Tetrahedron 67 (2011) 9541–9554

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

endo-Mode cyclizations of vinylogous *N*-acyliminium ions as a route to the synthesis of condensed thiazolidines

Milovan Stojanović [a,b], Rade Marković [a,c], Erich Kleinpeter [b], Marija Baranac-Stojanović [a,b,c,*]

[a] *Center for Chemistry ICTM, P.O. Box 473, 11000 Belgrade, Serbia*
[b] *Chemisches Institut der Universität Potsdam, Karl-Liebknecht Str. 24-25, D-14476 Potsdam (Golm), Germany*
[c] *Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158, 11000 Belgrade, Serbia*

ARTICLE INFO

Article history:
Received 12 July 2011
Received in revised form 14 September 2011
Accepted 3 October 2011
Available online 10 October 2011

Keywords:
Vinylogous *N*-acyliminium ion
endo-Mode cyclization
Condensed thiazolidines
Quantum chemical calculations

ABSTRACT

endo-Mode cyclizations of vinylogous *N*-acyliminium ions incorporating heteroatom-based nucleophiles have been examined as a route to the synthesis of condensed thiazolidines. The scope of these reactions and stereochemical outcome are discussed and explained using quantum chemical calculations.

1. Introduction

Iminium ions have proven to be valuable intermediates in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. Indeed, the well-known Mannich reaction[1] and its intramolecular variant—the Pictet–Spengler reaction,[2] used for a long time as α-aminoalkylation reactions, are based on the reactive iminium species. Iminium ion cyclizations have been widely exploited as a powerful method for the construction of a huge variety of heterocyclic systems.[3] Diverse nucleophiles, such as π-nucleophiles (aromatic rings, carbon–carbon double, and triple bonds), σ-nucleophiles and heteroatom-based nucleophiles, have been used to react with various acyclic and cyclic iminium ions in both *exo*- and *endo*-mode cyclizations (Fig. 1). Heterocycles produced via the addition of heteroatoms as nucleophiles onto the iminium ions not only are well-known and important compounds, particularly in the field of medicinal chemistry, but also represent stable potential iminium ions equivalents due to reversibility of the addition process. Despite the fact that, according to Baldwin's rules,[4] 5-*endo*-*trig* cyclizations are classified as 'unfavoured' for the first-row elements,[4b] they can occur with iminium ions as reactive species.[3a–c,h,j,5]

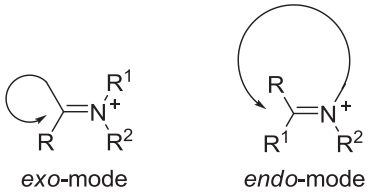


Fig. 1. *exo*- and *endo*-Mode cyclizations.

Suitable structural variations in the iminium ion precursor, like introduction of a second heteroatom, enlarges the scope of the iminium ion methodology. For example, cyclizations involving thiazolidine-based iminium ions can result in the formation of a variety of derivatives of interesting pharmacological structure.[6] In addition, further desulfurization of thiazolidine-containing polycycles is a valuable method for synthesis of various ring structures, some of which are not easily accessible by other routes.[6c,7]

The iminium ions can be divided into two main categories: *N*-alkyl-[3a] (R^3, R^4=alkyl, aryl, Fig. 2) and *N*-acyliminium ions[3b,c] (R^3=alkyl, aryl, R^4=COR, CO_2R, SO_2R, Fig. 2). Introduction of an electron-withdrawing group on nitrogen leads to more electrophilic iminium carbon, which makes *N*-acyliminium ions much more reactive as electrophiles than simple *N*-alkyliminium ions. A subtype of *N*-acyliminium ions with carbon–carbon double bond conjugating an acyl group to nitrogen is referred to as *vinylogous N-acyliminium ions* (Fig. 3). Literature covering this type of iminium

* Corresponding author. Tel.: +381 11 3336740; fax: +381 11 2636061; e-mail address: mbaranac@chem.bg.ac.rs (M. Baranac-Stojanović).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.011

ions is rather scarce, with just a few reports published thus far. It has been shown that they can react with added nucleophiles,[8] or initiate ring-closing reaction with π-nucleophile, such as an olefin[9] or aromatic ring.[10]

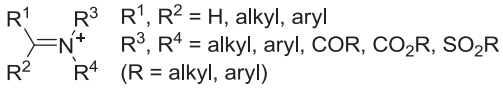


Fig. 2. *N*-Alkyl and *N*-acyliminium ions.

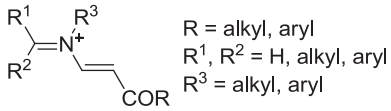
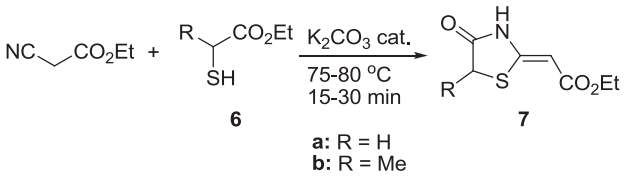


Fig. 3. Vinylogous *N*-acyliminium ions.

In the course of our studies on the reactivity of 2-alkylidene-4-oxothiazolidines we have observed that vinylogous *N*-acyliminium ion **3** derived from compound **1** can undergo cyclization reaction in a 5-*exo* mode giving rise to bicyclic product **5**, albeit in low yield (Scheme 1).[11] The iminium ion **3** is formed from the hydroxy derivative **2**, produced by the regioselective reduction of one carbonyl of the vinylogous imide function. The resistance of another carbonyl to reduction is considered to reside in its deactivation due to the push–pull effect of the carbon–carbon double bond.[12] Now, the iminium function enhances the electrophilicity of the ester group in **3** allowing its reduction to **4**, even at rt.[13] Subsequent 5-*exo*-*trig* cyclization affords the *cis*-fused tetrahydrofurothiazolidine **5**. This finding prompted us to further explore the ability of these new vinylogous *N*-acyliminium ions to participate in cyclization reactions with suitably positioned nucleophiles. We examined reactions with a range of heteroatom-based nucleophiles in both *endo*- and *exo*-mode. Herein, we present the results of *endo*-mode reactions together with quantum chemical calculations used to rationalize the experimental observations.

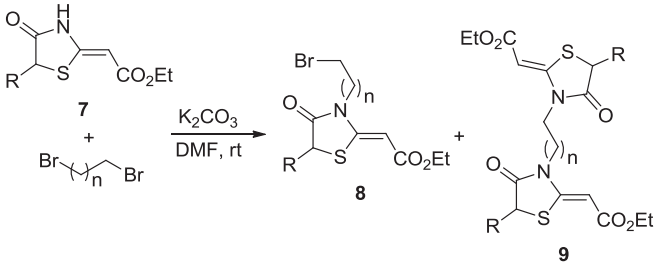
Table 1
Comparison of synthesis of 4-oxothiazolidines **7** with and without solvent



Product	Reaction conditions and yield[a] (%)	
7a-*Z* (R=H)	EtOH, reflux, 5 h (67)	No solvent, 75–80 °C, 30 min (87)
7b-*Z* (R=Me)	EtOH, reflux, 6 h (42)	No solvent, 75–80 °C, 15 min (76)

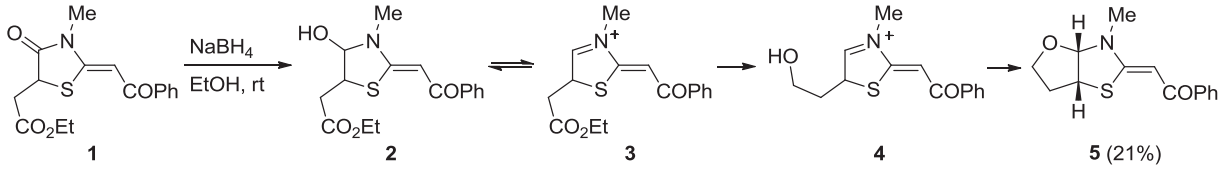
[a] Yield of isolated products.

Table 2
N-Alkylation of 4-oxothiazolidines **7** with α,ω-dibromides



R	*n*	Time (h)	Product **8**[a] (%)	Dimer **9**[a] (%)
H	1	5	**8a** (72)	/
Me	1	5	**8b** (82)	**9a** (6)
H	2	2	**8c** (70)	**9b**(18)
Me	2	2.5	**8d** (70)	**9c** (21)
H	3	4	**8e** (83)	**9d** (4)
Me	3	1.5	**8f** (80)	**9e** (7)

[a] Yield of isolated products.



Scheme 1.

2. Results and discussion

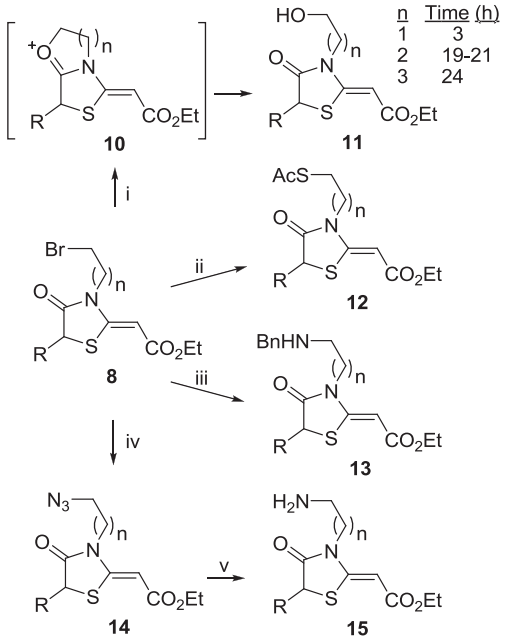
2.1. Synthesis of 4-oxothiazolidines

Starting 4-oxothiazolidines **7** were prepared by the base-catalyzed reaction of ethyl cyanoacetate and α-mercapto esters **6**, with a slight modification of our published procedure for the synthesis of 4-oxothiazolidine compounds.[14] In contrast to the published procedure, these syntheses were run without solvent, which resulted in significant shortening of the reaction time and increase in the yields of the products (Table 1). The products were obtained exclusively as *Z* isomers.[15]

2.2. Cyclization reactions

Preparation of precursors for the *endo*-mode cyclizations began with the N-alkylation of 4-oxothiazolidines **7** with α,ω-dibromides[16] (Table 2). *N*-Bromoalkyl derivatives **8** were obtained along with the dimeric products **9**. Thus, it was necessary to employ 4–5.4 molar excess of the alkylating agent to suppress the dialkylating process and effect the best yields of **8**.

The obtained alkyl bromides **8** were then converted into precursors possessing O, S, or N as a nucleophilic atom (Scheme 2 and Table 3). Hydrolysis using 0.75 M DMF/H_2O solution of HCl, based on the method of Geluk and Schlatmann,[17] afforded alcohols **11a–e** in moderate to high yields (51–92%). The observed experimental rates of hydrolysis (Scheme 2), which decrease in the order (n=1)>(n=2)>(n=3), points to the neighboring-group participation of carbonyl oxygen of the lactam group. When n=1, formation of a favorable five-membered cyclic intermediate **10** can facilitate the hydrolytic reaction. When n=2 and 3, the participation of carbonyl oxygen is diminished due to the greater loss of entropy accompanying the formation of six- and seven-membered rings, resulting in much longer reaction times (n=1 (3 h); n=2 (19–21 h); n=3 (24 h)). Substrates **12a–f** containing sulfur as a nucleophile were prepared in high yields (93–100%) by the reaction of bromides **8** with KSAc in acetone, at rt.[18] They were deprotected with NaOEt/EtOH[19] prior to the formation of iminium ions (see Experimental section). Two type of precursors with nitrogen-based



Scheme 2. Reagents and conditions: (i) DMF/H_2O (1:1, v/v), HCl, Δ; (ii) KSAc (1.1–1.25 equiv), acetone, rt, 10–15 min; (iii) $BnNH_2$ (5 equiv), Et_3N (1.4 equiv), DMF, rt, 18 h; (iv) NaN_3 (2–2.9 equiv), DMF, rt, 1–1.5 h; (v) Ph_3P (1.5 equiv), MeOH, reflux, 1 h.

Table 3
Yields of products **11**–**15**

R	*n*	Product[a] (%)	R	*n*	Product[a] (%)
H	1	**11a** (66)	H	2	**13a** (77)
Me	1	**11b** (72)	Me	2	**13b** (92)
H	2	**11c** (92)	H	1	**14a** (91)
Me	2	**11d** (62)	H	2	**14b** (94)
Me	3	**11e** (51)	H	3	**14c** (89)
H	1	**12a** (98)	H	1	**15a** (62)
Me	1	**12b** (100)	H	2	**15b** (70)
H	2	**12c** (95)	H	3	**15c** (63)
Me	2	**12d** (94)			
H	3	**12e** (93)			
Me	3	**12f** (98)			

[a] Yield of isolated products.

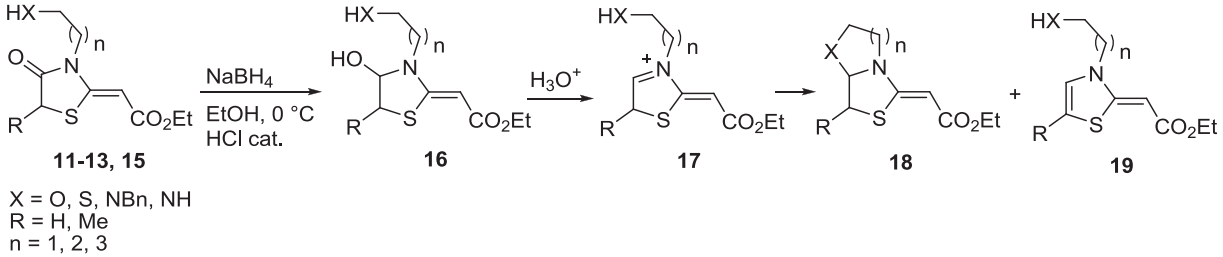
nucleophiles were prepared. Compounds **13a**,**b**, having a secondary amino group as an internal nucleophile, were synthesized in good to high yields (77–92%) from alkyl bromides **8** and benzylamine.[20] Substrates **15a**–**c**, possessing a primary amino group were obtained in two steps. First, bromides **8** were allowed to react with NaN_3 in DMF, at rt.[21] Azides **14a**–**c** were isolated in high yields (89–94%) and then subjected to reduction using Ph_3P in MeOH at reflux[22] to give **15a**–**c** in moderate yields (62–70%).

With all precursors in hand, the next step was to examine iminium ion-initiated reactions. Vinylogous *N*-acyliminium ions **17** were generated according to the procedure of Speckamp[6b,23] (Scheme 3). Thus, the ring carbonyl group was reduced to give the hydroxy derivatives **16** with $NaBH_4$ in EtOH at 0 °C, in the presence of a catalytic amount of concd HCl. They were used without isolation for the subsequent dehydration to the iminium ions **17**, which was achieved by the addition of 1 M HCl in EtOH. Two type of products were formed from the iminium ions **17**: bicyclic derivatives **18** and thiazolines **19** (Scheme 3 and Table 4). Each reaction yielded one of them as a sole product (in two cases, however, a complex mixture was obtained; entries 2 and 14). The products **19** arise from the C(5) deprotonation of the cationic intermediate **17** and they failed to participate in iminium ion cyclization. In fact, the observed β-elimination often occurs in the cyclizations involving *N*-acyliminium ions, especially if they are relatively sluggish because of a less reactive nucleophile or steric hindrance. In many instances, particularly under protic acid conditions, this side reaction is reversible. The reluctance of **19** to participate in cyclization[24] can be accounted for by the development of a partial aromaticity in the thiazoline ring[25] (Scheme 4).

The 5-*endo*-mode cyclization occurred only with sulfhydryl group as a nucleophile, albeit in low yield (28–35%, Table 4, entries 6 and 7), but failed with both oxygen and nitrogen nucleophiles (entries 1, 2, and 14). This is in consistence with Baldwin's rules[4] according to which 5-*endo*-mode cyclizations for the first-row elements are unfavorable, but can occur with second-row elements, i.e., sulfur.[4b] Though, 5-*endo*-mode cyclizations can be observed in iminium ion chemistry, as already discussed in the introduction. The formation of six-membered ring via a favorable 6-*endo*-mode cyclization occurred for OH, SH, and NH_2 nucleophiles in low to good yields (36–66%, entries 3, 4, 8, 9, and 15), but failed with NHBn; instead, stable thiazoline derivatives **19c** and **19d** were formed (76–78%, entries 12 and 13). Cyclization to seven-membered ring, although stereochemically allowed,[4] was feasible only for sulfur nucleophiles affording the bicyclic derivatives **18g** and **18h** in moderate to good yields (57–69%, entries 10 and 11). In the case of O and N nucleophiles the reaction resulted in formation of thiazolines **19b** and **19e** in good yields (72–80%, entries 5 and 16).

In short, *endo*-mode cyclization was applicable to formation of five- to seven-membered rings for sulfur nucleophiles. For hydroxy and primary amino group it was restricted to the synthesis of (5,6)-membered ring systems, i.e., closing of six-membered ring. Interestingly, NHBn did not cyclize to a favorable six-membered ring, but gave thiazolines **19c** and **19d**.

The stereochemistry of bicyclic compounds **18b**, **18d**, **18f**, and **18h** was assigned by NOESY NMR techniques, where distinct NOEs between H-4 and H-5 of the thiazolidine ring were observed for cis isomers, and between H–4 and C(5)–CH_3 for trans isomers. Low to moderate diastereoselectivity (Table 4, entries 4, 9, and 11) is a consequence of the reversibility of the reaction and small energy difference between the cis and trans isomers, i.e., thermodynamic control. In the case of **18d**, however, a kinetic control was observed (entry 7). The free energies of the two diastereomers were predicted by DFT calculations at the B3LYP/6-31G(d) level of theory[26] with inclusion of EtOH as a solvent[27] (only relative energies are

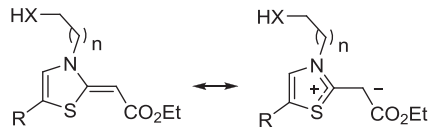


Scheme 3. *endo*-Mode cyclizations of vinylogous *N*-acyliminium ions **17**.

Table 4
Yields of products **18** and **19** obtained from vinylogous *N*-acyliminium ions **17**

Entry	Substrate	R	*n*	X	Product **18**[a] (%)	Ratio trans/cis exp[b] (calcd)[c]	Relative free energy[d] (kcal/mol) trans/cis	Product **19** (%)[a]
1	**11a**	H	1	O				**19a** (63)
2	**11b**	Me	1	O	Complex mixture			
3	**11c**	H	2	O	**18a** (36)			
4	**11d**	Me	2	O	**18b** (63)	75/25 (79/21)	0/0.79	
5	**11e**	Me	3	O				**19b** (80)
6	**12a**	H	1	S	**18c** (28)			
7	**12b**	Me	1	S	**18d** (35)	15/85 (93/7)	0/1.49	
8	**12c**	H	2	S	**18e** (66)			
9	**12d**	Me	2	S	**18f** (60)	56/44 (86/14)	0/1.1	
10	**12e**	H	3	S	**18g** (57)			
11	**12f**	Me	3	S	**18h** (69)	78/22 (86/14)	0/1.08	
12	**13a**	H	2	NBn				**19c** (76)
13	**13b**	Me	2	NBn				**19d** (78)
14	**15a**	H	1	NH	Complex mixture			
15	**15b**	H	2	NH	**18i** (62)			
16	**15c**	H	3	NH				**19e** (72)

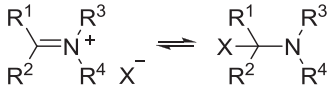
[a] Yield of isolated products.
[b] Determined by an integration of the corresponding signals in ^{1}H NMR spectra.
[c] Calculated ratio based on free energy difference (obtained at the B3LYP/6-31G(d) level in EtOH) between cis and trans isomers.
[d] Based on the optimized structures at the B3LYP/6-31G(d) level of theory in EtOH.



19

Scheme 4. Resonance structures of thiazoline derivatives **19**.

given in Table 4). The calculated isomer ratio, based on these energies, is given along with the experimentally observed ratio. In general, iminium ions are supposed to exist in equilibrium with a covalent adduct, the structure of which depends on the type of nucleophiles present in solution (Scheme 5). This type of equilibrium has been experimentally proved by Yamamoto et al. in their studies of the reaction of α-alkoxy carbamates with Lewis acids.[28] In the case of our reactions run in the nucleophilic solvent EtOH, the covalent species are, most probably, 4-ethoxy derivatives **20**,[29] enriched in the thermodynamically more stable trans isomer (Scheme 6). For example, the calculated energy difference between *cis* and *trans* **20** (X=S, *n*=1) amounts 1.85 kcal/mol, which corresponds to a trans/cis ratio 96/4. Nucleophile attacks the iminium carbon from the side opposite to the ethoxy group, which leads to formation of a cis/trans mixture of bicyclic products **18** enriched in thermodynamically less stable cis isomer. Obviously, this attack is reversible process so that the two isomers equilibrate via iminium ion **17** as an intermediate (Scheme 6). Judging from the isolated isomer ratio for **18b**, **18f**, and **18h** (Table 4) the reaction times (30 min, 90 min, and 45 min for the reduction step for **18b**, **18f**, and **18h**, respectively, and 1 h for the treatment with HCl) were insufficient for complete equilibration. In the case of **18d** the major isomer isolated was the higher energy cis isomer, even after a total of 2 h (1 h for reduction and 1 h for the treatment with HCl). Apparently, this (5,5)-membered ring system equilibrated with the slowest rate.[30]



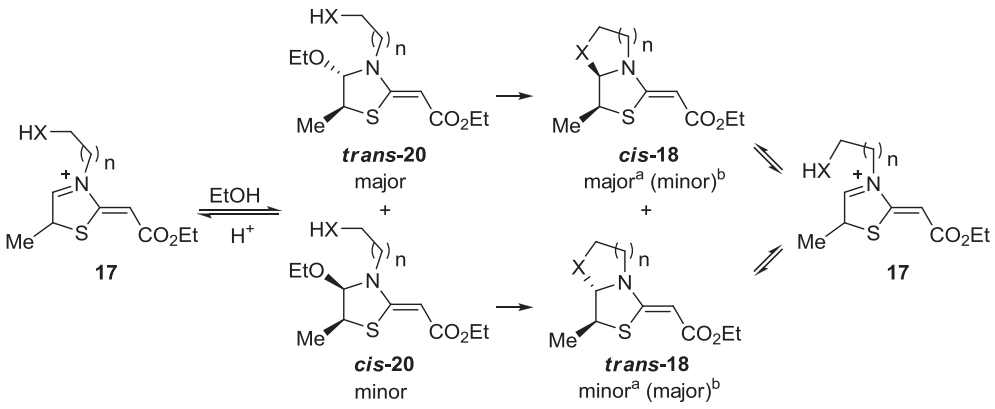
Scheme 5. Equilibrium between an iminium ion and covalent adduct in solution.

The reason for different rates of equilibration lies in stereoelectronic factors. Most stable conformations of *cis*-**18b**, *cis*-**18d**, *cis*-**18f**, and *cis*-**18h** are shown in Fig. 4. Six-membered ring adopts chair conformation, seven-membered ring twist-chair conformation and five-membered ring envelope conformation. In all derivatives conformation of the thiazolidine ring is half-chair with S(1)–C(2)–N(3) in one plane. The position of C(5)–CH_3 is pseudoequatorial in (5,6)- and (5,7)-membered ring systems, but pseudoaxial in (5,5)-membered system. It is apparent that in both (5,6)- and (5,7)-membered systems the nitrogen lone pair proves to be a p-like orbital more or less in-plane with the breaking C(4)–X bond and thus facilitating the formation of the iminium ion. In (5,5)-membered molecule, the nitrogen lone pair orbital and the breaking bond lie in different planes making it much less prone to equilibration.

Next, we turned our attention to computational methods to rationalize why some substrates did not cyclize, but gave thiazolines instead. We envisioned the reaction to occur in the following sequence (Scheme 7): (i) formation of an iminium ion **17** existing in equilibrium with the covalent adduct **20**,[28] (ii) approach of a nucleophile to a reactive center (conformations **17b** and **20b**), and (iii) formation of products **18** or **19** where EtOH acts as a base abstracting proton either from the heteroatom, which leads to the cyclization or from C(5) of the thiazolidine ring leading to the elimination.

First we sought for activation parameters for the cyclization and elimination processes. To do this, iminium ion structures **17b** were optimized at the B3LYP/6-31G(d) level.[26] Then EtOH was added and supramolecules **21** and **22**[31] (Fig. 5) were optimized using the same method and basis set. Transition state geometries were found by the 'reaction coordinate method'.[32] In this method, one parameter, chosen as a reaction coordinate, is constrained for the appropriate degree of freedom while all other variables are freely optimized. In the studied reactions, the reaction coordinate was taken to be the distance between the hydrogen and heteroatom in **21** (H–X) and hydrogen and C(5) of the thiazolidine ring in **22** (H–C(5)) and the reaction path was calculated by the successive increase in this distance. In the case of substrates containing amino groups as nucleophiles the reaction path was calculated by successive decrease in the distance between nitrogen and iminium carbon, without the added EtOH molecule.

Activation free energies (ΔG_{act}), presented in Table 5, were calculated from the difference in energies of the transition states and starting supramolecular geometries. The activation barriers for the cyclization of intermediates **21d**–**f** incorporating sulfur nucleophiles (8.87–9.32 kcal/mol) compared to the barrier for the elimination reaction (13.08 kcal/mol) are in agreement with the



[a] Immediately after the cyclization. [b] After the equilibration (except for **18d**).

Scheme 6. Formation and equilibration of cis and trans stereoisomers of **18b**, **18d**, **18f**, and **18h**.

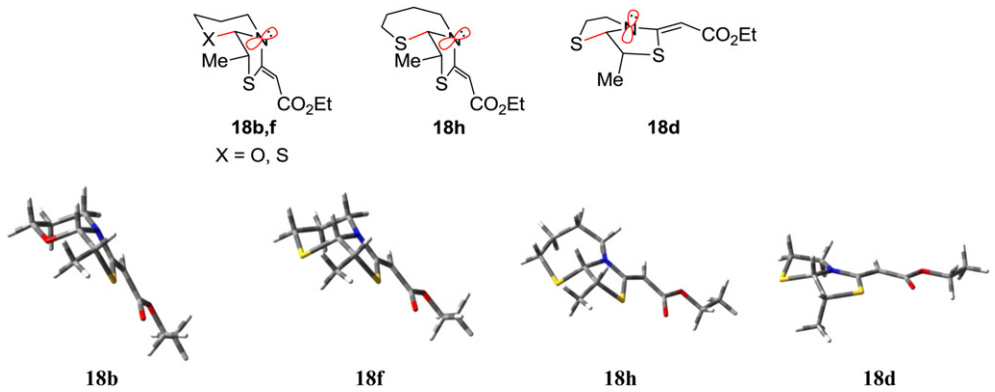
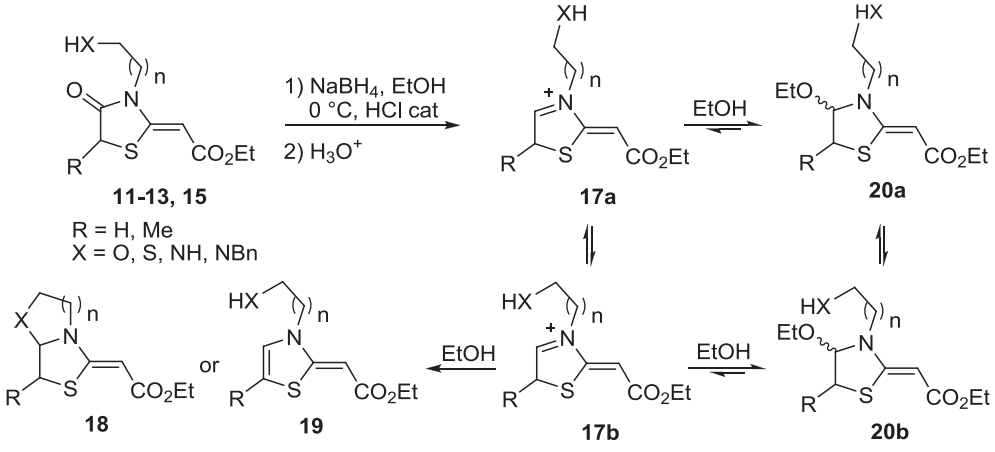


Fig. 4. Most stable conformations of cis isomers of **18b**, **18d**, **18f**, and **18h**.



Scheme 7.

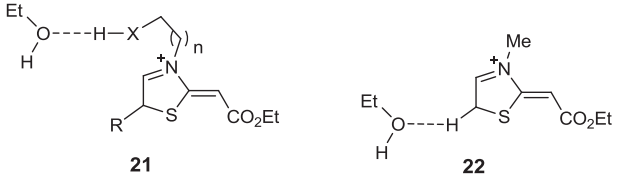


Fig. 5. Initial supramolecular structures used for the calculation of activation parameters.

observed experimental data: all precursors cyclized to the expected bicyclic products (Table 4). The barrier for the formation of five-membered ring with oxygen nucleophile (intermediate **21a**, Table 5) is much higher than the barrier for the β-elimination, thus explaining the thiazoline formation from the precursor **11a** (Table 4, entry 1). The activation free energy found for closing of six- and seven-membered rings from intermediates **21b** and **21c**, incorporating OH nucleophile, are quite similar and lower than the energy required for the β-elimination. However, six-membered

Table 5
The activation free energy for the cyclization step[a,b]

Starting structure	R	*n*	X	ΔG_{act}
21a	H	1	O	18.47
21b	H	2	O	10.62
21c	Me	3	O	10.79
21d	H	1	S	9.32
21e	H	2	S	8.93
21f	H	3	S	8.87
21g	H	1	NH	3.42
21h	H	2	NH	0.00[c]
21i	H	2	NBn	0.00[c]
21j	H	3	NH	3.99
22				13.08

[a] Obtained at the B3LYP/6-31G(d) level in gas phase.
[b] Values are in kcal/mol.
[c] Optimization of iminium ion structures **17b** resulted in cyclic products.

ring was formed, but seven-membered was not (Table 4, entries 3–5). This fact is accounted for by the total higher entropy loss accompanying the formation of seven-membered ring from the open-chain intermediates **17a**/**20a** (Scheme 7), having a higher degree of freedom of internal rotation around single bonds than the cyclic product, thus making the β-elimination more feasible. For all intermediates with nitrogen nucleophiles **21g–j** the estimated barriers, based on the NH_2/NBn approach to the iminium carbon, are quite low (0–3.99 kcal/mol). Yet, only **15b** cyclized to the (5,6)-membered **18i** (Table 4, entries 12–16).

Assuming that amino species are protonated under the acidic reaction conditions and that the deprotonation, leading to the formation of the expected cyclization products, occurs near the reaction center just before the generation of the iminium ion, we next examined the energy difference between the protonated zigzag conformation **20a** and reactive conformation **20b** (Scheme 7) of amino precursors **13a** and **15a–c**. In the gas phase, the reactive conformations **20b** of all compounds were found to be energetically much more favored than the corresponding zigzag conformations **20a** ($\Delta\Delta H_{gas\ phase}$ in Table 6). This is due to the existence of an attractive, non-bonded $=C\cdots H-N^+$ interaction between the exocyclic carbon of the CC double bond and protonated amino group, evident from the C···H distances ($d_{C\cdots H}$ (Å) in Table 6, Fig. 6), which are considerably shorter than the sum of Van der Waals radii (2.9 Å). The nature of the interaction is dual. It involves an electrostatic attraction between the negatively charged exocyclic carbon[12] and positively charged hydrogen, and $\pi\rightarrow\sigma^*_{N-H}$ orbital interactions, as shown by the second order perturbation theory analysis of Fock matrix in NBO basis[33] (Table 6). Further, the solvation effect was simulated[34] by considering that zigzag conformations are stabilized by three hydrogen bonds with the solvent, while the reactive conformations **20b** have two such interactions, the third remained the above mentioned $=C\cdots H-N^+$ interaction. Consequently, the energy difference between the two conformations should be the difference in one $=C\cdots H-N^+$ interaction and $O\cdots H-N^+$ hydrogen bond ($\Delta\Delta H_{EtOH}$ in Table 6; the energy of one hydrogen bond was estimated to be −17.26 kcal/mol, see Computational details). As expected, the zigzag conformations are now preferred and the smallest energy difference was found for **15b**, the only precursor, which was able to cyclize affording the bicyclic product **18i**.

Table 6
Enthalpy difference between reactive conformation **20b** and the zigzag conformation **20a** of precursors **13a** and **15a–c** in the gas phase and by simulating solvation effects, C···H distance and hyperconjugation energy

Substrate	$\Delta\Delta H_{gas\ phase}$[a]	$\Delta\Delta H_{EtOH}$[a]	$d_{C\cdots H}$ (Å)	$E\ (\pi\rightarrow\sigma^*_{N-H})$[a,b]
13a	−10.61	6.65	2.01	14.39
15a	−8.00	9.26	2.40	11.31
15b	−14.45	2.81	1.82	25.58
15c	−9.07	8.19	2.50	2.18

[a] Values are in kcal/mol.
[b] Obtained by NBO analysis.

3. Conclusions

In summary, we have shown that *endo*-mode cyclizations of vinylogous *N*-acyliminium ions, possessing O, S, and N as internal nucleophiles, can be applied for the synthesis of thiazolidine-fused heterocycles. While the cyclization to form five- to seven-membered rings was feasible for SH as a nucleophile, it was restricted to closing of six-membered ring with OH and NH_2. The attempted 5- and 7-*endo* cyclizations with these nucleophiles ended in the formation of thiazoline derivatives, which was also the case using NHBn nucleophile in 6-*endo* cyclization.

The observed trend was rationalized by quantum chemical calculations of activation energy for cyclization versus β-elimination of the intermediate iminium ions. The activation free energy, predicted at the B3LYP/6-31G(d) level, needed for the formation of the oxazolidine-fused ring (18.47 kcal/mol) was found to be higher than the energy required for thiazoline formation (13.08 kcal/mol). While all other barriers are lower than the β-elimination barrier (more so for sulfur, 8.87–9.32 kcal/mol, than for oxygen nucleophiles, 10.62–10.79 kcal/mol), the fact that oxazepine-fused heterocycle was not formed is accounted for by the total higher entropy loss accompanying the closing of seven-membered ring. In the case of precursors containing *N*-nucleophiles the calculated activation barriers were very low (0–3.99 kcal/mol), yet only 6-*endo* cyclization with NH_2 took place. This fact was rationalized by computing the energy difference between the zigzag **20a** and reactive conformation **20b** of protonated amino-containing 4-ethoxy intermediates. The reactive conformation **20b**, in which *N*-nucleophilic group is placed close to the reactive center, is stabilized by non-bonded $=C\cdots H-N^+$ interaction between the exocyclic carbon of the CC double bond and protonated amino group. The strongest stabilization was found for the intermediate derived from **15b**, which was the only precursor able to cyclize.

The stereochemical outcome of cyclization reactions was found to originate from thermodynamic control and small energy difference between the cis and trans isomers of **18b**, **18f**, and **18h**. In the case of **18d**, however, a kinetic control was observed. The rate of equilibration of two isomers was dictated by stereoelectronic factors. The most favorable alignment of nitrogen p-like lone pair and breaking C–X bond was achieved in (5,6)- and (5,7)-membered

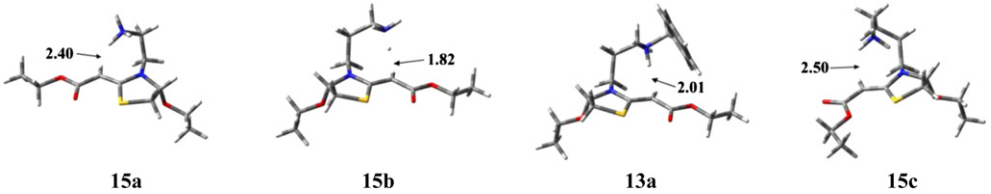


Fig. 6. Reactive conformations **20b** of amino-containing intermediates **13a** and **15a–c**.

systems, which equilibrated more rapidly than (5,5)-membered system.

4. Computational details

Ab initio MO calculations and the Natural Bond Orbital (NBO) Population Analysis[33] were done using Gaussian 03 program package.[35] Geometries of intermediates and products were fully optimized at the B3LYP/6-31G(d) level[26] and the minimum energy structures confirmed by all positive vibrational force constants. The solvent effects (EtOH ε=24.55) were included in the calculations by the SCRF theory using IEFPCM model.[27] Transition state structures were found by the 'reaction coordinate method'.[32] In this method, one parameter, chosen as a reaction coordinate, is constrained for the appropriate degree of freedom while all other variables are freely optimized. Initial supramolecular structures, consisting of an iminium ion and suitably placed EtOH, were fully optimized at the same level of theory. The reaction coordinate was taken to be the distance between the hydrogen and heteroatom in **21** (H–X) and hydrogen and C(5) of the thiazolidine ring in **22** (H–C(5)) and the reaction path was calculated by the successive increase in this distance (for 0.01, 0.02 or 0.05 Å, depending on the reaction). In the case of substrates containing amino groups as internal nucleophiles the conformations **17b** were optimized and the reaction path calculated by the successive decrease in the distance between the nitrogen and iminium carbon (for 0.1 Å). The transition state structures were verified by having only one negative frequency. The activation parameters were calculated from the difference in energies of the transition state structures and the initial supramolecules. Energy of one O···H–N hydrogen bond (formed between EtOH and an ammonium group, −17.26 kcal/mol) was estimated by first optimizing the zigzag conformation **17a** (Scheme 7) with three hydrogen-bonded EtOH molecules. Then, from the obtained energy, the energy of free **17a** and energy of three EtOH molecules were subtracted and divided by three.

5. Experimental

5.1. General

Melting points were determined on a Stuart SMP10 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 recorded on a Varian Gemini 2000 spectrometer (^1H at 200 MHz, ^{13}C at 50.3 MHz) and on a Bruker Ultrashield Advance III (^1H at 500.26 MHz, ^{13}C at 125.79 MHz) in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard. Elemental analyses were performed at the microanalysis laboratory at the Centre for Chemistry ICTM. HRMS was carried out on 6210 TOF LC/MS coupled with HPLC 1200 Series Agilent Technologies. Thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl and spots were visualized by iodine or by 50% H_2SO_4. Column chromatography was carried out on SiO_2 (silica gel 60 Å, 12–26, ICN Biomedicals). All solvents were distilled before use. DMF was distilled over CaH_2.

5.2. General procedure for synthesis of 4-oxothiazolidines 7

A mixture of ethyl cyanoacetate (1 equiv), α-mercapto ester (1.05 equiv), and K_2CO_3 (0.05 equiv) was heated with stirring at the temperature of an oil bath of 75–80 °C for 15–30 min (see below) and then cooled to rt. After adding of water/EtOH 7/3 (v/v) to the solidified reaction mixture stirring was continued for 1 h at rt. Filtration gave pure products **7**.

*5.2.1. (Z)-Ethyl 2-(4-oxothiazolidin-2-ylidene)acetate (**7a**).* Compound **7a** was obtained from ethyl cyanoacetate (5.31 g, 47.0 mmol), ethyl mercaptoacetate (6.25 g, 52.0 mmol) and K_2CO_3 (450 mg; 3.26 mmol) according to general procedure (reaction time 30 min), as a white solid (7.70 g; 87%), mp 152–153 °C (lit.[36] 154–155 °C); R_f=0.52 (toluene/ethyl acetate 7:3); ^1H NMR[37] (200 MHz, DMSO-d_6): δ 1.18 (t, J=7.2 Hz, 3H, CH_3), 3.78 (s, 2H, CH_2S), 4.06 (q, J=7.2 Hz, 2H, CH_2O), 5.44 (s, 1H, =CH), 11.58 (br s, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 14.6 (CH_3), 32.6 (CH_2S), 59.2 (CH_2O), 88.6 (=CH), 159.2 (C=), 167.3 (CO_{ester}), 174.5 (CO_{lactam}); IR (KBr): ν=3246, 1722, 1660, 1151 cm^{-1}.

*5.2.2. (Z)-Ethyl 2-(5-methyl-4-oxothiazolidin-2-ylidene)acetate (**7b**).* Compound **7b** was obtained from ethyl cyanoacetate (1.59 g, 14.1 mmol), ethyl 2-mercaptopropionate (1.99 g, 14.8 mmol), and K_2CO_3 (94.5 mg; 0.68 mmol) according to general procedure (reaction time 15 min), as a white solid (2.17 g; 76%), mp 120–121 °C (lit.[36] 123 °C); R_f=0.48; 0.73 (toluene/ethyl acetate 7:3; two spots due to Z/E isomerization);[15] ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.0 Hz, 3H, CH_3CH_2), 1.63 (d, J=7.0 Hz, 3H, CH_3CH), 3.97 (q, J=7.0 Hz, 1H, CHS), 4.20 (q, J=7.0 Hz, 2H, CH_2O), 5.64 (s, 1H, =CH), 9.62 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3CH_2), 18.8 (CH_3CH), 41.8 (CHS), 60.1 (CH_2O), 91.3 (=CH), 154.6 (C=), 167.9 (CO_{ester}), 178.2 (CO_{lactam}); IR (KBr): ν=3156, 1726, 1657, 1164 cm^{-1}.

5.3. General procedure for synthesis of *N*-bromoalkyl derivatives 8

An alkylating agent was added to a stirred mixture of 4-oxothiazolidine **7** and K_2CO_3 in DMF, and stirring was continued at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2 (10–15 mL), washed with water (3×10 mL), saturated aq NaCl (1×10 mL), and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography.

*5.3.1. (Z)-Ethyl 2-(3-(2-bromoethyl)-4-oxothiazolidin-2-ylidene)acetate (**8a**).* Compound **8a** was obtained from **7a** (222 mg; 1.18 mmol), K_2CO_3 (170 mg; 1.23 mmol; 1.04 equiv), 1,2-dibromoethane (1.00 g; 5.33 mmol; 4.5 equiv) in DMF (2.5 mL) according to general procedure (reaction time 5 h, TLC: petrolether/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 60:40) gave pure **8a**, as a white solid (250 mg; 72%), mp 106–107 °C; R_f=0.47 (petrolether/ethyl acetate 4:1); ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.4 Hz, 3H, CH_3), 3.47 (t, J=7.6 Hz, 2H, CH_2Br), 3.74 (s, 2H, CH_2S) 4.07 (t, J=7.6 Hz, 2H, NCH_2), 4.22 (q, J=7.4 Hz, 2H, CH_2O), 5.53 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 25.0 (CH_2Br), 31.5 (CH_2S), 44.3 (NCH_2), 60.2 (CH_2O), 90.7 (=CH), 157.2 (C=), 167.4 (CO_{ester}), 172.2 (CO_{lactam}); IR (KBr): ν=1719, 1680, 1562, 1182, 1137 cm^{-1}; HRMS: calcd for $C_9H_{13}BrNO_3S$ $[M+H]^+$ 293.9794, found 293.9798.

*5.3.2. (Z)-Ethyl 2-(3-(2-bromoethyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**8b**).* Compound **8b** was obtained from **7b** (242 mg; 1.20 mmol), K_2CO_3 (176 mg; 1.27 mmol; 1.06 equiv), 1,2-dibromoethane (894 mg; 4.76 mmol; 4.0 equiv) in DMF (3.0 mL) according to general procedure (reaction time 5 h, TLC: petrolether/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 70:30) gave pure **8b**, as a white solid (306 mg; 82%), mp 105–106 °C; R_f=0.78 (petrolether/ethyl acetate 3:2); ^1H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3CH_2), 1.63 (d, J=7.0 Hz, 3H, CH_3CH), 3.47 (t, J=7.4 Hz, 2H, CH_2Br), 3.92 (q, J=7.0 Hz, 1H, CHS), 4.06 (t, J=7.4 Hz, 2H, NCH_2), 4.22 (q, J=7.2 Hz, 2H, CH_2O), 5.51 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3CH_2), 19.1 (CH_3CH), 25.2 (CH_2Br), 40.3 (CHS), 44.2 (NCH_2), 60.2 (CH_2O), 90.2 (=CH), 155.9 (C=), 167.4 (CO_{ester}), 175.4 (CO_{lactam}); IR

(KBr): ν=1719, 1683, 1586, 1304, 1179, 1143 cm^{-1}; Anal. Calcd for $C_{10}H_{14}BrNO_3S$ (308.19): C, 38.97; H, 4.58; N, 4.54; S, 10.40, found: C, 39.27; H, 4.41; N, 4.62; S, 10.61.

*5.3.3. (2Z,2′Z)-Diethyl 2,2′-(3,3′-(ethane-1,2-diyl)bis(5-methyl-4-oxothiazolidin-3-yl-2-ylidene))diacetate (**9a**).* Compound **9a** was obtained as a by-product in the N-alkylation of **7b** with 1,2-dibromoethane, as a white solid (15.4 mg; 6%), mp 186–188 °C; R_f=0.52 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 6H, 2× CH_3CH$_2$), 1.58 (d, J=7.0 Hz, 6H, 2× CH_3CH), 3.89–4.10 (m, 4H, 2× NCH$_2$), 3.84 (q, J=7.0 Hz, 1H, CHS), 3.85 (q, J=7.0 Hz, 1H, CHS), 4.21 (q, J=7.2 Hz, 4H, 2× CH$_2$O), 5.49 (s, 1H, =CH), 5.50 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 18.5 (*C*H$_3$CH), 40.1 (CHS), 40.1 (NCH$_2$), 60.1 (CH$_2$O), 89.6 (=CH), 156.5 (C=), 167.3 (CO$_{ester}$), 176.1 (CO$_{lactam}$); IR (KBr): ν=1715, 1686, 1570, 1292, 1150 cm^{-1}; HRMS: calcd for $C_{18}H_{25}N_2O_6S_2$ [M+H]$^+$ 429.1148, found 429.1140.

*5.3.4. (Z)-Ethyl 2-(3-(3-bromopropyl)-4-oxothiazolidin-2-ylidene) acetate (**8c**).* Compound **8c** was obtained from **7a** (218 mg; 1.16 mmol), K_2CO_3 (169 mg; 1.22 mmol; 1.05 equiv), 1,3-dibromopropane (1.19 g; 5.88 mmol; 5.1 equiv) in DMF (3.0 mL) according to general procedure (reaction time 2 h, TLC: toluene/ethyl acetate 7:3). Column chromatography (eluent: gradient toluene/ethyl acetate 100:0 to 70:30) gave pure **8c**, as a white solid (250 mg; 70%), mp 74–75 °C; R_f=0.36 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.4 Hz, 3H, CH$_3$), 2.12–2.25 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 3.43 (t, J=6.6 Hz, 2H, CH$_2$Br), 3.72 (s, 2H, CH$_2$S), 3.83 (t, J=7.4 Hz, 2H, NCH$_2$), 4.22 (q, J=7.4 Hz, 2H, CH$_2$O), 5.58 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH$_3$), 29.3 (CH$_2$*C*H$_2$CH$_2$), 29.6 (CH$_2$Br), 31.6 (CH$_2$S), 42.2 (NCH$_2$), 60.1 (CH$_2$O), 90.6 (=CH), 157.60 (C=), 167.6 (CO$_{ester}$), 172.5 (CO$_{lactam}$); IR (KBr): ν=1723, 1679, 1567, 1180, 1144 cm^{-1}; HRMS: calcd for $C_{10}H_{15}BrNO_3S$ [M+H]$^+$ 307.9950, found 307.9949.

*5.3.5. (2Z,2′Z)-Diethyl 2,2′-(3,3′-(propane-1,3-diyl)bis(4-oxothiazolidin-3-yl-2-ylidene))diacetate (**9b**).* Compound **9b** was obtained as a by-product in the N-alkylation of **7a** with 1,3-dibromopropane, as a white solid (44.4 mg; 18%), mp 159–160 °C; R_f=0.22 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.0 Hz, 6H, 2× CH$_3$), 1.90–2.05 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 3.73 (t, J=7.2 Hz, 4H, 2× NCH$_2$), 3.73 (s, 4H, 2× CH$_2$S), 4.21 (q, J=7.0 Hz, 4H, 2× CH$_2$O), 5.44 (s, 2H, 2× =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH$_3$), 23.7 (CH$_2$CH$_2$CH$_2$), 31.6 (CH$_2$S), 40.6 (NCH$_2$), 60.1 (CH$_2$O), 90.4 (=CH), 157.5 (C=), 167.4 (CO$_{ester}$), 172.4 (CO$_{lactam}$); IR (KBr): ν=1717, 1684, 1571, 1171 cm^{-1}; HRMS: calcd for $C_{17}H_{23}N_2O_6S_2$ [M+H]$^+$ 415.0992, found 415.0983.

*5.3.6. (Z)-Ethyl 2-(3-(3-bromopropyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**8d**).* Compound **8d** was obtained from **7b** (208 mg; 1.03 mmol), K_2CO_3 (150 mg; 1.08 mmol; 1 equiv), 1,3-dibromopropane (1.03 g; 5.1 mmol; 4.9 equiv) in DMF (3.0 mL) according to general procedure (reaction time 2.5 h, TLC: petrolether/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 60:40) gave pure **8d**, as a white solid (234 mg; 70%), mp 101–102 °C; R_f=0.61 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.61 (d, J=7.2 Hz, 3H, CH_3CH), 2.12–2.25 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 3.42 (t, J=6.4 Hz, 2H, CH$_2$Br), 3.83 (t, J=7.4 Hz, 2H, NCH$_2$), 3.90 (q, J=7.2 Hz, 1H, CHS), 4.22 (q, J=7.2 Hz, 2H, CH$_2$O), 5.56 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$CH), 29.4 (CH$_2$*C*H$_2$CH$_2$), 29.6 (CH$_2$Br), 40.3 (CHS), 42.2 (NCH$_2$), 60.1 (CH$_2$O), 90.1 (=CH), 156.3 (C=), 167.6 (CO$_{ester}$), 175.7 (CO$_{lactam}$); IR (KBr): ν=1715, 1689, 1574, 1309, 1173, 1146 cm^{-1}; HRMS: calcd for $C_{11}H_{17}BrNO_3S$ [M+H]$^+$ 322.0107, found 322.0096.

*5.3.7. (2Z,2′Z)-Diethyl 2,2′-(3,3′-(propane-1,3-diyl)bis(5-methyl-4-oxothiazolidin-3-yl-2-ylidene))diacetate (**9c**).* Compound **9c** was obtained as a by-product in the N-alkylation of **7b** with 1,3-dibromopropane, as a white solid (47.0 mg; 21%), mp 141–142 °C; R_f=0.16 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 6H, 2× CH_3CH$_2$), 1.62 (d, J=7.0 Hz, 6H, 2 x CH_3CH), 1.89–2.02 (m, 4H, 2× CH$_2$C*H*$_2$CH$_2$), 3.72 (t, J=7.2 Hz, 4H, 2× NCH$_2$), 3.92 (q, J=7.0 Hz, 2H, 2× CHS), 4.20 (q, J=7.2 Hz, 4H, 2× CH$_2$O), 5.42 (s, 2H, 2× =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$CH), 24.0 (CH$_2$CH$_2$CH$_2$), 40.3 (CHS), 40.7 (NCH$_2$), 60.0 (CH$_2$O), 90.0 (=CH), 156.1 (C=), 167.4 (CO$_{ester}$), 175.6 (CO$_{lactam}$); IR (KBr): ν=1694, 1575, 1312, 1173 cm^{-1}; HRMS: calcd for $C_{19}H_{27}N_2O_6S_2$ [M+H]$^+$ 443.1305, found 443.1294.

*5.3.8. (Z)-Ethyl 2-(3-(4-bromobutyl)-4-oxothiazolidin-2-ylidene)acetate (**8e**).* Compound **8e** was obtained from **7a** (203 mg; 1.09 mmol), K_2CO_3 (160 mg; 1.23 mmol; 1.13 equiv), 1,4-dibromobutane (1.18 g; 5.44 mmol; 5.4 equiv) in DMF (2.5 mL) according to general procedure (reaction time 4 h, TLC: petrolether/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 60:40) gave pure **8e**, as a white solid (289 mg; 83%), mp 76–77 °C; R_f=0.71 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH$_3$), 1.71–1.96 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 3.44 (t, J=6.2 Hz, 2H, CH$_2$Br), 3.71 (t, J=7.0 Hz, 2H, NCH$_2$), 3.72 (s, 2H, CH$_2$S), 4.22 (q, J=7.2 Hz, 2H, CH$_2$O), 5.51 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH$_3$), 25.0 (*C*H$_2$CH$_2$Br), 29.5 (NCH$_2$*C*H$_2$), 31.7 (CH$_2$S), 32.5 (CH$_2$Br), 42.5 (NCH$_2$), 60.1 (CH$_2$O), 90.6 (=CH), 157.8 (C=), 167.6 (CO$_{ester}$), 172.4 (CO$_{lactam}$); IR (KBr): ν=1710, 1672, 1560, 1177, 1136, 1040 cm^{-1}; HRMS: calcd for $C_{11}H_{17}BrNO_3S$ [M+H]$^+$ 322.0107, found 322.0097.

*5.3.9. (2Z,2′Z)-Diethyl 2,2′-(3,3′-(butane-1,4-diyl)bis(4-oxothiazolidin-3-yl-2-ylidene))diacetate (**9d**).* Compound **9d** was obtained as a by-product in the N-alkylation of **7a** with 1,4-dibromobutane, as a white solid (15.7 mg; 4%), mp 186–187 °C; R_f=0.42 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.0 Hz, 6H, 2× CH$_3$), 1.65 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 3.70 (m, 4H, 2× CH$_2$S), 3.72 (s, 4H, 2× NCH$_2$), 4.22 (q, J=7.0 Hz, 4H, 2× CH$_2$O), 5.48 (s, 2H, 2× =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH$_3$), 23.6 (CH$_2$CH$_2$CH$_2$CH$_2$), 31.7 (CH$_2$S), 42.7 (NCH$_2$), 60.1 (CH$_2$O), 90.6 (=CH), 157.8 (C=), 167.6 (CO$_{ester}$), 172.6 (CO$_{lactam}$); IR (KBr): ν=1713, 1683, 1562, 1141, 1041 cm^{-1}; HRMS: calcd for $C_{18}H_{25}N_2O_6S_2$ [M+H]$^+$ 429.1148, found 429.1141.

*5.3.10. (Z)-Ethyl 2-(3-(4-bromobutyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**8f**).* Compound **8f** was obtained from **7b** (205 mg; 1.02 mmol), K_2CO_3 (149 mg; 1.08 mmol; 1.06 equiv), 1,4-dibromobutane (1.08 g; 5.44 mmol; 5 equiv) in DMF (2.0 mL) according to general procedure (reaction time 1.5 h, TLC: petrolether/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 60:40) gave pure **8f**, as a white solid (273 mg; 80%), mp 77–78 °C; R_f=0.51 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.61 (d, J=7.2 Hz, 3H, CH_3CH), 1.71–1.96 (m, 4H, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 3.44 (t, J=6.2 Hz, 2H, CH$_2$Br), 3.71 (t, J=6.8 Hz, 2H, NCH$_2$), 3.94 (q, J=7.2 Hz, 1H, CHS), 4.21 (q, J=7.2 Hz, 2H, CH$_2$O), 5.49 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.2 (*C*H$_3$CH), 25.1 (*C*H$_2$CH$_2$Br), 29.5 (NCH$_2$*C*H$_2$), 32.5 (CH$_2$Br), 40.4 (CHS), 42.5 (NCH$_2$), 60.1 (CH$_2$O), 90.2 (=CH), 156.5 (C=), 167.6 (CO$_{ester}$), 175.8 (CO$_{lactam}$); IR (KBr): ν=1712, 1684, 1568, 1312, 1179,

1141 cm^{-1}; HRMS: calcd for $C_{12}H_{19}BrNO_3S$ $[M+H]^+$ 336.0264, found 336.0252.

*5.3.11. (2Z,2′Z)-Diethyl 2,2′-(3,3′-(butane-1,4-diyl)bis(5-methyl-4-oxothiazolidin-3-yl-2-ylidene))diacetate (**9e**).* Compound **9e** was obtained as a by-product in the N-alkylation of **7b** with 1,4-dibromobutane, as a white solid (16.9 mg; 7%), mp 155–156 °C; R_f=0.18 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.1 Hz, 6H, 2× CH_3CH$_2$), 1.61 (d, J=7.4 Hz, 6H, 2× CH_3CH), 1.64 (m, 4H, CH$_2$CH_2CH_2CH$_2$), 3.67–3.75 (m, 4H, 2× NCH$_2$), 3.90 (q, J=7.4 Hz, 2H, 2× CHS), 4.22 (q, J=7.1 Hz, 4H, 2× CH$_2$O), 5.47 (s, 2H, 2× =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.1 (*C*H$_3$CH), 23.6 (CH$_2$CH$_2$CH$_2$CH$_2$), 40.4 (CHS), 42.7 (NCH$_2$), 60.1 (CH$_2$O), 90.1 (=CH), 156.4 (C=), 167.6 (CO$_{ester}$), 175.8 (CO$_{lactam}$); IR (KBr): ν=1711, 1687, 1567, 1311, 1180, 1145 cm^{-1}; HRMS: calcd for $C_{20}H_{29}N_2O_6S_2$ $[M+H]^+$ 457.1462, found 457.1456.

5.4. General procedure for synthesis of alcohols 11

A solution of bromide **8** in 0.75 M HCl in DMF/H_2O (1:1 v/v) was heated at the temperature of an oil bath of 100 °C until the disappearance of the starting material (TLC). The reaction mixture was then diluted with $CHCl_3$ (10 mL), washed with water (3×10 mL), 5% aq $NaHCO_3$ (1×10 mL), saturated aq NaCl (1×10 mL) and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by stirring with *n*-hexane for 2 h at rt, or by column chromatography.

*5.4.1. (Z)-Ethyl 2-(3-(2-hydroxyethyl)-4-oxothiazolidin-2-ylidene) acetate (**11a**).* Compound **11a** was prepared from **8a** (39.8 mg; 0.13 mmol) in 3 mL DMF/H_2O 1:1 (v/v) to which 200 μL concd HCl was added, according to general procedure (reaction time 3 h, TLC: toluene/ethyl acetate 7:3). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 50:50) gave pure **11a**, as a white solid (20.5 mg; 66%), mp 107–108 °C; R_f=0.23 (toluene/ethyl acetate 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, CH$_3$), 2.40 (br s, 1H, OH), 3.75 (s, 2H, CH$_2$S), 3.82–3.90 (m, 4H, CH$_2$CH$_2$), 4.20 (q, J=7.2 Hz, 2H, CH$_2$O), 5.60 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH$_3$), 31.7 (CH$_2$S), 45.7 (NCH$_2$), 59.0 (CH$_2$OH), 60.1 (CH$_2$O), 90.8 (=CH), 158.2 (C=), 167.8 (CO$_{ester}$), 173.4 (CO$_{lactam}$); IR (KBr): ν=3497, 1703, 1678, 1569, 1368, 1167 cm^{-1}; HRMS: calcd for $C_9H_{14}NO_4S$ $[M+H]^+$ 232.0638, found 232.0644.

*5.4.2. (Z)-Ethyl 2-(3-(2-hydroxyethyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**11b**).* Compound **11b** was prepared from **8b** (100 mg; 0.33 mmol) in 3 mL DMF/H_2O 1:1 (v/v) to which 200 μL concd HCl was added, according to general procedure (reaction time 3 h, TLC: petrolether/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 60:40) gave pure **11b**, as a white solid (59.7 mg; 72%), mp 93–94 °C; R_f=0.27 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.62 (d, J=7.2 Hz, 3H, CH_3CH), 1.93 (br s, 1H, OH), 3.80–3.92 (m, 4H, CH$_2$CH$_2$), 3.94 (q, J=7.2 Hz, 1H, CHS), 4.21 (q, J=7.2 Hz, 2H, CH$_2$O), 5.58 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.1 (*C*H$_3$CH), 40.4 (CHS), 45.7 (NCH$_2$), 59.2 (CH$_2$OH), 60.1 (CH$_2$O), 90.4 (=CH), 156.8 (C=), 167.7 (CO$_{ester}$), 176.7 (CO$_{lactam}$); IR (KBr): ν=3451, 1706, 1682, 1568, 1306, 1160, 1041 cm^{-1}; HRMS: calcd for $C_{10}H_{16}NO_4S$ $[M+H]^+$ 246.0795, found 246.0785.

*5.4.3. (Z)-Ethyl 2-(3-(3-hydroxypropyl)-4-oxothiazolidin-2-ylidene) acetate (**11c**).* Compound **11c** was prepared from **8c** (45.7 mg; 0.15 mmol) in 3 mL DMF/H_2O 1:1 (v/v) to which 200 μL concd HCl was added, according to general procedure (reaction time 21 h, TLC: toluene/ethyl acetate 7:3). The crude product was purified by stirring with *n*-hexane. Filtration gave pure **11c** as a white solid (33.4 mg; 92%), mp 94–95 °C; R_f=0.28 (toluene/ethyl acetate 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.4 Hz, 3H, CH$_3$), 1.79–1.91 (m, 2H, CH$_2$CH_2CH$_2$), 3.61 (t, J=6.0 Hz, 2H, CH_2OH), 3.75 (s, 2H, CH$_2$S), 3.84 (t, J=6.4 Hz, 2H, NCH$_2$), 4.21 (q, J=7.4 Hz, 2H, CH$_2$O), 5.59 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH$_3$), 29.0 (CH$_2$CH$_2$CH$_2$), 31.7 (CH$_2$S), 40.2 (NCH$_2$), 58.7 (CH$_2$OH), 60.1 (CH$_2$O), 90.9 (=CH), 157.7 (C=), 167.7 (CO$_{ester}$), 173.4 (CO$_{lactam}$); IR (KBr): ν=3446, 1684, 1564, 1369, 1155, 1043 cm^{-1}; HRMS: calcd for $C_{10}H_{16}BrNO_4S$ $[M+H]^+$ 246.0795, found 246.0802.

*5.4.4. (Z)-Ethyl 2-(3-(3-hydroxypropyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**11d**).* Compound **11d** was prepared from **8d** (100 mg; 0.31 mmol) in 3 mL DMF/H_2O 1:1 (v/v) to which 200 μL concd HCl was added, according to general procedure (reaction time 19 h, TLC: petrolether/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 80:20 to 50:50) gave pure **11d**, as a white solid (50.2 mg; 62%), mp 104–105 °C; R_f=0.26 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.62 (d, J=7.2 Hz, 3H, CH_3CH), 1.79–1.91 (m, 2H, CH$_2$CH_2CH$_2$), 2.58 (br s, 1H, OH), 3.59 (t, J=5.0 Hz, 2H, CH_2OH), 3.84 (dd, J_1=11.2 Hz, J_2=6.8 Hz, 2H, NCH$_2$), 3.94 (q, J=7.2 Hz, 1H, CHS), 4.21 (q, J=7.2 Hz, 2H, CH$_2$O), 5.57 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (*C*H$_3$CH$_2$), 19.2 (*C*H$_3$CH), 29.0 (CH$_2$*C*H$_2$CH$_2$), 40.1 (CHS), 40.5 (NCH$_2$), 58.6 (CH$_2$OH), 60.1 (CH$_2$O), 90.6 (=CH), 156.3 (C=), 167.6 (CO$_{ester}$), 176.9 (CO$_{lactam}$); IR (KBr): ν=3511, 1716, 1671, 1565, 1311, 1192, 1162 cm^{-1}; HRMS: calcd for $C_{11}H_{18}NO_4S$ $[M+H]^+$ 260.0951, found 260.0943.

*5.4.5. (Z)-Ethyl 2-(3-(4-hydroxybutyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**11e**).* Compound **11e** was prepared from **8f** (93.1 mg; 0.28 mmol) in 3 mL DMF/H_2O 1:1 (v/v) to which 200 μL concd HCl was added, according to general procedure (reaction time 24 h, TLC: petrolether/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 40:60) gave pure **11e**, as a colorless oil (38.7 mg; 51%); R_f=0.21 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.60 (d, J=7.2 Hz, 3H, CH_3CH), 1.51–1.77 (m, 4H, CH$_2$CH_2CH_2CH$_2$), 1.80 (s, 1H, OH), 3.69 (t, J=6.0 Hz, 2H, CH_2OH), 3.72 (t, J=6.4 Hz, 2H, NCH$_2$), 3.89 (q, J=7.2 Hz, 1H, CH$_3$C*H*), 4.21 (q, J=7.2 Hz, 2H, CH$_2$O), 5.51 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.1 (*C*H$_3$CH), 23.1 (*C*H$_2$CH$_2$Br), 29.4 (NCH$_2$*C*H$_2$), 40.4 (CHS), 43.3 (NCH$_2$), 60.0 (CH$_2$O), 62.0 (CH$_2$OH), 90.1 (=CH), 156.1 (C=), 167.7 (CO$_{ester}$), 175.8 (CO$_{lactam}$); IR (KBr): ν=3399, 1716, 1689, 1570, 1310, 1150 cm^{-1}; HRMS: calcd for $C_{12}H_{20}NO_4S$ $[M+H]^+$ 274.1108, found 274.1095.

5.5. General procedure for synthesis of *S*-acyl derivatives 12

A solution of bromide **8** and KSAc in dry acetone was stirred at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2 (10–15 mL), washed with water (3×10 mL), saturated aq NaCl (1×10 mL), and dried over Na_2SO_4. Evaporation of the solvent gave pure products.

*5.5.1. (Z)-Ethyl 2-(3-(2-(acetylthio)ethyl)-4-oxothiazolidin-2-ylidene)acetate (**12a**).* Compound **12a** was obtained from **8a** (66.6 mg; 0.23 mmol) and KSAc (29.4 mg; 0.33 mmol; 1.1 equiv) in acetone (2.0 mL) according to general procedure (reaction time 15 min, TLC: petrolether/ethyl acetate 4:1) as a white solid (64.5 mg; 98%), mp 120–121 °C; R_f=0.14 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J=7.0 Hz, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$COS), 3.00–3.08 (m, 2H, CH$_2$SCO), 3.79–3.86 (m, 2H, NCH$_2$), 3.72 (s, 2H, CH$_2$S), 4.23 (q, J=7.0 Hz, 2H, CH$_2$O), 5.90 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH$_3$), 25.3 (*C*H$_2$SCO), 30.5 (*C*H$_3$COS), 31.6 (CH$_2$S), 42.2 (NCH$_2$), 60.1 (CH$_2$O), 91.2 (=CH), 157.2 (C=), 167.8 (CO$_{ester}$), 172.3 (CO$_{lactam}$), 195.5 (COS); IR (KBr): ν=1719,

1686, 1561, 1189, 1141 cm^{-1}; HRMS: calcd for $C_{11}H_{16}NO_4S_2$ $[M+H]^+$ 290.0515, found 290.0505.

*5.5.2. (Z)-Ethyl 2-(3-(2-(acetylthio)ethyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**12b**).* Compound **12b** was obtained from **8b** (92.8 mg; 0.31 mmol) and KSAc (43.0 mg; 0.38 mmol; 1.2 equiv) in acetone (2.0 mL) according to general procedure (reaction time 15 min, TLC: petrolether/ethyl acetate 4:1) as a white solid (93.0 mg; 100%), mp 85–86 °C; R_f=0.26 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.61 (d, J=7.3 Hz, 3H, CH_3CH), 2.38 (s, 3H, CH_3COS), 3.01–3.08 (m, 2H, CH_2SCO), 3.79–3.86 (m, 2H, NCH_2), 3.90 (q, J=7.3 Hz, 1H, CHS), 4.23 (q, J=7.2 Hz, 2H, CH_2O), 5.86 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$CH), 25.4 (*C*H$_2$SCO), 30.5 (*C*H$_3$COS), 40.3 (CHS), 42.2 (NCH_2), 60.1 (CH_2O), 90.7 (=CH), 155.9 (C=), 167.8 (CO_{ester}), 175.5 (CO_{lactam}), 195.5 (COS); IR (KBr): ν=1724, 1686, 1573, 1310, 1149 cm^{-1}; Anal. Calcd for $C_{12}H_{17}NO_4S_2$: C, 47.50; H, 5.65; N, 4.62; S, 21.14, found: C, 47.17; H, 5.69; N, 4.63; S, 20.83.

*5.5.3. (Z)-Ethyl 2-(3-(3-(acetylthio)propyl)-4-oxothiazolidin-2-ylidene)acetate (**12c**).* Compound **12c** was obtained from **8c** (61.7 mg; 0.2 mmol) and KSAc (28.7 mg; 0.25 mmol; 1.25 equiv) in acetone (2.0 mL) according to general procedure (reaction time 15 min, TLC: toluene/ethyl acetate 4:1) as a white solid (57.9 mg; 95%), mp 105–106 °C; R_f=0.36 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 3H, CH_3), 1.83–1.98 (m, 2H, $CH_2CH_2CH_2$), 2.36 (s, 3H, CH_3COS), 2.90 (t, J=7.0 Hz, 3H, CH_2SCO), 3.71 (s, 2H, CH_2S), 3.73 (t, J=7.4 Hz, 2H, NCH_2), 4.21 (q, J=7.2 Hz, 2H, CH_2O), 5.50 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 26.1 (*C*H$_2$SCO), 26.4 ($CH_2CH_2CH_2$), 30.5 (*C*H$_3$COS), 31.6 (*C*H$_2$S), 42.2 (NCH_2), 60.0 (CH_2O), 90.5 (=CH), 157.7 (C=), 167.6 (CO_{ester}), 172.4 (CO_{lactam}), 195.2 (COS); IR (KBr): ν=1721, 1682, 1566, 1358, 1142 cm^{-1}; HRMS: calcd for $C_{12}H_{18}NO_4S_2$ $[M+H]^+$ 304.0672, found 304.0663.

*5.5.4. (Z)-Ethyl 2-(3-(3-(acetylthio)propyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**12d**).* Compound **12d** was obtained from **8d** (100 mg; 0.31 mmol) and KSAc (43.4 mg; 0.38 mmol; 1.2 equiv) in acetone (2.0 mL) according to general procedure (reaction time 10 min, TLC: petrolether/ethyl acetate 4:1) as a white solid (92.0 mg; 94%), mp 63–64 °C; R_f=0.41 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, CH_3CH$_2$), 1.58 (d, J=7.2 Hz, 3H, CH_3CH), 1.80–1.95 (m, 2H, $CH_2CH_2CH_2$), 2.33 (s, 3H, CH_3COS), 2.86 (t, J=7.0 Hz, 2H, CH_2SCO), 3.70 (t, J=7.2 Hz, 2H, NCH_2), 3.86 (q, J=7.2 Hz, 1H, CHS), 4.18 (q, J=7.0 Hz, 2H, CH_2O), 5.45 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.0 (*C*H$_3$CH), 26.2 (*C*H$_2$SCO), 26.5 ($CH_2CH_2CH_2$), 30.6 (*C*H$_3$COS), 40.3 (CHS), 42.2 (NCH_2), 60.0 (CH_2O), 90.1 (=CH), 156.4 (C=), 167.6 (CO_{ester}), 175.7 (CO_{lactam}), 195.3 (COS); IR (KBr): ν=1708, 1680, 1563, 1359, 1178, 1144 cm^{-1}; Anal. Calcd for $C_{13}H_{19}NO_4S_2$: C, 49.19; H, 6.03; N, 4.41; S, 20.20, found: C, 48.89; H, 5.86; N, 4.39; S, 20.33.

*5.5.5. (Z)-Ethyl 2-(3-(4-(acetylthio)butyl)-4-oxothiazolidin-2-ylidene)acetate (**12e**).* Compound **12e** was obtained from **8e** (68.1 mg; 0.21 mmol) and KSAc (25.6 mg; 0.22 mmol; 1.05 equiv) in acetone (2.0 mL) according to general procedure (reaction time 15 min, TLC: petrolether/ethyl acetate 4:1) as a colorless oil (62.0 mg; 93%); R_f=0.47 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.0 Hz, 3H, CH_3), 1.57–1.74 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.34 (s, 3H, CH_3COS), 2.90 (t, J=6.8 Hz, 2H, CH_2SCO), 3.67 (t, J=7.2 Hz, 2H, NCH_2), 3.71 (s, 2H, CH_2S), 4.22 (q, J=7.0 Hz, 2H, CH_2O), 5.48 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 25.3 (CH_2CH_2S), 26.7 (*C*H$_2$SCO), 28.2 (NCH_2CH_2), 30.6 (*C*H$_3$COS), 31.7 (CH_2S), 42.9 (NCH_2), 60.0 (CH_2O), 90.4 (=CH), 157.9 (C=), 167.7 (CO_{ester}), 172.4 (CO_{lactam}), 195.7 (COS); IR (KBr): ν=1718, 1687, 1570, 1358, 1177, 1140 cm^{-1}; HRMS: calcd for $C_{13}H_{20}NO_4S_2$ $[M+H]^+$ 318.0828, found 318.0822.

*5.5.6. (Z)-Ethyl 2-(3-(4-(acetylthio)butyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**12f**).* Compound **12f** was obtained from **8f** (101 mg; 0.3 mmol) and KSAc (42.4 mg; 0.37 mmol; 1.2 equiv) in acetone (3.0 mL) according to general procedure (reaction time 10 min, TLC: petrolether/ethyl acetate 4:1) as a colorless oil (98.1 mg; 98%); R_f=0.56 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.60 (d, J=7.2 Hz, 3H, CH_3CH), 1.59–1.73 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.33 (s, 3H, CH_3COS), 2.90 (t, J=6.8 Hz, 2H, CH_2SCO), 3.67 (t, J=7.0 Hz, 2H, NCH_2), 3.89 (q, J=7.2 Hz, 1H, CHS), 4.21 (q, J=7.2 Hz, 2H, CH_2O), 5.46 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (*C*H$_3$CH$_2$), 19.1 (*C*H$_3$CH), 25.4 (CH_2CH_2S), 26.7 (*C*H$_2$SCO), 28.2 (NCH_2CH_2), 30.6 (*C*H$_3$COS), 40.4 (CHS), 42.2 (NCH_2), 60.0 (CH_2O), 90.0 (=CH), 156.5 (C=), 167.6 (CO_{ester}), 175.6 (CO_{lactam}), 195.6 (COS); IR (KBr): ν=1715, 1687, 1570, 1176, 1141 cm^{-1}; HRMS: calcd for $C_{14}H_{22}NO_4S_2$ $[M+H]^+$ 332.0985, found 332.0981.

5.6. General procedure for synthesis of secondary amines 13

A solution of bromide **8**, benzylamine and Et_3N in DMF was stirred at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2 (15 mL), washed with water (3×10 mL), saturated aq NaCl (1×10 mL), and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography.

*5.6.1. (Z)-Ethyl 2-(3-(3-(benzylamino)propyl)-4-oxothiazolidin-2-ylidene)acetate (**13a**).* Compound **13a** was obtained from **8c** (77.3 mg; 0.25 mmol), benzylamine (137 mg; 1.28 mmol; 5.1 equiv), and Et_3N (36.0 mg; 0.36 mmol; 1.4 equiv) in DMF (3.0 mL) according to general procedure (reaction time 18 h, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 20:80) gave pure **13a**, as a colorless oil (64.6 mg; 77%); R_f=0.37 (ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H, CH_3), 1.72–1.86 (m, 2H, $CH_2CH_2CH_2$), 2.64 (t, J=6.8 Hz, 2H, *C*H$_2$NHBn), 3.66 (s, 2H, CH_2Ph), 3.76 (s, 2H, CH_2S), 3.77 (t, J=7.0 Hz, 2H, NCH_2), 4.20 (q, J=7.2 Hz, 2H, CH_2O), 5.62 (s, 1H, =CH), 7.23–7.34 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 26.7 ($CH_2CH_2CH_2$), 31.6 (CH_2S), 41.4 (NCH_2), 45.9 (CH_2NHBn), 53.8 (CH_2Ph), 59.9 (CH_2O), 90.6 (=CH), 126.9 (*p*-Ph), 128.1 (*o*-Ph), 128.3 (*m*-Ph), 140.0 (C_1Ph), 158.0 (C=), 167.7 (CO_{ester}), 172.5 (CO_{lactam}); IR (KBr): ν=3313, 3027, 1716, 1684, 1568, 1308, 1156, 739, 700 cm^{-1}; HRMS: calcd for $C_{17}H_{23}N_2O_3S$ $[M+H]^+$ 355.1424, found 355.1426.

*5.6.2. (Z)-Ethyl 2-(3-(3-(benzylamino)propyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetate (**13b**).* Compound **13b** was obtained from **8d** (48.8 mg; 0.15 mmol), benzylamine (78.4 mg; 0.73 mmol; 4.9 equiv), and Et_3N (21.6 mg; 0.21 mmol; 1.4 equiv) in DMF (3.0 mL) according to general procedure (reaction time 18 h, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 40:60 to 20:80) gave pure **13b**, as a colorless oil (48.6 mg; 92%); R_f=0.46 (ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, CH_3CH$_2$), 1.58 (d, J=7.3 Hz, 3H, CH_3CH), 1.73–1.87 (m, 2H, $CH_2CH_2CH_2$), 2.62 (t, J=6.6 Hz, 2H, *C*H$_2$NHBn), 3.76 (s, 2H, CH_2Ph), 3.77 (t, J=7.0 Hz, 2H, NCH_2), 3.86 (q, J=7.3 Hz, 1H, CHS), 4.20 (q, J=7.2 Hz, 2H, CH_2O), 5.60 (s, 1H, =CH), 7.22–7.34 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3CH_2), 19.1 (*C*H$_3$CH), 26.8 ($CH_2CH_2CH_2$), 40.4 (CHS), 41.4 (NCH_2), 45.8 (CH_2NHBn), 53.9 (CH_2Ph), 60.0 (CH_2O), 90.2 (=CH), 127.0 (*p*-Ph), 128.2 (*o*-Ph), 128.4 (*m*-Ph), 140.0 (C_1Ph), 156.6 (C=), 167.8 (CO_{ester}), 175.9 (CO_{lactam}); IR (KBr): ν=3314, 3063, 3028, 1642, 1524, 1456,

1380, 1166, 1140, 741, 700 cm^{-1}; HRMS: calcd for $C_{18}H_{25}N_2O_3S$ $[M+H]^+$ 349.1580, found 349.1581.

5.7. General procedure for synthesis of azides 14

A solution of bromide **8** and NaN_3 in DMF was stirred at rt until the disappearance of the starting material (TLC). The reaction mixture was then diluted with $CHCl_3$ (10–15 mL), washed with water (3×10 mL), saturated aq NaCl (1×10 mL), and dried over Na_2SO_4. Evaporation of the solvent gave pure products.

*5.7.1. (Z)-Ethyl 2-(3-(2-azidoethyl)-4-oxothiazolidin-2-ylidene)acetate (**14a**).* Compound **14a** was obtained from **8a** (128 mg; 0.43 mmol) and NaN_3 (56.0 mg; 0.86 mmol; 2 equiv) in DMF (3.0 mL) according to general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 7:3) as a white solid (101 mg; 91%), mp 90–91 °C; R_f=0.61 (toluene/ethyl acetate 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, 3H, J=7.2 Hz, CH_3), 3.55 (t, J=6.2 Hz, 2H, CH_2N_3), 3.75 (s, 2H, CH_2S), 3.88 (t, J=6.2 Hz, 2H, NCH_2), 4.22 (q, J=7.2 Hz, 2H, CH_2O), 5.55 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 31.5 (CH_2S), 42.3 (NCH_2), 47.3 (CH_2N_3), 60.2 (CH_2O), 90.7 (=CH), 157.5 (C=), 167.5 (CO_{ester}), 172.5 (CO_{lactam}); IR (KBr): ν=2106, 1720, 1682, 1571, 1157 cm^{-1}; HRMS: calcd for $C_9H_{13}N_4O_3S$ $[M+H]^+$ 257.0703, found 257.0705.

*5.7.2. (Z)-Ethyl 2-(3-(3-azidopropyl)-4-oxothiazolidin-2-ylidene)acetate (**14b**).* Compound **14b** was obtained from **8c** (41.7 mg; 0.14 mmol) and NaN_3 (26.4 mg; 0.41 mmol; 2.9 equiv) in DMF (2.0 mL) according to general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 7:3) as a colorless oil (34.5 mg; 94%); R_f=0.68 (toluene/ethyl acetate 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.0 Hz, 3H, CH_3), 1.81–1.95 (m, 2H, $CH_2CH_2CH_2$), 3.40 (t, J=6.0 Hz, 2H, CH_2N_3), 3.73 (s, 2H, CH_2S), 3.77 (t, J=6.8 Hz, 2H, NCH_2), 4.22 (q, J=7.0 Hz, 2H, CH_2O), 5.53 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 25.9 ($CH_2CH_2CH_2$), 31.6 (CH_2S), 40.8 (NCH_2), 48.7 (CH_2N_3), 60.1 (CH_2O), 90.5 (=CH), 157.6 (C=), 167.6 (CO_{ester}), 172.4 (CO_{lactam}); IR (KBr): ν=2098, 1717, 1683, 1570, 1153 cm^{-1}; HRMS: calcd for $C_{10}H_{15}N_4O_3S$ $[M+H]^+$ 271. 0859, found 271.0854.

*5.7.3. (Z)-Ethyl 2-(3-(4-azidobutyl)-4-oxothiazolidin-2-ylidene)acetate (**14c**).* Compound **14c** was obtained from **8e** (131 mg; 0.4 mmol) and NaN_3 (53.0 mg; 0.81 mmol; 2 equiv) in DMF (3.0 mL) according to general procedure (reaction time 1.5 h, TLC: toluene/ethyl acetate 7:3) as a colorless oil (103 mg; 89%); R_f=0.61 (toluene/ethyl acetate 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.54–1.80 (m, 4H, $CH_2CH_2CH_2CH_2$), 3.35 (t, J=6.2 Hz, 2H, CH_2N_3), 3.72 (s, 2H, CH_2S), 3.70 (t, J=7.0 Hz, 2H, NCH_2), 4.22 (q, J=7.2 Hz, 2H, CH_2O), 5.50 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 23.7 (NCH_2CH_2), 26.0 ($CH_2CH_2N_3$), 31.6 (CH_2S), 42.8 (NCH_2), 50.7 (CH_2N_3), 60.1 (CH_2O), 90.5 (=CH), 157.7 (C=), 167.6 (CO_{ester}), 172.4 (CO_{lactam}); IR (KBr): ν=2097, 1718, 1684, 1568, 1151 cm^{-1}; HRMS: calcd for $C_{11}H_{17}N_4O_3S$ $[M+H]^+$ 285.1016, found 285.1017.

5.8. General procedure for synthesis of amines 15

A solution of azide **14** and Ph_3P in MeOH was refluxed until the disappearance of the starting material (TLC). The reaction mixture was then diluted with CH_2Cl_2 (15 mL), a few drops of concd HCl were added and it was extracted with water (3×10 mL). The water layer was neutralized with Na_2CO_3, extracted with CH_2Cl_2 (3×10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave pure products.

*5.8.1. (Z)-Ethyl 2-(3-(2-aminoethyl)-4-oxothiazolidin-2-ylidene)acetate (**15a**).* Compound **15a** was obtained from **14a** (59.5 mg; 0.23 mmol) and Ph_3P (90.5 mg; 0.34 mmol; 1.5 equiv) in MeOH (5.0 mL) according to general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 7:3) as a colorless oil (32.7 mg; 62%); R_f=0.38 (ethyl acetate/MeOH 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 3H, CH_3), 2.11 (br s, 2H, NH_2), 2.96 (t, J=6.8 Hz, 2H, CH_2NH_2), 3.74 (s, 2H, CH_2S), 3.76 (t, J=6.8 Hz, 2H, NCH_2), 4.21 (q, J=7.2 Hz, 2H, CH_2O), 5.55 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (CH_3), 31.7 (CH_2S), 38.6 (CH_2NH_2), 46.0 (NCH_2), 60.0 (CH_2O), 90.6 (=CH), 158.0 (C=), 167.7 (CO_{ester}), 172.9 (CO_{lactam}); IR (KBr): ν=3367, 1717, 1683, 1568, 1142 cm^{-1}; HRMS: calcd for $C_9H_{15}N_2O_3S$ $[M+H]^+$ 231.0798, found 231.0818.

*5.8.2. (Z)-Ethyl 2-(3-(3-aminopropyl)-4-oxothiazolidin-2-ylidene) acetate (**15b**).* Compound **15b** was obtained from **14b** (33.6 mg; 0.12 mmol) and Ph_3P (49.0 mg; 0.19 mmol; 1.5 equiv) in MeOH (5.0 mL) according to general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 7:3) as a pale pink solid (20.6 mg; 70%), mp 158–159 °C; R_f=0.32 (ethyl acetate/MeOH 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, CH_3), 1.86–1.97 (m, 2H, $CH_2CH_2CH_2$), 3.47–3.56 (m, 4H, $CH_2CH_2CH_2$), 3.75 (br s, 2H, NH_2), 3.81 (s, 2H, CH_2S), 4.19 (q, J=7.2 Hz, 2H, CH_2O), 5.21 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 19.3 ($CH_2CH_2CH_2$), 32.5 (CH_2S), 43.3 (CH_2NH_2), 44.6 (NCH_2), 59.7 (CH_2O), 85.4 (=CH), 154.5 (C=), 160.6 (CO_{ester}), 168.3 (CO_{lactam}); IR (KBr): ν=3425, 3276, 1716, 1674, 1582, 1165 cm^{-1}; HRMS: calcd for $C_{10}H_{17}N_2O_3S$ $[M+H]^+$ 245.0954, found 245.0959.

*5.8.3. (Z)-Ethyl 2-(3-(4-aminobutyl)-4-oxothiazolidin-2-ylidene)acetate (**15c**).* Compound **15c** was obtained from **14c** (77.1 mg; 0.27 mmol) and Ph_3P (107 mg; 0.41 mmol; 1.5 equiv) in MeOH (5.0 mL) according to general procedure (reaction time 1 h, TLC: toluene/ethyl acetate 7:3) as a colorless oil (44.2 mg; 63%); R_f=0.40 (ethyl acetate/MeOH 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J=7.2 Hz, 3H, CH_3), 1.44–1.55 (m, 2H, $CH_2CH_2NH_2$) 1.56–1.74 (m, 2H, NCH_2CH_2), 1.89 (br s, 2H, NH_2), 2.74 (t, J=7.0 Hz, 2H, CH_2NH_2), 3.69 (t, J=7.2 Hz, 2H, NCH_2), 3.71 (s, 2H, CH_2S), 4.21 (q, J=7.2 Hz, 2H, CH_2O), 5.51 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (CH_3), 23.7 (NCH_2CH_2), 30.3 ($CH_2CH_2NH_2$), 31.6 (CH_2S), 41.4 (CH_2NH_2), 43.2 (NCH_2), 59.9 (CH_2O), 90.4 (=CH), 157.9 (C=), 167.6 (CO_{ester}), 172.4 (CO_{lactam}); IR (KBr): ν=3400, 1716, 1683, 1568, 1158 cm^{-1}; HRMS: calcd for $C_{11}H_{19}N_2O_3S$ $[M+H]^+$ 259.1111, found 259.1110.

5.9. Deprotection of *S*-acyl derivatives 12 prior to the generation of an iminium ion

S-Acyl derivatives **12** were deprotected by 0.2 M NaOEt/EtOH (1 equiv of NaOEt) at rt for 15 min (TLC: toluene/ethyl acetate 4:1) and used, without isolation, for the formation of an iminium ion.

5.10. General procedure for generation of an iminium ion and work-up of reaction mixture

To a mixture of a substrate and $NaBH_4$ in abs EtOH at 0 °C three drops of 0.4 M aq HCl were added every 10–15 min until the completion of the reduction (TLC). The reaction mixture was then acidified by dropwise addition of 1 M ethanolic HCl (until H_2 evolution had ceased) and stirring was continued for 30 min at 0 °C. After dilution with water stirring was continued at rt for additional 30 min. The reaction mixture was then neutralized with $NaHCO_3$, extracted with CH_2Cl_2 (3×10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave crude products, which were purified by column chromatography.

*5.10.1. (Z)-Ethyl (tetrahydrothiazolo[4,3-b][1,3]oxazin-6(2H)-ylidene)acetate (**18a**).* Compound **18a** was obtained from **11c** (40.0 mg; 0.16 mmol) and $NaBH_4$ (82.3 mg; 2.2 mmol; 13.6 equiv) in

EtOH (6.0 mL) according to general procedure (reduction time 45 min, TLC: toluene/ethyl acetate 7:3). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 70:30) gave pure **18a** (13.4 mg; 36%) as a colorless oil; R_f=0.64 (toluene/ethyl acetate 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, CH_3), 1.44–1.47 (m, 1H, CH_2CHHCH_2), 1.95–2.05 (m, 1H, CH_2CHHCH_2), 2.98 (dd, J_1=12.0 Hz, J_2=3.5 Hz, 1H, C*H*HS), 3.24 (dd, J_1=12.0 Hz, J_2=5.5 Hz, 1H, CH*H*S), 3.30 (dt, J_1=13.0 Hz, J_2=3.0 Hz, 1H, OC*H*HCH$_2$CH$_2$N), 3.74–3.79 (m, 2H, OCH*H*CH$_2$C*H*HN), 4.12–4.15 (m, 1H, CH*H*N), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 5.03 (s, 1H, =CH), 5.04 (dd, J_1=5.5 Hz, J_2=3.5 Hz, 1H, OCHN); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (CH_3), 23.2 ($CH_2CH_2CH_2$), 32.8 (CH_2S), 44.6 (NCH_2), 59.2 (CH_2O), 67.5 (CH_2OCH), 82.4 (=CH), 92.5 (OCHN), 162.8 (C=), 169.0 (CO_{ester}); IR (KBr): ν=1671, 1551, 1151, 1049 cm^{-1}; HRMS: calcd for $C_{10}H_{16}NO_3S$ $[M+H]^+$ 230.0845, found 230.0840.

*5.10.2. (Z)-Ethyl (8-methyltetrahydrothiazolo[4,3-b][1,3]oxazin-6(2H)-ylidene)acetate (**18b**).* Compound **18b** was obtained from **11d** (44.0 mg; 0.17 mmol) and $NaBH_4$ (88.0 mg; 2.33 mmol; 13.7 equiv) in EtOH (4.0 mL) according to general procedure (reduction time 30 min, TLC: toluene/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 50:50) gave pure **18b** (24.7 mg; 63%; trans/cis 3:1) as a colorless oil; R_f=0.68 (petrolether/ethyl acetate 3:2); ^{1}H NMR (500 MHz, $CDCl_3$): cis isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.35 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.46–1.50 (m, 1H, CH_2CHHCH_2), 1.95–2.04 (m, 1H, CH_2CHHCH_2), 3.24 (dt, 1H, J_1=13.5 Hz, J_2=3.5 Hz, OC*H*HCH$_2$CH$_2$N), 3.59 (dq, J_1=7.0 Hz, J_2=5.5 Hz, 1H, CHS), 3.68–3.76 (m, 2H, OCH*H*CH$_2$C*H*HN), 4.12–4.19 (m, 1H, CH*H*N), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 4.79 (d, J=5.5 Hz, 1H, OCHN), 5.00 (s, 1H, =CH), trans isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.38 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.46–1.50 (m, 1H, CH_2CHHCH_2), 1.95–2.04 (m, 1H, CH_2CHHCH_2), 3.22 (dt, J_1=13.0 Hz, J_2=3.5 Hz, 1H, OC*H*HCH$_2$CH$_2$N), 3.36 (dq, J_1=7.0 Hz, J_2=4.0 Hz, 1H, CHS), 3.68–3.76 (m, 2H, OCH*H*CH$_2$C*H*HN), 4.12–4.19 (m, 1H, CH*H*N), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 4.55 (d, J=4.0 Hz, 1H, OCHN), 4.98 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): cis isomer δ 13.6 (CH_3CH), 14.6 (CH_3CH_2), 23.0 ($CH_2CH_2CH_2$), 40.7 (CHS), 44.8 (NCH_2), 59.2 (CH_2O), 67.4 (CH_2OCH), 82.4 (=CH), 93.3 (OCHN), 162.4 (C=), 169.0 (CO), trans isomer δ 14.5 (CH_3CH_2), 18.5 (CH_3CH), 23.1 ($CH_2CH_2CH_2$), 42.8 (CHS), 44.6 (NCH_2), 59.2 (CH_2O), 67.4 (CH_2OCH), 82.1 (=CH), 98.1 (OCHN), 162.4 (C=), 169.0 (CO); IR (KBr, cis and trans isomer): ν=1674, 1553, 1455, 1371, 1151, 1050 cm^{-1}; HRMS: calcd for $C_{11}H_{18}NO_3S$ $[M+H]^+$ 244.1002, found 244.0997.

*5.10.3. (Z)-Ethyl (tetrahydrothiazolo[4,3-b]thiazol-5-ylidene)acetate (**18c**).* Compound **18c** was obtained from **12a** (45.9 mg; 0.16 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (92.0 mg; 2.4 mmol; 15.2 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 1 h, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 80:20) gave pure **18c** (10.2 mg; 28%) as a colorless oil; R_f=0.61 (toluene/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, CH_3), 3.08–3.36 (m, 3H, NC*H*HC*H*$_2$S), 3.23 (dd, J_1=11.6 Hz, J_2=4.0 Hz, 1H, C*H*HS), 3.51 (dd, J_1=11.6 Hz, J_2=6.2 Hz, 1H, CH*H*S), 3.99–4.09 (m, 1H, NCH*H*), 4.17 (q, J=7.0 Hz, 2H, CH_2O), 5.16 (s, 1H, =CH), 5.27 (dd, J_1=6.2 Hz, J_2=4.0 Hz, 1H, SCHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5 (CH_3), 31.9 (CH_2CH_2S), 33.3 (CH_2S), 51.2 (NCH_2), 59.5 (CH_2O), 71.3 (SCHN), 85.1 (=CH), 164.4 (C=), 168.7 (CO); IR (KBr): ν=1674, 1558, 1462, 1163, 1141, 1046 cm^{-1}; HRMS: calcd for $C_9H_{14}NO_2S_2$ $[M+H]^+$ 232.0460, found 232.0464.

*5.10.4. (Z)-Ethyl (7-methyltetrahydrothiazolo[4,3-b]thiazol-5-ylidene)acetate (**18d**).* Compound **18d** was obtained from **12b** (77.3 mg; 0.25 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (130 mg; 3.4 mmol; 13.8 equiv) in EtOH (3.0 mL) according to general procedure (reduction time 1 h, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 80:20) gave pure **18d** (22.0 mg; 35%; trans/cis 1:5.7) as a colorless oil; R_f=0.58 (toluene/ethyl acetate 7:3); ^{1}H NMR (500 MHz, $CDCl_3$): cis isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.46 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 3.05–3.07 (m, 1H, C*H*HS), 3.24–3.34 (m, 2H, CH*H*S and NC*H*H), 3.89 (dq, J_1=7.0 Hz, J_2=5.5 Hz, 1H, CHS), 4.00–4.02 (m, 1H, NCH*H*), 4.15 (q, J=7.0 Hz, 2H, CH_2O), 5.10 (s, 1H, =CH), 5.28 (d, 1H, J=5.5 Hz, SCHN), trans isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.49 (d, J=6.5 Hz, 3H, C*H*$_3$CH), 3.09–3.12 (m, 1H, C*H*HS), 3.15–3.20 (m, 1H, CH*H*S), 3.26–3.32 (m, 1H, NC*H*H), 3.66 (dq, J_1=6.5 Hz, J_2=5.5 Hz, 1H, CHS), 3.97 (ddd, 1H, J_1=11.5 Hz, J_2=6.0 Hz, J_3=3.0 Hz NCH*H*), 4.15 (q, J=7.0 Hz, 2H, CH_2O), 4.89 (d, J=5.5 Hz, 1H, SCHN), 5.07 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): cis isomer δ 14.5 (*C*H$_3$CH$_2$), 17.0 (*C*H$_3$CH), 31.0 (CH_2S), 41.3 (CHS), 51.0 (NCH_2), 59.4 (CH_2O), 76.8 (SCHN), 84.8 (=CH), 163.8 (C=), 168.6 (CO), trans isomer δ 14.5 (*C*H$_3$CH$_2$), 20.1 (*C*H$_3$CH), 32.0 (CH_2S), 45.2 (CHS), 50.7 (NCH_2), 59.4 (CH_2O), 77.8 (SCHN), 84.4 (=CH), 163.8 (C=), 168.6 (CO); IR (KBr, cis and trans isomer): ν=1674, 1556, 1454, 1329, 1144, 1090 cm^{-1}; HRMS: calcd for $C_{10}H_{16}NO_2S_2$ $[M+H]^+$ 246.0617, found 246.0627.

*5.10.5. (Z)-Ethyl (tetrahydrothiazolo[4,3-b][1,3]thiazin-6(2H)-ylidene) acetate (**18e**).* Compound **18e** was obtained from **12c** (50.5 mg; 0.17 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (101 mg; 2.7 mmol; 15.9 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 45 min, TLC: toluene/ethyl acetate 7:3). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 80:20) gave pure **18e** (27.4 mg; 66%) as a white solid, mp 108–109 °C; R_f=0.38 (petrolether/ethyl acetate 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, CH_3), 1.65–2.05 (m, 2H, $CH_2CH_2CH_2$), 2.76–2.84 (m, 1H, SC*H*HCH$_2$CH$_2$N), 2.83 (dd, J_1=11.8 Hz, J_2=2.0 Hz, 1H, C*H*HS), 3.04–3.19 (m, 1H, SCH*H*CH$_2$CH$_2$N), 3.19–3.34 (m, 1H, NC*H*H), 3.39 (dd, J_1=11.8 Hz, J_2=7.0 Hz, 1H, CH*H*S), 3.80–3.87 (m, 1H, NCH*H*), 4.19 (q, J=7.0 Hz, 2H, CH_2O), 5.05 (s, 1H, =CH), 5.09 (dd, J_1=7.0 Hz, J_2=2.0 Hz, 1H, SCHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (CH_3), 22.0 ($CH_2CH_2CH_2$), 29.1 (SCH$_2$CH$_2$CH$_2$N), 33.0 (CH_2S), 46.8 (NCH_2), 59.3 (CH_2O), 67.5 (SCHN), 83.5 (=CH), 162.3 (C=), 168.9 (CO); IR (KBr): ν=1663, 1531, 1459, 1144, 1102 cm^{-1}; HRMS: calcd for $C_{10}H_{16}NO_2S_2$ $[M+H]^+$ 246.0617, found 246,0618.

*5.10.6. (Z)-Ethyl (8-methyltetrahydrothiazolo[4,3-b][1,3]thiazin-6(2H)-ylidene)acetate (**18f**).* Compound **18f** was obtained from **12d** (48.0 mg; 0.15 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (100 mg; 2.64 mmol; 15.5 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 1.5 h, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 70:30) gave pure **18f** (23.4 mg; 60%; trans/cis 1.3:1) as a colorless oil; R_f=0.34; 0.42 (petrolether/ethyl acetate 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): cis isomer δ 1.27 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.38 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.64–1.68 (m, 1H, CH_2CHHCH_2), 1.86–1.96 (m, 1H, CH_2CHHCH_2), 2.84–2.87 (m, 1H, C*H*HS), 2.99–3.05 (m, 1H, CH*H*S), 3.28–3.31 (m, 1H, NC*H*H), 3.79–3.90 (m, 2H, NCH*H* and CHS), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 5.01 (s, 1H, =CH), 5.09 (d, J=6.0 Hz, 1H, SCHN), trans isomer δ 1.27 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.43 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.71–1.75 (m, 1H, CH_2CHHCH_2), 1.86–1.96 (m, 1H, CH_2CHHCH_2), 2.78–2.81 (m, 1H, C*H*HS), 3.04–3.10 (m, 1H, CH*H*S), 3.18–3.26 (m, 2H, NC*H*H and CHS), 3.79–3.86 (m, 1H, NCH*H*), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 4.75 (d, J=2.0 Hz, 1H, SCHN), 5.00 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): cis isomer δ 13.5 (*C*H$_3$CH), 14.6 (*C*H$_3$CH$_2$), 22.0 ($CH_2CH_2CH_2$), 28.4 (CH_2S), 41.4 (CHS), 47.0 (NCH_2), 59.2 (CH_2O), 73.1 (SCHN), 83.3 (=CH), 162.7 (C=), 168.7 (CO), trans isomer δ 14.5 (*C*H$_3$CH$_2$), 21.3 (*C*H$_3$CH), 22.4 ($CH_2CH_2CH_2$), 29.0 (CH_2S), 43.2 (CHS), 46.8 (NCH_2), 59.2 (CH_2O), 73.9 (SCHN), 83.0 (=CH), 162.2 (C=), 168.8 (CO); IR (KBr, cis and trans

isomer): ν=1670, 1554, 1445, 1364, 1154, 1114 cm^{-1}; HRMS: calcd for $C_{11}H_{18}NO_2S_2$ $[M+H]^+$ 260.0774, found 260.0771.

*5.10.7. (Z)-Ethyl (hexahydrothiazolo[4,3-b][1,3]thiazepin-7(2H)ylidene) acetate (**18g**).* Compound **18g** was obtained from **12e** (41.0 mg; 0.13 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (82.0 mg; 2.2 mmol; 16.7 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 45 min, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 80:20) gave pure **18g** (19.1 mg; 57%) as a white solid, mp 85–87 °C; R_f=0.64 (petrolether/ethyl acetate 3:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, CH_3), 1.73–2.06 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.69–2.74 (m, 2H, $SCH_2CH_2CH_2CH_2N$), 3.11 (dd, J_1=11.8 Hz, J_2=4.8 Hz, 1H, C*H*HS), 3.48 (dd, J_1=11.8 Hz, J_2=7.0 Hz, 1H, CH*H*S), 3.50–3.53 (m, 2H, NCH_2), 4.16 (q, J=7.0 Hz, 2H, CH_2O), 4.93 (s, 1H, =CH), 5.13 (dd, J_1=7.0 Hz, J_2=4.8 Hz, 1H, SCHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.6 (CH_3), 25.8 ($SCH_2CH_2CH_2CH_2N$), 29.8 ($SCH_2CH_2CH_2CH_2N$), 31.7 ($SCH_2CH_2CH_2CH_2N$), 35.7 (CH_2S), 47.4 (NCH_2), 59.1 (CH_2O), 69.7 (SCHN), 81.1 (=CH), 161.9 (C=), 167.0 (CO); IR (KBr): ν=1666, 1552, 1462, 1181, 1160 cm^{-1}; HRMS: calcd for $C_{11}H_{18}NO_2S_2$ $[M+H]^+$ 260.0774, found 260.0765.

*5.10.8. (Z)-Ethyl (9-methylhexahydrothiazolo[4,3-b][1,3]thiazepin-7(2H)ylidene)acetate (**18h**).* Compound **18h** was obtained from **12f** (74.0 mg; 0.22 mmol), deprotected prior to the addition of a reducing agent, and $NaBH_4$ (144 mg; 3.8 mmol; 17.3 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 45 min, TLC: toluene/ethyl acetate 4:1). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 80:20) gave pure **18h** (42.1 mg; 69%; trans/cis 3.5:1) as a light yellow oil; R_f=0.44; 0.47 (petrolether/ethyl acetate 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): cis isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.44 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.74–1.79 (m, 1H, $SCH_2CH_2CHHCH_2N$), 1.86–2.00 (m, 2H, $SCH_2CHHCHHCH_2N$), 2.01–2.08 (m, 1H, $SCH_2CHHCH_2CH_2N$), 2.62–2.79 (m, 2H, SCH_2), 3.54–3.56 (m, 2H, NCH_2), 3.87 (dq, J_1=7.0 Hz, J_2=6.0 Hz, 1H, CHS), 4.15 (q, J=7.0 Hz, 2H, CH_2O), 4.90 (s, 1H, =CH), 5.02 (d, J=6.0 Hz, 1H, SCHN), trans isomer δ 1.26 (t, J=7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.43 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 1.74–1.79 (m, 1H, $SCH_2CH_2CHHCH_2N$), 1.86–2.00 (m, 2H, $SCH_2CHHCHHCH_2N$), 2.01–2.08 (m, 1H, $SCH_2CHHCH_2CH_2N$), 2.62–2.79 (m, 2H, SCH_2), 3.47 (dq, J_1=7.0 Hz, J_2=6.0 Hz, 1H, CHS), 3.54–3.56 (m, 2H, NCH_2), 4.15 (q, J=7.0 Hz, 2H, CH_2O), 4.60 (d, J=6.0 Hz, 1H, SCHN), 4.91 (s, 1H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$): cis isomer δ 14.6 (*C*H$_3$CH$_2$), 15.5 (*C*H$_3$CH), 25.2 ($SCH_2CH_2CH_2CH_2N$), 31.0 ($SCH_2CH_2CH_2CH_2N$), 32.0 (SCH_2), 42.7 (CHS), 48.2 (NCH_2), 59.0 (CH_2O), 76.0 (SCHN), 81.6 (=CH), 161.5 (C=), 168.9 (CO), trans isomer δ 14.6 (*C*H$_3$CH$_2$), 19.5 (*C*H$_3$CH), 26.1 ($SCH_2CH_2CH_2CH_2N$), 29.1 ($SCH_2CH_2CH_2CH_2N$), 31.3 (SCH_2), 41.7 (CHS), 47.2 (NCH_2), 59.0 (CH_2O), 76.1 (SCHN), 80.3 (=CH), 161.5 (C=), 168.9 (CO); IR (KBr, cis and trans isomer): ν=1665, 1538, 1449, 1342, 1150, 1127, 1044 cm^{-1}; HRMS: calcd for $C_{12}H_{20}NO_2S_2$ $[M+H]^+$ 274.0935, found 274.0931.

*5.10.9. (Z)-Ethyl (hexahydrothiazolo[3,4-a]pyrimidin-6-ylidene)acetate (**18i**).* Compound **18i** was obtained from **15b** (36.6 mg; 0.15 mmol) and $NaBH_4$ (84.0 mg; 2.2 mmol; 14.8 equiv) in EtOH (7.0 mL) according to general procedure (reduction time 1 h, TLC: ethyl acetate/MeOH 1:1). Column chromatography (eluent: gradient ethyl acetate/MeOH 100:0 to 85:15) gave pure **18i** (21.3 mg; 62%) as a light pink oil; R_f=0.61 (ethyl acetate/MeOH 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, J=7.0 Hz, 3H, CH_3), 1.59–1.72 (m, 2H, $CH_2CH_2CH_2$), 2.07 (s, 1H, NH), 2.76 (dd, J_1=11.0 Hz, J_2=7.5 Hz, 1H, C*H*HS), 2.83–2.89 (m, 1H, C*H*HNH), 3.10 (ddd, J_1=J_2=12.5 Hz, J_3=3.5 Hz, 1H, CH*H*NH), 3.21–3.22 (m, 1H NC*H*H), 3.24 (dd, J_1=11.0 Hz, J_2=6.5 Hz, 1H, CH*H*S), 3.74–3.77 (m, 1H NCH*H*), 4.15 (q, J=7.0 Hz, 2H, CH_2O), 4.42 (dd, J_1=7.5 Hz, J_2=6.5 Hz, 1H, NHC*H*N), 4.96 (s, 1H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (CH_3), 20.6 ($CH_2CH_2CH_2$), 32.7 (CH_2S), 44.6 (CH_2NH), 45.7 (NCH_2), 59.2 (CH_2O), 78.0 (NHCHN), 81.5 (=CH), 162.7 (C=), 169.2 (CO); IR (KBr): ν=3288, 1666, 1554, 1456, 1368, 1176, 1147 cm^{-1}; HRMS: calcd for $C_{10}H_{17}N_2O_2S$ $[M+H]^+$ 229.1005, found 229.1001.

*5.10.10. (Z)-Ethyl 2-(3-(2-hydroxyethyl)thiazol-2(3H)-ylidene)acetate (**19a**).* Compound **19a** was obtained from **11a** (23.1 mg; 0.1 mmol) and $NaBH_4$ (45.0 mg; 1.19 mmol; 11.9 equiv) in EtOH (3.0 mL) according to general procedure (reduction time 2 h, TLC: toluene/ethyl acetate 1:1). Column chromatography (eluent: gradient toluene/ethyl acetate 100:0 to 30:70) gave pure **19a** (13.5 mg; 63%) as a white solid, mp 56–58 °C; R_f=0.22 (toluene/ethyl acetate 3:7); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H, CH_3), 3.84–3.95 (m, 4H, CH_2CH_2), 4.16 (q, J=7.2 Hz, 2H, CH_2O), 5.01 (br s, 1H, =CH), 6.26 (d, J=4.4 Hz, 1H, =CHS), 6.75 (d, J=4.4 Hz, 1H, =CHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7 (CH_3), 50.9 (NCH_2), 58.8 (CH_2OH), 59.0 (CH_2O), 75.3 (=*C*HCO$_2$Et), 104.6 (=CHS), 129.7 (=CHN), 162.4 (C=), 169.1 (CO); IR (KBr): ν=3399, 3115, 1622, 1519, 1163 cm^{-1}; HRMS: calcd for $C_9H_{14}NO_3S$ $[M+H]^+$ 216.0689, found 216.0684.

*5.10.11. (Z)-Ethyl 2-(3-(4-hydroxybutyl)-5-methylthiazol-2(3H)-ylidene)acetate (**19b**).* Compound **19b** was obtained from **11e** (37.4 mg; 0.16 mmol) and $NaBH_4$ (65.0 mg; 1.72 mmol; 12.3 equiv) in EtOH (5.0 mL) according to general procedure (reduction time 30 min, TLC: petrolether/ethyl acetate 3:2). Column chromatography (eluent: gradient petrolether/ethyl acetate 100:0 to 20:80) gave pure **19b** (28.0 mg; 80%) as a colorless oil; R_f=0.31 (toluene/ethyl acetate 3:7); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H, C*H*$_3$CH$_2$), 1.51–1.64 (m, 2H, NCH_2CH_2), 1.73–1.87 (m, 2H, CH_2CH_2OH), 2.15 (d, J=1.4 Hz, 3H, C*H*$_3$C), 2.29 (br s, 1H, OH), 3.67 (t, J=6.4 Hz, 4H, CH_2OH and NCH_2), 4.17 (q, J=7.2 Hz, 2H, CH_2O), 4.96 (br s, 1H, =CHCO$_2$Et), 6.34 (d, J=1.4 Hz, 1H, =CHN); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.9 (*C*H$_3$C), 14.7 (*C*H$_3$CH$_2$), 24.0 (CH_2CH_2OH), 29.4 (NCH_2CH_2), 48.4 (NCH_2), 58.8 (CH_2O), 61.9 (CH_2OH), 74.4 (=*C*HCO$_2$Et), 117.4 (=CHS), 124.6 (=CHN), 162.6 (C=), 169.0 (CO); IR (KBr): ν=3399, 1635, 1522, 1171, 1141 cm^{-1}; HRMS: calcd for $C_{12}H_{20}NO_3S$ $[M+H]^+$ 258.1158, found 258.1157.

*5.10.12. (Z)-Ethyl 2-(3-(3-(benzylamino)propyl)thiazol-2(3H)-ylidene)acetate (**19c**).* Compound **19c** was obtained from **13a** (28.3 mg; 0.08 mmol) and $NaBH_4$ (58.1 mg; 1.53 mmol; 18.1 equiv) in EtOH (3.0 mL) according to general procedure (reduction time 1 h, TLC: ethyl acetate/MeOH 1:1). Column chromatography (eluent: gradient ethyl acetate/MeOH 100:0 to 70:30) gave pure **19c** (20.6 mg; 76%) as a colorless oil; R_f=0.53 (ethyl acetate/MeOH 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, CH_3), 1.82–1.95 (m, 2H, $CH_2CH_2CH_2$), 2.64 (t, J=6.6 Hz, 2H, CH_2NHBn), 3.77 (s, 2H, CH_2Ph), 3.84 (t, J=6.8 Hz, 2H, NCH_2), 4.20 (q, J=7.2 Hz, 2H, CH_2O), 5.09 (s, 1H, =CHCO$_2$Et), 6.21 (d, J=4.6 Hz, 1H, =CHS), 6.60 (d, J=4.6 Hz, 1H, =CHN), 7.28–7.35 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.0 (CH_3), 27.1 ($CH_2CH_2CH_2$), 45.4 (CH_2NHBn), 46.2 (NCH_2), 53.0 (CH_2Ph), 58.2 (CH_2O), 74.6 (=*C*HCO$_2$Et), 104.7 (=CHS), 127.1 (*p*-Ph), 128.5 (*o*-Ph), 128.6 (*m*-Ph), 130.5 (=CHN), 140.2 (C_1Ph), 162.0 (C=), 168.1 (CO); IR (KBr): ν=3416, 1639, 1523, 1160, 1051, 764, 698 cm^{-1}; HRMS: calcd for $C_{17}H_{23}N_2O_2S$ $[M+H]^+$ 319.1475, found 319.1471.

*5.10.13. (Z)-Ethyl 2-(3-(3-(benzylamino)propyl)-5-methylthiazol-2(3H)-ylidene)acetate (**19d**).* Compound **19d** was obtained from **13b** (22.8 mg; 0.07 mmol) and $NaBH_4$ (46.0 mg; 1.22 mmol; 18.7 equiv) in EtOH (2.0 mL) according to general procedure (reduction time 30 min, TLC: ethyl acetate). Column chromatography (eluent: gradient petrolether/ethyl acetate 50:50 to 0:100) gave pure **19d** (16.9 mg; 78%) as a colorless oil; R_f=0.36 (ethyl acetate/EtOH 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J=7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.77–1.90 (m, 2H, $CH_2CH_2CH_2$), 2.11 (d, J=1.4 Hz, 3H, CH_3C), 2.62 (t, J=6.4 Hz, 2H, CH_2NHBn), 3.74 (t, J=6.8 Hz, 2H, NCH_2), 3.77 (s, 2H, CH_2Ph), 4.18 (q, J=7.4 Hz, 2H, CH_2O), 5.00 (s, 1H, =CH),

6.23 (d, J=1.4 Hz, 1H, =CHN), 7.25–7.33 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.9 (CH_3C), 14.8 (CH_3CH_2), 27.5 ($CH_2CH_2CH_2$), 45.5 (CH_2NHBn), 46.1 (NCH_2), 53.9 (CH_2Ph), 58.7 (CH_2O), 74.4 (=CH), 117.1 (=CS), 124.8 (=CHN), 127.0 (*p*-Ph), 128.2 (*o*-Ph), 128.4 (*m*-Ph), 140.2 (C_1Ph), 162.6 (C=), 167.0 (CO); IR (KBr): ν=3310, 1641, 1525, 1381, 1164, 1139, 737, 699 cm^{-1}; HRMS: calcd for $C_{18}H_{25}N_2O_2S$ $[M+H]^+$ 333.1631, found 333,1627.

*5.10.14. (Z)-Ethyl 2-(3-(4-aminobutyl)thiazol-2(3H)-ylidene)acetate (**19e**).* Compound **19e** was obtained from **15c** (38.9 mg; 0.15 mmol) and $NaBH_4$ (87.0 mg; 2.3 mmol; 14.4 equiv) in EtOH (3.5 mL) according to general procedure (reduction time 30 min, TLC: ethyl acetate/MeOH 4:1). Column chromatography (eluent: gradient ethyl acetate/MeOH 100:0 to 0:100) gave pure **19e** (27.8 mg; 72%) as a white solid; R_f=0.08 (ethyl acetate/MeOH 1:1); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.17 (t, J=7.2 Hz, 3H, CH_3), 1.32–1.51 (m, 2H, $CH_2CH_2NH_2$), 1.55–1.68 (m, 2H, NCH_2CH_2), 1.72 (s, 2H, NH_2), 2.58–2.64 (t, 2H, CH_2NH_2), 3.79 (t, J=6.8 Hz, 2H, NCH_2), 4.01 (q, J=7.2 Hz, 2H, CH_2O), 5.05 (br s, 1H, =$CHCO_2Et$), 6.57 (d, J=4.4 Hz, 1H, =CHS), 7.14 (d, J=4.4 Hz, 1H, =CHN); ^{13}C NMR (50 MHz, DMSO-d_6): δ 15.0 (CH_3), 24.6 (NCH_2CH_2), 28.4 ($CH_2CH_2NH_2$), 40.4 (CH_2NH_2), 47.9 (NCH_2), 58.0 (CH_2O), 74.5 (=$CHCO_2Et$), 104.6 (=CHS), 130.5 (=CHN), 161.9 (C=), 168.0 (CO); HRMS: calcd for $C_{11}H_{19}N_2O_2S$ $[M+H]^+$ 243.1167, found 243.1172.

Acknowledgements

This work was supported by the Ministry of Science of the Republic of Serbia, Grant No. 142007 (to R.M.), and Deutscher Akademischer Austauschdienst (DAAD)—project ID: 504 252 70.

Supplementary data

X, Y, Z Coordinates of optimized structures of products, intermediates, ground states, and transition states. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.10.011.

References and notes

1. (a) Tramontini, M. *Synthesis* **1973**, 703; (b) Reichert, B. *Die Mannich Reaktion*; Springer: Berlin, 1959; (c) Blicke, F. F. *Org. React.* **1942**, *1*, 303.
2. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
3. For a review on iminium ions, see: (a) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311 for reviews on *N*-acyliminium ions, see: (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431; (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817 for selected examples, see: (d) King, F. D.; Aliev, A. E.; Caddick, S.; Tocher, D. A.; Courtier-Murias, D. *Org. Biomol. Chem.* **2009**, *7*, 167; (e) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036; (f) Tang, Y.; Fettinger, C.; Shaw, J. T. *Org. Lett.* **2009**, *11*, 3802; (g) Min, B. J.; Gu, X.; Yamamoto, T.; Petrov, R. R.; Qu, H.; Lee, Y. S.; Hruby, V. J. *Tetrahedron Lett.* **2008**, *49*, 2316; (h) Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5428; (i) Chiou, W.-H.; Mizutani, N.; Ojima, I. *J. Org. Chem.* **2007**, *72*, 1871; (j) Nielsen, T. E.; Le Quement, S.; Meldal, M. *Org. Lett.* **2005**, *7*, 3601.
4. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; (b) Baldwin, J. E.; Cutting, J. .; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
5. For examples, with heteroatom-based nucleophiles, see: (a) Yamada, S.; Takahashi, Y. *Tetrahedron Lett.* **2009**, *50*, 5395; (b) Bahajaj, A. A.; Moore, M. H.; Vernon, J. M. *Tetrahedron* **2004**, *60*, 1235; (c) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *Tetrahedron* **2004**, *60*, 1247; (d) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547; (e) Cornille, F.; Fobian, Y. M.; Slomczynska, U.; Beusen, D. D.; Marshall, G. R.; Moeller, K. D. *Tetrahedron Lett.* **1994**, *35*, 6989; (f) Kobayashi, S.; Isobe, M.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1921.
6. (a) Hamersma, J. A. M.; Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron* **1985**, *41*, 1999; (b) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron* **1982**, *38*, 3255; (c) Hamersma, J. A. M.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 1347.
7. (a) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron* **1985**, *41*, 2861; (b) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3811.
8. Fasseur, D.; Rigo, B.; Cauliez, P.; Debacker, M.; Couturier, D. *Tetrahedron Lett.* **1990**, *31*, 1713.
9. Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367.
10. Winterfeldt, E. *Synthesis* **1975**, 617. Ref. 129.
11. (a) Marković, R.; Baranac, M.; Steel, P.; Kleinpeter, E.; Stojanović, M. *Heterocycles* **2005**, *65*, 2635; (b) Marković, R.; Baranac, M.; Stojanović, M. *Synlett* **2004**, 1034.
12. For a selected literature on push–pull alkenes, see: (a) Rattananakin, P.; Pittman, C. R., Jr.; Collier, W. E.; Saebø, S. *Struct. Chem.* **2007**, *18*, 399; (b) Kleinpeter, E. *J. Serb. Chem. Soc.* **2006**, *71*, 1; (c) Kleinpeter, E.; Klod, S.; Rudorf, W.-D. *J. Org. Chem.* **2004**, *69*, 4317; (d) Sandström, J. *Top. Stereochem.* **1983**, *14*, 83.
13. $NaBH_4$ does not reduce esters under ambient conditions. Such reduction is possible under reflux conditions or by enhancing its reactivity by the addition of certain additives. For examples, with additives, see: (a) Periasami, M.; Thirumalaikumar, M. *J. Organomet. Chem.* **2000**, *609*, 137; (b) Prasad, A. B. S.; Kanth, J. V. B.; Periassamy, M. *Tetrahedron* **1992**, *48*, 4623; (c) Yamakawa, T.; Masaki, M.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2730 For examples, of using reflux temperature, see: (d) da Costa, J. C. S.; Pais, K. C.; Fernandes, E. L.; de Oliveira, P. S. M.; Mendonça, J. S.; de Souza, M. V. N.; Peralta, M. A.; Vasconcelos, T. R. A. *Arkivoc* **2006**, *i*, 128; (e) Boechat, N.; da Costa, J. C. S.; Mendonça, J. S.; de Oliveira, P. S. M.; de Souza, M. V. N. *Tetrahedron Lett.* **2004**, *45*, 6021; (f) Bachi, M. O.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439 and Ref 11 in the present paper. Reduction of an ester at rt is possible without any additive if a substrate contains hydroxy or keto group in the vicinity of the ester function. These groups can complex with $NaBH_4$ thereby activating it. For examples, see: (g) Patra, A.; Batra, S.; Bhaduri, A. P. *Synlett* **2003**, 1611; (h) Kim, J.; De Castro, K. A.; Lim, M.; Rhee, H. *Tetrahedron* **2010**, *66*, 3995.
14. (a) Marković, R.; Baranac, M.; Jovanović, V.; Džambaski, Z. *J. Chem. Educ.* **2004**, *81*, 1026; (b) Marković, R.; Baranac, M.; Džambaski, Z.; Stojanović, M.; Steel, P. J. *Tetrahedron* **2003**, *59*, 7803 The synthesis of **7a** and **7b** was not published previously, by us.
15. For the determination of configuration around the carbon–carbon double bond in these and similar compounds, and isomerization studies, see: (a) Marković, R.; Baranac, M.; Juranić, N.; Macura, S.; Cekić, I.; Minić, D. *J. Mol. Struct.* **2006**, *800*, 85; (b) Marković, R.; Shirazi, A.; Džambaski, Z.; Baranac, M.; Minić, D. *J. Phys. Org. Chem.* **2004**, *17*, 118; (c) Marković, R.; Džambaski, Z.; Baranac, M. *Tetrahedron* **2001**, *57*, 5833; (d) Marković, R.; Baranac, M. *Heterocycles* **1998**, *48*, 893 and Ref 14 in the present paper.
16. Some *endo*-mode cyclizations have been communicated: Stojanović, M.; Marković, R. *Synlett* **2009**, 1997.
17. Geluk, H. V.; Schlatmann, J. L. M. A. *Tetrahedron* **1968**, *24*, 5361.
18. Zheng, T.-C.; Burkart, M.; Richardson, D. E. *Tetrahedron Lett.* **1999**, *40*, 603.
19. Van Maarseveen, J. H.; Scheeren, H. W.; Kruse, C. G. *Tetrahedron* **1993**, *49*, 2325.
20. Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647.
21. (a) Marco-Contelles, J.; Rodrígues-Fernándes, M. *J. Org. Chem.* **2001**, *66*, 3717; (b) Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, 413.
22. Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317.
23. Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.
24. Similar dehydration, which slows down or completely blocks the cyclization, has also been observed in reactions starting from imidazolidin-2-ones and thiazolidin-2-ones as iminium ion precursors. For examples, see: (a) Liao, Z. K.; Kohn, K. *J. Org. Chem.* **1984**, *49*, 4745; (b) Kohn, K.; Liao, Z. K. *J. Org. Chem.* **1982**, *47*, 2787 and Refs. 6b and 6c in the present paper.
25. Baranac-Stojanović, M.; Kleinpeter, E. *J. Org. Chem.* **2011**, *76*, 3861.
26. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.
27. (a) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327; (b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.
28. Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121.
29. In certain cases the ethoxy derivative was isolated. See, for example, Refs. 11a and 23 in the present paper.
30. It was confirmed that the equilibration do occur by recording ^{1}H NMR spectrum of the isolated product **18d** after several months standing in a freezer, yielding a mixture trans/cis 73/28.
31. It is assumed that activation parameters for the thiazoline formation from differently *N*-substituted intermediates would not differ much, so the *N*-Me derivative was chosen for the computation.
32. (a) Karaman, R. *Bioorg. Chem.* **2010**, *38*, 165 and references cited therein; (b) Karaman, R. *Tetrahedron Lett.* **2008**, *49*, 5998 and references cited therein.
33. (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 1736; (b) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735; (c) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066; (d) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211.
34. Taxak, N.; Parmar, V.; Patel, D. S.; Kotasthane, A.; Bharatam, P. V. *J. Phys. Chem. A* **2011**, *115*, 891.
35. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennuci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Babuol, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzales, C.; Pople, J. A. *Gaussian 03 (Revision C.02)*; Gaussian: Wallingford CT, 2004.
36. Satzinger, G. *Liebigs Ann. Chem.* **1963**, *665*, 150.
37. Ceder, O.; Stenhede, U.; Dahlquist, K.-I.; Waisvisz, J. M.; van der Hoeven, M. G. *Acta Chem. Scand.* **1973**, *27*, 1914.