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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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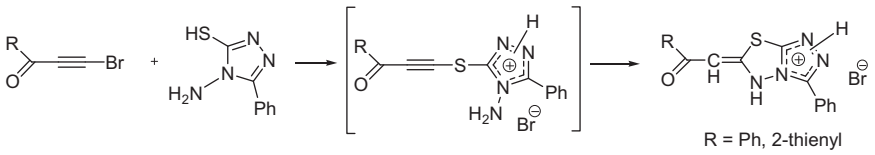
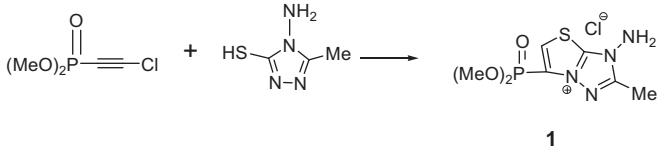
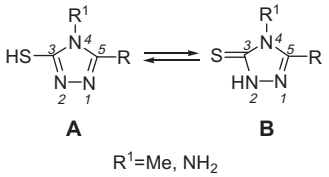


Scheme 1. Reaction of the 4-amino-3-mercapto-5-phenyl-1,2,4-triazole with 1-bromo-2-acyl acetylenes.



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.

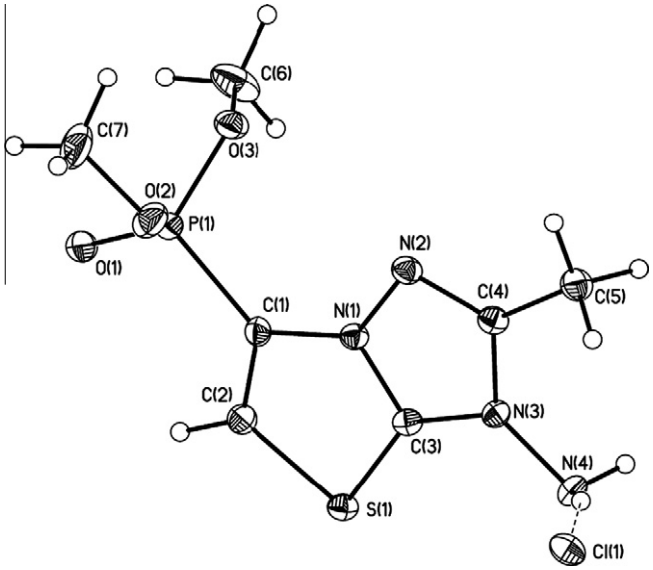


Figure 1. Crystal structure of compound **1** (SHELXTL/ORTEP).

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]

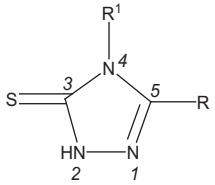
The structure of the previously synthesized[6] salt **1** was proved by an X-ray diffraction study[8] (Fig. 1). The structures of compounds **2–5** follow from the similarities of their NMR and mass spectral characteristics to those of compound **1** (see Table 4).

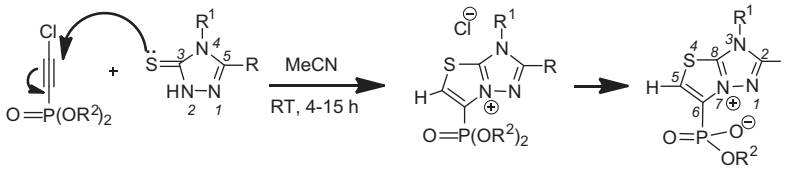
In the ^{1}H NMR spectra of compounds **1–5** the sole proton C-5-H on the thiazolotriazolium ring resonated at a low field at ~8.5 ppm as a doublet due to spin–spin coupling with the phosphorus nucleus, J_{HP} 8.0 Hz. The HCO protons in the R^2 group of the $(R^2O)_2P(O)$ fragment resonated as typical 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

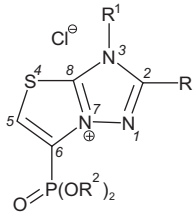
Table 1
^{15}N NMR spectral data of 1,2,4-triazole derivatives

	R	R^1	^{15}N chemical shifts (ppm) and spin–spin coupling constants ($^1J_{NH}$, Hz)			
			N^1	N^2	N^4	NH_2
	Me	NH_2	265.42 s	197.32 d (108.2)	188.89 s	66.62 t (70.1)
	Et	NH_2	265.30	197.54	187.54	66.22
	Pr	NH_2	265.90	197.33	187.04	66.20
	2-$MeOC_6H_4$	NH_2	270.68 d ($^2J_{NH}$ 7.7)	255 d (107.8)	189.55 s	69.00 t (70.0)
	H	CH_3	278.48	204.94	168.58	—
	NH_2	H	232.03 d ($^2J_{NH}$ 12.5)	192.28 d (107.0)	157.28 d (101.3)	45.80 t (69.0)
	CH_3 (S–K salt)	NH_2	292.41	286.92	184.93	67.69



Scheme 4. Synthesis of compounds **1**–**5**, compounds **6**–**8**.

Table 2
2,3-Substituted 6-(dialkoxyphosphoryl)-3*H*-thiazolo[3,2-*b*][1,2,4]triazol-7-ylium chlorides

	Product	R	R^1	R^2	Time (h)	Yield (%)
	**1**	Me	NH_2	Me	4–5	2–5[a]
	2	Me	NH_2	Et	10–12	67
	3	Me	NH_2	*i*-Pr	12–15	57
	4	H	Me	Et	1–1.5	39[a]
	5	H	Me	*i*-Pr	1–1.5	24[a]

[a] Low yield obtained due to conversion into zwitterions.

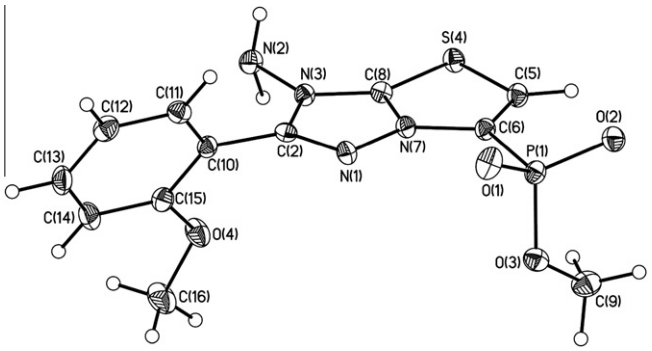
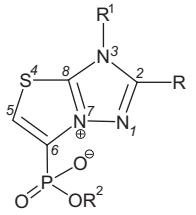


Figure 2. Crystal structure of zwitterion **7** (SHELXTL/ORTEP).

Table 3
Examples of zwitterions **6**–**10**

	Product	R	R^1	R^2	Time (h)	Yield (%)
	**6**	Me	NH_2	Me	4–5	72[a]
	7	2-$MeOC_6H_4$	NH_2	Me	6–8	48[a]
	8	H	Me	Me	6–8	52[a]
	9	Pr	NH_2	H	16	48[b]
	10	2-$MeOC_6H_4$	NH_2	H	16	50[b]

[a] Yield obtained by heating in ethanol or water.
[b] Yield obtained by heating in concentrated hydrochloric acid.

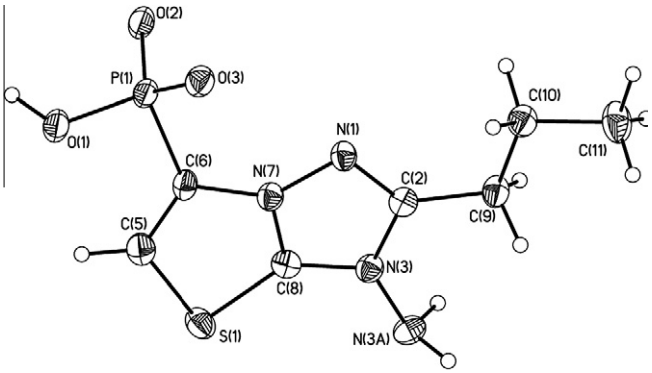


Figure 3. Crystal structure of zwitterion **9** (SHELXTL/ORTEP).

zwitterions **6**, **8** and **10** follow from the similarities of their NMR characteristics to those of compounds **1**, **7** and **9** (see Table 4). The main peaks in the ESI-MS spectra of compounds **6–9** correspond to the protonated molecules.

The obtained results allowed us to hypothesize that the reaction in an aprotic medium involves formation of a sulfenium cation with cleavage of chloride. The positively charged sulfur polarizes the triple bond oppositely to that which occurred in the original 1-chloroacetylene-2-phosphonate, which leads to almost simultaneous attack by the second nucleophilic site, the N-2 nitrogen atom, on the acetylene carbon atom C-2, with proton transfer to C-1. The reaction is completed by redistribution of electron density leading to neutral sulfur and positively charged N-7 atoms.

We observed that in contrast to previous results, the same reactions of thiolotriazoles with chloroacetylenephosphonates, but carried out in anhydrous acetonitrile in the presence of potassium

Table 4
NMR spectral parameters and mass ions in the ESI-MS spectra of compounds **1–10**

Compound	NMR spectral parameters: δ, ppm (J, Hz)[a]						ESI-MS, m/z
	C-5-H ($^3J_{HP}$)	C-2	C-5 ($^2J_{CP}$)	C-6 ($^1J_{CP}$)	C-8 ($^3J_{CP}$)	P	
1	8.53 (5.6)	161.39	132.28 (21.8)	123.72 (215.2)	155.83 (11.0)	2.68	262.73 [*M*-Cl]$^{+}$[b]
2	8.43 (8.0)	160.92	131.66 (18.1)	124.27 (217.3)	154.98 (12.0)	−0.90	291.0698 [*M*-Cl]$^{+}$[c]
3	8.36 (8.0)	160.91	131.26 (18.1)	125.24 (218.3)	154.98 (11.0)	−3.90	319.2907 [*M*-Cl]$^{+}$[c]
4	8.03 (8.0)	150.35	133.15 (17.1)	124.27 (219.3)	154.48 (12.0)	−1.02	276.0580 [*M*-Cl]$^{+}$[c]
5	8.49 (8.0)	150.38	132.77 (18.1)	125.31 (219.3)	154.55 (11.0)	−4.02	304.0894 [*M*-Cl]$^{+}$[c]
6	7.93 (8.0)	160.15	125.84 (15.0)	130.43 (187.1)	154.57 (10.0)	−3.92	249.0226 [*M*+H]$^{+}$[c]
7	7.99 (4.0)	158.78	125.67 (14.1)	131.57 (184.8)	154.92 (10.0)	−4.07	363.0314 [*M*+Na]$^{+}$[c]
8	7.97 (4.0)	149.71	127.41 (15.1)	130.30 (187.1)	154.06 (9.0)	−3.97	234.0124 [*M*+H]$^{+}$[c]
9	7.45 (8.0)	162.51	125.04 (16.0)	130.84 (193.1)	154.11 (9.0)	−7.81	263.0415 [*M*+H]$^{+}$[c]
10	7.92 (8.0)	158.64	124.61 (15.1)	132.68 (188.1)	154.69 (9.0)	−6.37	326.75 [M]$^{+}$[b]

[a] Bruker Avance 400, 400.13 MHz (^{1}H), 100.61 MHz (^{13}C), 161.98 MHz (^{31}P), 40.54 MHz (^{15}N), solvents D_2O and DMSO-d_6.
[b] TSQ Quantum Access MAX.
[c] Bruker micrOTOF.

carbonate, or in a protic solvent (methanol or acetonitrile-methanol mixture), or using potassium triazolothiolate, resulted in difficult to separate mixtures that included, in addition to the thiazolotriazolium derivatives, compounds containing, by NMR spectroscopy, PCH= and PCH_2 groups, as well as other substances. Obviously, in these cases, parallel reactions proceed with attack of both nucleophilic sites on the haloacetylenic carbon atom. In the presence of a proton-donor (solvent) or a base (potassium thiolate), the sulfenium cation was not formed or was rapidly converted into a sulfide group, which exhibited an electron-donor effect causing a change in the reaction regioselectivity.

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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.2012.05.157.

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7. *Typical experimental procedure for the synthesis of compounds* **1–5** and **6–8**. To a solution of 5 mmol of a dialkyl chloroacetylenephosphonate in 10 ml of anhydrous MeCN under vigorous stirring at room temperature was added 5 mmol of 4-amino(methyl)-3-thiolo-5-alkyl(aryl)-1,2,4-triazole. The suspension was stirred vigorously at room temperature for 3–15 h. The resulting precipitate was filtered and washed with Et_2O to afford the thiazolotriazolium salt **1–5** (see Table 2). The solvent was removed from the filtrate under vacuum, and the viscous crystalline residue was recrystallized from a mixture of MeOH–2-propanol (1:1). The resulting crystals were the corresponding zwitterions **6–8** (see Table 3). The zwitterions with ethoxy- and isopropoxyphosphoryl groups (not considered in this Letter) can be obtained from the corresponding thiazolotriazolium salts by heating in EtOH or H_2O for 2–3 h at 70–80 °C. *3-Amino-6-(dimethoxyphosphoryl)-2-methyl-3H-thiazolo[3,2-b][1,2,4]triazol-7-ylium chloride* (**1**). IR (KBr, cm^{-1}): 567, 617, 702, 760, 818, 845, 968, 1049, 1192, 1238, 1269, 1373, 1404, 1524, 1558, 1651, 2951, 3013, 3121. ^{1}H NMR (400.13 MHz, D_2O): δ 2.72 (s, 3H, CH_3), 3.94 (d, $^3J_{HP}$ 11.6 Hz, 6H, OCH_3), 8.53 (d, $^3J_{HP}$ 5.6 Hz, 1H, H-ring). ^{13}C NMR (100.61 MHz, D_2O): δ 10.10 (s, CH_3), 55.55 (d, $^2J_{CP}$ 6.0 Hz, OCH_3), 123.72 (d, $^1J_{CP}$ 215.2 Hz, C^6), 132.28 (d, $^2J_{CP}$ 21.8 Hz, C^5), 155.83 (d, $^3J_{CP}$ 11.0 Hz, C^8), 161.39 (s, C^2). ^{31}P NMR (161.98 MHz, D_2O): δ 2.68. ESI-MS: calcd for $C_7H_{12}ClN_4O_3PS$: 298.6869; found: 262.73 (*M*-Cl)$^+$. *3-Amino-6-(diethoxyphosphoryl)-2-methyl-3H-thiazolo[3,2-b][1,2,4]triazol-7-ylium chloride* (**2**). IR (KBr, cm^{-1}): 542.9, 580, 761, 970, 1004, 1089, 1066, 1239, 1264, 1298, 1398, 1442, 1558, 1634, 2938, 2990, 3095, 3186. ^{1}H NMR (400.13 MHz, D_2O): δ 1.30 (t, $^3J_{HH}$ 8.0 Hz, 6H, OCH_2CH_3), 2.67 (s, 3H, CH_3), 4.29 (dq, $^3J_{HH}$ 8.0 Hz, $^3J_{HP}$ 12.0 Hz, 4H, OCH_2), 8.43 (d, $^3J_{HP}$ 8.0 Hz, 1H, H-ring). ^{13}C NMR (100.61 MHz, D_2O): δ 9.83 (s, CH_3), 15.51 (d, $^3J_{CP}$ 6.0 Hz, $OCH_2\underline{C}H_3$), 66.33 (d, $^2J_{CP}$ 6.0 Hz, OCH_2), 124.27 (d, $^1J_{CP}$ 217.3 Hz, C^6), 131.66 (d, $^2J_{CP}$ 18.1 Hz, C^5), 154.98 (d, $^3J_{CP}$ 12.0 Hz, C^8), 160.92 (s, C^2). ^{31}P NMR (161.98 MHz, D_2O): δ −0.90. ESI-MS: calcd for $C_9H_{16}ClN_4O_3PS$: 326.7401; found: 291.0698 (*M*-Cl)$^+$. *3-Methyl-6-(diethoxyphosphoryl)-3H-thiazolo[3,2-b][1,2,4]triazol-7-ylium chloride* (**4**). IR (KBr, cm^{-1}): 557, 574, 795, 936, 984, 1016, 1043, 1069, 1164, 1253, 1269, 1299, 1454, 1567, 1835, 2910, 2995, 3116. ^{1}H NMR (400.13 MHz, D_2O): δ 1.32 (t, $^3J_{HH}$ 8.0 Hz, 6H, CH_3), 4.10 (s, 3H, NCH_3), 4.32 (dq, $^3J_{HH}$ 8.0 Hz, $^3J_{HP}$ 12.0 Hz, 4H, OCH_2), 8.03 (d, $^3J_{HP}$ 8.0 Hz, 1H, H-ring), 9.07 (s, 1H, N=CH). ^{13}C NMR (100.61 MHz, D_2O): δ 15.53 (d, $^3J_{CP}$ 6.0 Hz, OCH_2CH_3), 34.72 (s, NCH_3), 66.45 (d, $^2J_{CP}$ 6.0 Hz, OCH_2), 124.27 (d, $^1J_{CP}$ 219.3 Hz, C^6), 133.15 (d, $^2J_{CP}$ 17.1 Hz, C^5), 150.35 (s, C^2), 154.48 (d, $^3J_{CP}$ 12.0 Hz, C^8). ^{31}P NMR (161.98 MHz, D_2O): δ −1.02. ESI-MS: calcd for $C_9H_{15}ClN_3O_3PS$: 311.7254; found: 276.0580 (*M*-Cl)$^+$. *Methyl 3-amino-2-methyl-3H-thiazolo[3,2-b][1,2,4]triazol-7-ylium-6-phosphonate* (**6**). IR (KBr, cm^{-1}): 548, 555, 586, 762, 962, 1044, 1099, 1106, 1182, 1251, 1651, 1670, 3107, 3259, 3378, 3401. ^{1}H NMR (400.13 MHz, D_2O): δ 2.63 (s, 3H, CH_3), 3.52 (d, $^3J_{HP}$ 12.0 Hz, 3H, OCH_3), 7.93 (d, $^3J_{HP}$ 8.0 Hz, 1H, H-ring). ^{13}C NMR (100.61 MHz, D_2O): δ 9.77 (s, CH_3), 52.91 (d, $^2J_{CP}$ 6.0 Hz, OCH_3), 125.84 (d, $^2J_{CP}$ 15.0 Hz, C^5), 130.43 (d, $^1J_{CP}$ 187.1 Hz, C^6), 154.57 (d, $^3J_{CP}$ 10.0 Hz, C^8), 160.15 (s, C^2). ^{15}N NMR (40.54 MHz, D_2O): δ 66.06 (s, NH_2), 173.43 (s, N^3), 232.84 (d, $^2J_{NP}$ 6.6 Hz, N^7), 269.09 (s, N^1). ^{31}P NMR (161.98 MHz, D_2O): δ −3.92. ESI-MS: calcd for $C_6H_9N_4O_3PS$: 248.1994; found: 249.0226 (*M*+H)$^+$.
8. The X-ray crystal structure for compound **1** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 848044. Formula: $C_7H_{12}ClN_4O_3PS$. Crystal system monoclinic, space group P2(1)/c. Unit cell parameters: a = 15.3837(11) Å, b = 6.0034(4) Å, c = 14.5397(10) Å, α = 90°, β = 110.5360(10)°, γ = 90°. V = 1257.47(15) Å^3; T = 100(2) K; Z = 4; ρ_{calc} = 1.578 Mg/m^3; μ = 0.599 mm^{-1} (for MoKα, λ = 0.71073 Å); F(000) = 616; full-matrix least-squares on F^2; data = 3710; parameters = 157; restraints = 0; wR(all) = 0.0837; GoF(all) = 1.034.

9. *Typical procedure for obtaining zwitterions* **9** and **10**. A solution of 2.5 mmol of compound **6–8** in 5–10 ml of concentrated HCl was heated at a temperature of 80–90 °C for 16 h. The solvent was removed under vacuum and the residue was recrystallized from a mixture of EtOH–H_2O (2:1) (see Table 3). *3-Amino-2-(o-methoxyphenyl)-6-phosphono-3H-thiazolo[3,2-b][1,2,4]triazolo-7-ylium (internal salt)* (**10**). IR (KBr, cm^{-1}): 558, 694, 744, 762, 968, 1010, 1056, 1170, 1257, 1286, 1302, 1350, 1493, 1573, 1609, 2974, 3152. ^{1}H NMR (400.13 MHz, D_2O): δ 3.86 (s, 3H, OCH_3), 7.14 (t, $^3J_{HH}$ 8.0 Hz, *m*-CH, 1H), 7.22 (d, $^3J_{HH}$ 8.0 Hz, *m*-CH, 1H), 7.54 (dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.5 Hz, *o*-CH, 1H), 7.58 (dt, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.5 Hz, *p*-CH, 1H), 7.92 (d, $^3J_{HP}$ 8.0 Hz, 1H, H-ring). ^{13}C NMR (100.61 MHz, D_2O): δ 56.13 (s, OCH_3), 110.56 (s, *ipso*-C), 112.33 (s, *m*-C), 121.33 (s, *m*-C), 124.61 (d, $^2J_{CP}$ 15.1 Hz, C^5), 132.00 (s, *o*-C), 132.68 (d, $^1J_{CP}$ 188.1 Hz, C^6), 135.11 (s, *p*-C), 154.69 (d, $^3J_{CP}$ 9.0 Hz, C^8), 157.57 (s, *ipso*-C), 158.64 (s, C^2). ^{15}N NMR (40.54 MHz, D_2O): δ 68.39 (s, NH_2), 173.91 (s, N^3), 234.54 (d, $^2J_{NP}$ 6.4 Hz, N^7), 272.16 (s, N^1). ^{31}P NMR (161.98 MHz, D_2O): δ −6.37. ESI-MS: calcd for $C_{11}H_{11}N_4O_4PS$: 326.2682; found: 326.75 $(M)^+$.

10. The X-ray crystal structure for compound **10** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 867704. Formula: $C_{12}H_{13}N_4O_4PS$. Crystal system orthorhombic, space group Pbca. Unit cell parameters: a = 8.5974(5) Å, b = 13.6503(8) Å, c = 23.7719(14) Å, α = 90°, β = 90°, γ = 90°. V = 2789.8(3) Å^3; T = 100(2) K; Z = 8; ρ_{calc} = 1.620 Mg/m^3; μ = 0.372 mm^{-1} (for MoKα, λ = 0.71073 Å); $F(000)$ = 1408; full-matrix least-squares on F^2; data = 3701; parameters = 219; restraints = 8; wR(all) = 0.0826; *GoF*(all) = 1.150.

11. The X-ray crystal structure for compound **9** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 867702. Formula: $C_7H_{11}N_4O_3PS$. Crystal system orthorhombic, space group Pbca. Unit cell parameters: a = 12.5994(9) Å, b = 8.8703(6) Å, c = 19.2231(14) Å, α = 90°, β = 90°, γ = 90°. V = 2148.4(3) Å^3; T = 100(2) K; Z = 8; ρ_{calc} = 1.621 Mg/m^3; μ = 0.449 mm^{-1} (for MoKα, λ = 0.71073 Å); $F(000)$ = 1088; full-matrix least-squares on F^2; data = 2594; parameters = 149; restraints = 0; wR(all) = 0.1107; *GoF*(all) = 1.085.