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Unusual mode of reactivity of 2-alkylidene-4-oxothiazolidine *S*-oxides under the Pummerer reaction conditions

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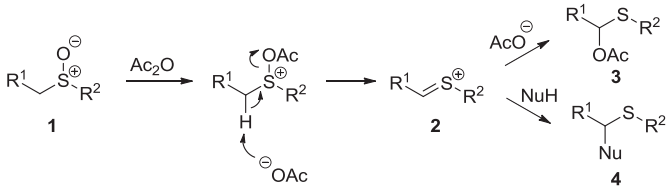
ABSTRACT

The reactivity of 2-alkylidene-4-oxothiazolidine *S*-oxides under the Pummerer reaction conditions, using Ac_2O, TFAA, $SOCl_2$ and $SOBr_2$ as initiators, has been examined. Almost all reactions proceeded with absolute regioselectivity yielding α-substituted sulfides or vinyl-chloro derivatives. The mechanism for the formation of the latter products was postulated and proved experimentally.

1. Introduction

Heteroatom-stabilized carbocations, owing to their electron deficiency and high reactivity, are valuable intermediates in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. A notable example is the Pummerer rearrangement reaction, which has received considerable attention from both mechanistic and synthetic points of view.[1] It utilizes thionium ion **2** as an intermediate, generally formed by treating a sulfoxide **1** bearing an α-hydrogen with an acid anhydride (Scheme 1). The thionium ion can be trapped by a counter anion, or other nucleophilic species present in the reaction medium yielding α-substituted sulfides **3** or **4**, respectively.



Scheme 1. The Pummerer rearrangement reaction.

Pummerer chemistry has undergone remarkable progress, and it now includes various reaction types, such as additive, vinylogous, connective, aromatic, interrupted, asymmetric and domino Pummerer reactions.[1] Inter- and intramolecular variants, including carbon and heteroatom nucleophiles, have found broad application in the functionalization of existing molecules, or for the construction of a wide variety of heterocyclic systems.

As part of our project dealing with the chemistry of pharmacologically important thiazolidine-containing systems,[2] we investigated the Pummerer reactions of sulfoxides **5** (Scheme 2), directed toward further functionalization of the 2-alkylidene-4-oxothiazolidine system. The sulfonium ion **6**, formed upon sulfoxide activation, can react in two ways: the classical Pummerer reaction leading to the α-substituted product **7** and/or additive Pummerer reaction, typical for α,β-unsaturated sulfoxides lacking a γ-hydrogen,[1] which results in the addition product **8**.

Here, we report the reactions of **5** with Ac_2O, TFAA, $SOCl_2$ and $SOBr_2$ as activators and discuss reaction mechanisms, with special emphasis on the regioselectivity.

2. Results and discussion

The starting sulfoxides **5** were prepared as previously described.[3] When treated with the standard Pummerer reaction

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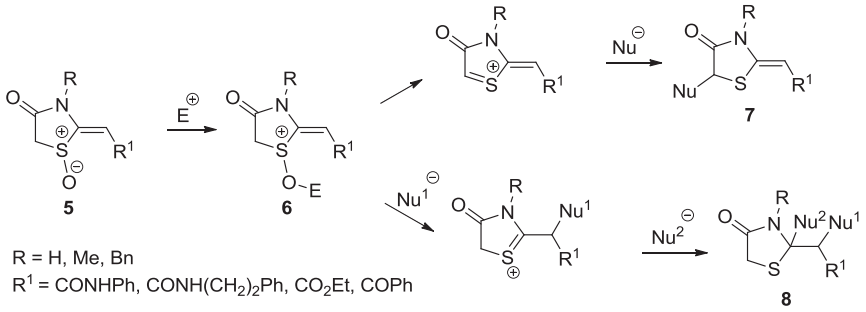
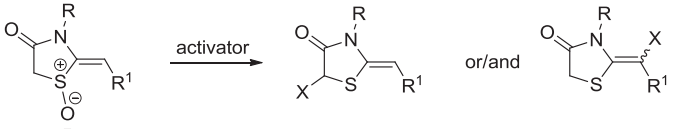


Scheme 2. Possible reaction pathways for Pummerer-type reactions of sulfoxides **5**.

initiator, Ac_2O, substrates **5a** and **5b** reacted only at elevated temperature, when the anhydride was used as a solvent, and yielded exclusively α-substituted sulfides **9a** and **9b** (Table 1, entries 1–3). The more electrophilic trifluoroacetic anhydride initiated the reaction under milder conditions providing the α-trifluoroacetoxy derivative, which could be detected only by ^{1}H NMR and ^{13}C NMR spectroscopy of the crude reaction mixture. It hydrolyzed completely during the column chromatography purification to give the cyclic hemithioacetal **9c**, as the final product (entry 4). The reaction of sulfoxides **5a**–**f** with thionyl chloride in CH_2Cl_2 solution, at low to room temperature, took a different reaction path—vinyl chlorides **10a**–**f** were formed as sole products (entries 5–10). By contrast, exposure of **5a** to thionyl bromide, under the same reaction conditions, followed the classical Pummerer rearrangement pathway affording the α-bromo sulfide **9d**, with absolute regioselectivity (entry 11). Under more vigorous conditions, in toluene at 110 °C, the same type of regioselectivity could be achieved with thionyl chloride (entries 12–14).

Table 1
Pummerer reactions of sulfoxides **5**



5 9 10

Entry		R	R^1	Reaction conditions		**9** (%)[a]		**10** (%)[a]
1	**5a**	Me	CO_2Et	Ac_2O, CH_2Cl_2, −10 °C→rt		0		0
2	**5a**	Me	CO_2Et	Ac_2O, 100 °C	**9a**	65 (X=OAc)		0
3	**5b**	Me	COPh	Ac_2O, 100 °C	**9b**	65 (X=OAc)		0
4	**5a**	Me	CO_2Et	TFAA, CH_2Cl_2, 0 °C; reaction workup	**9c**	72 (X=OH)[b]		0
5	**5a**	Me	CO_2Et	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10a**	59 (X=Cl) *Z*/*E* 0:100
6	**5b**	Me	COPh	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10b**	68 (X=Cl) *Z*/*E* 60:40
7	**5c**	Me	CONHPh	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10c**	58 (X=Cl) *Z*/*E* 0:100
8	**5d**	Me	$CONH(CH_2)_2Ph$	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10d**	54 (X=Cl) *Z*/*E* 0:100
9	**5e**	Bn	CO_2Et	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10e**	58 (X=Cl) *Z*/*E* 0:100
10	**5f**	H	CO_2Et	$SOCl_2$, CH_2Cl_2, −10 °C→rt		0	**10f**	45 (X=Cl) *Z*/*E* 100:0
11	**5a**	Me	CO_2Et	$SOBr_2$, CH_2Cl_2, −10 °C→rt	**9d**	64 (X=Br)		0
12	**5a**	Me	CO_2Et	$SOCl_2$, toluene, 110 °C	**9e**	51 (X=Cl)[c]	**10a**	24 (X=Cl)[c]
13	**5b**	Me	COPh	$SOCl_2$, toluene, 110 °C	**9f**	81 (X=Cl)		0
14	**5d**	Me	$CONH(CH_2)_2Ph$	$SOCl_2$, toluene, 110 °C	**9g**	48 (X=Cl)		0

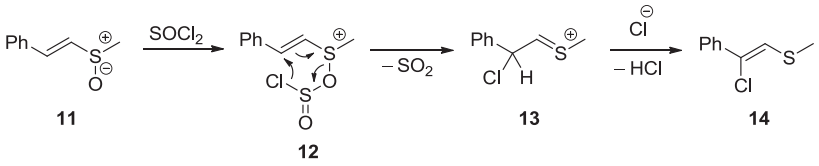
[a] Yields of isolated products.
[b] The initially formed trifluoroacetoxy derivative underwent hydrolysis during the workup process.
[c] Yields are determined on the basis of the ^{1}H NMR spectrum of a mixture of products, which could not be separated by column chromatography. Overall yield 75%.

To the best of our knowledge, the formation of a vinyl chloride under the Pummerer reaction conditions has only one precedent in the reaction of **11** with thionyl chloride[4] and was rationalized by an intramolecular chloride transfer to the β-vinylic carbon of the activated sulfoxide **12** (Scheme 3). The additive Pummerer sequence was obviously interrupted by a proton loss from **13** to produce the alkene **14**.

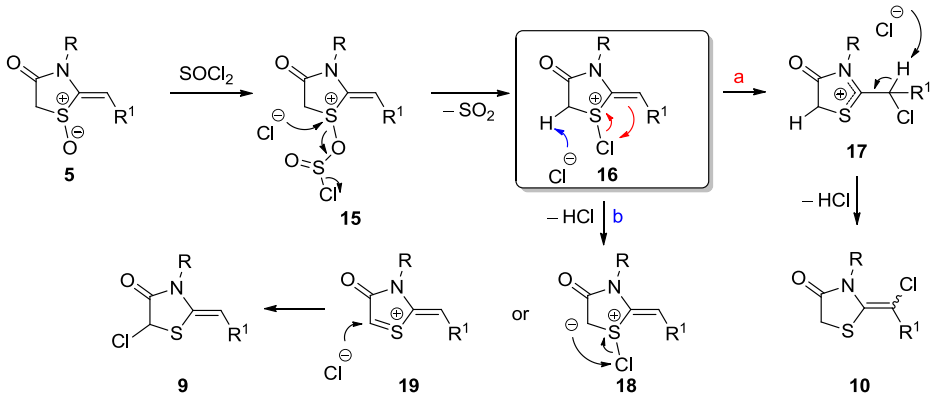
A very similar mechanism was invoked to explain the introduction of a chlorine atom into the 2-position of pyrrol-3-yl and indole-3-yl sulfoxides,[5] or to initiate the additive Pummerer reaction of α,β-unsaturated sulfoxides.[6]

However, we need to explain why the reaction of sulfoxides **5** with thionyl chloride, under mild conditions, was the only one that took a different route. Since the products **9a**–**c** were formed with absolute regioselectivity, we assumed that nucleophilic attack at the α-carbon is much more favourable than at the β-vinylic position. Thus, we speculated about another mechanism according to which the sulfur of the sulfonium ion **15** is attacked by the chloride anion forming, after elimination of SO_2 and Cl^-, the chlorosulfonium salt **16** (Scheme 4). The intermediacy of the chlorosulfonium species upon treatment of a sulfoxide with thionyl chloride has been proposed.[7] They are capable of transferring a positive chlorine onto a nucleophilic site.[7d,e,8] Thus, we believe that the β-vinylic carbon is actually attacked intramolecularly by an electrophilic chlorine, followed by proton loss to afford vinyl chlorides **10** (Scheme 4, path a). The driving force for such an interrupted additive mechanism should be the formation of stabilized, conjugated system. An intermolecular transfer to the sulfoxide double bond does not seem possible, since we showed that sulfoxide **5a** did not react with NCS under similar reaction conditions (CH_2Cl_2, 0 °C to rt).

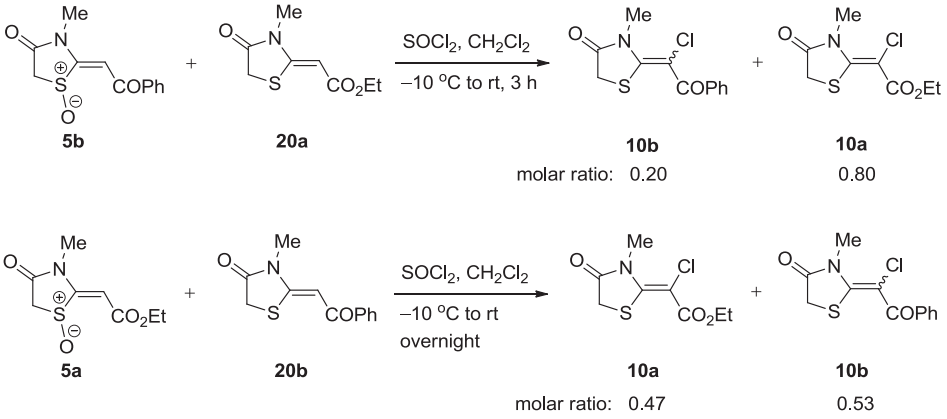
Next, we needed to prove that intermediate **16** was indeed formed during the reaction course, and that it could act as a chloronium ion source. Therefore, two crossover experiments were done (Scheme 5). In the first, an equimolar mixture of sulfoxide **5b** and thiazolidine **20a** was treated with thionyl chloride under the same reaction conditions as those given in Table 1. In the second, an equimolar mixture of sulfoxide **5a** and thiazolidine **20b** was used. Both reactions resulted in the formation of two vinyl chlorides, **10a** and **10b**. The shorter reaction time and the larger amount of the product formed by the chlorination of thiazolidine **20a** shows that the chlorosulfonium intermediate **16**, derived from the sulfoxide **5b**, is a more effective chlorinating agent than the



Scheme 3. Reaction of vinyl sulfoxide **11** with thionyl chloride.



Scheme 4. Mechanism for the reaction of sulfoxides **5** with thionyl chloride.



Scheme 5. Crossover experiments employed to show the intermediacy of the chlorosulfonium salt **16** in the course of the reactions of sulfoxides **5a**–**f** with thionyl chloride.

corresponding salt formed from **5a**. These results are in accord with the stronger electron-accepting ability of COPh, which makes the corresponding chlorosulfonium salt **16** less electronically favoured (relative to the one containing the ester group at the β-vinylic carbon). The proof for an intermolecular chlorine transfer in these reactions comes from the fact that thiazolidines **20a** and **20b** did not react with thionyl chloride alone. However, these experiments still did not exclude the mechanism depicted in Scheme 3. Thus, the vinyl chlorides **10b** (the first experiment, Scheme 5) and **10a** (the second experiment, Scheme 5) could arise from an intramolecular chloride anion transfer to the β-vinylic carbon of the sulfonium ion **15**, followed by proton loss. If they could chlorinate the double bond of another thiazolidine molecule, **20a** and **20b**, respectively, a mixture of vinyl chlorides **10a** and **10b** would be formed. Thus, the final proof for the intermediacy of the chlorosulfonium species **16** came from the following experiment: a mixture of vinyl chloride **10b**, thiazolidine **20a** and thionyl chloride in CH_2Cl_2 was stirred at −10 °C to rt for 3 h (identical conditions as in the crossover experiments, given in Scheme 5). An analysis of the reaction mixture by NMR spectroscopy revealed that vinyl chloride **10a** was not formed, i.e., there was no intermolecular chlorine transfer between the two thiazolidine molecules.

There was also a possibility that in the crossover experiments Cl^+ was exchanged between the sulfur atoms of two thiazolidine molecules, leading to the mixture of chlorosulfonium salts **16**.[7e,9] If such an exchange is followed by Cl^- attack at the β-vinylic carbon, a vinyl chloride would be formed. Owing to the resonance interaction between the sulfur (and nitrogen) with the double bond, β-carbon is more nucleophilic than the sulfur atom and we believe that Cl^+ is transferred directly to the double bond of another thiazolidine. Additional experiments have showed that the double bond of substrates **5** can be chlorinated to chlorides **10** with a source of electrophilic chlorine, such as NCS.

In the case of thionyl bromide, this type of reactivity is sterically hindered ($A^{1,3}$ strain) and α-bromo sulfide **9d** was the sole product. When the sulfoxides **5a**,**b** and **5d** were exposed to thionyl chloride at much higher temperature (toluene, 110 °C), the regioselectivity was shifted to the classical Pummerer rearrangement yielding the

α-chloro derivatives **9e**–**g** (Table 1, entries 12–14). The fact that the heating of vinyl chlorides **10a**,**b** and **10d** with thionyl chloride in toluene did not yield the α-chloro derivatives **9e**–**g**, excluded a possibility of a thermodynamic control of the reaction, but pointed to a change in the reaction mechanism. Hence, **9e**–**g** were formed either via the ylide **18** or thionium ion **19**, which is attacked by the chloride ion, as depicted in Scheme 4, path b. Thus, proper choice of reaction conditions allows one to control the regioselectivity of the thionyl chloride-induced reactions. Crossover experiments have shown that there was no intermolecular halogen transfer in the α-functionalization reactions leading to **9e**–**g** (toluene, 110 °C).

It is important to note that chlorination of the vinylic β-position proceeded stereoselectively, with respect to the configuration around the double bond, as evidenced from the NMR spectroscopic data of isolated products where one set of signals appeared. The only exception was compound **10b**, which was isolated as a mixture of isomers in a 60:40 molar ratio. An assessment of the stereochemistry around the double bond was not possible directly from NMR spectroscopic data, since the structures lacked protons suitable for NOE measurements. For this reason, we used computational methods, which can predict NMR chemical shifts with high accuracy.[10] The two isomers of **10b** were optimized at the B3LYP/6-31+G** level of theory,[11] using the Gaussian 09 program package.[12] Solvent effects were modelled as IEF-PCM.[13] NMR chemical shifts were computed using the GIAO method.[14] The most diagnostic chemical shift values of the two isomers, which differ by 0.2–5.8 ppm, are listed in Table 2. An excellent correlation between the experimental and the calculated chemical shift differences between the isomers (Fig. 1) allowed us to identify the prevailing isomer as having a *Z* configuration. This was further corroborated by the computed energy difference of 0.79 kcal/mol (Table 3), favouring the same isomer.

Table 2
Selected experimental and calculated[a] ^{1}H NMR and ^{13}C NMR chemical shifts of the two isomers of **10b**

Compound **10b**		^{1}H NMR (ppm)				^{13}C NMR (ppm)			
		NCH_3		CH_2S		C=		CO_{ketone}	
		$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6
Z-Isomer	Exp	3.07	2.83	3.91	4.09	149.0	151.5	187.8	187.3
	Calcd	3.05	3.05	3.75	3.84	159.0	160.4	185.7	186.7
E-Isomer	Exp	3.76	3.56	3.77	3.90	155.6	157.3	192.3	191.3
	Calcd	3.73	3.74	3.58	3.67	164.0	165.3	188.7	189.7

[a] At the B3LYP/6-31+G** theory level.

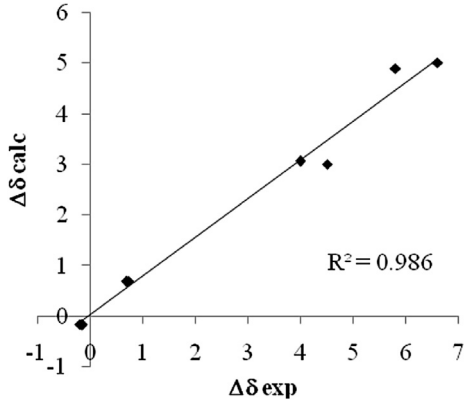


Fig. 1. Computed chemical shift differences of *Z*- and *E*-isomers of **10b** against the experimental ones. The values of chemical shifts, the differences of which are plotted in this graph, are given in Table 2.

Table 3
Computed relative energies[a] of the *Z*- and *E*-isomers of vinyl chlorides **10**

Compound	Relative energy (kcal/mol) *Z*/*E*
10a	1.34/0
10b	0/0.79
10c	1.24/0
10d	1.42/0
10e	0.78/0
10f	0/2.47

[a] At the B3LYP/6-31+G** level, in the gas phase.

Since **10a** and **10c**–**e** were isolated as a single isomer, they were assigned *E*-stereochemistry by analogy of the NCH_3 and CH_2S chemical shift values[15] with those of **10b**-*E*. The computed relative energies (Table 3) confirmed that in all cases the *E*-isomer was more stable. The large difference in energy, which range from 1.24 to 2.47 kcal/mol,[16] is in accord with the formation of only one isomer. However, in the case of **10f**, the *Z*-isomer is energetically favoured by the formation of an intramolecular hydrogen bond.

3. Conclusions

The reactions of 2-alkylidene-4-oxothiazolidine *S*-oxides with Ac_2O, TFAA, $SOCl_2$ and $SOBr_2$ proceeded with absolute regioselectivity leading to α-substituted sulfides **9** or vinyl-chloro derivatives **10**. The only exception was the reaction of **5a** with $SOCl_2$ in refluxing toluene, which gave a 2:1 mixture of regioisomers **9e**/**10a**. The formation of vinyl chlorides **10** was rationalized by the intermediacy of chlorosulfonium salt **16**, which can act as a chloronium ion source. The *Z*/*E* stereoselectivity of this latter reaction arises from a thermodynamic control, as proved by computational studies. The observed and defined regioselectivity should be of interest for further synthetic applications of Pummerer-type reactions based on this or similar systems, containing pharmacologically important thiazolidine ring.

4. Experimental

4.1. General

Melting points were determined on a Stuart SMP10 apparatus. 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 (^{1}H at 200 MHz, ^{13}C at 50.3 MHz) and on a Bruker Ultrashield Advance III (^{1}H at 500.26 MHz, ^{13}C at 125.79 MHz) in DMSO-d_6 or $CDCl_3$. Chemical shifts are given in parts per million downfield 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 Time-of-Flight LC/MS (G1969A, Agilent Technologies) coupled with 1200 Series HPLC system (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.

4.2. General procedure for the synthesis of α-acetoxy sulfides 9a and 9b

A solution of sulfoxide **5** (0.1 mmol) in acetic anhydride (1–1.5 mL) was heated at 100 °C in an oil bath. After the completion of the reaction (TLC), the reaction mixture was evaporated under reduced pressure, the residue was dissolved in ethyl acetate (5 mL) and the obtained solution was neutralized with an equal volume of

aq K_2CO_3 (5%). The layers were separated and the water layer was extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with water (2×5 mL), brine (1×5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (gradient toluene/ethyl acetate).

*4.2.1. (Z)-Ethyl (5-acetoxy-3-methyl-4-oxothiazolidine-2-ylidene) ethanoate (**9a**).* Compound **9a** was obtained from **5a** (65.2 mg; 0.3 mmol) in Ac_2O (3 mL) according to the general procedure (reaction time 8 h) as a white solid (53.8 mg; 65%); mp 82–84 °C; R_f=0.55 (toluene/ethyl acetate 7:3); IR (ATR): ν=3086, 2982, 1733, 1689, 1586, 1426, 1369, 1333, 1282, 1215, 1178, 1125, 1046, 802, 679 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 1.21 (t, 3H, CH_3CH$_2$, J=7.1 Hz), 2.15 (s, 3H, CH_3CO) 3.17 (s, 3H, NCH_3), 4.12 (q, 2H, OCH_2, J=7.1 Hz), 5.76 (s, 1H, =CH), 6.30 (s, 1H, CHS); ^{13}C NMR (DMSO-d_6, 50.3 MHz): δ 14.4 (*C*H$_3$CH$_2$), 20.4 (*C*H$_3$CO), 30.2 (NCH_3), 59.9 (OCH_2), 72.5 (CHS), 92.1 (=CH), 155.1 (C=), 166.8 (CO_{ester}), 168.8 and 170.1 (CO_{lactam} and CO_{acyl}); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.30 (t, 3H, CH_3CH$_2$, J=7.2 Hz), 2.17 (s, 3H, CH_3CO), 3.24 (s, 3H, NCH_3), 4.22 (q, 2H, OCH_2, J=7.2 Hz), 5.58 (s, 1H, =CH), 6.16 (s, 1H, CHS); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 14.2 (*C*H$_3$CH$_2$), 20.3 (*C*H$_3$CO), 30.0 (NCH_3), 60.3 (OCH_2), 72.1 (CHS), 92.8 (=CH), 154.5 (C=), 166.9 (CO_{ester}), 168.6 and 169.6 (CO_{lactam} and CO_{acyl}); HRMS: calcd for $C_{10}H_{14}NO_5S$ $[M+H]^+$ 260.0587, found 260.0590.

*4.2.2. (Z)-(5-Acetoxy-3-methyl-4-oxothiazolidine-2-ylidene)-1-phenylethanone (**9b**).* Compound **9b** was obtained from **5b** (30.1 mg; 0.121 mmol) in Ac_2O (2 mL) according to the general procedure (reaction time 6 h) as a yellow solid (22.8 mg; 65%); mp 174–176 °C; R_f=0.53 (toluene/ethyl acetate 8:2); IR (ATR): ν=3040, 2921, 1754, 1731, 1641, 1529, 1345, 1201, 1040, 967, 765, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.17 (s, 3H, CH_3CO), 3.37 (s, 3H, NCH_3), 6.16 (s, 1H, CHS), 6.74 (s, 1H, =CH), 7.43–7.56 (m, 3H, *m*- and *p*-Ph), 7.92–7.96 (m, 2H, *o*-Ph); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 20.4 (*C*H$_3$CO), 30.4 (NCH_3), 72.0 (CHS), 97.0 (=CH), 127.6 (*o*-Ph), 128.6 (*m*-Ph), 132.6 (*p*-Ph), 138.0 (C1–Ph), 157.5 (C=), 169.4 and 169.6 (CO_{lactam} and CO_{acyl}), 188.8 (CO_{ketone}); ^1H NMR (DMSO-d_6, 500 MHz): δ 2.16 (s, 3H, CH_3CO), NCH_3 is covered by the H_2O from the solvent, 6.31 (s, 1H, CHS), 7.06 (s, 1H, =CH), 7.54–7.62 (m, 3H, *m*- and *p*-Ph), 8.07 (d, 2H, *o*-Ph); ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ 20.2 (*C*H$_3$CO), 30.4 (NCH_3), 72.2 (CHS), 97.0 (=CH), 127.8 (*o*-Ph), 128.7 (*m*-Ph), 132.7 (*p*-Ph), 137.6 (C1–Ph), 157.5 (C=), 169.1 and 169.9 (CO_{lactam} and CO_{acyl}), 188.1 (CO_{ketone}); HRMS: calcd for $C_{14}H_{14}NO_4S$ $[M+H]^+$ 292.0638, found 292.0642.

4.3. (*Z*)-Ethyl (5-hydroxy-3-methyl-4-oxothiazolidine-2-ylidene)ethanoate (9c)

TFAA (105.0 mg; 70 μL; 0.60 mmol) was added to a stirred solution of **5a** (54.3 mg; 0.25 mmol) in CH_2Cl_2 (3 mL), which was cooled in an ice bath. The stirring was continued at 0 °C for 2 h and the solvent was evaporated under reduced pressure. Toluene (10 mL) was added and TFAA removed as an azeotrope at reduced pressure. The ^1H NMR and ^{13}C NMR spectra of thus obtained crude product revealed the presence of α-trifluoroacetoxy derivative: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.31 (t, 3H, CH_3, J=7.0 Hz), 3.27 (s, 3H, NCH_3), 4.23 (q, 2H, OCH_2, J=7.0 Hz), 5.67 (s, 1H, =CH), 6.38 (s, 1H, CHS); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 14.1 (*C*H$_3$CH$_2$O), 30.3 (NCH_3), 60.8 (OCH_2), 72.9 (CHS), 94.1 (=CH), 113.9 (q, CF_3, $^1J_{C-F}$=286 Hz), 152.7 (C=), 156.3 (q, CF_3CO, $^2J_{C-F}$=44 Hz), 166.6 and 166.9 (CO_{lactam} and CO_{ester}). It hydrolyzed completely during the column chromatography purification (gradient toluene/ethyl acetate 100:0 to 70:30) to give **9c** (39.4 mg; 72%) as a pale yellow solid; mp 92–95 °C; R_f=0.30 (toluene/ethyl acetate 7:3); IR (ATR): ν=3302, 2989, 1688, 1578, 1332, 1295, 1182, 1080, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.30 (t, 3H, J=7.0 Hz), 3.19 (s, 3H, NCH_3), 4.20 (q, 2H, OCH_2, J=7.0 Hz), 4.70 (broad s, 1H, OH), 5.53 (s, 1H, =CH), 5.73 (s, 1H, CHS); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 14.3 (CH_3), 30.1 (NCH_3), 60.5 (OCH_2), 73.49 (CHS), 92.4 (=CH), 155.1 (C=), 167.3 (CO_{ester}), 172.8 (CO_{lactam}); ^1H NMR (DMSO-d_6, 500 MHz): δ 1.19 (t, 3H, CH_3CH$_2$, J=7.2 Hz), 3.10 (s, 3H, NCH_3), 4.09 (q, 2H, OCH_2, J=7.2 Hz), 5.62 (s, 1H, =CH), 5.71 (s, 1H, CHS), 9.15 (broad s, 1H, OH); ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ 14.3 (*C*H$_3$CH$_2$), 29.8 (NCH_3), 59.4 (OCH_2), 73.3 (CHS), 90.6 (=CH), 155.9 (C=), 166.5 (CO_{ester}), 172.4 (CO_{lactam}); HRMS: calcd for $C_8H_{12}NO_4S$ $[M+H]^+$ 218.0482, found 218.0479.

4.4. (*Z*)-Ethyl (5-bromo-3-benzyl-4-oxothiazolidin-2-ylidene) ethanoate (9d)

Thionyl bromide (91.5 mg; 34 μL; 0.44 mmol) was added to a stirred solution of **5a** (86.9 mg; 0.4 mmol) in CH_2Cl_2 (10 mL), which was cooled at −10 °C. The stirring was continued at −10 °C for 15 min and then at rt for 4 h. The solvent and the excess thionyl bromide were evaporated under reduced pressure. The crude product was purified by column chromatography (gradient petrol ether (bp 60–80 °C)/ethyl acetate 100:0 to 85:15) to give pure **9d** (48.8 mg; 64%) as a pale yellow solid; mp 72–73 °C; R_f=0.60 (petrol ether/ethyl acetate 8:2); IR (ATR): ν=3074, 2982, 2933, 1717, 1679, 1574, 1425, 1362, 1336, 1277, 1192, 1169, 1139, 1115, 1039, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31 (t, 3H, CH_3CH$_2$, J=7.2 Hz), 3.25 (s, 3H, NCH_3), 4.23 (q, 2H, OCH_2, J=7.2 Hz), 5.62 (s, 1H, =CH), 5.74 (s, 1H, CHS); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 14.2 (*C*H$_3$CH$_2$), 30.4 (NCH_3), 41.8 (CHS), 60.5 (OCH_2), 93.1 (=CH), 153.9 (C=), 167.0 (CO_{ester}), 169.8 (CO_{lactam}); HRMS: calcd for $C_8H_{11}BrNO_3S$ $[M+H]^+$ 279.9638, found 279.9634.

4.5. General procedure for the synthesis of α-chloro sulfides 9e–g

Thionyl chloride (0.11 mmol) was added to a stirred suspension of **5** (0.1 mmol) in toluene (2–2.5 mL), which was heated at 110 °C in an oil bath. The stirring was continued at 110 °C until the disappearance of the starting material (TLC). The solvent and the excess thionyl chloride were evaporated under reduced pressure. The crude product was purified by column chromatography (gradient petrol ether (bp 60–80 °C)/ethyl acetate).

*4.5.1. (Z)-Ethyl (5-chloro-3-benzyl-4-oxothiazolidin-2-ylidene)ethanoate (**9e**).* Compound **9e** was obtained from **5a** (43.4 mg; 0.2 mmol) and $SOCl_2$ (26.2 mg; 16 μL; 0.22 mmol) in toluene (5 mL) according to the general procedure (reaction time 4 h) as a light yellow solid (51%, based on the NMR spectrum of a mixture with **10g**); R_f=0.60 (petrol ether/ethyl acetate 7:3); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.31 (t, 3H, CH_3CH$_2$, J=7.0 Hz), 3.25 (s, 3H, NCH_3), 4.23 (m, 2H, OCH_2), 5.61 (s, 1H, =CH), 5.67 (s, 1H, CHS); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 14.2 (*C*H$_3$CH$_2$), 30.6 (NCH_3), 55.8 (CHS), 60.5 (OCH_2), 93.0 (=CH), 153.6 (C=), 167.0 (CO_{ester}), 169.1 (CO_{lactam}); HRMS: calcd for $C_8H_{11}ClNO_3S$ $[M+H]^+$ 236.0143, found: 236.0149.

*4.5.2. (Z)-(5-Chloro-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**9f**).* Compound **9f** was obtained from **5b** (62.3 mg; 0.25 mmol) and $SOCl_2$ (32.7 mg; 20 μL; 0.27 mmol) in toluene (5 mL) according to the general procedure (reaction time 1 h) as a yellow solid (54.8 mg; 81%); mp 153–155 °C; R_f=0.58 (toluene/ethyl acetate 8:2); IR (ATR): ν=3427, 3059, 2960, 1722, 1633, 1523, 1417, 1342, 1230, 1116, 920, 762, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.38 (s, 3H, CH_3), 5.62 (s, 1H, CHS), 6.77 (s, 1H, =CH), 7.44–7.57 (m, 3H, *m*-Ph and *p*-Ph), 7.92–7.96 (m, 2H, *o*-Ph); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 30.9 (NCH_3), 55.3 (CHS), 97.1 (=CH), 127.7 (*o*-Ph), 128.7 (*m*-Ph), 132.8 (*p*-Ph), 137.6 (C1–Ph), 156.7 (C=),

169.7 (CO_{lactam}), 188.9 (CO_{ketone}); HRMS: calcd for $C_{12}H_{11}ClNO_2S$ $[M+H]^+$ 268.0194, found 268.0183.

*4.5.3. (Z)-(5-Chloro-3-methyl-4-oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (**9g**).* Compound **9g** was obtained from **5d** (58.5 mg; 0.2 mmol) and $SOCl_2$ (26.2 mg; 16 μL; 0.22 mmol) in toluene (5 mL) according to the general procedure (reaction time 1 h) as a yellow solid (29.3 mg; 48%); mp 89–92 °C; R_f=0.45 (toluene/ethyl acetate 7:3); IR (ATR): ν=3314, 3083, 3028, 2943, 1726, 1651, 1585, 1463, 1337, 1293, 1226, 1122, 1028, 811, 741, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.84 (t, 2H, CH_2Ph, J=7.0 Hz), 3.16 (s, 3H, CH_3), 3.58 (m, broad, 2H, NCH_2), 5.48 (s, 1H, =CH), 5.57 (s, 1H, CHS), 5.78 (s, broad, 1H, NH) 7.18–7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 30.5 (CH_3), 35.6 (CH_2Ph), 40.6 (NCH_2), 56.2 (CHS), 95.0 (=CH), 126.5 (*p*-Ph), 128.6 (*o*-Ph), 128.7 (*m*-Ph), 138.6 (C1–Ph), 150.2 (C=), 166.0 (CO_{amide}), 169.1 (CO_{lactam}); HRMS: calcd for $C_{14}H_{16}ClN_2O_2S$ $[M+H]^+$ 311.0616, found 311.0616.

4.6. General procedure for the synthesis of vinyl chlorides 10a–f

Thionyl chloride (0.11 mmol) was added to a stirred solution of **5** (0.1 mmol) in CH_2Cl_2 (2.3–3.5 mL), which was cooled at −10 °C. The stirring was continued at −10 °C for 15–30 min and then at rt until the disappearance of the starting material (TLC). The solvent and the excess thionyl chloride were evaporated under reduced pressure. The crude product was purified by column chromatography (gradient petrol ether (bp 60–80 °C)/ethyl acetate).

*4.6.1. (E)-Ethyl 2-chloro-2-(3-methyl-4-oxothiazolidin-2-ylidene) ethanoate (**10a**).* Compound **10a** was obtained from **5a** (174.4 mg; 0.802 mmol) and $SOCl_2$ (105.1 mg; 62 μL; 0.883 mmol) in CH_2Cl_2 (20 mL) according to the general procedure (reaction time 5 h) as a yellow solid (112.0 mg; 59%); mp 118–120 °C; R_f=0.60 (petrol ether/ethyl acetate 7:3); IR (KBr): ν=3426, 2968, 2931, 1723, 1674, 1532, 1297, 1222, 1117, 1055, 1021, 871, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36 (t, 3H, CH_3CH_2, J=7.0 Hz), 3.64 (s, 3H, NCH_3), 3.70 (s, 2H, CH_2S), 4.29 (q, 2H, OCH_2, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 14.1 (CH_3CH_2), 31.8 (CH_2S), 34.7 (NCH_3), 61.9 (OCH_2), 93.0 (=CCl), 153.5 (C=), 165.1 (CO_{ester}), 173.8 (CO_{lactam}); ^1H NMR (DMSO-d_6, 200 MHz): δ 1.24 (t, 3H, CH_3CH_2, J=7.3 Hz), 3.49 (s, 3H, NCH_3), 3.86 (s, 2H, CH_2S), 4.20 (q, 2H, OCH_2, J=7.3 Hz); ^{13}C NMR (DMSO-d_6, 50.3 MHz): δ 14.4 (CH_3CH_2), 31.7 (CH_2S), 34.6 (NCH_3), 61.6 (OCH_2), 90.6 (=CCl), 155.6 (C=), 164.6 (CO_{ester}), 174.5 (CO_{lactam}); HRMS: calcd for $C_8H_{11}ClNO_3S$ $[M+H]^+$ 236.0143, found 236.0132.

*4.6.2. (Z)- and (E)-2-Chloro-2-(3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (**10b**).* Compound **10b** was obtained from **5b** (149.6 mg; 0.6 mmol) and $SOCl_2$ (78.5 mg; 47 μL; 0.66 mmol) in CH_2Cl_2 (15 mL) according to the general procedure (reaction time 5 h) as a yellow solid (109.6 mg; 68%; mixture of isomers: *Z*/*E* 60:40 molar ratio); mp 93–96 °C; R_f=0.38 (petrol ether/ethyl acetate 8:2); IR (ATR) ν=3434, 3059, 2981, 1725, 1640, 1533, 1485, 1415, 1346, 1237, 1118, 1004, 917, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): *Z*-isomer δ 3.07 (s, 3H, CH_3), 3.91 (s, 2H, CH_2S), 7.55 (m, 2H, *m*-Ph), 7.65 (t, 1H, *p*-Ph, J=7.5 Hz), 7.96 (d, 2H, *o*-Ph, J=7.0 Hz); *E*-isomer δ 3.76 (s, 3H, CH_3), 3.77 (s, 2H, CH_2S), 7.48 (m, 2H, *m*-Ph), 7.55 (t, 1H, *p*-Ph, J=7.8 Hz), 7.72 (d, 2H, *o*-Ph, J=7.5 Hz); ^{13}C NMR ($CDCl_3$, 125.8 MHz): *Z*-isomer δ 32.2 (CH_2S), 34.1 (CH_3), 102.5 (=CCl), 128.5 (*m*-Ph), 129.4 (*o*-Ph), 133.4 (*p*-Ph), 136.3 (C1–Ph), 149.0 (C=), 172.6 (CO_{lactam}), 187.8 (CO_{ketone}); *E*-isomer δ 31.6 (CH_2S), 34.8 (CH_3), 100.2 (=CCl), 127.8 (*m*-Ph), 128.2 (*o*-Ph), 131.1 (*p*-Ph), 138.3 (C1–Ph), 155.6 (C=), 173.9 (CO_{lactam}), 192.3 (CO_{ketone}); ^1H NMR (DMSO-d_6, 500 MHz): *Z*-isomer δ 2.83 (s, 3H, CH_3), 4.09 (s, 2H, CH_2S), 7.45–7.84 (m, 5H, Ph); *E*-isomer δ 3.56 (s, 3H, CH_3), 3.90 (s, 2H, CH_2S), 7.45–7.84 (m, 5H, Ph); ^{13}C NMR (DMSO-d_6, 125.8 MHz): *Z*-isomer δ 32.3 (CH_2S), 33.9 (CH_3), 100.6 (=CCl), 128.7 (*m*-Ph), 129.4 (*o*-Ph), 133.4 (*p*-Ph), 136.48 (C1–Ph), 151.5 (C=), 173.4 (CO_{lactam}), 187.3 (CO_{ketone}); *E*-isomer δ 31.4 (CH_2S), 34.4 (CH_3), 98.3 (=CCl), 127.7 (*m*-Ph), 128.0 (*o*-fenil), 130.9 (*p*-Ph), 138.7 (C1–Ph), 157.3 (C=), 174.4 (CO_{lactam}), 191.3 (CO_{ketone}); HRMS (ESI): $C_{12}H_{11}ClNO_2S$ $[M+H]^+$ 268.0194, found 268.0196.

*4.6.3. (E)-2-Chloro-2-(3-methyl-4-oxothiazolidin-2-ylidene)-N-phenylethanamide (**10c**).* Compound **10c** was obtained from **5c** (200.0 mg; 0.757 mmol) and $SOCl_2$ (99.0 mg; 61 μL; 0.832 mmol) in CH_2Cl_2 (24 mL) according to the general procedure (reaction time 6 h) as a white solid (123.5 mg; 58%); mp 115–116 °C (decomposes); R_f=0.63 (toluene/acetone 7:3); IR (ATR): ν=3374, 3060, 2962, 2932, 1702, 1639, 1598, 1520, 1436, 1312, 1209, 1124, 1058, 1008, 889, 752, 689 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 3.52 (s, 3H, CH_3), 3.79 (s, 2H, CH_2S), 7.10 (t, 1H, *p*-Ph, J=7.2 Hz), 7.32 (m, 2H, *m*-Ph), 7.62 (d, 2H, *o*-Ph, J=8.5 Hz), 9.65 (s, 1H, NH_{amide}); ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ 31.4 (CH_2S), 34.3 (CH_3), 92.6 (=CCl), 121.3 (*o*-Ph), 124.0 (*p*-Ph), 128.4 (*m*-Ph), 138.2 (C1–Ph), 151.5 (C=), 162.9 (CO_{amide}), 174.2 (CO_{lactam}); HRMS: calcd for $C_{12}H_{12}ClN_2O_2S$ $[M+H]^+$ 283.0302, found 283.0306.

*4.6.4. (E)-2-Chloro-2-(3-methyl-4-oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (**10d**).* Compound **10d** was obtained from **5d** (100.0 mg; 0.342 mmol) and $SOCl_2$ (44.8 mg; 27 μL; 0.377 mmol) in CH_2Cl_2 (12 mL) according to the general procedure (reaction time 25 min) as a yellow solid (57.6 mg; 54%); mp 97–98 °C (decomposes); R_f=0.67 (toluene/acetone 7:3); IR (ATR): ν=3368, 3060, 2027, 2932, 1720, 1669, 1518, 1457, 1343, 1300, 1243, 1124, 873, 750, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.87 (t, 2H, CH_2Ph, J=7.0 Hz), 3.59 (s, 3H, CH_3), 3.58–3.62 (m, 2H, NCH_2), 3.64 (s, 2H, CH_2S), 6.61 (broad s, 1H, NH_{amide}), 7.20–7.33 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 32.0 (CH_2S), 34.5 (CH_3), 35.7 (CH_2Ph), 41.3 (NCH_2), 94.0 (=CCl), 126.6 (*p*-Ph), 128.7 (*o*-Ph), 128.8 (*m*-Ph), 138.6 (C1–Ph), 150.1 (C=), 164.3 (CO_{amide}), 173.9 (CO_{lactam}); ^1H NMR (DMSO-d_6, 500 MHz): δ 2.77 (t, 2H, CH_2Ph, J=7.7 Hz), 3.36–3.39 (m, 2H, NCH_2), 3.46 (s, 3H, CH_3), 3.72 (s, 2H, CH_2S), 7.18–7.32 (m, 5H, Ph), 8.11 (t, 1H, NH_{amide}, J=5.7 Hz); ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ 31.3 (CH_2S), 34.2 (CH_3), 35.1 (CH_2Ph), 41.1 (NCH_2), 93.0 (=CCl), 126.2 (*p*-Ph), 128.3 (*o*-Ph), 128.7 (*m*-Ph), 139.3 (C1–Ph), 149.6 (C=), 163.8 (CO_{amide}), 174.1 (CO_{lactam}); HRMS: calcd for $C_{14}H_{16}ClN_2O_2S$ $[M+H]^+$ 311.0616, found 311.0623.

*4.6.5. (E)-Ethyl 2-chloro-2-(3-benzyl-4-oxothiazolidin-2-ylidene) ethanoate (**10e**).* Compound **10e** was obtained from **5e** (62.9 mg; 0.214 mmol) and $SOCl_2$ (28.1 mg; 17 μL; 0.236 mmol) in CH_2Cl_2 (5 mL) according to the general procedure (reaction time 5 h) as a white oil (39.1 mg; 58%); R_f=0.45 (petrol ether/ethyl acetate 8:2); IR (ATR): ν=3056, 3031, 2976, 2925, 1730, 1666, 1516, 1261, 1158, 1055, 861, 724, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.32 (t, 3H, CH_3, J=7.2 Hz), 3.79 (s, 2H, CH_2S), 4.25 (q, 2H, OCH_2, J=7.2 Hz), 5.55 (s, 2H, CH_2Ph), 7.15 (d, 2H, *o*-Ph, J=7.0 Hz), 7.26 (t, 1H, *p*-Ph, J=7.5 Hz), 7.33 (m, 2H, *m*-Ph); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 14.2 (CH_3), 31.7 (CH_2S), 48.7 (CH_2Ph), 62.1 (OCH_2), 93.4 (=CCl), 126.1 (*o*-Ph), 127.4 (*p*-Ph), 128.7 (*m*-Ph), 136.3 (C1–Ph), 152.2 (C=), 165.1 (CO_{ester}), 174.2 (CO_{lactam}); HRMS: calcd for $C_{14}H_{15}ClNO_3S$ $[M+H]^+$ 312.0456, found 312.0453.

*4.6.6. (Z)-Ethyl 2-chloro-2-(4-oxothiazolidin-2-ylidene)ethanoate (**10f**).* Compound **10f** was obtained from **5f** (51.1 mg; 0.25 mmol) and $SOCl_2$ (32.0 mg; 20 μL; 0.28 mmol) in CH_2Cl_2 (7 mL) according to the general procedure (reaction time 3 h) as a white oil (25.3 mg; 45%); R_f=0.58 (petrol ether/ethyl acetate 7:3); IR (KBr): ν=3439, 3257, 2982, 2934, 1730, 1671, 1597, 1312, 1281, 1230, 1185, 1053, 760, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.33 (t, 3H, CH_3, J=7.2 Hz), 3.78 (s, 2H, CH_2S), 4.27 (q, 2H, OCH_2, J=7.2 Hz), 10.42 (s, 1H, NH); ^{13}C

NMR ($CDCl_3$, 50.3 MHz): δ 14.1 (CH_3), 32.9 (CH_2S), 62.0 (OCH_2), 94.7 (=CCl), 153.7 (C=), 163.7 (CO_{ester}), 172.4 (CO_{lactam}); ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.24 (t, 3H, CH_3, J=7.1 Hz), 4.00 (s, 2H, CH_2S), 4.23 (q, 2H, OCH_2, J=7.1 Hz), 10.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50.3 MHz): δ 14.4 (CH_3), 33.3 (CH_2S), 61.6 (OCH_2), 92.9 (=CCl), 155.8 (C=), 162.2 (CO_{ester}), 174.0 (CO_{lactam}); HRMS: calcd for $C_7H_9ClNO_3S$ $[M+H]^+$ 221.9986, found 221.9982.

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Supplementary data

Absolute energies and *x*, *y*, *z* coordinates of the optimized structures. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.004.

References and notes

1. For reviews on Pummerer reactions, see: (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832–5844; (b) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35–76; (c) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003–5034; (d) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432; (e) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353–1377.
2. (a) Jain, A. K.; Vaidya, A.; Ravichandran, V.; Kashaw, S. K.; Agrawal, R. K. *Bioorg. Med. Chem.* **2012**, *20*, 3378–3395; (b) Prabhakar, Y. S.; Solomon, V. R.; Gupta, M. K.; Katti, S. B. *Top. Heterocycl. Chem.* **2006**, *4*, 161–249.
3. Džambaski, Z.; Marković, R.; Kleinpeter, E.; Baranac-Stojanović, M. *Tetrahedron* **2013**, *69*, 6436–6447.
4. Russel, G. A.; Sabourin, E.; Mikol, G. J. *J. Org. Chem.* **1966**, *31*, 2854–2858.
5. Garcia, J.; Ortiz, C.; Greenhouse, R. *J. Org. Chem.* **1988**, *53*, 2634–2637.
6. Kosugi, H.; Uda, H.; Yamagiwa, S. *J. Chem. Soc., Chem. Commun.* **1976**, 71–72.
7. (a) Fujihara, H.; Akaishi, R.; Furukawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4451–4452; (b) Masuda, T.; Furukawa, N.; Oae, S. *Chem. Lett.* **1977**, 1103–1106; (c) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247–260; (d) Moore, H. W.; Snyder, H. R. *J. Org. Chem.* **1964**, *29*, 97–99; (e) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572–577.
8. (a) Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713–2715; (b) Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U. M. *J. Chem. Res., Synop.* **1986**, 426–427; (c) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* **1986**, 868–870; (d) Schmidt, D. L.; Heeschen, J. P.; Klingler, T. C.; McCarty, L. P. *J. Org. Chem.* **1985**, *50*, 2840–2847.
9. (a) Max Hull, C.; Bargar, T. W. *J. Org. Chem.* **1975**, *40*, 3152–3154; (b) Bovio, A.; Miotti, U. *J. Chem. Soc., Perkin Trans. 2* **1978**, 172–177; (c) Miotti, U. *J. Chem. Soc., Perkin Trans. 2* **1991**, 617–622.
10. Jain, R.; Bally, T.; Rablen, P. R. *J. Org. Chem.* **2009**, *74*, 4017–4023.
11. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785–789.
12. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09 (Revision C.01)*; Gaussian: Wallingford, CT, 2010.
13. (a) Cancés, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041; (b) Mennucci, B.; Cancés, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506–10517.
14. (a) Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789–807; (b) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.
15. Only CH_2S for **10e**.
16. The energy difference for **10e**, which is slightly lower, corresponds to the most stable rotamers around the N–CH_2 bond and is obviously raised if other rotamers are taken into account.