme 3. A plausible reaction mechanism.

Due to the presence of the labile proton in the tetrazole moiety of the intermediate sulfenyl chloride, in addition to the main pathway involving attack of the N-4 atom on the phosphorus-substituted acetylene carbon atom, elimination of hydrogen chloride occurs to form the product of chlorine substitution, followed by addition of a second molecule of thiotetrazole to give the corresponding phosphorylated 1,2-bis(thiotetrazolyl)-substituted alkene. However, the involvement of the thiotetrazole thiol forms in this process cannot be completely denied. The formation of fused cyclic compounds **1**–**9** is associated only with the thione form of the thiotetrazole through the formation of a sulfenium ion, which leads to the reverse polarization of the acetylene bond compared to the initial chloroacetylenephosphonate.[2]

In conclusion, phosphorylated thiazolotetrazolium chlorides **1**–**9** have not been described previously in the literature. The structures of these substances suggest a potentially wide range of biological activity. Nonphosphorylated analogs were obtained in the 1970s through multi-stage syntheses as the salts, mainly as the perchlorate or sulfite salts. The latter were found to be biologically active.[10]

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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4. 1-Phenyl-5-thiotetrazole and 1-methyl-5-thiotetrazole are commercially available (Alfa Aesar). 1-Amino-5-thiotetrazole was synthesized as described in: Wagatsuma, M.; Hatsuno, S.; Yamaguchi, T.; Ohshima, S. U.S. Patent 4,576,938, 1986.
5. *Typical experimental procedure for the synthesis of compounds **1**–**9**.* To a solution of 5 mmol of a dialkyl chloroacetylenephosphonate in 10 ml of anhydrous

MeCN was added 5 mmol of 1-amino(methyl/phenyl)-5-thiolo-1,2,3,4-tetrazole under vigorous stirring at room temperature. The resulting suspension was stirred vigorously at room temperature for 13–18 h. The obtained precipitate was filtered off (for compounds with a methyl substituent) and washed with Et_2O to afford the thiazolotetrazolium salts **1**–**9**. Products with a phenyl substituent were clear solutions. The solvent was removed under vacuum, and the viscous residue was recrystallized from MeOH/*i*-PrOH (1:1) for compound **1a**, and from EtOH/H_2O (1:1) for other compounds.

6. The X-ray crystal structure for compound **1a** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 932040. Formula: $C_5H_{11}N_4O_5PS$. Crystal system orthorhombic, space system $P2_12_12_1$. Unit cell parameters: $a = 6.89430(17)$ Å, $b = 9.1278(3)$ Å, $c = 17.2139(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$. $V = 1083.27(5)$ Å^3; $T = 100(2)$ K; $Z = 4$; $\rho_{calc} = 1.657$ Mg/m3; $\mu = 4.253$ mm^{-1} (for CuKα, $\lambda = 1.54184$ Å); $F(000) = 560$; full-matrix least-squares on F^2; data = 2148; parameters = 163; restraints = 2; R(all) = 0.0253; wR(all) = 0.0639; *GoF*(all) = 1.007.
7. *Typical experimental procedure for the synthesis of compounds* ***10*****–*****12***. To a mixture of 2.5 mmol of a dialkyl chloroacetylenephosphonate in 10 ml of anhydrous MeOH and a catalytic amount of KO^{t}Bu (0.3 mmol) was added 5 mmol of 1-amino(methyl/phenyl)-5-thiolo-1,2,3,4-tetrazole. The mixture was stirred at room temperature for 1 h and then at 50–60 °C for 8–10 h. The solvent was removed under vacuum and the viscous residue was recrystallized from aqueous EtOH. The yields of alkenes **10**–**12** were 80–85%.
8. The X-ray crystal structure for compound **12** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 932042. Formula: $C_{20}H_{21}N_8O_3PS_2$. Crystal system triclinic, space group $p1$. Unit cell parameters: $a = 9.2740(9)$ Å, $b = 10.0813(10)$ Å, $c = 13.9866(13)$ Å, $\alpha = 96.614(5)°$, $\beta = 109.330(5)°$, $\gamma = 103.610(5)°$. $V = 1172.4(2)$ Å^3; $T = 296(2)$ K; $Z = 2$; $\rho_{calc} = 1.463$ Mg/m^3; $\mu = 0.336$ mm^{-1} (for MoKα, $\lambda = 0.71073$ Å); $F(000) = 536$; full-matrix least-squares on F^2; data = 7022; parameters = 379; restraints = 0; R(all) = 0.0460; wR(all) = 0.1138; *GoF*(all) = 1.011.
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