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High regioselectivity in the heterocyclization of β-oxonitriles to 4-oxothiazolidines: X-ray structure proof

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Abstract—Base-catalyzed reactions of β-oxonitriles **1** with diethyl mercaptosuccinate favour heterocyclization to afford 2-alkylidene-4-oxothiazolidines **3**, rather than 2-alkylidene-4-oxo-1,3-thiazinanes **4**. The observed regioselectivity is based on spectroscopic and experimental evidence, including a single-crystal X-ray structure determination.

1. Introduction

The widespread occurrence and diverse biological activity of thiazolidine-containing natural products have initiated the development of numerous methods for their synthesis.[1,2] They are also useful intermediates for the synthesis of different heterocyclic compounds.[2a,3]

Heterocycles synthesized from functionalized thiazolidines include benzothiophene derivatives,[4] indenothiophenes[5] and 2,1-benzisothiazole derivatives.[6] We have reported recently a one-pot cyclization reaction leading to a range of new 2-alkylidene-4-oxothiazolidines **3** from diethyl mercaptobutandioate and activated nitriles **1** (Scheme 1).[7] These functionalized heterocycles having the β-enaminocarbonyl moiety are formed through the addition–cyclization reaction sequence shown in Scheme 1. A plausible intermediate **2**, generated in situ, possessing two electrophilic and two nucleophilic centres, could in turn direct intramolecular cyclization toward formation of four heterocycles, i.e. 4-oxothiazolidine derivative **3**, 4-oxo-1,3-thiazinane derivative **4**, or a derivative of tetrahydrothiophene **5** and/or tetrahydrothiopyran **6**, as well as other macrocyclic compounds. However, the exclusive formation of oxothiazolidine enamino derivatives **3** in low to moderate yields (24–68%) is observed without any detectable traces of compounds **4**–**6**.

As a continuation of our mechanistic and synthetic studies on push–pull 4-oxothiazolidines, reported here is: (i) a detailed study of the regioselectivity and stereochemistry in the reaction of β-oxonitriles **1** with α and β-mercapto esters; (ii) the stereochemical assignment of the title compounds **3** is confirmed by an X-ray crystallographic analysis carried out on (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanoate (**3d**); (iii) finally, the optimized procedure to obtain compounds **3** in improved yields is presented.

2. Results and discussion

2.1. Mechanistic aspects and spectroscopic properties

There is a distinct similarity between the isolated 2-alkylidene-4-oxothiazolidine derivatives **3a-d** and 2-alkylidene-4-oxothiazinane derivatives **4a-d** as possible products. The ^{1}H NMR sharp signal within the range of ~5.40–6.90 ppm and a singlet between ~9 and 12 ppm for all compounds examined (Table 1), indicate, regardless of the ring size, the presence of the olefinic proton of a trisubstituted C=C bond and the lactam proton, respectively. In addition, the shift values of the NH protons fit either structure **3** or **4**, but rule out the heterocycles **5** and **6** or the tautomers **5A** and **6A**, including other possible tautomers as well.

The singlet in the ^{13}C NMR spectra between 89 and 95 ppm (Table 2) is assigned by the DEPT technique to the C(2′) atom of the C=C exocyclic bond, whereas three resonances (~167–188 ppm) in each compound suggest the presence of three carbonyl groups. The lowest field signal in the ^{13}C NMR spectra of all 4-oxothiazolidinones **3a-c** at 187.77 ppm, indicates a conjugated keto carbonyl function

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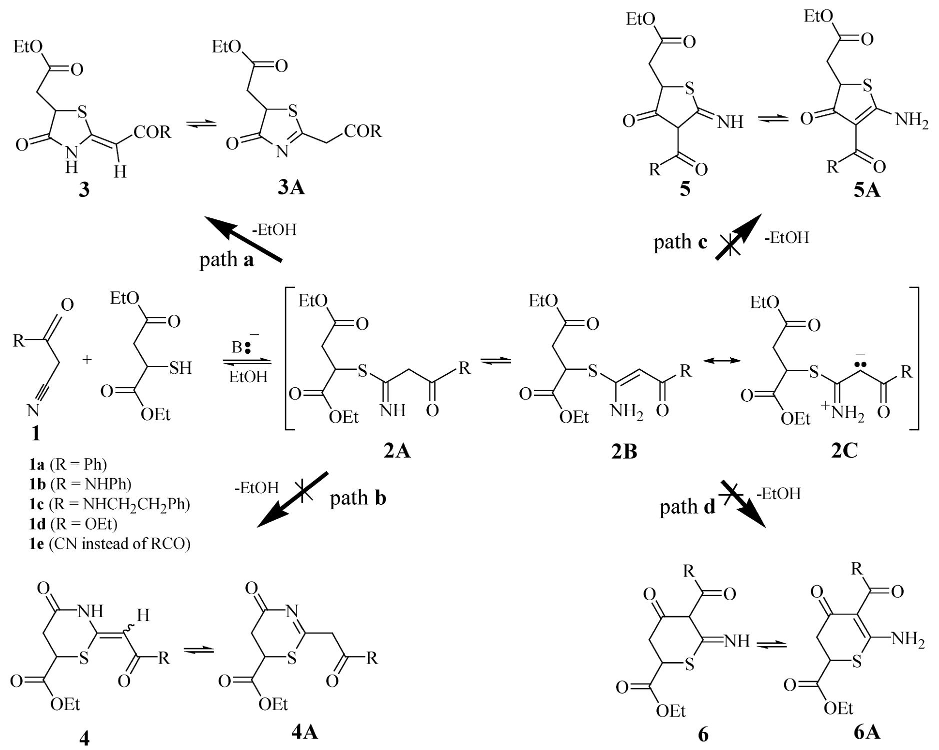
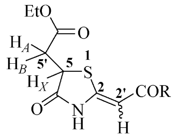


Scheme 1.

Table 1. Selected ^{1}H chemical shifts (ppm) of cyclic derivatives **3a** (R=Ph), **3b** (R=NHPh), **3c** (R=$NHCH_2CH_2Ph$) and **3d** (R=OEt)

Compound	C(2′)H	NH(ring)	C(5′)H_A	C(5′)H_B	C(5)H_X
(*Z*)-**3a** ($CDCl_3$)	6.85 (s)	9.88 (s)	3.00 (dd) J_{AB}=17.5 Hz, J_{AX}=8.2 Hz	3.15 (dd) J_{AB}=17.5 Hz, J_{BX}=4.3 Hz	4.22 (dd) J_{AX}=8.2 Hz, J_{BX}=4.3 Hz
(*Z*)-**3b** (DMSO-d_6)	5.79 (s)	11.58 (s)	2.92 (dd) J_{AB}=17.5 Hz, J_{AX}=8.0 Hz	3.02 (dd) J_{AB}=17.5 Hz, J_{BX}=4.6 Hz	4.19 (dd) J_{AX}=8.0 Hz, J_{BX}=4.6 Hz
(*Z*)-**3c** (DMSO-d_6)	5.55 (s)	11.30 (s)	2.85 (dd) J_{AB}=17.2 Hz, J_{AX}=8.4 Hz	2.97 (dd) J_{AB}=17.2 Hz, J_{BX}=4.3 Hz	Not observable
(*Z*)-**3d** (DMSO-d_6)	5.44 (s)	11.60 (s)	2.95 (dd) J_{AB}=17.6 Hz, J_{AX}=7.8 Hz	3.04 (dd) J_{AB}=17.6 Hz, J_{BX}=4.6 Hz	4.28 (dd) J_{AX}=7.8 Hz, J_{BX}=4.6 Hz

Table 2. Selected ^{13}C NMR chemical shifts (ppm) of cyclic derivatives (*Z*)-**3a**-**3c** in DMSO-d_6



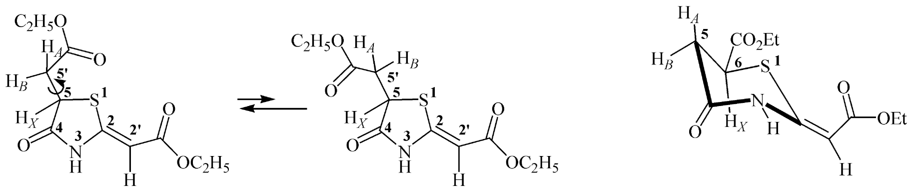
3

3a (R = Ph)
3b (R = NHPh)
3c (R = $NHCH_2CH_2Ph$)
3d (R = OEt)

Compound	CH_2COO (in **3**)	CHS	=CH	C(2)=	$\Delta\delta_{C2,C2'}$	CO_{exo}	CO_{ring}	CO_{ester}
(*Z*)-**3a**	36.40	42.54	94.94	161.56	66.62	187.77	170.72	176.30
(*Z*)-**3b**	37.19	42.44	93.34	153.54	60.20	165.89	170.88	175.68
(*Z*)-**3c**	37.37	42.29	93.23	150.82	57.59	167.05	170.90	175.49
(*Z*)-**3d**	36.50	42.61	88.86	157.84	67.98	167.24	170.42	175.41

of the derivative **3a**. The ^{13}C NMR spectra of **5** (or **5A**) and **6** (or **6A**) are not compatible with these spectral features. In accordance with this interpretation, the ^{1}H and ^{13}C NMR spectra (vide infra) correspond to either compounds **3** or **4** to the exclusion of the tautomers **3A** or **4A**.

The formation of the five-membered heterocyclic products **3** rather than the competing six-membered 4-oxo-1,3-thiazinanes **4** was unequivocally established by the comparative analysis of their mass spectrometric fragmentation patterns. The appearance of the strong molecular ions and the most significant peaks at *m*/*z*=228, 182, 128, 73, and 55 in nearly all spectra can be rationalized by the analogous fragmentation processes for compounds of the types **3** or **4**. The examination of the mass spectra also revealed the presence of a peak at *m*/*z*=87 in all isolated products which



Scheme 2.

corresponds to composition $C_4H_7O_2$. This fragment is obviously formed by the loss of $CH_2COOC_2H_5$ from the molecular ion of the corresponding 4-oxothiazolidine-5-acetate derivative **3**. Therefore, if the isolated heterocycles had been the (*Z*)-4-oxo-1,3-thiazinanes **4a-d**, this fragment would not have been detected.

The structure assignment regarding the ring size in heterocycles **3a-d** is supported by the analysis of the coupling constants of the diastereotopic CH_AH_B protons, as shown explicitly for the (*Z*)-isomer **3d** (Table 1).[8] These protons have different chemical shift values, i.e. 2.95 ppm for H_A, and 3.04 ppm for H_B. The spectrum exhibits an ABX spin-coupling system with significant geminal coupling ($^2J_{AB}$=17.6 Hz). The third proton H_X with chemical shift value of 4.28 ppm is split differently to the vicinal methylene protons H_A and H_B ($^3J_{AX}$=7.8 Hz; $^3J_{BX}$=4.6 Hz). The splitting pattern for each proton consists of a doublet of doublets. The unequal vicinal couplings $^3J_{AX}$ and $^3J_{BX}$ reflect hindered rotation around C(5)–C(5′) due to steric reasons. The value of $^3J_{AX}$ strongly suggests the five-membered ring. In the case of the six-membered ring in a conformation **C** of the hypothetical 4-oxo-1,3-thiazinane derivative (*Z*)-**4d**, having nearly antiperiplanar protons H_A and H_X, the $^3J_{AX}$ should have a higher value (~11–13 Hz for neighboring diaxial protons in cyclohexane derivatives). Two conformers **A** and **B** are considered for (*Z*)-**3d** (Scheme 2).

The dominant conformation **A** is relatively devoid of steric congestion. In the less stable rotamer **B**, as seen by an inspection of Dreiding models, the ester group at C(5′) experiences an unfavorable interaction with the lactam carbonyl. Such destabilization can be avoided by rotation around the C(5)–C(5′) bond, leading to the dominant rotamer **A**.

With respect to the configuration of the double bond, one-dimensional nuclear Overhauser effect measurements showed that irradiation of the singlet at δ 6.85 of the **3a** isomer (or **4a**), immediately after dissolution in $CDCl_3$, gave an enhancement of 4.4% to the aromatic region and an enhancement of 1.7% to the lactam proton singlet at δ 8.88. This is in agreement with the (*Z*)-configuration as the correct assignment. Heterocycles **3a-d** are obtained as pure (*Z*)-diastereomers in ethanol as solvent. Classified as push–pull alkenes due to the presence of electron-donating and electron-withdrawing groups bonded to the intervening C=C bond, they undergo facile *Z*/*E* isomerization in nonpolar solvents.[9,10] Thus, the NOE experiment was then conducted 1 day later on a solution of the *Z*/*E* mixture, containing about 85% of the (*E*)-**3a** isomer. Irradiation of the vinyl singlet at δ 6.32 of the major (*E*)-**3a** isomer showed, as expected, a NOE enhancement of the aromatic region, but not the singlet at δ 12.06 assigned to the lactam proton of (*E*)-**3a**. It is noteworthy that no tautomeric imino 4-oxothiazolidines of type **3A** are formed at all.[11]

2.2. Crystal structure of ethyl (Z)-(5-ethoxycarbonyl-methyl-4-oxothiazolidin-2-ylidene)ethanoate (3d)

Figure 1 shows a perspective view of the X-ray crystal structure of the thiazolidinone derivative **3d**. The tautomeric enamine form was definitively determined by location and refinement of the NH hydrogen. The central thiazolidinone ring is planar (mean deviation from planarity=0.014 Å, maximum deviation 0.023 Å). The molecular packing is controlled by intermolecular hydrogen bonds between the NH group and the C4 carbonyl of an adjacent molecule related by a crystallographic two-fold screw axis [H3···O41=2.00(3) Å; N3···O41=2.765(2) Å; N3–H···O41=165(2)°].

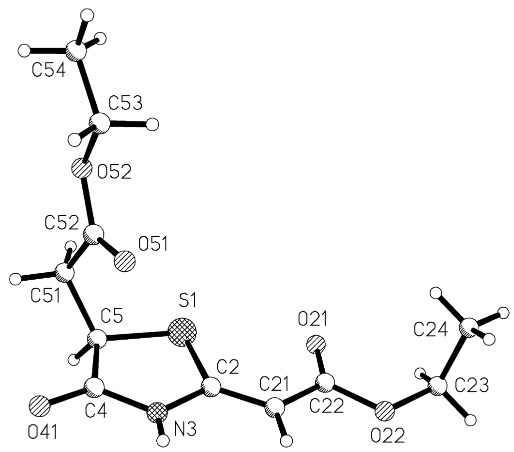
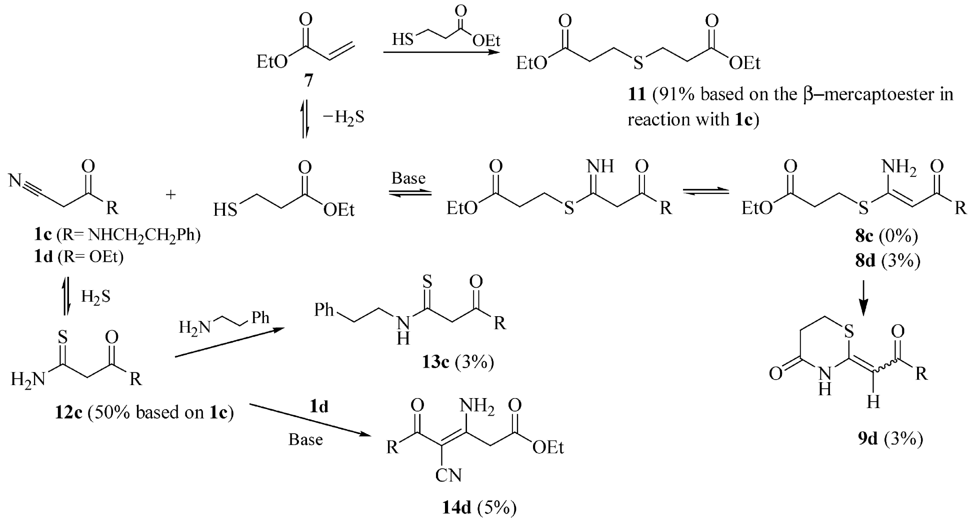


Figure 1. Perspective view of ethyl (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanoate (**3d**), showing the crystallographic numbering scheme.

The X-ray analysis of derivative **3d** proved the *Z*-configuration of the double bond. The C2 side-chain is also essentially coplanar with the five-membered ring which brings O21 into close proximity with the sulfur atom (O21···S1=2.873(2) Å). This distance is less than the sum of the van der Waals radii (3.22 Å) but greater than that previously observed in similar thiadiazolones.[12]

2.3. Reactions of β-oxonitriles with ethyl 3-mercapto-propanoate

To verify the 100% regioselectivity of the base-catalyzed

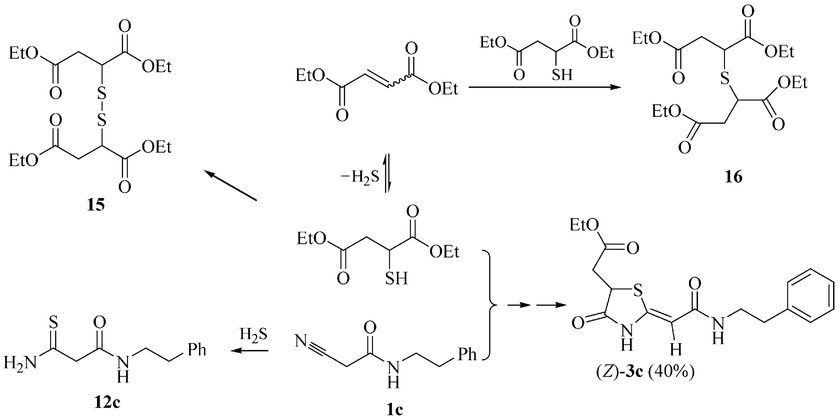


Scheme 3. *Conditions*: reactions conducted in 96% ethanol; molar ratio **1c**/ester: 1/1.7 and **1d**/ester: 1/3; reflux time: 11 h; catalyst: anh. K_2CO_3; the structures of byproducts **11**–**14** are fully confirmed on the spectroscopic basis.

heterocyclization of β-oxonitriles **1** with diethyl mercaptosuccinate affording the 5-substituted-4-oxothiazolidine derivatives **3** (Scheme 1, path a), the base-catalyzed reactions of β-oxonitriles **1c** and **1d** with ethyl 3-mercaptopropanoate were attempted (Scheme 3). If the adduct **8c** was formed in the first step of an addition-cyclization reaction sequence with the cyano derivative **1c**, then intramolecular cyclization should give the 4-oxo-4*H*-1,3-thiazinane derivative **9c**. Despite many attempts to obtain cyclic compound presumably via the intermediate **8c**, only simple acyclic products **11**–**13** and unreacted nitrile **1c** in 25% yield (Scheme 3), accompanied by its ethanolysis products, were isolated. The heterocyclization reaction responsible for the formation of six-membered heterocycle **9c** was completely supressed at the expense of much faster side reactions. On the other hand, in the reaction of the more reactive β-oxonitrile **1d** with the same β-mercaptoester, ethyl (*E*)-(4-oxo-[1,3]thiazinan-2-ylidene)ethanoate (**9d**) was isolated and fully characterized, however in very low yield (3%). In this case, the expected intermediate, i.e. ethyl (*Z*)-3-amino-3-(2-ethoxycarbonylethylsulfanyl)propenoate (**8d**) leading to **9d**, has been isolated for the first time, again in a negligible amount (3%). Although the analogous primarily formed addition adducts **2a-e** depicted in Scheme 1 are not isolable, they readily undergo intramolecular cyclization only by path a, affording under kinetic control the five-membered cyclization products **3a-e**. This is again in accord with the lesser cyclization tendency of intermediates **2a-e** to give the six-membered heterocycles **4a-e** (path b) which were never detected.

Finally, we turned our attention to improve low to modest yields (24–54%) of the purified 4-thiazolidinone derivatives **3a-d**. Initial attempts toward the conversion of β-oxonitriles **1a-d** to **3a-d** (Scheme 1) involved treatment of the corresponding nitrile with diethyl mercaptosuccinate in a 1/1 molar ratio, in boiling ethanol. Employing the model substance **1c**, the reaction gave, as depicted in Scheme 4, cyclization product **3c** in 40% yield, along with products **12c**, **15** and **16** by secondary processes.

After experimentation, it was found that the use of a large molar excess of diethyl mercaptosuccinate relative to nitrile derivative **1c** (molar ratio **1c**/mercapto derivative 1.00/1.73) improved the yield of the cyclization product to 60%. Under these conditions better yields (62–77%) were also obtained with activated nitriles **1a-b** and **1d** (Table 3). A possible explanation of the role of the mercapto derivative for the increased yields, is that the increased concentration secures at the same time sufficient quantity of mercaptodiester for



Scheme 4.

Table 3. Molar ratio effect on yields of cyclization products **3a-d** according to Scheme 1

Nitrile **1**	Diester/**1** mole ratio	Reaction time (h)	Product	Yield[a] (%)
1a	1.10	7	**3a**	47
1a	1.75	7	**3a**	68
1b	1.00	5	**3b**	24
1b	1.72	5	**3b**	77
1c	1.00	7.5	**3c**	40
1c	1.73	5	**3c**	60
1d	1.00	9	**3d**	54
1d	1.54	7	**3d**	62

[a] Purified products.

concurrent secondary reactions and heterocyclization. In the case of very reactive malononitrile (**1e**) the yield of purified thiazolidinone derivative **3e** was quite good (68%) even with the 1/1 molar ratio.

In conclusion, we have shown that among four possible heterocycles **3**–**6**, which on the grounds of mechanistic consideration could be formed by the base-catalyzed reaction of activated β-oxonitriles **1** with diethyl mercapto-succinate in ethanol, the favoured formation of the five-membered heterocyclic derivatives, i.e. (*Z*)-4-oxo-thiazolidines **3** occurs without any detectable traces of other heterocyclic compounds. Efficient heterocyclization is kinetically controlled over the heterocyclization to 2-alkyl-idene-4-oxo-1,3-thizinanes **4** and competing side reactions.

3. 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}). Samples for IR spectral measurements were prepared as KBr disks. The NMR spectra were obtained using a Varian Gemini 2000 instrument (^1H at 200 MHz, ^{13}C at 50.3 MHz). ^{13}C NMR resonance assignments were aided by the use of the DEPT technique to determine numbers of attached hydrogens. 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 recorded using a Finnigan MAT 8230 BE spectrometer at 70 eV (EI). Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. The UV spectra were measured on a Beckman DU-50 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl, and the spots were visualized by iodine. Column chromatography was carried out on SiO_2 (silica gel 60 Å, 12-26, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

3.1. General procedure A for the preparation of 4-oxothiazolidine derivatives 3a-e

To a stirred suspension of activated β-oxonitrile **1a-e** (Scheme 1) and freshly distilled diethyl mercaptosuccinate (~0–10% molar excess) in 5–10 mL of ethanol, a catalytic amount of K_2CO_3 was added (reagents for the starting compounds **1** were obtained by standard procedure). *CAUTION*. All reactions involving mercapto ester, due to the unpleasant odor, should be carried out in a well-ventilated hood. The mixture was brought to reflux and reaction mixture was stirred for 2–9 h. The mixture was cooled down to rt and the precipitated product was collected by filtration, washed with ethanol and recrystallized from 96% ethanol to provide the final product **3a-e** in 24–68% yield. Alternatively the filtered solution was concentrated under reduced pressure and the residue was chromatographed (toluene/ethyl acetate, 10/0→1/10, v/v) affording the desired cyclic product **3**. The structural assignments of all isolated products were made on the basis of spectroscopic data (IR, ^1H and ^{13}C NMR, MS, UV) and elemental analysis. Compounds **3a-c** were previously described.[7a]

General procedure B. The above procedure was adopted with the modification that a large excess of diethyl mercaptosuccinate (~1.7 mmol) relative to β-oxonitrile **1a-d** (1 mmol) was used, which improved the yield of cyclization products to 60–77% (Table 3). The yields of all products refer to purified compounds.

3.1.1. Ethyl (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanoate (3d). The title compound was obtained as a white solid in 54% yield (3.47 g) from 4.98 g (24.2 mmol) of diethyl mercaptosuccinate and 2.74 g (24.2 mmol) of ethyl cyanoacetate according to procedure A (reaction time 9 h). Mp 105–106°C; IR (KBr): ν_{max} 3188, 3122, 3079, 2985, 1739, 1722, 1691, 1605, 1474, 1380, 1298, 1196, 1144, 1093, 1029, 817, 725, 676 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (6H, t, $2CH_3$, J=7.2 Hz), 2.93 (1H, dd, H_A, J_{AB}=17.3 Hz, J_{AX}=8.5 Hz), 3.13 (1H, dd, H_B, J_{AB}=17.3 Hz, J_{BX}=4.1 Hz), 4.19 (4H, q, $2CH_2O$, J=7.2 Hz), C(5)–H signal buried below the quartet centered at δ 4.19, 5.59 (1H, s, =CH(2′)), 9.35 (1H, s, NH); ^{13}C NMR (50.3 MHz, DMSO-d_6): δ 14.16, 14.54, 36.50, 42.61, 59.29, 60.87, 88.86, 157.84, 167.24, 170.42, 175.41. Mass spectrum (EI) m/z (rel. intensity): 273 (M^+, 11), 227 (46), 182 (22), 154 (100), 127 (14), 87 (15), 68 (15), 55 (21). Analytically pure sample was obtained by crystallization of the isolated solid from a 4/1 ethanol/water solvent mixture. Anal. calcd for $C_{11}H_{15}NO_5S$: C, 48.30; H, 5.52; N, 5.12; S, 11.73. Found: C, 48.12; H, 5.35; N, 5.36; S, 11.95.

3.1.2. Ethyl (*E*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)ethanoate (3d). In the case of heterocycles **3a-d** they are obtained as pure (*Z*)-diastereomers in ethanol as solvent. Classified as push–pull alkenes due to the interaction of the two electron-donating groups and electron-withdrawing group through the intervening C=C bond, they undergo facile *Z*/*E* isomerization in nonpolar solvents. Thus, the *Z*/*E* mixture of **3d** becomes progressively enriched in more stable *E*-isomer (Table 4) during the course of relatively slow isomerization process (~2–3 days) at rt. Accordingly, two sets of signals observed in the ^1H NMR spectrum in $CDCl_3$ are compatible with the presence of both configurational isomers.

^1H NMR (200 MHz, $CDCl_3$) for (*E*)-**3d**: δ 1.27 (3H, t, J=7.0 Hz, CH_3), 1.28 (3H, t, J=7.0 Hz, CH_3), 2.86 (1H, dd,

Table 4. *Z/E* Isomerization data based on selected ^{1}H NMR signals for (*Z*)-**3d** and (*E*)-**3d** isomers in $CDCl_3$

	(*Z*)-**3d**	(*E*)-**3d**	*Z/E* ratio (%); time (days)
NH	9.35[a]	10.63	96/4 (after few minutes)
=CH(2′)	5.59	5.12	43/57 (2)
			10/90 (6)

[a] The chemical shift of the lactam proton in (*Z*)-**3d** is not fixed; in principle an increase in the extent of intermolecular hydrogen bonding, which depends on concentration, temperature and solvent, moves this proton to lower field.

H_A, J_{AB}=17.6 Hz, J_{AX}=9.8 Hz), 3.23 (1H, dd, H_B, J_{AB}=17.6 Hz, J_{BX}=3.5 Hz), 4.17 (2H, q, *J*=7.0 Hz, CH_2O), 4.20 (2H, q, *J*=7.0 Hz, CH_2O), 4.27 (1H, dd, H_X, J_{AX}=9.8 Hz, J_{BX}=3.5 Hz), 5.12 (1H, s, =CH), 10.63 (1H, s, NH).

3.2. Crystal structure determination of ethyl (*Z*)-(5-ethoxycarbonylmethyl-4-oxothiazolidin-2-ylidene)-ethanoate 3d

Crystallographic data (excluding structure factors) for the structure **3d** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 208829. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.2.1. (5-Ethoxycarbonylmethyl-4-oxothiazoliodin-2-ylidene) ethanonitrile (3e). The title compound was obtained as a mixture of diastereomers as a white solid in 81% yield (4.70 g) from 5.28 g (25.6 mmol) of diethyl mercaptosuccinate, 1.69 g (25.6 mmol) of freshly distilled malononitrile and 0.19 g (1.39 mmol) of anh. K_2CO_3 in ethanol (31 mL) according to procedure A (reaction time ~2 h). Purification of the crude product by crystallization from ethanol afforded 3.92 g (68%) of thiazolidinone **3e** as small white needles, mp 142–144°C (melting point varies depending on the ratio of isomers); IR (KBr): ν_{max} 3164, 3131, 3075, 2994, 2933, 2827, 2210, 1737, 1712, 1620, 1383, 1282, 1223, 1192, 1157, 817, 746, 722 cm^{-1}. (*Z*)-**3e** isomer: ^{1}H NMR (DMSO-d_6): δ 1.19 (3H, t, *J*=7.1 Hz, CH_3), 3.05–3.08 (2H, m, J_{AX}=6.9 Hz, J_{BX}=5.3 Hz, CH_2COO; chemical shifts of H_A and H_B protons are very close and J_{AB} cannot be determined), 4.10 (2H, q, *J*=7.1 Hz, CH_2O), 4.59 (1H, dd, J_{AX}=6.9 Hz, J_{BX}=5.3 Hz, H_X), 4.93 (1H, s, =CH), 12.05 (1H, s, NH); ^{13}C NMR (DMSO-d_6): δ 14.15 (CH_3), 36.27 (*C*H_2COO), 44.68 (CHS), 60.96 (CH_2O), 66.72 (=CH), 118.00 (CN), 159.82 (C=), 170.30 (CO_{ring}), 175.03 (CO_{ester}); (*E*)-**3e** isomer: δ 1.18 (3H, t, *J*=7.2 Hz, CH_3), 4.08 (2H, q, CH_2O, *J*=7.2 Hz), 4.52 (1H, dd, J_{AX}=6.8 Hz, J_{BX}=5.4 Hz, H_X), 4. 87 (1H, s, =CH), 12.05 (1H, s, NH), precise assignment of H_A and H_B protons was not possible; NMR (DMSO-d_6): δ 14.15 (CH_3), 36.27 (*C*H_2COO), 44.20 (CHS), 60.96 (CH_2O), 64.64 (=CH), 116.63 (CN), 159.82 (C=), 170.30 (CO_{ring}), 175.37 (CO_{ester}); CIMS: *m/z* 227 (M+1); UV (DMSO): λ_{max} (ε) 270.0 nm (23.000). Anal. calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.45; N, 12.38; S, 14.17. Found: C, 47.68; H, 4.65; N, 12.46; S, 14.04.

3.3. Heterocyclization of activated nitriles 1c and 1d with ethyl 3-mercaptopropanoate

Heterocyclization of ethyl cyanoacetate (**1d**) *with ethyl 3-mercaptopropanoate*. A stirred suspension of ethyl cyanoacetate (0.30 g, 2.65 mmol), ethyl 3-mercapto-propanoate (0.61 g, 4.57 mmol) and a catalytic amount of K_2CO_3 (0.02 g, 0.14 mmol) in ethanol (4 mL) was brought to reflux. After stirring at reflux temperature for 7 h (TLC showed incomplete reaction) the reaction mixture was cooled down and upon evaporation under reduced pressure to half of its original volume, potasium cyanoacetate precipitated (0.036 g, 0.28 mmol, mp 176–177°C). The solid was filtered off and concentration of the ethanol solution left a pale-yellow residue (0.648 g), which was chromatographed on silica gel (ca. 50 g). Elution with toluene–EtOAc (solvent gradient 90/10–70/30, v/v) furnished 0.29 g of the starting ester (48% of the total amount), 77 mg of ethyl cyanoacetate (26% of the total amount). The following are characterizations of the remaining products.

3.3.1. Ethyl 3-amino-3-(2-ethoxycarbonylethylsulfanyl)-propenoate (8d). 22 mg (3%) as a yellow oil. IR (KBr) ν_{max} 3413, 3311, 3198, 3030, 2982, 2922, 2870, 2822, 1732, 1662, 1601, 1529, 1448, 1376, 1347, 1252, 1155 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.16 (3H, t, *J*=7.1 Hz, CH_3), 1.19 (3H, t, *J*=7.1 Hz, CH_3), 2.64 (2H, t, *J*=6.9 Hz, CH_2), 3.09 (2H, t, *J*=6.9 Hz, CH_2), 3.99 (2H, q, CH_2O, *J*=7.1 Hz), 4.08 (2H, q, *J*=7.1 Hz, CH_2O), 4.50 (1H, s, =CH), 7.67 (2H, broad s, NH_2); ^{13}C NMR (DMSO-d_6): δ 14.2 (CH_3), 14.7 (CH_3), 25.3 (CH_2S), 33.7 (*C*H_2CO), 58.2 (CH_2O), 60.5 (CH_2O), 80.7 (=CH), 161.4 (C=), 168.2 (C=*C*CO), 171.22 (CO); MS (EI): *m/z* (rel. intensity): 247 (32) (M^+), 202 (28), 174 (17), 156 (26), 147 (100), 134 (14), 114 (28), 101 (25), 86 (45), 73 (28), 61 (26).

3.3.2. Ethyl (*E*)-(4-oxo-[1,3]thiazinan-2-ylidene)ethanoate (9d). 13 mg (3%) as a yellowish crystals, mp 66–67°C. IR (KBr): ν_{max} 3195, 3073, 1689, 1656, 1583, 1445, 1366, 1230, 1188, 1155, 793 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.19 (3H, t, *J*=7.1 Hz, CH_3), 2.85 (2H, m, CH_2), 3.21 (2H, m, CH_2); the coupling constants of multiplets at 2.85 and 3.21 ppm cannot be determined as signals are of the higher order and the chemical shifts are the centres of signals resembling triplets; 4.10 (2H, q, *J*=7.1 Hz, CH_2O), 5.12 (1H, s, =CH), 11.11 (1H, s, NH); ^{13}C NMR (DMSO-d_6): δ 14.4 (CH_3), 23.0 (CH_2S), 33.2 (*C*H_2CO), 59.9 (CH_2O), 90.1 (=CH), 154.5 (C=), 167.4 (C=*C*CO), 168.1 (CO).; MS (EI): *m/z* (rel. intensity): 201 (62) (M^+), 173 (10), 156 (33), 129 (75), 55 (100); UV (DMSO): λ_{max} (ε) 298.4 nm (17900). Anal. calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96; S, 15.93. Found: C, 48.06; H, 5.63; N, 6.92; S, 15.88.

3.3.3. Diethyl 3-amino-2-cyanopent-2-enedioate (14d). 15 mg (5%); yellow crystals, mp 52–54°C (lit. 54–55°C).[13] IR (KBr): ν_{max} 3383, 3324, 3288, 3219, 2983, 2937, 2871, 2824, 2209, 1737, 1681, 1630, 1530, 1449, 1370, 1329, 1273, 1196, 1103, 1024 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.21 (6H, t, *J*=7.1 Hz, CH_3), 3.56 (2H, s, CH_2), 4.13 (2H, q, *J*=7.1 Hz, CH_2O), 4.14 (2H, q, *J*=7.1 Hz, CH_2O), 8.85 (1H, broad s, N*H*H), 9.09 (1H, broad s, NH*H*); ^{13}C NMR (DMSO-d_6): δ 14.2 (CH_3), 14.5 (CH_3), 40.1 (CH_2), 59.9

(CH_2O), 61.4 (CH_2O), 71.2 (=C(CN)CO), 118.5 (CN), 166.2 (H_2NC=), 167.1 (C=C*C*O), 167.5 (CO). MS (EI): *m*/*z* (rel. intensity): 226 (50) (M^(^), 180 (40), 152 (100), 123 (57), 108 (51), 98 (42).

3.4. Heterocyclization of cyano *N*-2-(phenylethyl)-ethanamide (1c) with ethyl 3-mercaptopropanoate

The reaction of the nitrile **1c** (0.300 g, 1.6 mmol) with a large excess of ethyl 3-mercaptopropanoate (0.64 g, 4.8 mmol), following the same procedure as described for ethyl cyanoacetate, did not afford the expected cyclic product **8c** even after the prolonged reaction time (11 h). Instead, in addition to unreacted nitrile **1c** (25%), a minor amount of ethyl *N*-phenethyl-2-phenethylthiocarbamoyl-ethanamide (**13c**), 0.51 g (91% based on ethyl 3-mercapto-propanoate) of ethyl 3-(2-ethoxycarbonylethyl-sulfanyl)propanoate (**11**) and 0.18 g (50% based on **1c**) of *N*-phenethyl-2-thiocarbamoylethanamide (**12c**) were isolated (Scheme 3).

3.5. By-product characterization in the heterocyclization of cyano *N*-2-(phenylethyl)ethanamide (1c) with diethyl mercaptosuccinate

Following a similar general heterocyclization of **1c** (1.126 g, 5.5 mmol) employing a slight molar excess of diethyl mercaptosuccinate (procedure A), the reaction mixture was brought to reflux (7.5 h), then cooled down to rt and left overnight, whereby a small amount of cyclic product **3c** (0.115 g) precipitated. The filtered solution was concentrated and silica gel chromatography (toluene/ethyl acetate 7/3, v/v) provided the following compounds.

3.5.1. *N*-Phenethyl-2-thiocarbamoylethanamide (12c). The title compound (0.082 g) as a white solid, mp 88–9°C; IR (KBr) ν_{max}/cm^{-1} 3333, 3282, 2931, 1660, 1648, 1618, 1561, 1497, 1432, 1199, 1155, 1030, 737, 696 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.72 (2H, t, J=7.3 Hz, CH_2Ph), 3.24–3.35 (2H, m, NCH_2, $J(CH_2CH_2)$=7.3 Hz, $J(NHCH_2)$=5.5 Hz), 3.44 (2H, s, $CSCH_2CO$), 7.16–7.34 (5H, m, aromatic), 8.17 (1H, t, NH, J=5.5 Hz), 9.31 (1H, br s, SCN*H*H), 9.61 (1H, br s, SCNH*H*); ^{13}C NMR (DMSO-d_6): δ 35.78 (CH_2Ph), NCH_2 not visible, 47.00 (NCH_2), 52.29 (CS*C*H_2CO), 126.92 (*p*-Ph), 129.14 (*o*-Ph), 129.49 (*m*-Ph), 140.18 (C_1-Ph), 167.40 (CO), 200.88 (CS); MS (CI) *m*/*z* 223 (M+1); MS (EI) *m*/*z* (rel. intensity) 222 (M^+, 21), 131 (8), 120 (13), 118 (100), 105 (21), 104 (43), 103 (15), 102 (48), 101 (65), 91 (34), 77 (16), 75 (9), 60 (17), 59 (8), 43 (23), 30 (41). Anal. calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.11; H, 6.15; N, 12.43.

3.5.2. Tetraethyl thiodisuccinate (16). The title compound (0.477 g, 46% of the starting diethyl mercaptosuccinate) as a pale yellow oil. IR (film) ν_{max}/cm^{-1} 3453, 2984, 1734, 1467, 1447, 1260, 1028, 796, 730, 689, 645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.71 (2H, t, J=7.4 Hz, CH_2Ph), 2.88 (2H, t, J=7.5 Hz, CH_2Ph), CH_2NH overlapped by H_2O from DMSO, 3.50 (2H, s, $CSCH_2CO$), 3.62–3.77 (2H, m, NHC*H*$_2$), 7.16–7.35 (10H, m, aromatic), 8.16 (1H, t, J=5.6 Hz), 10.26 (1H, br t, NH); ^{13}C NMR (DMSO-d_6): δ 33.16 (CH_2Ph), 35.18 (CH_2Ph), 40.66 (NCH_2), 47.00 (NCH_2), 51.94 (CS*C*H_2CO), 126.36 (*p*-Ph), 126.53 (*p*-Ph), 128.57 (*o*-Ph), 128.66 (*o*-Ph), 128.88 (*m*-Ph), 128.91 (*m*-Ph), 139.20 (C_1-Ph), 139.60 (C_1-Ph), 167.02 (CO), 195.80 (CS); MS (CI) 327 (M+1); MS (EI) *m*/*z* (rel. intensity) 326 (M^+, 16), 293 (4), 235 (39), 222 (6), 206 (12), 164 (4), 163 (2), 148 (3), 120 (22), 118 (100), 105 (85), 104 (92), 91 (22), 77 (23) 59 (19), 43 (12); tetraethyl-2,2′-dithiodisuccinate (**15**) (small amount in the mixture with thiodisuccinate **16**). In addition to these products, pure cyclic compound **3c** (0.264 g), a mixture of **3c** and starting nitrile **1c** (0.385 g) and pure unreacted nitrile (0.125 g) were also isolated.

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11. Regioselective α-bromination of (*Z*)-5-substituted-2-alkyl-

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