REGIOSELECTIVE SYNTHESIS AND SPECTRAL CHARACTERIZATION OF ETHYL (*Z*)- AND (*E*)-2-ALKYLIDENE-4-OXOTHIAZOLIDINE-5-ACETATE DERIVATIVES. SOLVENT EFFECTS ON THE *Z-E* ISOMERIZATION

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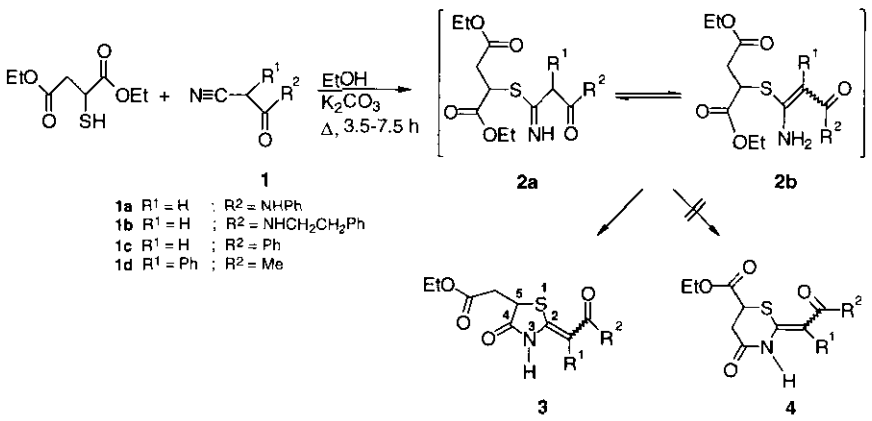
Abstract - The title compounds containing an exocyclic double bond of exclusively the *Z*-configuration were prepared in anhydrous ethanol by the regio-selective base catalyzed reaction of diethyl 2-mercaptobutanedioate with nitrile precursors possessing an acidic α-hydrogen. The ^{1}H NMR data indicating the presence of both geometrical isomers in primarily nonpolar media favoring the *E*-form are presented in terms of the solvent influence on intra- and intermolecular H-bonding and stereochemical outcome of the reaction.

Various 4-oxothiazolidines, possessing a trisubstituted exocyclic double bond at C-2, have attracted considerable interest due to their structural diversity and wide variety of their biological activities.[1] Likewise these derivatives can be useful synthetic intermediates that offer access for preparing different heterocyclic systems.[1,2] Although examination of the literature data indicates that thiazolidine derivatives of this type exist nearly exclusively as conjugated enamines,[3] there appears to be no direct and unambiguous evidence concerning the stereochemistry of the exocyclic double bond.[4,5]

Thus, the purpose of this paper is to report the regioselective synthesis and spectral characterization of as yet unreported (*Z*)- and (*E*)-5-ethoxycarbonylmethyl-4-oxothiazolidin-2-alkylidene derivatives (**3a-c**) (Scheme 1), resembling known pharmacologically active agents,[1] from the oxo nitriles (**1**) and diethyl 2-mercaptobutanedioate. A number of pure *Z*-isomers of this class have been characterized,[6,7] but the separation and the spectral data of the *E*-counterparts are either very sparse, or absent.[1,8]

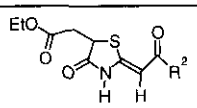


Scheme 1

In this context, the nature and role of the solvent of different polarity on formation of intra- and intermolecular hydrogen bonds,[9,10] which profoundly influence the stereochemistry of the tri- or tetrasubstituted exocyclic double bond at C-2, were given particular scrutiny. Since unisolable intermediates (**2**), formed *via* the nucleophilic addition of diethyl 2-mercaptobutanedioate to the activated nitrile substrates (**1**), contain two electrophilic centers, not only the formation of the 4-oxothiazolidinone derivatives (**3**) but also the intramolecular formation of 6-membered lactams (**4**) can be expected. The reaction of the cyano derivatives (**1**), prepared by standard methods,[11] with diethyl 2-mercapto-butanedioate was achieved under mild experimental conditions in the presence of catalytic amounts of K_2CO_3 in anhydrous ethanol. The structural assignments of the isolated products (**3**) were made on the basis of spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analysis.

An examination of the data in Table 1 reveals that in ethanol as protic polar solvent, 4-oxothiazolidine derivatives (**3a-c**) were formed exclusively, as indicated by comparative analysis of ^{1}H NMR (entries 1,3 and 9) and ^{13}C NMR spectra of recrystallized products which exhibited a single series of signals in DMSO-d_6. The stereochemistry of the double bond in the isolated products (**3a-c**), identified initially as *Z*, was based on established fact that the olefinic proton, positioned *syn* to a lactam nitrogen in comparable compounds,[6] resonates at considerably lower field relative to the *E*-isomers. It is important to point out that the initial *Z*-stereoisomers (**3a-c**) isomerize in solvents differing in polarity, thus resulting in a mixture containing the corresponding *E*-derivatives for spectral comparison (Table 1, entries 2, 4, 10). Additional NMR correlations (*vide infra*) for assigning *Z*-configuration were possible in order to recognize a general trend consistent with the δ values of selected hydrogens in the series (**3a-c**). As for the cyclization process resulting in the formation of **3a-c**, it was evident from trial experiments, utilizing **1b** as a precursor, that the reaction slows down after approximately 4 h because of by-product accumulation.

Table 1. Selected spectroscopic and analytical data of 4-oxothiazolidine-2-alkylidene derivatives (**3a-c**)

 3-Z[a]	mp °C Yield (%)	^{13}C NMR (50.3 MHz, DMSO)	Analysis (%) Calcd/ Found C	H	N	S
3a-Z	183-185	175.68, 170.88, 165.89, 153.54, 140.43, 129.27,	56.12	5.03	8.75	10.01
(R^2 = NHPh)	43.0	123.08, 119.18, 93.34, 61.16, 42.44, 37.19, 14.59	56.15	5.17	8.87	10.15
3b-Z	152-153	175.49, 170.90, 167.05, 150.82, 140.24, 129.24, 128.94,	58.60	5.79	8.04	9.20
(R^2=NHCH$_2$CH$_2$Ph)	42.0	126.66, 92.23, 61.12, 42.29, 40.65, 37.37, 35.99, 14.59	58.76	5.81	8.08	9.20
3c-Z	126-127	187.77, 176.30, 170.72, 161.56, 138.74, 132.62,	59.00	4.95	4.59	10.50
(R^2 = Ph)	48.0	129.31, 127.53, 94.94, 61.15, 42.54, 36.40, 14.49	58.76	5.02	4.68	10.54

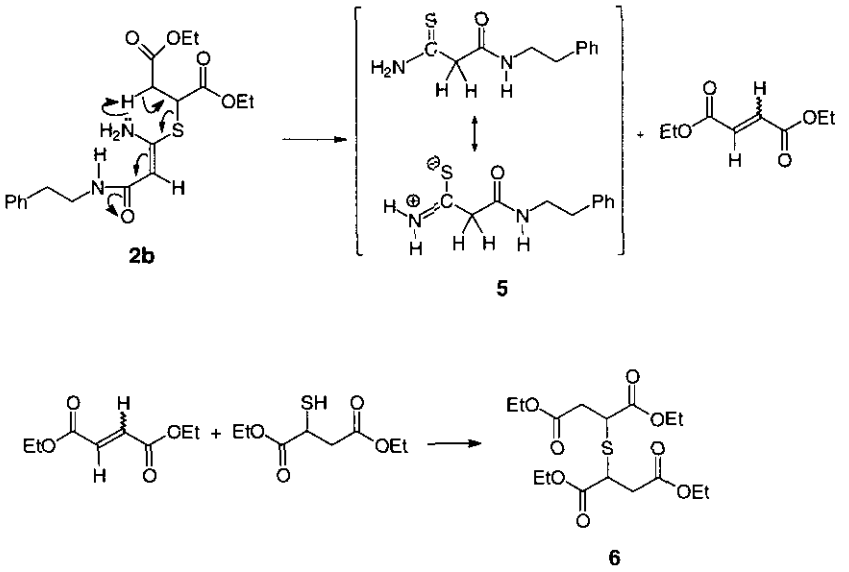
^{1}H NMR (200 MHz) data of Z- and E-isomers (**3a-c**)[b]

entry	compound	NH (lactam)	NH (amide)	HC=	HC-S
1	**3a**-Z(DMSO-d$_6$)	11.57	9.84	5.79	4.18
2	**3a**-E(DMSO-d$_6$)	11.31	9.90	5.36	4.48
3	**3b**-Z(DMSO-d$_6$)	11.30	7.85	5.55	4.11
4	**3b**-E(DMSO-d$_6$)	11.49	8.15	5.15	4.44
5	**3b**-Z(Me$_2$CO-d$_6$)	10.13	7.05	5.68	4.12
6	**3b**-E(Me$_2$CO-d$_6$)[c]	11.64		5.18	4.36
7	**3b**-Z(CDCl$_3$)	9.44	5.81	5.54	4.18
8	**3b**-E(CDCl$_3$)	11.43	5.29	4.90	4.25
9	**3c**-Z(DMSO-d$_6$)	11.93		6.78	4.28
10	**3c**-Z(Me$_2$CO-d$_6$)	10.69		6.95	4.26
11	3c-E(Me$_2$CO-d$_6$)			6.60	4.50
12	**3c**-Z(CDCl$_3$)	9.88		6.85	4.20
13	**3c**-E(CDCl$_3$)	12.06		6.32	4.29

[a] Preliminary results indicate that under the experimental conditions employed (Scheme) only in the case of **1b**, regioisomeric six-membered derivative (**4b**) was formed (< 5%); compounds (**3a**-**3c**) of the exclusively Z-configuration are isolated from reaction mixture and recrystallized from EtOH; the yields refer to analytically pure samples. [b] Although **3d** (R^2 = Me, and Ph instead of the olefinic H), was obtained, as a Z,E-mixture, in low yield (21% after the purification by column chromatography) due to the extensive polymerization, the structural assignment was apparent from the careful consideration of the ^{1}H NMR spectrum in DMSO-d$_6$. [c] NH (amide) proton is hidden behind aromatic protons.

Thus, after isolation of the cyclization compound (**3b**), residual amount of product and unreacted amide (**1b**) remained in the mother liquor, along with two other side products, detected by TLC. One by-product, isolated by column chromatography from highly polar fractions, was identified as *N*-β-phenylethyl-2-thiocarbamoylethanamide (**5**). The structure of **5** was confirmed by IR, MS and ^{1}H NMR where, besides the characteristic two broad resonances associated with the NH_2 protons (δ 9.60 and 9.30), triplet at δ

8.16 (J = 5.6 Hz) assigned to NH, and singlet at δ 3.42 for H_2C-2 protons, the multiplet at δ 3.30 ($HNC\underline{H}_2CH_2$, $J_{NH\text{-}CH}$ = 6.3 Hz; $J_{CH\text{-}CH}$ = 7.0 Hz) and triplet at δ 2.71 ($CH_2C\underline{H}_2Ph$, J = 7.6 Hz) were present. Scheme 2 provides the mechanistic rationale for formation of *N*-β-phenylethyl-2-thiocarbamoyl-ethanamide (**5**). Nucleophilic addition of the mercapto-diester to activated nitrile precursor (**1b**) gives rise to the intermediate (**2b**) (Scheme 1) which, by a β-elimination, gives the amide derivative (**5**) and unsaturated diester. Consistent with this interpretation, the tetraethyl thiodisuccinate (**6**) isolated as a mixture of *meso*- and racemic forms (see Experimental), is the product of Michael addition of diethyl 2-mercaptobutanedioate to the unsaturated ester.



Scheme 2

In an attempt to check the chemical homogeneity of (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-phenylethanamide (**3a**), after isolation and crystallization from EtOH, by TLC (toluene/EtOAc; 3:2, v/v, with or without a trace of HOAc), two spots were observed (R_f = 0.73 and 0.29). Facile interconversion of the **3a**-*Z*- into the **3a**-*E*-isomer forming a mixture of both forms, accounts for the presence of two components. Two dimensional TLC of the same **3a**-*Z*-isomer showed the presence of 4 components split into 2 pairs having identical low and high R_f values, *i.e.* 0.29 and 0.73, suggesting again the presence of a *Z*/*E* mixture from isomerization of each isomer. When the crude (*Z*)-(5-ethoxy-carbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-phenylethanamide (**3a**) was purified by silica gel column chromatography, using relatively nonpolar toluene/EtOAc solvent gradient (95/5 to 60:40, v/v), thiazolidinone derivative (**3a**) crystallized almost instantly upon elution from the column because of the

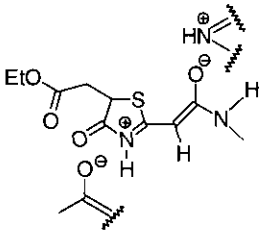
very low solubility in toluene/EtOAc mixture. Not unexpectedly, the ^{1}H NMR spectrum of **3a** in DMSO-d_6, showed two sets of signals, due to rearrangement around the exocyclic double bond,[13] giving **3a**-*Z*- and **3a**-*E*-isomers (Table 1, entries 1 and 2). The *Z*/*E* ratio of the geometrical isomers (**3a**-*Z*) and (**3a**-*E*) was 27:73, as determined by integration of resolved chemical shifts of either the lactam NH, C(5)-H or the HC= protons in the ^{1}H NMR spectrum. The ratio changed with time and converged after 31 h to only the **3a**-*Z*-isomer (Table 2). Specifically, the isomerization to a single **3a**-*Z*-isomer was observed in DMSO-d_6 following a progressive appearance of a singlet at 5.79 ppm assigned to olefinic hydrogen of **3a**-*Z* and a complete disappearance of the 5.36 signal ascribed to **3a**-*E*.

Table 2. The proportion of the *Z*-and *E*-forms (**3a-c**) determined by ^{1}H-NMR in various solvents at rt

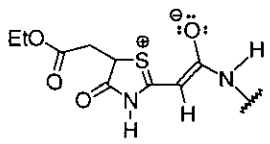
Compd	Initial *Z*/E ratio (%)	Solvent	*Z*/E ratio (%); time (h)			
3a	27/73[b]	DMSO-d_6	29/71 ; 0.5	41/59 ; 2.5	79/21 ; 21.0	100/0 ; 31.0
3b	100/0	DMSO-d_6	94/6[a]			
3b	100/0	Me_2CO-d_6	61/39 (4 days) ; 52/48[a] (8 days)			
3b	100/0	$CDCl_3$	22/78 [a]			
3c	100/0	DMSO-d_6	100/0			
3c	100/0	Me_2CO-d_6	76/24 [a]			
3c	100/0	$CDCl_3$	11/89 [a]			

[a] The equilibrated *Z*/*E* ratio at rt. [b] Isolated by column chromatography (*vide ante*).

This indicates, most likely, the existence of a mesomeric structure (**7a**) stabilized by intermolecular hydrogen bonds.[12,13] The low temperature X-Ray structure of a related 2-methylenethiazolidin-4-one derivatives reported by Steel *et al.*[3] proved the importance of the dipolar structure of type **7a**. A proper description of the configurational stability of the structurally similar *Z*-geometrical isomers (**3a-c**) requires, however, a consideration of an another structure (**7b**), stabilized by attractive electrostatic interactions between the *syn*-configurated alkylthio electron-donating group and electron-withdrawing carbonyl group.[14] Nevertheless, strong intermolecular H-bonding with DMSO provides the most significant contribution to the stability of the *Z*-form, as indicated by analysis of the ^{1}H NMR spectra of **3b**-*Z*-isomer in various solvents. The chemical shift of lactam NH-proton of the **3b**-*Z*-isomer in DMSO-d_6, Me_2CO-d_6 and $CDCl_3$ appears as a singlet at *11.30*, *10.13* and *9.44* ppm, respectively (Table 1, entries 3, 5 and 7). The large NMR downfield shift observed in DMSO-d_6 relative to $CDCl_3$ (*ca.* $\Delta\delta$ 1.58 ppm)



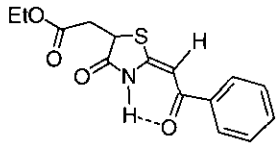
7a



7b

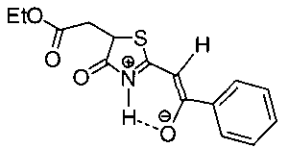
(the absorption in Me_2CO-d_6 being in an intermediate position; $\Delta\delta$ 1.18 ppm), indicate a highly deshielded proton in DMSO-d_6. That directly reflects the strongest intermolecular interactions of the NH-lactam hydrogen with DMSO-d_6 molecules, which are characterized by the high proton accepting ability. In terms of the strengthening of intermolecular H-bonding along solvent series $CDCl_3$, Me_2CO-d_6 and DMSO-d_6, a consistent set of the solvent-dependent NMR data for the NH (amide)-proton absorption has also been observed (Table 1, entries 3, 5 and 7). For example, **3b**-*Z*-isomer in $CDCl_3$ exhibits a triplet centered at 5.81 ppm, due to the vicinal CH_2 group, while the chemical shifts for the same proton are shifted downfield in Me_2CO-d_6 and DMSO-d_6, *i.e.* δ 7.05 and 8.85, respectively. The changes in chemical shift of NH proton in different solvents reflect again the degree of solvent-promoted disruption of the intermolecular H-bonding in $CDCl_3$ solution *versus* strengthening in Me_2CO-d_6 and DMSO-d_6.

The difference of the selected chemical shifts observed in the ^{1}H NMR spectra of the **3a**-*Z*- and *E*-isomers was also exploited for the determination of *Z*/*E* ratios of the analogous thiazolidinones (**3b**) and (**3c**). Thus, when the pure **3c**-*Z*-isomer was examined in $CDCl_3$, a new set of signals of the **3c**-*E* -isomer (Table 1, entries 12 and 13), was detected, indicating the presence of *Z*/*E* mixture in a ratio of *ca.* 11/89, in favor of the *E*-isomer (see Table 2). Evidently, intermolecular H-bonding, present in the *Z*-isomers (**3a-c**), can be suppressed by dissolving the substance in a lipophilic solvent, promoting conversion of the pure *Z*-isomer into a *Z*/*E* mixture enriched in *E*-isomer.[15] On the other hand, an increased effectiveness of aprotic and polar solvents, such as acetone, to delocalize the charges by the solvation, favors the dipolar form of the structure (**3c**) as a predominant species, possessing the *E*-configuration.



predominant neutral chelated form

of **3c**-*E* in $CDCl_3$



predominant dipolar chelated form

of **3c**-*E* in Me_2CO-d_6

Regarding the *Z*/*E* ratio of **3c** in acetone, **3c**-*Z* isomer is the major one, *i.e.* *Z*/*E* ratio = 76/24, while in more polar DMSO this is the only isomer present (Table II). This indicates that the 4-oxothiazolidine system (**3a-c**) with an electron-accepting group on one side and a donor group on the opposite side of the exocyclic double bond, displays many of the properties of H-bonding associated with the changes in the ratios of *Z*- and *E*-isomers induced by changes in the chemical environment and alteration of the polar character of the solvent.

Previous ^{1}H NMR studies[4-6] have totally neglected or indicated a negligible chemical shift difference between geminal C-5 protons in configurational isomers of 4-oxothiazolidine derivatives without substituent on the C-5. However, as can be seen in Table 1 the C(5)-H of **3a**-*E*-isomer in DMSO-d_6 appears at 4.48 ppm as two doublets (ABX system) due to splitting by the adjacent diastereotopic CH_2 protons (J_{AX} = 4.6 Hz; J_{BX} = 7.7 Hz). The corresponding NMR signal of the **3a**-*Z*-isomer is shifted upfield by 0.3 ppm relative to the **3a**-*E*-isomer. A rationale for this upfield shift, with an average chemical shift difference between *Z*- and *E*-isomers (**3a-c**) of about 0.29 ppm, is the presence of the aforementioned dipolar structure of type (**7a**) stabilized by strong intermolecular hydrogen bonds, which is reflected in the diamagnetic location of the C(5)-H in the *Z*-isomers. This is consistent with the observation that in $CDCl_3$ solution containing an equilibrated *Z*/*E* mixture (Table 2), the C(5)-H of **3c**-*Z*-isomer (Table 1, entries 8 and 9) experiences a diamagnetic shift of only 0.09 ppm associated with a much smaller charge separation and diamagnetic effect, than in polar DMSO.

Therefore, from the above results, the unequivocal assignment of the stereochemistry of 4-oxothiazolidine derivatives (**3a-c**), possessing an α,β-unsaturated ene-amide lactam structure with β-alkylthio substituent susceptible to extended delocalization, is possible. In addition, advantage can be taken for preparative purposes, of the different behavior in the equilibration between the *E*- and *Z*-isomers: thus, performing the reaction in polar ethanol favors formation of *Z*-isomers and *vice-versa* in hydrophobic solvents ($CHCl_3$, toluene) a mixture of both isomers, but enriched in the *E*-isomer, can be expected.

EXPERIMENTAL

General Methods. Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer 1725X and are reported as wave numbers (cm^{-1}). Samples for IR spectral measurements were prepared as KBr disks. NMR spectra were recorded on a Varian Gemini 2000 spectrometer (^{1}H at 200 MHz, ^{13}C at 50.3 MHz). Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the solvents specified. Low-resolution mass spectra were determined using a Finnigan MAT 8230 BE spectrometer. UV spectra were

measured on a Varian Super Scan 3 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on SiO_2 (Kodak Chromogram Sheet / 13181, 100 μ), and the spots were visualized by UV or iodine. Column chromatography was carried out on SiO_2 (silica gel 60Å, 12-26, ICN Biomedicals). Elemental analyses were performed at the Laboratory for microanalysis at the Department of Chemistry, University of Belgrade.

***(Z)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-phenylethanamide (3a-*Z*).** In a typical procedure to a stirred suspension of 0.538 g (3.36 mmol) of cyano *N*-phenylethanamide, obtained by standard procedure, and 0.700 g (3.4 mmol; ~ 1% molar excess) of diethyl 2-mercaptobutanedioate in absolute ethanol (5 mL), a catalytic amount of potassium carbonate (9.3 mg; 0.067 mmol) was added. The mixture was brought to reflux, additional amount of ethanol (2 mL) added to dissolve the residual amount of *N*-phenylethanamide and solution allowed to reflux for 3.5 h with continuous stirring. The solution was cooled down to rt and the separated solid was filtered, washed with ethanol and dried to provide the total of 0.664 g (61.7%) of **3a**-*Z*. The half of the crude product thus obtained, 0.332 g, was recrystallized twice from 96% EtOH to give 0.231 g (43%) of the pure **3a**-*Z* isomer as colorless crystals, mp 183-185 °C; IR (KBr): ν_{max} = 3370, 3169, 3060, 3020, 2983, 1718, 1696, 1667, 1582, 1533, 1373, 1248, 1196, 1148, 1079, 796, 730, 690 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.19 (t, 3H, H_3C, J = 7.2 Hz), 2.83-3.08 (ddd, 2H, $\underline{H_a}\underline{H_b}C$-$CH_xS$, J_{AB} = 17.3 Hz, J_{AX} = 4.6 Hz, J_{BX} = 8.0 Hz), 4.10 (q, 2H, CH_2O, J = 7.2 Hz), 4.18 (dd, 1H, CH_xS, shielded, J_{AX} = 4.6 Hz, J_{BX} = 8.0 Hz), 5.79 (s, 1H, =CH), 6.98 (t, 1H, HC(4'), J = 3.7 Hz), 7.26 (t, 2H, HC(3') and HC(5'), J = 3.8 Hz), 7.58 (d, 2H, HC(2') and HC(6'), J = 4.3 Hz), 9.84 (s, 1H, NH, *exo*), 11.57 (9s, 1H, NH, ring). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 14.59, 37.19, 42.44, 61.16, 93.34, 119.18, 123.08, 129.27, 140.43, 153.54, 165.89, 170.88, 175.68. EIMS: *m/z* (rel. intensity) 320 (M^+, 37), 275 (8), 228 (15), 182 (16), 93 (100), 77 (20). UV (DMSO): λ_{max} (ε) 306.0 nm (31000). Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.12; H, 5.03; N, 8.75; S, 10.01. Found: C, 56.15; H, 5.17; N, 8.87; S, 10.15.

***(E)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-phenylethanamide (3a-*E*).** Column chromatography of another half of crude **3a** (0.332 g) employing toluene/ethyl acetate solvent gradient (95/5 to 60:40, v/v) afforded 0.211 g of a mixture containing the corresponding **3a**-*E*-isomer for spectral comparison, in a 26.6/73.4 *E*/*Z* ratio, as determined by ^1H NMR analysis (Table 1). IR (KBr): ν_{max} = 3331, 3091, 2981, 2929, 1727, 1710, 1646, 1610, 1595, 1542, 1495, 1257, 1220, 1182, 1165, 1076, 769, 693, 678 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.18 (t, 3H, H_3C, J = 7.1 Hz), 2.95-3.18 (ddd, 2H, $\underline{H_a}\underline{H_b}C$-$CH_xS$, J_{AB} = 17.4 Hz, J_{AX} = 4.6 Hz, J_{BX} = 7.7 Hz), 4.10 (q, 2H, CH_2O, J = 7.2 Hz), 4.48 (dd, 1H, CH_xS, J_{AX} = 4.6 Hz, J_{BX} = 7.7 Hz), 5.36 (s, 1H, =CH), 7.04 (t, 1H, HC(4'), J = 3.4 Hz), 7.30 (t, 2H,

HC(3') and HC(5'), J= 3.6Hz), 7.59 (d, 2H, HC(2') and HC(6') J= 4.1Hz), 9.90 (s, 1H, NH, *exo*), 11.31 (9s, 1H, NH, ring).

***(Z)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-2-phenylethylethanamide (3b-*Z*).** A stirred mixture of 1.00 g (5.3 mmol) of cyano *N*-2-phenylethylethanamide (**1b**) and 1.096 g (5.9 mmol) of diethyl 2-mercaptobutanedioate in absolute ethanol (7 mL) was refluxed for 7 h under nitrogen in the presence of a catalytic amount of potassium carbonate (58 mg; 0.42 mmol) until complete consumption of mercapto diester (TLC). After cooling to the rt, small amount (2 mL) of ethanol was added. The precipitate was collected, washed with ethanol and dried to give 0.605 g (33.1%) of **3b**-*Z* as a solid, which gave an analytical sample by recrystallization from ethanol; mp 152-153 °C; IR (KBr): ν_{max} = 3300, 3060, 3030, 2925, 2880, 1737, 1696, 1630, 1560, 1469, 1373, 1289, 1093, 1079, 807, 742, 692 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.19 (t, 3H, CH_3, J= 7.2 Hz), 2.69 (t, 2H, CH_2Ph, J= 7.4 Hz), 2.77-3.04 (ddd, 2H, $\underline{H_a}\underline{H_b}C$-$CH_xS$, J_{AB} = 17.2 Hz, J_{AX} = 4.3 Hz, J_{BX} = 8.4 Hz), 3.22-3.34 (m, NCH_2, J= 7.4 Hz, J= 5.4 Hz), 4.09 (q, 2H, CH_2O, J= 7.2 Hz), 4.11 (dd, 1H, CH_xS, shielded, J_{AX} = 4.3 Hz, J_{BX} = 8.4 Hz), 5.55 (s, 1H, =CH), 7.18 (t, 1H, HC(4'), J= 2.3 Hz), 7.22 (t, 2H, HC(3') and HC(5'), J= 3.7 Hz) 7.32 (d, 2H, HC(2') and HC(6'), J= 2.4 Hz), 7.85 (t, 1H, NH, *exo*, J= 5.4 Hz), 11.30 (s, 1H, NH, ring). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 14.59, 35.99, 37.37, 40.65, 42.29, 61.12, 92.23, 126.67, 128.94, 129.24, 140.24, 150.82, 167.05, 170.90, 175.49. EIMS: *m/z* (rel. intensity) 348 (M^+, 4), 303 (6), 228 (99), 182 (81), 153 (88), 103 (base peak), 128 (41), 77 (36). UV(DMSO) λ_{max} (ϵ) 282 nm (25000). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; S, 9.20. Found: C, 58.76; H, 5.81; N, 8.08; S, 9.20. The remaining filltered solution was concentrated *in vacuo* and the resultant yellowish oil was chromatographed on SiO_2 (160 g) using toluene/EtAOc (7:3) to give the additional amount of **3b**-*Z* (0.636 g, 34.8%), thus increasing the total yield of **3b**-*Z* to 1.241 g (67.9%). *N*-β-Phenylethyl-2-thiocarbamoylethanamide (**5**) (52 mg) as a white solid, mp 142-144 °C, and tetraethyl thiodisuccinate (**6**) (isolated as a oily mixture of the racemic and *meso*-forms) (0.279 g) were obtained as a side products. Column chromatography also afforded unreacted starting amide (**1b**) (0.150 g) and an inseparable mixture.

***N*-β-Phenylethyl-2-thiocarbamoylethanamide (5).** mp 142-144 °C; IR (KBr): ν_{max} = 3333, 3282, 3158, 3028, 2931, 1719, 1660, 1646, 1618, 1561, 1432, 1155, 1030, 803, 737, 696 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.71 (t, 2H, CH_2Ph, J= 7.6 Hz), 3.30 (m, 2H, $HNCH_2$, J_{NH-CH} = 5.6 Hz, J_{CH-CH} = 7.0 Hz), 3.42 (s, 2H, CH_2CO), 7.16-7.34 (m, 5H 8.16 (t, 1H, NH, J= 5.6 Hz), 9.30 and 9.60 (2 br s, 2H, NH_2CS). ^{13}C NMR (50.3 MHz DMSO-d_6): δ = 200.72, 167.24, 140.02, 129.32, 128.99, 126.77, 52.14, 41.06, 35.62. MS: *m/z* = 223 (M+1).

Tetraethyl thiodisuccinate (6) (isolated as a pale yellow oil). IR (KBr): ν_{max} = 3453, 2984, 1734, 1467, 1447, 1260, 1028, 796, 730, 689, 645 cm^{-1}; two distinguishable sets of signals appear in the ^{1}H NMR

spectrum (200 MHz, DMSO-d_6) (first series of signals): δ = 1.17 (t, 6H, CH_3, J = 7.2Hz), 1.20 (t, 6H, $SCHCOOCH_2C\underline{H}_3$, J= 7.0 Hz), 2.65-2.95 (ddd, 4H, $(\underline{H_aH_b}C\text{-}CH_x)_2S$, J_{AB} = 17.1 Hz, J_{AX} = 5.9 Hz, J_{BX} = 9.5 Hz), 3.89 (m, 2H, $(H_aH_bC\text{-}C\underline{H_x})_2S$, J_{AX} = 5.9 Hz, J_{BX} = 9.5 Hz), 4.06 (q, 4H, OCH_2, J = 7.1 Hz); in a second series of signals corresponding to *meso-* or racemic compound (**6**) the following absorptions are observed: δ = 2.70-2.97 (ddd, 4H, $(\underline{H_aH_b}C\text{-}CH_x)_2S$, J_{AB} = 17.0 Hz, J_{AX} = 6.0 Hz, J_{BX} = 9.4 Hz), 3.93 (m, 2H, $(H_aH_bC\text{-}C\underline{H_x})_2S$, J_{AX} = 6.0 Hz, J_{BX} = 9.4 Hz), 4.12 (q, 4H, OCH_2, J = 7.1 Hz). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 171.31, 170.54, 61.67, 60.03, 42.10, 41.79, 36.96, 36.52, 14.50, 14.35 (as for ^{1}H NMR spectrum, two pairs of separate chemical shifts assigned to C(2) and C(3) are noticed. EIMS: *m/z* (relative intensity) 378 (M^+,12), 333 (27), 304 (61), 206 (79), 173 (base peak).

(E)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-*N*-2-phenylethylethanamide (3b-*E*).** Isomerization of **3b-*Z in DMSO-d_6 afforded the equilibrated mixture containing **3b-*E*** isomer (*Z/E* ratio = 94/6, Table 2) for spectral characterization. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.19 (t, 3H, H_3C, J = 7.2 Hz), 2.69 (t, 2H, CH_2Ph, J = 7.4 Hz), 2.77-3.04 (ddd, 2H, $\underline{H_aH_b}C\text{-}CH_xS$, J_{AB} = 17.2 Hz, J_{AX} = 4.3 Hz, J_{BX} = 8.4 Hz), 3.22-3.34 (m, NCH_2, J = 7.4 Hz, J = 5.4 Hz), 4.09 (q, 2H, CH_2O, J = 7.2 Hz), 4.44 (dd, 1H, CH_xS, J_{AX} = 4.3 Hz, J_{BX} = 8.4 Hz), 5.15 (s, 1H, =CH), 7.18 (t, 1H, HC(4'), J = 2.3 Hz), 7.22 (t, 2H, HC(3') and HC(5'), J = 3.7 Hz) 7.32 (d, 2H, HC(2') and HC(6'), J = 2.4 Hz), 7.85 (t, 1H, NH, *exo*, J = 5.4 Hz), 11.49 (s, 1H, NH, ring). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.04, 35.69, 37.95, 40.37, 42.15, 61.51, 91.09, 126.59, 128.71, 128.74, 138.71, 150.81, 166.56, 170.34, 173.39.

(Z)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (3c-*Z*).** Diethyl 2-mercaptobutanedioate (1.43 g, 6.97 mmol) was added to a suspension of cyanoacetophenone (1.00 g, 6.90 mmol) and catalytic amount of potassium carbonate (24 mg, 0.18 mmol) in dry ethanol (10 mL). The reaction mixture was stirred at 45 °C for 15 min and then the solutrion was allowed to reflux. The course of the reaction was carefully monitored by TLC. Upon the completion of the reaction (5 h) the reaction mixture was cooled to rt and the precipitate separated by filtration was washed with ethanol and dried to give 0.85 g of crude **3c-*Z isomer. The filtrate was evaporated *in vacuo* and the residue purified by silica gel column chromatography (toluene/ethyl acetate; 7:3 v/v as a eluent) to yield additional amount (0.37 g) of **3c-*Z***. Recrystallization from ethanol of both solids afforded 1.01 g (48%) of the pure **3c-*Z*** isomer as colorless crystals, mp 126-127 °C; IR (KBr): ν_{max} = 3125, 3110, 3102, 3082, 2986, 2918, 1718, 1610, 1595, 1575, 1465, 1410, 1375, 1247, 1055, 889, 782, 704, 682 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.20 (t, 3H, H_3C, J = 7.0 Hz), 2.91-3.14 (ddd, 2H, $\underline{H_aH_b}C\text{-}CH_xS$, J_{AB} = 17.6 Hz, J_{AX} = 4.6 Hz, J_{BX} = 7.6 Hz), 4.12 (q, 2H, CH_2O, J = 7.0 Hz), 4.28 (dd, 1H, CH_xS, shielded, J_{AX} = 4.6 Hz, J_{BX} = 7.6 Hz), 6.78 (s, 1H, =CH), 7.46-7.62 (m, 3H, HC(3'), HC(5') and HC(4')), 7.81-7.86 (m, 2H, HC(2') and HC(6')), 11.93 (br s, 1H, NH). ^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 14.49, 36.40, 42.54, 61.15, 94.94, 127.53, 129.31,

132.62, 138.74, 161.557, 170.72, 176.30, 187.77. EIMS: *m/z* (rel. intensity) 305 (M^+, 38), 260 (8), 232 (26), 146 (10), 87 (7), 77 (18). UV(DMSO) λ_{max} (ϵ) 335 nm (19000). Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59; S, 10.50. Found: C, 58.76; H, 5.02; N, 4.68; S, 10.54.

***(E)*-(5-Ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (3c-*E*).**

Spectral characterization was performed using the equilibrated mixture containing **3c-*Z*** and **3c-*E*** isomer (*Z*/*E* ratio = 11/89, Table 2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, 3H, H_3C, J = 7.2 Hz), 2.83-3.34 (ddd, 2H, $\underline{H_a}\underline{H_b}C$-$CH_x$S, J_{AB} = 17.7 Hz, J_{AX} = 3.6 Hz, J_{BX} = 9.9 Hz), 4.22 (q, 2H, CH_2O, J = 7.2 Hz), 4.29 (dd, 1H, CH_xS, shielded, J_{AX} = 3.6 Hz, J_{BX} = 9.9 Hz), 6.32 (s, 1H, =CH), 7.41-7.59 (m, 3H, HC(3'), HC(5') and HC(4')), 7.88-7.93 (m, 2H, HC(2') and HC(6')), 12.06 (s, 1H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): 14.03, 37.54, 42.31, 61. 67, 94.54, 127.79, 128.61, 132.55, 137.94, 158.42, 170.09, 174.59, 188.29.

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