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SEQUENTIAL BROMINATION-REARRANGEMENT OF PUSH-PULL THIAZOLIDINES INDUCED BY PYRIDINIUM HYDROBROMIDE PERBROMIDE UNDER HOMOGENOUS REACTION CONDITIONS

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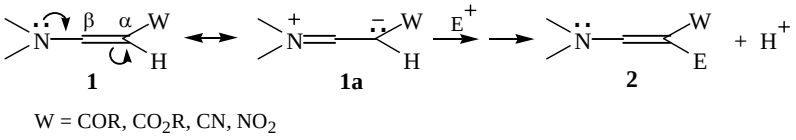
Abstract – Regiospecific bromination-rearrangement of the 5-substituted 2-alkylidene-4-oxothiazolidine derivatives induced by pyridinium hydrobromide perbromide (PHBP) provides a new synthetic approach to the corresponding push-pull thiazolidines with two exocyclic double bonds. In comparison to a heterogenous alternative, this conversion, taking place in acetonitrile under homogenous reaction conditions, has the advantage of almost quantitative yields and a substantial rate enhancement.

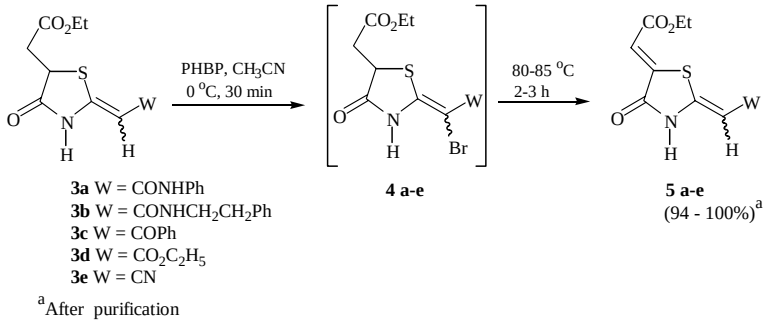
INTRODUCTION

Heterocyclic compounds which contain the β-enamino moiety (**1**) are the subject of numerous papers dealing with their functionalization and reactivity (Scheme 1).[1-4] Due to the n,π-interaction between the electron-donor and acceptor-groups leading to a polarized C=C bond, the electron density at the α-carbon atom in β-enamines is increased (resonance structure (**1a**)). Accordingly, the nucleophilicity of the heterocyclic β-enamines is enhanced, allowing the introduction of various electrophiles at the α-position.[5-7]
In recent publications[8-10] we reported the synthesis and *Z/E* isomerization study of the (*Z*)-5-substituted 2-alkylidene-4-oxothiazolidines (**3a-e**) (Scheme 2) which belong to the class of functionalized push-pull β-enamines.



Scheme 1

There is a considerable interest in synthetic and naturally occurring thiazolidine derivatives of that type, in part due to their broad range of biological activity.[11] In addition, ^{13}C NMR chemical shifts for the C(α) atoms (δ 89-95 ppm) and for the C(β) atoms (δ 151-162 ppm) in **3a-e**,[12,13] correlate with the enaminic susceptibility toward electrophiles. As a result, the regiocontrolled α-bromination of 4-oxothiazolidines (**3a-e**) affords the α-bromo-β-enamines (**4a-e**) (Scheme 2), which are synthetically useful α-acylvinyl anion equivalents,[14,15] is expected. In general, this reaction, carried out by various brominating reagents, usually requires a base such as pyridine,[16] DBU,[17] Et_3N,[18] DABCO,[19] K_2CO_3,[20] or $NaHCO_3$.[21] In the present case, the preformed vinyl bromides (**4a-e**) (or *in situ* formed) undergo novel rearrangement upon treatment with excess pyridine, giving rise to 4-oxothiazolidine derivatives (**5a-e**) (Scheme 2) in relatively low yields (Table 1, Method C).



Scheme 2

In this note, we describe the details of highly improved bromination-rearrangement conversion of 5-substituted-2-alkylidene-4-oxothiazolidines (**3**) to push-pull thiazolidines (**5**) (Scheme 2), induced by PHBP in MeCN under homogenous reaction conditions.

RESULTS AND DISCUSSION

Our previous results indicated that the regiospecific α-bromination of **3** [Br_2 in CCl_4, reflux, 30 min (**3b** and **3e**); Br_2 in dry EtOH, room temperature, 10 min (**3a** and **3c**)], yielding the α-bromo-β-enamines (**4**) (Scheme 2) in moderate yields (60-66%),[12,13] occurs without base,[22] except in the case of **3d** for which 1 equivalent of pyridine is required (Br_2 in $CHCl_3$, room temperature, 4 h). In this investigation we selected soluble PHBP in MeCN as the reagent for the bromination-rearrangement sequence due to its ease of

handling and mild reactivity.[23,24] It is also environmentally safer in comparison to elemental bromine. In addition, the amount of bromine is difficult to control, and excess reagent led to overbromination.

Table 1 summarizes the comparative results of the bromination-rearrangement reaction between thiazolidine derivatives (**3**) and PHBP under homogenous (Method A) and heterogenous reaction conditions (Method B). Method A gives markedly higher yields. In Method A the use of MeCN allows the complete solubility of PHBP, reactant, each intermediate and product. The reaction rates in MeCN are up to 20 times faster than in $CHCl_3$.

Table 1. Synthesis of thiazolidines (**5a-e**) with two exocyclic C=C bonds from **3a-e**[a] using PHBP[b]

Substrate	W	Yield (%)[c] Method A	2*Z*,5*Z*/2*E*,5*Z*[d] (Method A) Purified product (**5**)	Yield (%)[c] Method B[e]	Yield (%)[c] Method C[f]
3a	CONHPh	quant.	37/63	64	37
3b	$CONHCH_2CH_2Ph$	98	50/50	76	47
3c	COPh	quant.	10/90	81	39
3d	$CO_2C_2H_5$	quant.	32/68	54	40
3e	CN	94	79/21	46	40

[a] Starting compounds ((*Z*)-**3a-d** and **3e**) (*Z*/*E* mixture) were synthesized by a regioselective base-catalyzed reaction of the corresponding β-oxonitriles with diethyl mercaptosuccinate in ethanol under reflux.[5]

[b] The molar ratio of PHBP to thiazolidine substrate (**3**) was 1.2:1 (Method A).

[c] Irrespective of the method employed, yields refer to chromatographically isolated products (2*Z*,5*Z*/2*E*,5*Z* mixtures).

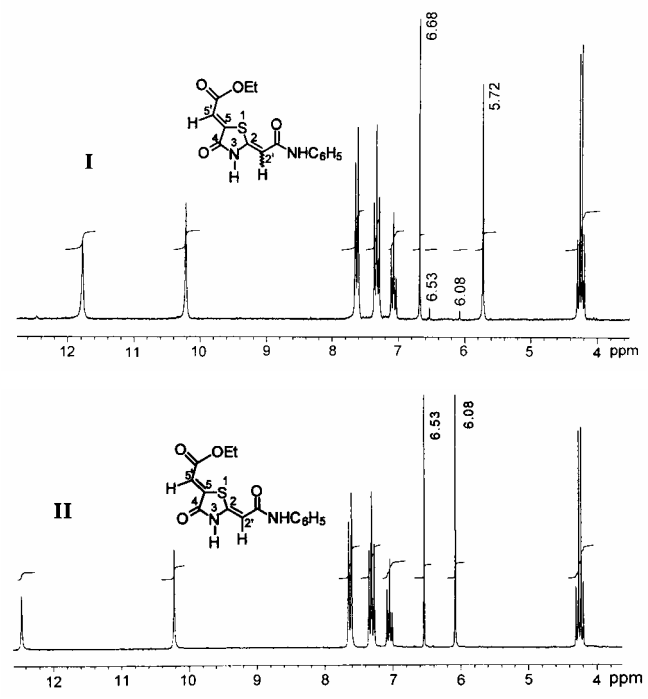
[d] The ratio of configurational isomers, determined by ^{1}H NMR spectroscopy, depends on the polarity of eluant used for the column chromatography purification; (*Z*)-configuration of the exocyclic double bond at C(5) in **5a-e** is fixed due to the repulsive interactions between the lactam carbonyl and carboethoxy group in *E*-configurated isomers.

[e] Method B: Reactions were carried out under heterogenous reaction conditions, using PHBP in $CHCl_3$; reaction time: 24-48 h at rt.

[f] Method C: The preformed vinyl bromides (**4**) were subjected to rearrangement in the presence of excess pyridine.

The highly reproducible sequential **3**→**4**→**5** transformation was carried out as a one-pot procedure yielding the final purified products in nearly quantitative yields. Purification of the crude products (**5a-e**) by column chromatography led to mixtures containing, in varying proportions, the 2*Z*,5*Z* and 2*E*,5*Z*-isomers. The facile *Z*/*E* isomerization of the C(2)-exocyclic double bond is an intrinsic structural property of precursors (**3a-e**) and products (**5a-e**), as well. The key factor controlling the *Z*/*E* ratio is the strength of inter- and intramolecular hydrogen bonds which, among other factors, depends on the medium polarity. With the exception of **3e** and **5e** (W = CN), the intramolecularly H-bonded 2*E*,5*Z*-**5a-d** isomers predominate in nonpolar solvents. For example, the equilibrated ratio of *ca.* 10/90 favoring the 2*E*,5*Z*-diastereomer in $CDCl_3$ was determined for **5c** (Table 1, column 4). As a rule, the replacement of the nonpolar solvent by a polar one (DMSO, DMF, MeCN) increases the stability and therefore the abundance of the 2*Z*,5*Z*-isomers. Figure 1. illustrates perfectly the effect of DMSO-d_6 on slow isomerization of the mixture consisting of 2*Z*,5*Z*-**5a** and 2*E*,5*Z*-**5a** isomers (^{1}H NMR spectrum I) in a ratio of 3/97, into the exclusively 5*Z*,5*Z*-**5a** isomer. The diastereomer ratios, before and after the isomerization, were determined by the integration of the C(α) olefinic protons which show different chemical shifts. The configurational stability of the 2*Z*,5*Z*-isomers (**5a-d**) is attributed to (*i*) the strong intermolecular H-bonding interactions

with the polar solvent and (*ii*) an equally dominant electrostatic oxygen-sulfur interaction of the 1,5-type within the structural unit S-C=C-C=O with the *cis*-configurated C=C bond.[25-27]

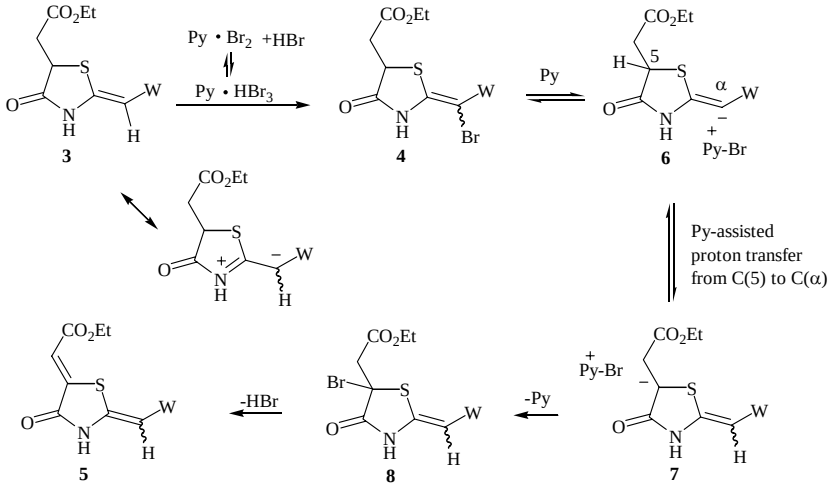


^{1}H NMR spectrum **I** shows the low intensity signals of the olefinic protons at 6.53 ppm (H-C5') and 6.08 ppm (H-C2') assigned to the minor (2*Z*,5*Z*)-**5a** isomer. Corresponding and larger peaks at 6.68 and 5.72 ppm are due to the major (2*E*,5*Z*)-**5a** isomer.

^{1}H NMR spectrum **II** is associated with the exclusively (2*Z*,5*Z*)-**5a** isomer after isomerization (a few days), as indicated by the complete disappearance of the 6.68 and 5.72 ppm signals ascribed to the (2*E*,5Z)-**5a** isomer.

Figure 1. Isomerization of the (2*E*,5Z)-**5a** and (2*Z*,5*Z*)-**5a** mixture (spectrum **I**) into the pure (2*Z*,5*Z*)-**5a** in DMSO-d_6 (spectrum **II**)

A plausible mechanism for the formation of thiazolidines (**5a-e**) is depicted in the Scheme 3.



Scheme 3

The first step is α-bromination of the thiazolidine derivatives (**(*Z*)-3a-d**) (*Z/E* mixture in the case of **3e**). Assuming that an equilibrium between Py·HBr_3 and Py·Br_2 is established in the presence of C=C bond,[28]

$Py{\cdot}Br_2$ is most likely the brominating reagent. The subsequent steps for pyridine-induced elimination-rearrangement sequence **4**→**5** were previously proposed.[13]

CONCLUSION

In conclusion, we have described an easy and efficient route to thiazolidines with two exocyclic double bonds from 5-substituted 2-alkylidene-4-oxothiazolidines. Experimental data indicate that the homogeneous bromination-rearrangement sequence using soluble PHBP in acetonitrile goes to (1) completion without need to isolate α-bromo-β-enamine intermediate; (2) it offers a simplified procedure which is cleaner and less polluting in comparison to a heterogenous alternative; (3) products are readily recovered (non-aqueous work-up); and (4) chromatographically isolated yields are very high (94-100%).

EXPERIMENTAL

Melting points were determined on a Micro-Heiztisch Boetius PHMK apparatus or Büchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer and are reported as wave numbers (cm^{-1}). The NMR spectra were obtained using a Varian Gemini 2000 instrument (^1H at 200 MHz, ^{13}C at 50.3 MHz). Low-resolution MS spectra were recorded using a Finnigan MAT 8230 BE spectrometer at 70 eV (EI). The UV spectra were measured on a Beckman DU-50 spectrophotometer. Flash chromatography was carried out on SiO_2 (silica gel 60Å, 12-26 mμ, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade. Reagents were used as obtained from commercial sources or purified according to standard procedures. Pyridinium Hydrobromide Perbromide was prepared as described in the literature.[23]

Pyridinium Hydrobromide Perbromide-induced bromination-rearrangement of 3a-e; General Procedure (Method A)

Thiazolidine derivative (**3**) (1 mmol) was dissolved in MeCN (15-20 mL) and cooled in an ice bath. PHBP (384 mg, 1.2 mmol) in MeCN (~10 mL) was added, with stirring over a 5 min period followed by a 30 min stirring period at 0 ºC. In all cases, the bromination gave the corresponding vinyl bromide (**4**) as the exclusive intermediate (TLC). The resulting mixture was warmed to 80-85°C and stirred for the additional 2-3 h until the disappearance of the *in situ* formed vinyl bromide (**4**). After evaporation of volatiles under reduced pressure, the crude product was purified by flash chromatography using toluene/EtOAc as eluent, to afford the thiazolidine product (**5**) as yellow solid.

(2*E*,5*Z*)- and (2*Z*,5*Z*)-(5-Ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)-*N*-phenylethanamide (5a)

From **3a** (64.0 mg, 0.20 mmol) in MeCN (4 mL) and PHBP (77 mg, 0.24 mmol) in MeCN (2 mL) after flash chromatography (toluene/EtOAc 3:1 to 1:1) a mixture of two diastereomers (**5a**) was isolated; yield

63.5 mg (100 %); mp 214-216 ºC. MS (EI): *m/z* (rel. intensity) 318 (M^+, 8), 273 (1), 226 (14), 198 (9), 180 (4), 159 (2), 131 (3), 103 (4), 93 (100), 85 (11), 77 (4), 68 (12), 67 (3), 66 (2), 65 (2). IR (KBr) of 2*E*,5*Z*-isomer: ν 3462, 3329, 3250, 3171, 3141, 3044, 3028, 2974, 2937, 2862, 1687, 1653, 1599, 1547, 1372, 1314, 1196, 1136, 852, 805, 756, 692 cm^{-1}; 2*Z*,5*Z*-isomer: ν 3444, 3323, 3197, 2987, 1708, 1674, 1654, 1619, 1600, 1548, 1373, 1321, 1202, 1149, 833, 751, 690 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer, distinct signals) = 1.27 (t, 3H, CH_3, *J* = 7.1 Hz), 4.25 (q, 2H, CH_2O, *J* = 7.1 Hz), 5.72 [s, 1H, =CH (C2)], 6.68 [s, 1H, =CH (C5)], 7.08 (t, 1H, *para* Ph, *J* = 7.3 Hz), 7.33 (t, 2H, *meta* Ph, *J* = 7.8 Hz), 7.63 (d, 2H, *ortho*-Ph, *J* = 7.8 Hz), 10.22 (s, 1H, NH_{exo}), 11.78 (s, 1H, NH_{ring}); δ (2*Z*,5*Z*-isomer, distinct signals) = 1.27 (t, 3H, CH_3, *J* = 7.0 Hz), 4.25 (q, 2H, CH_2O, *J* = 7.0 Hz), 6.08 [s, 1H, =CH (C2)], 6.54 [s, 1H, =CH (C5)], 7.05 (t, 1H, *para*-Ph, *J* = 7.4 Hz), 7.31 (t, 2H, *meta*-Ph, *J* = 7.8 Hz), 7.63 (d, 2H, *ortho*-Ph, *J* = 7.8 Hz), 10.23 (s, 1H, NH_{exo}), 12.47 (s, 1H, NH_{ring}). ^{13}C NMR (50 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer) = 14.3 (CH_3), 61.6 (CH_2O), 96.7 [=CH (C2)], 114.0 [=CH (C5)], 119.5 (*ortho*-phenyl), 123.7 (*para*-phenyl), 129.0 (*meta*-phenyl), 139.0 [C(1)-phenyl], 145.3 [C= (C5)], 148.0 [C= (C2)], 164.6 (CO_{ring}), 165.5 (CO_{ester}), 165.9 (CO_{exo}); δ (2*Z*,5*Z*-isomer) = 14.3 (CH_3), 61.3 (CH_2O), 97.3 [=CH (C2)], 113.6 [=CH (C5)], 119.1 (*ortho*-phenyl), 123.4 (*para*-phenyl), 129.0 (*meta*-phenyl), 139.5 [C(1)-phenyl], 145.2 (C= (C5)), 148.0 [C= (C2)], 164.6 (CO_{ring}), 165.5 (CO_{ester}), 165.9 (CO_{exo}). UV (DMSO), (for a mixture of two diastereomers): λ_{max} (ε) 276 nm (19,200); 374.5 (25.600). A small sample was recrystallized from toluene/EtOAc mixture 9:1 (v/v) to provide an analytically pure compound. Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80; S, 10.07. Found: C, 56.30; H, 4.62; N, 8.62; S, 9.62.

(2*E*,5*Z*)- and (2*Z*,5*Z*)-(5-Ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)-*N*-(2-phenylethyl)-ethanamide (5b)

From **3b** (70.0 mg, 0.20 mmol) in MeCN (4 mL) and PHBP (77 mg, 0.24 mmol) in MeCN (2 mL) after flash chromatography (toluene/EtOAc 3:1 to 1:1) a mixture of two diastereomers (**5b**) was isolated; yield 68 mg (98 %); mp 154-157 ºC. MS (EI): *m/z* (rel. intensity) 346 (M^+, 6), 301 (8), 300 (15), 273 (1), 255 (6), 242 (9), 226 (100), 198 (11), 180 (5), 159 (4), 131 (7), 105 (5), 104 (10), 103 (8), 91 (5), 85 (10), 77 (3), 68 (8), 67 (13). IR (KBr) of 2*E*,5*Z*-isomer: ν 3466, 3372, 3212, 3094, 3044, 3025, 2987, 2929, 2868, 1732, 1651, 1602, 1541, 1370, 1332, 1219, 1196, 868, 794, 761, 715, 697; 2*Z*,5*Z*-isomer: ν 3412, 3323, 3125, 3069, 3022, 2981, 2969, 2915, 2830, 1710, 1691, 1660, 1645, 1625, 1561, 1370, 1319, 1186, 848, 794, 761, 699 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer, distinct signals) = 1.26 (t, 3 H, CH_3, *J* = 7.2 Hz), 2.76 (t, 2H, CH_2Ph, *J* = 7.3 Hz), 3.34-3.43 [m, 2H, NCH_2, *J*(CH_2 CH_2) = 7.3 Hz, *J*($NHCH_2$) 5.5 Hz], 4.24 (q, 2H, CH_2O, *J* = 7.2 Hz), 5.55 [s, 1H, =CH (C2)], 6.65 [s, 1H, =CH (C5)], 7.20-7.34 (m, 5 H, Ph), 8.31 (t, 1H, NH_{exo}, *J* = 5.5 Hz), 11.89 (s, 1H, NH_{ring}); δ (2*Z*,5*Z*-isomer, distinct signals) = 1.26 (t, 3H, CH_3, *J* = 7.1 Hz), 2.74 (t, 2H, CH_2Ph, *J* = 7.3 Hz), 3.30-3.40 [m, 2H, NCH_2, *J*(CH_2

CH_2) = 7.3 Hz, *J*($NHCH_2$) 5.5 Hz], 4.23 (q, 2H, CH_2O, *J* = 7.1 Hz), 5.85 [s, 1H, =CH (C2)], 6.48 [s, 1H, =CH (C5)], 7.16-7.35 (m, 5H, Ph), 8.26 (t, 1H, NH_{exo}, *J* = 5.5 Hz), 12.21 (s, 1H, NH_{ring}). ^{13}C NMR (50 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer) = 14.3 (CH_3), 35.2 (CH_2Ph), C of NCH_2 overlapped signal, 61.6 (CH_2O), 96.5 [=CH (C2)], 113.7 [=CH (C5)], 126.4 (*para*-phenyl), 128.6 (*ortho*-phenyl), 128.9 (*meta*-phenyl), 139.5 [C(1)-phenyl], 145.0 [C= (C2) and (C5)], 165.4 (CO_{ring}), 165.7 (CO_{ester}), 165.9 (CO_{exo}); δ (2*Z*,5*Z*-isomer) = 14.3 (CH_3), 35.4 (CH_2Ph), C of NCH_2 overlapped signal, 61.2 (CH_2O), 97.3 [=CH (C2)], 113.0 [=CH (C5)], 126.4 (*para*-phenyl), 128.6 (*ortho*-phenyl), 128.9 (*meta*-phenyl), 139.7 [C(1)-phenyl)], 145.8 [C= (C2) and (C5)], 165.4 (CO_{ring}), 165.7 (CO_{ester}), 165.9 (CO_{exo}). UV (DMSO), (for a mixture of two diastereomers): λ_{max} (ε) 357 (19.400); another absorption maximum at 260 nm is masked by solvent absorption. A small sample was recrystallized from ethanol to provide an analytically pure compound. Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; S, 9.26. Found: C, 59.15; H, 5.28; N, 8.38; S, 9.51.

(2*E*,5*Z*)- and (2*Z*,5*Z*)-(5-Ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)-1-phenylethanone (5c)

According to general procedure, from **3c** (61 mg, 0.20 mmol) in MeCN (3 mL) and PHBP (77 mg, 0.24 mmol) in MeCN (2 mL) after flash chromatography (toluene/EtOAc 6:1) a mixture of two diastereomers (**5c**) was isolated; yield 60.5 mg (100 %); mp 167-169 ºC. MS (EI): *m/z* (rel. intensity) 303 (M^+, 100), 302 (66), 274 (10), 258 (12), 257 (18), 230 (6), 226 (17), 198 (6), 180 (1), 159 (2), 158 (5), 131 (12), 130 (8), 105 (19), 103 (9), 85 (16), 77 (17), 68 (5). IR (KBr) of mixture of *2Z,5Z*- and *2E,5Z*-isomers: ν 3442, 3193, 3079, 2987, 1727, 1689, 1639, 1616, 1550, 1369, 1318, 1220, 1196, 812, 762, 707, 651 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer, distinct signals) = 1.29 (t, 3H, CH_3, *J* = 7.0 Hz), 4.27 (q, 2H, CH_2O, *J* = 7.0 Hz), 6.67 [s, 1H, =CH (C2)], 6.97 [s, 1H, =CH (C5)], 7.53-7.65 (m, 3H, *meta*- and *para*-phenyl), 7.89-7.94 (m, 2H, *ortho*-phenyl), 12.71 (s, 1H, NH) ; δ (2*Z*,5*Z*-isomer) = 1.25 (t, 3H, CH_3, *J* = 7.1 Hz), 4.20 (q, 2H, CH_2O, *J* = 7.1 Hz), 6.91 [s, 1H, =CH (C2)], 7.05 [s, 1H, =CH (C5)], 7.53-7.65 (m, 3H, *meta*- and *para*-phenyl), 7.89-7.94 (m, 2H, *ortho*-phenyl), 12.49 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer) = 14.15 (CH_3), 61.9 (CH_2O), 97.1 [=CH (C2)], 117.3 [=CH (C5)], 128.0 (*ortho*-phenyl), 128.8 (*meta*-phenyl), 133.1 (*para*-phenyl), 137.6 [C(1)-phenyl], 139.5 [C= (C5)], 153.5 [C= (C2)], 165.7 (CO_{ring}), 166.2 (CO_{ester}), 189.0 (CO_{exo}). UV ($CHCl_3$), (for a mixture of two diastereomers): λ_{max} (ε) 286 nm (11,400); 368 (29,400). A small sample was recrystallized from ethanol to provide an analytically pure compound. Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.39; H, 4.32; N, 4.62; S, 10.57. Found: C, 59.19; H, 4.24; N, 4.90; S, 10.30.

(2*E*,5*Z*)- and (2*Z*,5*Z*)- Ethyl (5-ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)ethanoate (5d)

According to general procedure, from **3d** (55.1 mg, 0.20 mmol) in MeCN (4 mL) and PHBP (77.4 mg, 0.24 mmol) in MeCN (2 mL) after flash chromatography (toluene/EtOAc 6:1 to 3:1) mixture of two diastereomers (**5d**) was isolated; yield 54.6 mg (100 %); mp 146-148 ºC. MS (EI): *m/z* (rel. intensity) 271 (M^+, 46), 226 (53), 199 (77), 180 (37), 171 (18), 154 (18), 127 (39), 114 (14), 103 (34), 85 (100), 68 (50). IR (KBr) of 2*E*,5*Z*-isomer: ν 3449, 3424, 3381, 3223, 3088, 2989, 2921, 1730, 1686, 1604, 1370, 1318, 1269, 1206, 1135, 862, 818, 761, 698 cm^{-1}; 2*Z*,5*Z*-isomer: ν 3473, 3423, 3256, 3168, 3057, 2989, 2931, 2880, 1696, 1606, 1372, 1325, 1292, 1201, 1156, 861, 808, 759, 663 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ (2*E*,5*Z*-isomer, distinct signals) = 1.30 (t, 3H, CH_3, *J* = 7.1 Hz), 1.35 (t, 3H, CH_3, *J* = 7.1 Hz), 4.22 (q, 2H, CH_2O, *J* = 7.1 Hz), 4.31 (q, 2H, CH_2O, *J* = 7.1 Hz), 5.35 [s, 1H, =CH (C2)], 6.88 [s, 1H, =CH (C5)], 10.82 (s, 1H, NH); δ (2*Z*,5*Z*-isomer, distinct signals) = 1.32 (t, 3H, CH_3, *J* = 7.0 Hz), 1.35 (s, 3H, CH_3, *J* = 7.0 Hz), 4.25 (q, 2H, CH_2O, *J* = 7.0 Hz), 4.32 (q, 2H, CH_2O, *J* = 7.0 Hz), 5.83 [s, 1H, =CH (C2)], 6.80 [s, 1H, =CH (C5)], 10.54 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ (2*E*,5*Z*-isomer) = 14.0 (CH_3), 14.1 (CH_3), 60.6 (CH_2O), 61.7 (CH_2O), 92.6 [=CH (C2)], 116.2 [=CH (C5)], 140.2 [C= (C5)], 150.6 [C= (C2)], 164.7, 166.1, 166.9; δ (2*Z*,5*Z*-isomer) = 14.1 (CH_3), 14.2 (CH_3), 60.7 (CH_2O), 61.7 (CH_2O), 95.3 [=CH (C2)], 116.7 [=CH (C5)], 142.5 [C= (C5)], 150.7 [C= (C2)], 165.7, 166.8, 166.9. A small sample was recrystallized from ethanol to provide an analytically pure compound. Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.73; H, 4.79; N, 5.16. Found: C, 48.61; H, 4.84; N, 5.27.

(2*E*,5*Z*)- and (2*Z*,5*Z*)-(5-Ethoxycarbonylmethylidene-4-oxothiazolidin-2-ylidene)ethanonitrile (5e)

According to general procedure, from **3e** (68 mg, 0.30 mmol) in MeCN (4 mL) and PHBP (115 mg, 0.36 mmol) in MeCN (2 mL) after flash chromatography (toluene/EtOAc 5:1 to 3.5:1) mixture of two diastereomers (**5e**) was isolated; yield 63 mg (94 %); mp 199-201 ºC. MS (*EI*): m/z (rel. intensity) 224 (M^+, 100), 196 (20), 179 (72), 152 (51), 130 (18), 114 (18), 85 (37). IR (KBr) of both isomers: ν 3471, 3449, 3226, 3163, 3115, 3073, 2991, 2924, 2825, 2217, 1732, 1683, 1611, 1372, 1320, 1270, 1234, 1191, 861, 764, 736 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer, distinct signals) = 1.27 (t, 3H, CH_3, *J* = 7.1 Hz), 4.26 (q, 2H, CH_2O, *J* = 7.1 Hz), 5.39 [s, 1H, =CH (C2)], 6.69 [s, 1H, =CH (C5)], NH proton not visible; δ (2*Z*,5*Z*-isomer, distinct signals) = 1.26 (t, 3H, CH_3, *J* = 7.0 Hz), 4.24 (q, 2H, CH_2O, *J* = 7.0 Hz), 5.45 [s, 1H, =CH (C2)], 6.63 [s, 1H, =CH (C5)], NH proton not visible. ^{13}C NMR (50 MHz, DMSO-d_6): δ (2*E*,5*Z*-isomer) = 14.2 (CH_3), 61.9 (CH_2O), 72.4 [=CH (C2)], 115.0 [CH= (C5)], 117.0 (CN), 142.0 [C= (C5)], 155.2 [C= (C2)], 165.6, 165.9; δ (2*Z*,5*Z*-isomer) = 14.2 (CH_3), 61.7 (CH_2O), 70.4 [=CH (C2)], 114.2 [CH= (C5)], 115.7 (CN), 142.8 [C= (C5)], 153.9 [C= (C2)], 165.6, 165.9. UV ($CHCl_3$), (for a mixture of two diastereomers): λ_{max} (ε) 259 nm (10,400); 346 (18,300). A small sample was recrystallized from ethanol to provide an analytically pure compound. Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 48.38; H, 3.48; N, 12.35; S, 14.27.

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