Heteroatom Chemistry
Volume 16, Number 2, 2005

Regioselective Synthesis, Structure and Behavior in Solutions of Novel Phosphorylated Thiazolidin-4-ones

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Received 19 November 2004

ABSTRACT: *Regioselective syntheses of novel 2-(phosphoryl)methylidenethiazolidine-4-ones* **3a–c, 5** *by the condensation of phosphoryl acetic acid thioamides* **2a–c** *or substituted thioanilide* **4** *with dimethyl acetylenedicarboxylate are described. N^3-unsubstituted thiazolidine-4-ones* **3a–c** *were obtained as E,Z-isomers, while N^3-phenyl substituted heterocycle* **5** *was formed as Z,Z-isomer. The structures of thiazolidin-4-ones* **3a**-*E,Z and* **5**-*Z,Z are characterized by crystal structure determination. According to B3Pw91/6-31G* calculations, the isomers observed in crystals are thermodynamically preferable. In solutions, phosphorylated thiazolidines undergo isomerization (relative to C^2 carbon atom of the heterocycle) proceeded by either imine–enamine (N^3-unsubstituted compounds* **3a–c***) or push–pull mechanisms (N^3-substituted compound* **5***).* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:159–168, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20084

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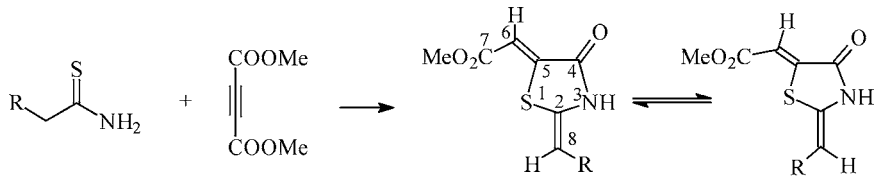
Contract grant sponsor: Russian Basic Research Foundation.
Contract grant numbers: 02-03-33073 and 03-03-32214.
Contract grant sponsor: President, Russian Federation.
Contract grant numbers: NSh-1100.2003.3 and YC-1209.2003.03.

INTRODUCTION

Condensation of thioureas with dimethyl acetylenedicarboxylate (DMAD) is known to be a convenient route to pharmacologically active 2-imino-5-methoxycarbonylthiazolidin-4-ones [1–7]. Recently malonothioamide derivatives were found to undergo a similar heterocyclization resulting in substituted 2,5-bis(substituted methylidene)-thiazolidine-4-ones **1** usually as a mixture of *Z,Z* and *E,Z* isomers (see Scheme 1) [8,9]. In a number of cases, the authors succeeded in isolating the individual isomers; most often the mixtures of isomers were obtained and investigated by NMR technique. Based on the ID NOE experiments, it was found that $C^5{=}C^6$ double bond in **1** exists in the *Z*-configuration [8], while the configuration of $C^2{=}C^8$ bond depends on the substituent R and the solvent in use. It was suggested that *E,Z*-isomers are stabilized in nonpolar solvents ($CDCl_3$; R is COOEt or $CONR'_2$) by the formation of the intramolecular hydrogen bond [8,9]. In contrast, the S···O contact stabilizes *Z,Z*-isomers in such solvents as ethanol or DMSO-d_6. However, the data and assignment of the configuration for the compounds in the [8] and [9] conflict with each other.

One may suggest that introduction of the phosphoryl moiety to the C^8 atom of such thiazolidin-4-one may not only allow novel biologically active compounds combining the useful properties of thiazolidin-4-one cycle and residue of phosphonous



R=CN, COOEt, $CONMe_2$, $CON(CH_2CH_2)_2O$, $CON(CH_2CH_2)_2CH_2$, CONHMe, $CONHCH_2Ar$

SCHEME 1

acid, but also help to elucidate the problems of isomerism in this heterocyclic system. Recently we published a procedure [10], which would allow for synthesizing high yields of a wide range of phosphorus-substituted carboxylic acid thioamides, which may serve as starting substrates in this reaction.

RESULTS AND DISCUSSION

We offer a simple and regioselective synthesis of the first representatives of thiazolidin-4-ones phosphorylated derivatives and describe their structure in a solid state on the bases of X-ray data. We also examine their isomerisation in solutions and discuss its possible mechanisms.

Synthesis and Establishment of the Structure

We have found that the interaction of phosphorylthioacetamides **2a–c** with DMAD in $CHCl_3$ proceeds under mild conditions (RT, 6 h) resulting in high yields of the novel 2-(phosphorylmethylidene)-thiazolidin-4-ones **3a–c**, as illustrated in Scheme 2.

In contrast to the similar condensation of non-phosphorylated carbothioamides, the reaction was found to proceed regioselectively and, according to spectroscopic analysis, resulted in only one isomer for the compounds **3a–c**. ^{31}P NMR spectra in $CDCl_3$ solution show singlet signals in the regions typical for the particular environment at the phosphorus atom in the specific compound **3** and one set of the corresponding signals in ^{1}H and ^{13}C NMR spectra in the same solvent. X-ray diffraction investigation (XRD) carried out for **3a** revealed that the *trans*-disposition of the phosphoryl group and the ring sulfur atom and the *cis*-disposition of the carbomethoxy substituent relative to the latter characterize the molecule (*E,Z*-isomer). Taking into consideration the general similarity of the spectral data, we also assigned the structures of the compounds **3b,c** to *E,Z*-isomers.

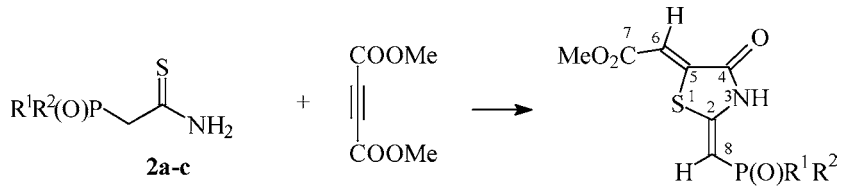
Use of diethyl 2-anilino-1-cyano-2-thioxoethylphosphonate **4** in condensation with DMAD instead of thioacetamide **2** yielded the phosphorylated thiazolidin-4-one **5** bearing the phenyl substituent at the nitrogen atom (see Scheme 3). In this case, the reaction was also regioselective but, according to the X-ray data, thiazolidine-4-one **5** was obtained as *Z,Z*-isomer only.

The compounds **3a–c** and **5** were isolated by recrystallization from ethyl acetate as light-yellow crystalline solids.

Thus, the interaction of phosphorus-substituted carbothioamides with DMAD was found to be the regioselective process.

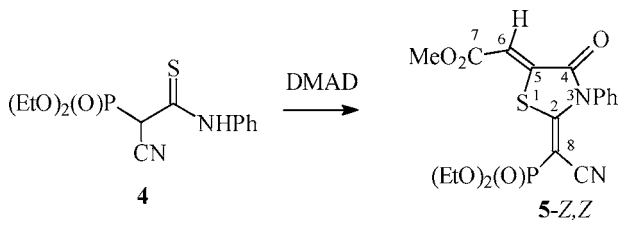
Molecular Geometry and Crystal Structure of **3a** *and* **5**

The bond lengths and angles in **3a**-*E,Z* (see Fig. 1, Table 1) are close to the typical values for thizolidine-4-one derivatives [6,7,11–13]. In particular, the thiazolidin-4-one cycle is planar and both C(2)=C(8) and C(5)=C(6) bond lengths are equal to 1.344(4) Å.



$R^1=R^2=OEt$ (**a**), Ph (**c**);
$R^1=Ph$, $R^2=OEt$ (**b**)

SCHEME 2



SCHEME 3

As it can be seen, the E,Z-isomer of **3a** is stabilized by the intramolecular N(3)—H(3)···O(1) hydrogen bond and S(1)···O(5) nonbonded contact (Fig. 1). The latter type of intramolecular interaction is also typical for the thiazolidin-4-one derivatives [6,7,11]. The nature of the such X—S···O contacts is usually explained in terms of the charge transfer from the oxygen lone pair (Lp_O) to the antibonding orbital of the X—S bond (σ^*_{X-S}) [12,13] which is in line with the specific direction of this contact in **3a** [C(2)S(1)O(5) is 164.8(2)°]. However, the S(1)···O(5) contact (2.800(2) Å) in **3a**-*E,Z* is significantly elongated in comparison with the ones in nonphosphorylated thiazolidin-4-one derivatives (2.613–2.696 Å) known in the literature [11,14–16]. Thus, the possibility that the S···O contact in **3a**-*E,Z* may be forced by its nature rather than caused by the charge transfer must not be ruled out.

With regard to the H-bonds, the analysis of crystal packing revealed that in addition to intramolecular H-bond the H(3N) atom forms the intermolecular H-bond assembling the molecules into a dimer (see Fig. 1). Moreover, the N···O distance for the intramolecular N—H···O bond (N···O 2.951(3) Å) exceeds the corresponding value for the intermolecular one (2.877(3) Å) and the N(3)H(3N)O(1A) angle (154°) is closer to the linear angle than the N(3)H(3N)O(1) one (118°).

The bonds lengths in **5**-*Z,Z* (see Fig. 2, Table 1) are slightly different from the corresponding ones in **3a**-*E,Z*. It seems that the differences result from both the presence of CN-group (elongation of the C(2)—C(8) bond up to 1.363(4) Å) in the molecule and the formation of intramolecular contacts of a different type (the shortening of the P(1)—O(1) bond). As one may see, the *cis*-disposition of the oxygen atom in the phosphoryl group and the S(1) atom in **5**-*Z,Z*-isomer leads to formation of S(1)···O(1)P(1) contact. The S···O distance in such a contact is slightly shorter (2.733(2) Å) in comparison with the distance S(1)···O(5) in the contacts formed by the carbonyl group [2.800(3) and 2.754(3) Å in **5**-*Z,Z* and **3a**-*E,Z*]. In addition, according to geometrical criteria, we cannot exclude the presence of the CN···C(14) contact. Actually, the C(14)···C(20) distance is shortened up to 2.826(5) Å and the C(8)C(20)N(21) angle decreases to 173.0(2)°.

Behavior of 2-(Phosphorylmethylidene)-thiazolidin-4-ones **3a–c** *in Solutions*

One would expect that **3a–c** will undergo *E,Z* → *Z,Z* isomerization in solutions similar to their nonphosphorylated analogs **1**. To investigate such a possibility, ^{31}P and ^{1}H NMR spectra of **3a–c** were recorded from the moment of the dissolving the

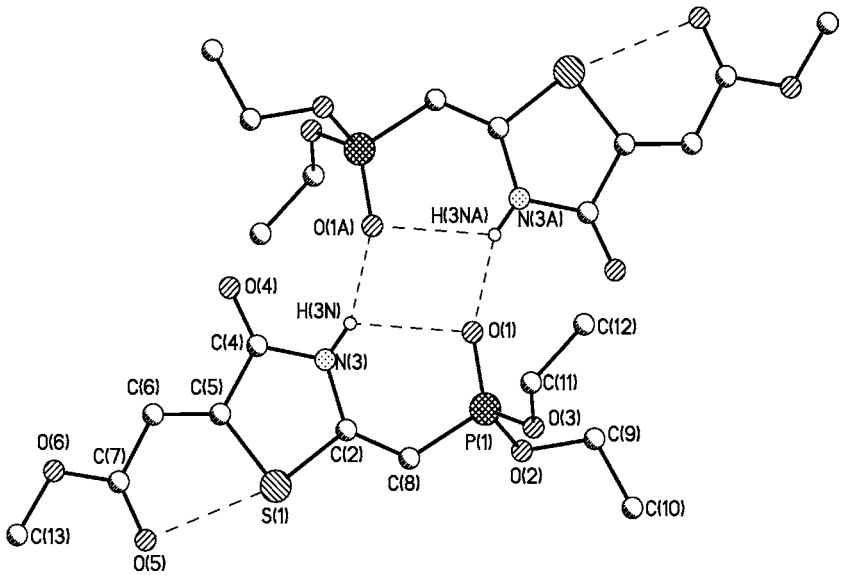


FIGURE 1 General view of N—H···O bonded dimer of **3a**-*E,Z* with hydrogen atoms omitted except for those that are involved in hydrogen bonding.

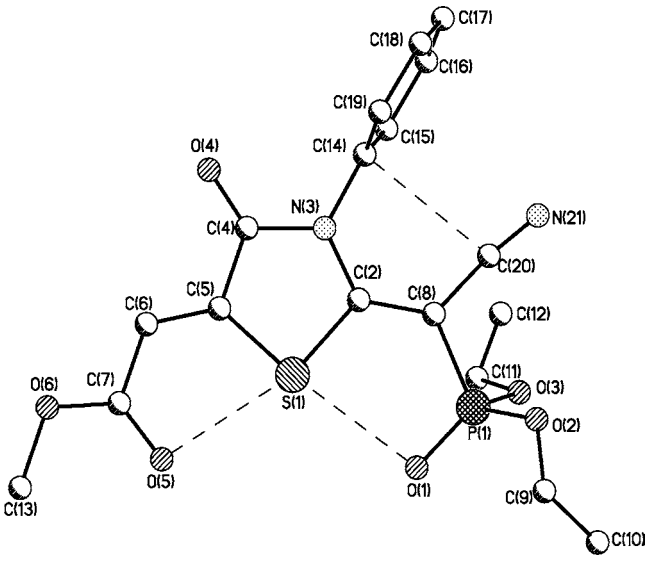


FIGURE 2 General view of **5**-*Z,Z* with hydrogen atoms omitted for clarity.

compound until the process reached the equilibrium position. The corresponding data are shown in Table 2. The most detailed study was performed using **3a**-*E,Z* as a representative compound with a range of solvents of different polarities.

During the time of observation, no changes were recorded in NMR spectra of **3a**-*E,Z* in $CDCl_3$ or C_6D_6 indicating that the equilibrium is fully shifted to this isomer in nonpolar solvents. The independence of the NH-chemical shift on the concentration in the ^{1}H NMR spectrum of **3a**-*E,Z* (2- and 3-fold dilution of the starting samples with the initial concentration 10^{-2} M) indicates the formation of the strong intramolecular H-bond, which stabilizes the **3a**-*E,Z*-isomer in these solutions.

The spectra registered in protein polar (CD_3OD) or aprotein bipolar solvent solutions, such as $CD_3C(O)CD_3$ or DMSO-d_6 (the mixture with CCl_4 in 8:2 or 1:1 ratio), demonstrated the signals corresponding to two isomers with one signal

TABLE 1 Geometrical Parametres in **3a** and **5** According to X-ray Diffraction Data and B3Pw91/6-31G* Calculations

	XRD	*B3Pw91/6-31G**			*XRD*	*B3Pw91/6-31G**	
	***3a**-E,Z*	***3a**-E,Z*	***3a**-E,Z (H-dimer)*	***3a**-Z,Z*	***5**-Z,Z*	***5**-Z,Z*	***5**-E,Z*
				Bond lengths (Å)			
S(1)–C(2)	1.778(3)	1.781	1.786	1.786	1.757(3)	1.786	1.786
S(1)–C(5)	1.734(3)	1.747	1.739	1.753	1.732(3)	1.746	1.739
P(1)–O(1)	1.471(2)	1.495	1.490	1.486	1.448(2)	1.484	1.487
P(1)–C(8)	1.763(3)	1.769	1.768	1.771	1.790(3)	1.804	1.817
C(2)–N(3)	1.387(3)	1.373	1.375	1.381	1.375(4)	1.381	1.377
C(2)–C(8)	1.344(4)	1.354	1.352	1.351	1.363(4)	1.374	1.373
N(3)–C(4)	1.377(3)	1.377	1.377	1.380	1.388(4)	1.402	1.408
C(4)–C(5)	1.507(4)	1.502	1.501	1.494	1.470(4)	1.485	1.487
C(5)–C(6)	1.344(4)	1.345	1.346	1.346	1.334(4)	1.347	1.346
C(6)–C(7)	1.464(4)	1.463	1.464	1.464	1.465(5)	1.465	1.465
				Bond angles (°)			
C(2)S(1)C(5)	91.8(1)	90.9	91.1	90.7	90.9(1)	90.7	91.2
N(3)C(2)S(1)	110.52(2)	110.8	110.9	110.1	111.6(2)	111.4	111.5
C(4)C(5)S(1)	110.9(2)	111.5	111.2	112.3	112.1(2)	112.2	111.6
C(8)P(1)O(1)	112.6(1)	113	112.9	114.3	112.2(1)	113.5	101
C(6)C(7)O(5)	124.0(2)	124	124.1	124.1	121.8	124	117
C(8)C(20)N(21)	–	–	–	–	173.0(3)	173.1	178.5
				Inter- and intra-molecular contacts (Å or °)			
O(5)···S(1) Å	2.800(3)	2.795	2.802	2.821	2.754(3)	2.813	2.776
O(5)S(1)C(2) (°)	164.8(2)	164.1	164.2	163.5	164.5(2)	163.7	164.6
O(1)···S(1) Å	–	–	–	2.910	2.733(3)	2.751	–
O(1)S(1)C(5) (°)	–	–	–	170.6	174.5(2)	174.7	–
H(3N)···O(1) Å	2.32	1.91	2.22	–	–	–	–
N(3)···O(1) Å	2.951(3)	2.745	2.940	–	–	–	–
N(3)H(3N)O(1) (°)	118	137	125	–	–	–	–
H(3N)···O(1A) Å	1.91	–	1.94	–	–	–	–
N(3)···O(1A) Å	2.877(3)	–	2.887	–	–	–	–
N(3)H(3N)O(1A) (°)	154	–	151	–	–	–	–
C(20)···C(14)	–	–	–	–	–	2.826(4)	2.853

TABLE 2 ^{31}P Shifts and Selected ^{1}H NMR Parameters for Phosphorylated Thiazolidinones **3a–c**, **5** in Different Solvents

Compound	*Solvent*	*E, Z/ Z, Z Ratio at the Equilibrium*	*Isomer*	δ_P	δC^8H, $d/^2J_{PH}$	δC^6H	δNH	δOCH_3
3a	$CDCl_3$	100/0	*E,Z*	18.26	4.80/7.2	6.81	10.76	3.83
3a	C_6D_6	100/0	*E,Z*	18.88	4.42/7.2	6.94	11.47	3.35
3a	DMSO- d_6/CCl_4(2:8)	20/80	*E,Z*	19.19	4.96/7.2	6.69	10.85	3.78
			Z,Z	19.19	5.16/7.2	6.56	12.20	3.78
3a	DMSO-d_6/CCl_4(1:1)	9/91	*E,Z*	19.16	5.27/7.6	6.67	12.30[a]	3.80
			Z,Z	19.16	5.19/7.8	6.55	[a]	3.80
3a	CD_3OD	23/77	*E,Z*	20.17	5.34/7.6	6.94	[b]	4.02
			Z,Z	19.20	5.43/7.6	6.88	[b]	4.02
3a	$CD_3C(O)CD_3$	60/40	*E,Z*	19.56	5.21/7.4	6.67	11.00 (br)	3.83
			Z	18.99	5.37/7.2	6.59	11.10 (br)	3.79
3b	$CDCl_3$	100/0	*E*	32.28	4.96/12.7	6.81	11.28	3.82
3b	DMSO- d_6/CCl_4(1:1)	8/92	*E*	33.23	5.63/12.1	6.66	12.03–12.30 (br)	3.96
			Z	31.04	5.45/12.1	6.54	[a]	[a]
3c	$CDCl_3$	100/0	*E*	29.64	5.26/16.2	6.81	11.51	3.82
3c	DMSO- d_6/CCl_4(1:1)	20/80	*E*	28.92	6.05/16.6	6.65	11.63(br)	3.80
			Z		5.80/16.6	6.53	12.29(br)	[a]
5	$CDCl_3$	16/84	*E*	5.87	–	7.01	–	3.90
			Z	11.68	–	6.98	–	3.88
5	CD_3OD	0/100	*Z*	14.08	–	7.13	–	4.07

[a]Coincides with the corresponding signal of *E,Z*-isomer.
[b]Do not observed due to fast exchange with the solvent.

substantially dominating (84–96%) initially (ca. 10 min) and becoming the minor over time. The ratio *E,Z*:*Z,Z* at the equilibrium position for **3a** is equal to 60:40 (acetone-d_6), 23:77 (CD_3OD), 20:80 (DMSO-d_6:CCl_4 = 2:8), 9:91 (DMSO-d_6:CCl_4 = 1:1); and the time required for the achievement of the equilibrium was equal to ca. 14 h in DMSO-d_6/CCl_4 = 1:1 mixed solvent, 6 days in acetone-d_6, and DMSO-d_6:CCl_4 = 2:8 mixture and 17 days in CD_3OD.

In ^{1}H NMR spectra, the position of C^8H in **3a**-*E,Z* is usually upfield shifted in comparison with the similar signal for *Z,Z*-isomer, while for C^6H the situation is opposite: the bigger value of the chemical shift corresponds to C^6H in **3a**-*E,Z*. Such characteristic disposition of isomer signals was not observed only in the mixture of DMSO-d_6:CCl_4 = 1:1 where the C^8H signal in **3a**-*E,Z* is downfield shifted relative to the one in **3a**-*Z,Z*.

It should be noted that intensities of C^8H signals of the *E,Z*- and *Z,Z*-isomers in the ^{1}H NMR spectra of **3a** in CD_3OD or acetone-d_6 solutions correspond to isomer ratio estimated by its ^{31}P NMR spectra but do not coincide with the intensity of the signals of the other protons for the same isomer. A similar situation is observed for NH signals (in acetone-d_6) having a broadened form. This fact may be explained by the fast prototropic exchange in NMR timeline between two isomers of heterocyclic amine **3a** via the corresponding imine. Therefore, the **3**-*E,Z* → **3**-*Z,Z* isomer transformation apparently proceeds via imine–enamine mechanism.

In general, the behavior of **3b,c** in solutions is similar to **3a** (see Table 2). Moreover, a similar characteristic disposition of the signals of vinyl protons of *E,Z* and *Z,Z* isomers was observed in ^{1}H NMR spectra. Note also that the value of $^{2}J_{PH}$ coupling constant increases in the series of thiazolidinones **3** with the increase of a number of P—C bonds in the surrounding of the phosphorus atom, i.e. when going from phosphonate **3a** to phosphinate **3b** and further to phosphine oxide **3c**.

Despite the fact that in MeOH the equilibrium is shifted to **3a**-*Z,Z* isomer, we failed to isolate the individual **3a**-*Z,Z* isomer by recrystallization from the above solvent. The single crystal obtained in this case presented the same **3a**-*E,Z* isomer that was obtained after recrystallization from EtOAc (vide supra), apparently indicating that *E,Z*-isomer is thermodynamically more stable in a solid state. This hypothesis was further proven by quantum-chemical calculations (see below). In other words, the crystallization process shifts the equilibrium and leads to formation of crystals of the more stable *E,Z*-isomer.

The ^{1}H, ^{13}C, and ^{31}P NMR spectra of **5** recorded immediately after dissolving in both polar and nonpolar solvents show that there is a set of signals corresponding to the single isomer (see Table 2). The spectral pattern of the samples in DMSO-d_6 did not change when stored over 1 month. Nevertheless, in $CDCl_3$ solution we observe a slow formation of the second isomer (6 days, *Z,Z*:*E,E* = 84:16). As imine–enamine tautomerism is impossible here, the

push–pull mechanism is the most probable (may be due to the introduction of promoting strong electron-acceptor cyano function to the C^8 atom).

Therefore, the isomerization in solutions is the characteristic feature of phosphorylated thiazolidine-4-ones and it may proceed via different routes depending on the substituent at the ring nitrogen atom.

Quantum Chemical Calculations

In order to estimate if the isomers observed in a solid state are the thermodynamically more preferable, we performed the B3Pw91/6-31G* calculations within the G98 program package [17a] for both isomers of **3a** and **5**. For simplicity, the ethoxy groups at the phosphorus atom in the molecules were substituted for the methoxy ones (Table 1). The geometry parameters obtained within the B3Pw91/6-31G* calculations are close to the experimental data, with the exception of elongated P(1)—O(1) bond lengths but the elongation of P=O bond in DFT calculations as well as in MP2 ones is typical [18]. Despite such a difference, the shorter value of the P=O bond in **5**-*Z,Z* in comparison with **3a**-*E,Z* is preserved in the isolated state.

As for the mentioned above S···O and C···CN contacts, the corresponding geometrical parameters in a crystal and an isolated state are similar to each other for both compounds. In contrast, the intramolecular N—H···O bond in the isolated molecule of **3a**-*E* is significantly shorter (N(3)···O(1) 2.745 Å) than the experimental value, but the optimization of the N—H···O bonded dimer ideally reproduces the experimental parameters both for the intra and the intermolecular H-bonds.

The general views of **3a**-*Z,Z* and **5**-*E,Z* according to B3Pw91/6-31G* calculations are shown at Fig. 3 and Fig. 4 correspondingly, while the structures of the H-bonded dimer of **3a**-*E,Z* and **5**-*Z,Z* isomer which are similar to experimental ones (see Fig. 1 and Fig. 2) are omitted.

The comparison of calculated values for bond lengths and angles in *E,Z* and *Z,Z* isomers of **3a** and **5** indicates that all parameters are insensitive to the mutual position of the P=O bond and the sulfur atom with the exception of the S(1)—C(5) bond. The latter is elongated in *Z,Z*-isomers, which correlates with the presence of the additional S(1)···O(1) interaction that may be interpreted as Lp_O - (σ^*_{S-C}) charge transfer.

According to the calculations, both **3a**-*E,Z* and **5**-*Z,Z* isomers found in the crystals correspond to the energy minimum. The difference in energy, taking into account zero potential energy (ZPE), between the *E,Z* and *Z,Z* isomers is equal to ca. 6.5 and 3.45 kcal/mol for **3a** and **5**, correspondingly. The stabilization of *E,Z* isomer of **3a** by N—H···O bonds is apparently more pronounced than the stabilization of **5**-*Z,Z* by S(1)···O(1) and C···CN contacts.

Furthermore, we estimated the energy of the intermolecular N—H···O bond in H-bonded dimer **3a**-*E,Z* which is equal to 3.37 kcal/mol when the ZPE is taken into account. This value should be considered as a rough approximation only because it includes the energies of intermolecular H-bonds, along with the changes in the strengths of intramolecular bonds.

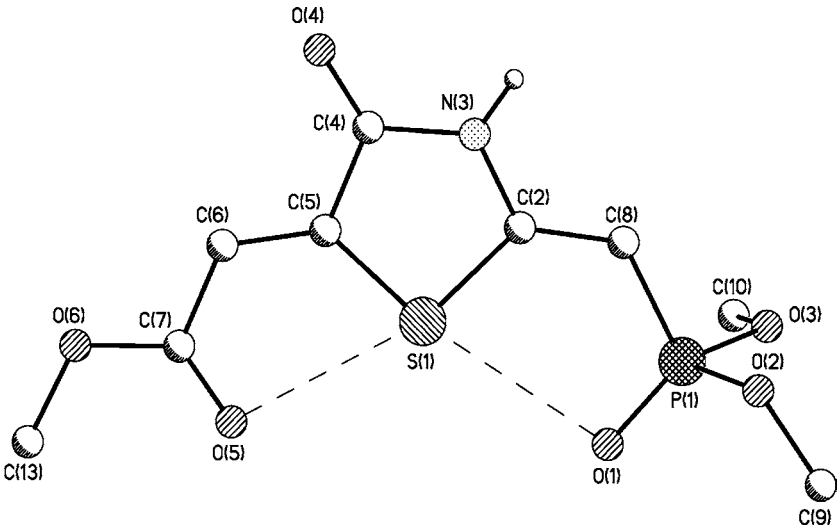


FIGURE 3 General view of **3a**-*Z,Z* according to B3Pw91/6-31G* calculations.

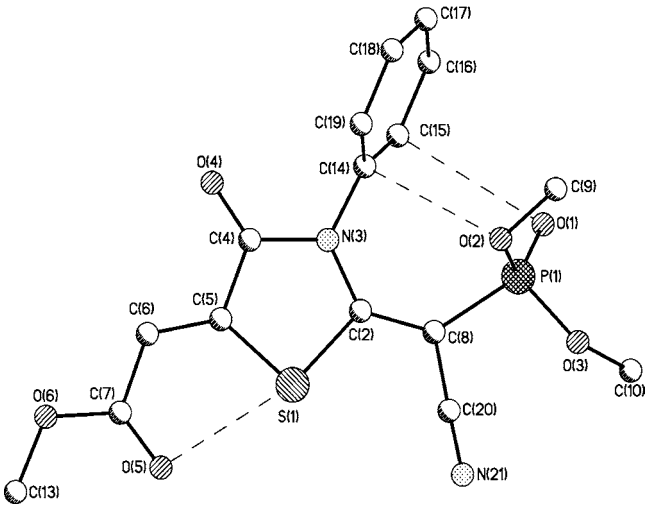


FIGURE 4 General view of **5**-*E*,*Z* according to B3Pw91/6-31G* calculations.

In order to analyze the nature of the intramolecular interactions (N—H···O, S···O, CN···Ph) in **3a** and **5** and estimate of their contribution into the stabilization of the specific isomer, we carried out a topological analysis of electron density function ($\rho(r)$) within R.F. Bader's "atom in molecules" theory [19]. This approach allowed successfully analyzing various inter- and intra-molecular contacts basing on the theoretical [20] and experimental [21] investigations of the $\rho(r)$ function.

The search of the critical point (CP) for the $\rho(r)$ function revealed that characteristic sets for both isomers of **3a** contain CP (3,−1) not only for all the expected bonds but also for S···O and N—H···O contacts, indicating that all of them correspond to attractive interactions. The analysis of the $\rho(r)$ function for N—H···O bonded dimer **3a**-*E*,*Z* revealed that both inter- and intra-molecular H-bonds are characterized by the presence of CP (3,−1). In addition to the N—H···O bonds in this dimer, the additional CP (3,−1) is located in the line O(1)···O(1A) (2.797 Å), indicating the presence of an additional interaction. It should be noted that O···O interaction of the similar type was previously observed in the case of keto-enol and enol-imine H-bonded dimers [22].

For the isomers of **5** the CP (3,−1) were found for contacts C(20)···C(14) in *Z*,*Z* isomer (Fig. 2) and O(1)···C(14) (3.091 Å), and O(3)···C(11) (3.041 Å) in *E*,*Z*-isomer in addition to S···O contacts (see Fig. 4).

All the above-mentioned intra- and intermolecular contacts in the isomers of **3a** and **5** are characterized by rather small values of $\rho(r)$ and positive values of Laplacian of electron density. Therefore, they correspond to the closed shell type of interatomic interactions whose energy, according to work [23], can be easily estimated based on the semiempirical correlation of potential energy density in CP(3,−1) with the energy of a contact. Using this approximation, we obtained the energies for all abovementioned contacts. Surprisingly, the differences in the sum of the energies corresponding to intramolecular contacts for *E*,*Z* and *Z*,*Z* isomers of both compounds under investigation are close to the calculated differences in energy between such isomers. These values are equal to 5.08 and 2.22 kcal/mol for **3a** and **5** correspondingly. The estimation of energy of dimer is more accurate and equal to 6.67 kcal/mol.

The maximum calculated value of the contact energy was observed for the intramolecular N—H···O bond (8.26 kcal/mole) in the isolated **3a**-*E*,*Z* molecule. For comparison, the energies of the S···O contacts are in the range of 3.40–4.20 kcal/mol and for the C···CN contact the energy is equal to 2.30 kcal/mol. Therefore, the application of AIM theory not only gives a possibility to reproduce the difference in the isomer energies with lower computational costs but also makes it possible to ascertain the reasons for their stabilization as well as dynamic behavior in solutions. Thus, in an isolated molecule of **3a**-*E*,*Z* the intermolecular N—H···O bond makes the main contribution into the stabilization of such isomer; in the corresponding dimer, the energy of the intermolecular H-bond is significantly reduced (to 4.0 kcal/mol) and the energy of the intramolecular H-bond is equal to 6.23 kcal/mol. Accordingly, the shift of the equilibrium to **3**-*Z*,*Z* isomers in solutions of polar solvents may be explained by the specific solvation of **3**-*E*,*Z* molecule, which first decreases the strengths of the intramolecular N—H···O bond and therefore reduces the difference in the energy between isomers.

CONCLUSION

The condensation of phosphorus-substituted carboxylic acid thioamides or thioanilides with dimethyl acetylenedicarboxylate proves to be an easily achieved synthetic route to novel 2-(phosphoryl)-methylene-thiazolidin-4-ones. Such regioselective interaction results in a more thermodynamically preferable isomer of final heterocycle whose type depends on the absence (*E*,*Z*-isomer) or presence (*Z*,*Z*-isomer) of the substituent at the nitrogen atom in the thiocarbamoyl group of the starting substrate. In solutions, these compounds undergo isomerization (relative to C^2 carbon atom of the heterocycle) proceeded either via amine–enamine (N^3-nonsubstituted compounds) or via push–pull mechanism (N^3-substituted compounds).

Biological tests of compounds **3a–c** and **5** are currently being conducted.

EXPERIMENTAL

General

The NMR (^{1}H, ^{13}C, and ^{31}P) spectra were recorded on a Bruker AMX-400 spectrometer using residual proton signals of deutero solvents as an internal standard (^{1}H, ^{13}C) and 85% H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the JMODECHO mode, the signals for the C atom bearing odd and even numbers of protons have the opposite polarities. IR spectra were recorded in KBr pellets on a Fourier-spectrometer "Magna-IR750"(Nicolet), resolution 2 cm^{-1}, 128 scans. Melting points are uncorrected. The starting thioacetamides 2 [10] and diethyl 2-anilino-1-cyano-2-thioxoethylphosphonate **4** [24] were obtained by the known procedures as reported. The assignment of the absorption bands in IR spectra was made according to [25,26]. All melting points are uncorrected.

(E)-2-[(Diethoxyphosphoryl)methylene]-(Z)-5-(methoxycarbonyl-methylene)thiazolidin-4-one **3a**. The mixture of dimethylacetylendicarboxilate (0.182 g, 1.2 mmol) and **2a** (0.253 g, 1.2 mmol) in $CHCl_3$ (10 mL) was stirred at room temperature for 6 h. The solvent was evaporated in vacuo, and the residue was recrystallized from ethyl acetate to afford the desired **3a**-*E,Z* as light-yellow solid. Yield 0.3 g (78%); mp 120–121°C. IR, KBr, ν/cm^{-1}: 1023 (C—O—C), 1049 (P—O—C), 1203, 1217 (P=O+νas CNC), 1310 (νs CNC), 1601 and 1604 (C=C), 1686 (C^7=O), 1727 (C^4=O), 3120 (br, NH). ^{13}C NMR ($CDCl_3$) δ: 16.1 (d, $^3J_{PC} = 6.8$ Hz, $\underline{C}H_3CH_2O$), 52.2 (s, OCH_3), 62.2 (d, $^2J_{PC} = 4.8$ Hz, OCH_2), 85.4 (d, $^1J_{PC} = 192.4$ Hz, C^8), 114.6 (s, C^6), 141.6 (s, C^5), 152.2 (d, $^2J_{PC} = 6.0$ Hz, C^2), 164.1 (s, C^7), 166.50 (s, C^4). Found: C 41.12; H 4.99; N 4.03; S 9.94. Calcad. for $C_{11}H_{16}NO_6PS$: C 41.12, H 5.02; N 4.36, S 9.98.

^{13}C NMR (CD_3COCD_3) δ, **3a**-*E,Z*: 15.92 (d, $^3J_{PC}$ = 6.4 Hz, $\underline{C}H_3CH_2O$), 52.2 (s, OCH_3), 62.3 (d, $^2J_{PC} = 4.8$ Hz, OCH_2), 86.1 (d, $^1J_{PC} = 186.5$ Hz, C^8), 114.0 (s, C^6), 142.6 (s, C^5), 152.0 (d, $^2J_{PC} = 5.8$, C^2), 164.1 (s, C^7), 166.6 (s, C^4); **3a**-*Z,Z*: 16.0 (d, $^3J_{PC}$ = 6.4 Hz, $\underline{C}H_3CH_2O$), 52.0 (s, OCH_3), 61.7 (d, $^2J_{PC}$ = 4.8 Hz, OCH_2), 88.2 (d, $^1J_{PC} = 204.4$ Hz, C^8), 113.5 (s, C^6), 144.6 (s, C^5), 152.0 (d, $^2J_{PC} = 5.8$, C^2), 164.9 (s, C^7), 166.5 (s, C^4).

(E)-2-{[Ethoxy(phenyl)phosphoryl]methylene}-(Z)-5-(methoxycarbonyl-methylene)thiazolidin-4-one **3b**. Using the procedure described for **3a**, with the exception that 0.292 g (1.2 mmol) of **2b** was used instead of **2a, 3b**-*E,Z* was obtained in 75% yield; mp 150–151°C (ethyl acetate). IR, KBr, ν/cm^{-1}: 552, 1026 br. (νC—O—C+ νP—O—C), 1178, 1199 (P=O+νas CNC), 1334 (νs CNC), 1689 and 1595 (C=C), 1685 (C^7=O), 1728 (C^4=O), 3066, 3168 (br, NH). ^{13}C NMR ($CDCl_3$) δ 16.3 (d, $^3J_{PC} = 6.4$ Hz, $\underline{C}H_3CH_2O$), 52.4 (s, OCH_3), 61.29 (d, $^2J_{PC} = 6.0$ Hz, OCH_2), 89.0 (d, $^1J_{PC} = 134.5$ Hz, C^8), 114.5 (s, C^6), 128.6 (d, $^3J_{PC} = 14.0$, *m*-C in C_6H_5P), 130.6 (d, $^2J_{PC} = 10.4$, *o*-C_6H_5P), 131.1 (d, $^1J_{PC} = 140.2$ Hz, *ipso*-C in C_6H_5P), 132.5 (s, *p*-C in C_6H_5P), 141.5 (s, C^5), 151.6 (s, C^2), 164.3 (s, C^7), 166.6 (s, C^4). Found: C 51.04; H 4.55; N 4.07. Calcad for $C_{15}H_{16}NO_5PS$: C 50.99, H 4.53; N 3.96.

(E)-2-[(Diphenylphosphoryl)methylene]-(Z)-5-(methoxycarbonyl-methylene)thiazolidin-4-one **3c**. Applying the above protocol, with the exception that 0.330 g (1.2 mmol) of **2c** was used instead of **2a, 3c**-*E,Z* was obtained in 80% yield; mp 223–224°C. IR, KBr, ν/cm^{-1}: 532, 542, 1012 (C—O—C), 1177 (P=O), 1201 (νas CNC), 1325 (νs CNC), 1570, 1595 (C=C), 1696 (C^7=O), 1721 (C^4=O), 3058 (br, NH). Found: C 59.19; H 4.11; N 3.68. Calcad for $C_{19}H_{16}NO_4PS$: C 59.22, H 4.15; N 3.63.

N-Phenyl-(Z)-2-[cyano(diethoxyphosphoryl)methylene]-(Z)-5-(methoxycarbonyl-methylene)thiazolidin-4-one **5**. Using the same procedure as described for **3a**, **4** (0.4 g, 1.2 mmol) was converted into **5**-*Z,Z* (0.25 g, 49%) isolated by recrystallization from ethyl acetate as light-yellow solid, mp 163–164°C. IR, ν/cm^{-1}: 1008 (C—O—C), 1044 (P—O—C), 1203 (N-Ph), 1220 (P=O), 1358 (νs CNC), 1537 (C^2=C^8), 1698 (C^4=O), 1712 (C^4=O···S), 1730, 1735 (shoulder) (C^7=O), 2196 (CN). ^{13}C NMR ($CDCl_3$, *Z*-**5**) δ 16.0 (d, $^3J_{PC} = 6.4$, $\underline{C}H_3CH_2O$), 52.7 (s, OCH_3), 62.2 (d, $^2J_{PC} = 5.6$ Hz, OCH_2), 76.2 (s, $^1J_{PC} = 201.6$ Hz, C^8), 111.5 (s, C^6), 118.7 (s, CN), 128.8 (s, *o*-C in C_6H_5N), 129.9 (s, *m*-C in C_6H_5N), 131.3 (s, *p*-C in C_6H_5N), 133.4 (s, ipso-C in C_6H_5N), 138.6 (s, C^5), 163.5 (d, $^2J_{PC} = 18.4$ Hz, C^2), 164.5 (s, C^7), 165.6 (s, C^4). Found: C 51.27; H 4.66; N 6.68. Calcad for $C_{18}H_{19}N_2O_6PS$: C 51.18, H 4.53; N 6.63.

X-ray Crystallography

Crystallographic data for **3a**-*E,Z* and **5**-*Z,Z* (single crystals crystallized from dilute ethyl acetate solution by slow evaporation of the solvent) are presented in Table 3. Both structures were solved by direct methods and refined by full-matrix least squares against F^2 in the anisotropic (H-atoms isotropic) approximation, using SHELXTL-97 package. The

TABLE 3 Crystallographic Data for **3a**-*E*,*Z* and **5**-*Z*,*Z*

	3a*-*E*,*Z		***5*-*Z*,*Z***
Formula	$C_{11}H_{16}NO_6PS$		$C_{18}H_{19}N_2O_6PS$
T (K)	120		298
Crystal system, space group	Triclinic, $P\,1$		Triclinic, $P\,1$
a (Å)	8.651(2)		5.9866(8)
b (Å)	9.745(2)		11.612(1)
c (Å)	10.309(2)		14.837(2)
α (°)	63.869(3)		89.642(3)
β (°)	68.379(4)		86.283(3)
γ (°)	70.134(4)		78.210(3)
V (Å^3), Z	708.8(2), 2		1007.5(2), 2
M	321.28		422.38
μ (cm^{-1})	3.65		2.77
F (000)	336		440
ρ_{calcd} (g cm^{-3})	1.505		1.392
$2\theta_{max}$ (°)	55		54
Diffractometer		Smart 1000 CCD	
Scan mode		ω-scan	
reflections measured (R_{int})	4745 (0.0269)		9568 (0.0513)
independent reflections	3104		4330
reflections with $I > 2\sigma(I)$	2603		2255
parameters	185		256
R_1	0.0584		0.0592
wR_2	0.1358		0.1354
GOF	1.041		0.992
Max./min peak (e Å^{-3})	0.730/-0.644		0.616/-0.217

absorption correction was applied semi-empirically from equivalents. The positions of hydrogen atoms in **3a**-*E*,*Z* and **5**-*Z*,*Z* were located from the Fourier density synthesis and included in refinement in riding model approximation.

Crystallographic data for the structures reported in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary no. CCDC-250119 for **3a**-*E*,*Z* and CCDC-250120 for **5**-*Z*,*Z*. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (Fax: (internat.) +44-1223/336-033; e-mail: deposit @ccdc.cam.ac.uk).

Theoretical Calculations

DFT calulations were carried out with Gaussian 98 program package [17a] in which fine grid (75302) is the default for evaluating integrals numerically and the (10^{-8} Hartree) disignation is the default for the SCF convergence. The threshold limit 1.5×10^{-5} and 6×10^{-5} a.u. was used for maximum force and displacement, respectively as a convergence criterion.

The optimization at B3Pw91 level of theory was followed by the evaluation of the harmonic vibration frequencies. Topological analysis of the $\rho(r)$ function (AIMPACK [17b]) was based on the wave functions obtained at B3Pw91 calculations.

ACKNOWLEDGMENT

We are grateful to Mrs. N. White (Department of Chemistry and Biochemistry, University of Maryland) for her helpful comments.

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