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Efficient synthesis of α-alkylidene-β-lactams via NaOH-promoted intramolecular aza-Michael addition of α-carbamoyl ketene-*S*,*S*-acetals in aqueous media

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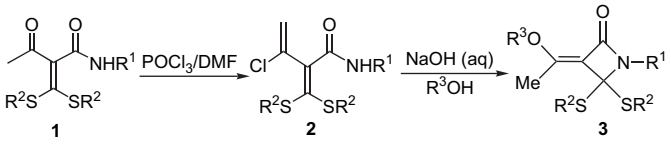
ABSTRACT

A facile and efficient synthesis of substituted α-alkylidene-β-lactams have been developed via a NaOH-promoted intramolecular aza-Michael addition of α-carbamoyl, α-(1-chlorovinyl) ketene-*S*,*S*-acetals and subsequent nucleophilic vinylic substitution (S_NV) reaction in alcoholic aqueous media.

1. Introduction

2-Azetidinone ring is a common structural feature of several families of β-lactam antibiotics (e.g., penicillins, cephalosporins, and carbapenems) that have been widely used as therapeutic agents, anti-cancer agents, and enzyme inhibitors.[1,2] Particularly, the recent discoveries of some natural monocyclic β-lactams (monobactams) displaying high anti-bacterial activity indicate that the 2-azetidinone ring is the key unit and the minimum requirement for biological activity.[3,4] The pharmacological importance of β-lactams and their utility as building blocks in organic synthesis have directed considerable research activity toward the synthesis of suitably substituted 2-azetidinone rings.[5,6] Intensive research has generated numerous synthetic approaches, involving ketene–imine cycloadditions (the Staudinger reaction),[7] ester enolate–imine condensations (the Gilman–Speeter reaction),[8] cyclization reactions of β-amino acids or esters,[9] coupling reactions of alkynes with nitrones,[8] photoinduced rearrangements,[10] carbene insertions,[11] and radical cyclizations,[12] among others. Nevertheless, to match the increasing scientific and practical demand for β-lactams, new and efficient methodologies for the construction of suitable substituted 2-azetidinone skeletons are still desirable.

Over the past few decades, the utility of α-oxo ketene-*S*,*S*-acetals as versatile intermediates in organic synthesis has been recognized.[13] During the course of our studies on the reaction of α-acyl ketene-*S*,*S*-acetals under Vilsmeier conditions,[14] we noted that the readily synthesized α-(1-chlorovinyl) ketene-*S*,*S*-acetals showed promising structural characteristics that could be exploited in further organic transformations. Inspired by these findings and our continuing interest in the utilization of β-oxo amide derivatives in the synthesis of carbo- and heterocycles,[15] we synthesized α-carbamoyl, α-(1-chlorovinyl) ketene-*S*,*S*-acetals **2** from α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1** and explored their synthetic potential. As a result, an efficient one-pot synthesis of highly substituted α-alkylidene-β-lactams **3** was developed from readily available **2** in aqueous media (Scheme 1). Herein, we wish to describe our results and present a proposed mechanistic scenario.



Scheme 1. Synthesis of α-alkylidene-β-lactams **3** from α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1**.

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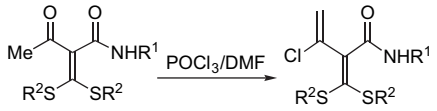
Table 1
Synthesis of compounds **2** from substrates **1** under Vilsmeier conditions



1 **2**

Entry	1	R^1	R^2	2	Yield[a] [%]
1	**1a**	C_6H_5	Me	**2a**	85
2	**1b**	C_6H_5	Et	**2b**	82
3	**1c**	4-MeC_6H_4	Me	**2c**	86
4	**1d**	4-MeC_6H_4	Et	**2d**	87
5	**1e**	4-$MeOC_6H_4$	Me	**2e**	86
6	**1f**	4-$MeOC_6H_4$	Et	**2f**	84
7	**1g**	4-ClC_6H_4	Me	**2g**	91
8	**1h**	4-ClC_6H_4	Et	**2h**	90
9	**1i**	2,4-$Me_2C_6H_3$	Me	**2i**	86
10	**1j**	2,4-$Me_2C_6H_3$	Et	**2j**	88
11	**1k**	Me	Me	**2k**	87
12	**1l**	Me	Et	**2l**	83

[a] Isolated yields.

2. Results and discussion

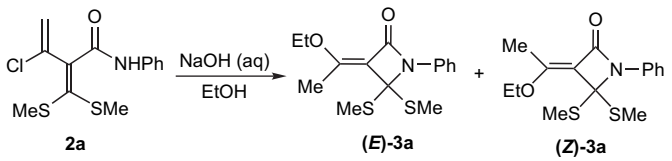
2.1. Synthesis of α-(1-chlorovinyl), α-carbamoyl ketene-*S*,*S*-acetals 2

The substrates, α-acyl, α-carbamoyl ketene-*S*,*S*-acetals **1**, were prepared from commercially available β-oxo amides in water in excellent yields following the procedure described in our previous work.[16] Upon treatment of compounds **1** with Vilsmeier reagent ($POCl_3$/DMF, 1.1 equiv) at 0 °C for 10 h, a series of compounds **2a**–**l** were synthesized in good yields (Table 1). The structure of **2a** was confirmed by the X-ray single-crystal analyses.[17]

2.2. Synthesis of substituted α-alkylidene-β-lactams 3

With compounds **2a**–**l** in hand, we selected 2-[bis (methylthio)methylene]-3-chloro-*N*-phenylbut-3-enamide **2a** as the model compound to examine its behavior under different basic conditions. Thus, the reaction of **2a** was performed in aqueous NaOH (2.0 equiv, 1.0 N)/ethanol at ambient temperature (20 °C) for 15 h. Workup and purification by column chromatography of the resulting mixture furnished two main products, which were characterized as (*E*)- and (*Z*)-3-(1-ethoxyethylidene)-4,4-bis(methylthio)-1-phenylazetidin-2-ones, i.e., **(*E*)-3a** and **(*Z*)-3a**, on the basis of their spectral and analytical data (Scheme 2). The structure and stereochemistry of **(*E*)-3a** were established by the X-ray single-crystal analysis (Fig. 1).[17] The results suggest that ethanol plays dual roles as a co-solvent and a nucleophilic species in the cyclization reaction.

It is of interest to note that the obtained compounds **(*E*)-** and **(*Z*)-3a** have remarkable structural and functional complexity since they contain the key skeleton of β-lactams. Certainly, the substituted α-alkylidene-β-lactams, as an important subset of azetidinones, have attracted significant interest among synthetic and medicinal



2a **(*E*)-3a** **(*Z*)-3a**

Scheme 2. The reaction of **2a** in NaOH (aq)/EtOH.

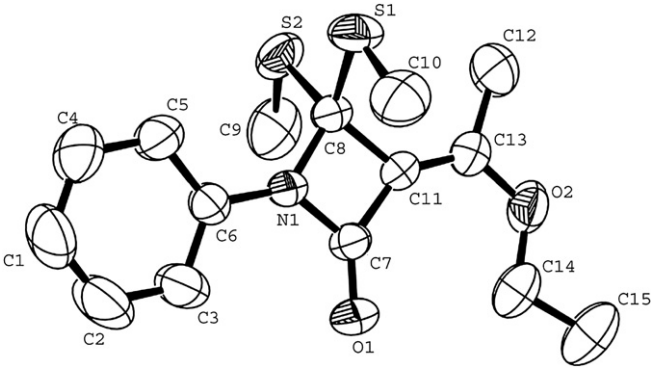


Figure 1. ORTEP drawing of **(*E*)-3a**.

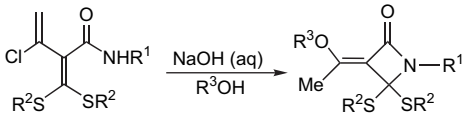
chemists over the years mainly because of their biologically activities and their utilities as useful building blocks in organic synthesis.[18–20]

The above findings encouraged us to investigate the reactions of **2a** for the construction of the 2-azetidinone skeletons under varied conditions. Thus, a series experiments were carried out with the aim at optimizing the reaction conditions, including the base, solvents, and reaction temperature. It was found that in the presence of K_2CO_3 (aq) in ethanol, the reaction proceeded sluggishly to afford both isomers of **3a** in much lower yields. Even no desired product **3a** was obtained when **2a** was treated with NaOH, NaH or NaOEt in absolute ethanol. We assumed that in the above cases, water might merely act as a better co-solvent for the employed base thus promoting the target cyclization. The accelerating properties of water when used as a convenient additive or co-solvent in other organic reactions have been reported elsewhere and therefore other roles should be considered.[21] Using ethanol as a reactant, we performed the reaction of **2a** with aqueous NaOH in other solvents such as CH_2Cl_2, DMF, THF, and water. By comparison, the optimal conditions were obtained when **2a** (2.0 mmol) was subjected to NaOH (aq, 1.0 N, 3.0 equiv) in ethanol (25 mL) at 30 °C for 12 h, whereby the yields of **(*E*)-** and **(*Z*)-3a** could reach 69 and 23%, respectively (Table 2, entry 1).

Having established the optimal conditions for the cyclization, we intended to determine its scope with respect to the amide and sulfanyl functionalities, and the nucleophilic species involved. Thus, substrates **2b**–**l** bearing varied amide groups were treated with aqueous NaOH in ethanol under the optimized reaction conditions as for **3a**. The effectiveness of the cyclization proved to be suitable for *N*-arylamides **2b**–**j** affording the corresponding compounds of type **3** in moderate to good yields (Table 2, entries 2–10). It is worth noting that in all the cases of **2b**–**j**, only isomer **(*E*)-3** was obtained. For *N*-alkylamides **2k** and **2l**, the reactions proceeded smoothly to furnish the corresponding **3k** and **3l**, in which both (*E*)- and (*Z*)-isomers were obtained with the (*E*)-isomer as the predominant one (Table 2, entries 11 and 12). All the results revealed that the cyclization reaction exhibited high stereoselectivity.

As an extension of the above cyclization, a series of reactions was performed on substrates **2** in methanol under the otherwise identical conditions. Thus, the corresponding substituted 2-azetidinones of type **(*E*)-3** were synthesized stereoselectively from amides **2a**–**l** in moderate to good yields (Table 2, entries 13–24). It was observed that, only in the case of *N*-alkylamide **2k**, both isomers **(*E*)-**, and **(*Z*)-3w** were obtained with the ratio of 5:2 (Table 2, entry 23). The validity of this 2-azetidinone synthesis was further evaluated in isopropanol by using **2a** as a representative example (Table 2, entry 25). However, when **2a** was subjected to aqueous NaOH in *tert*-butanol, the cyclization to the corresponding 2-azetidinone was unsuccessful, and only the intact substrate was recovered (Table 2, entry 26). This may be due to the weak nucleophilicity and the hindered stereo effect of the bulky *tert*-butyl

Table 2
Synthesis of α-alkylidene-β-lactams **3** from **2** in aqueous media



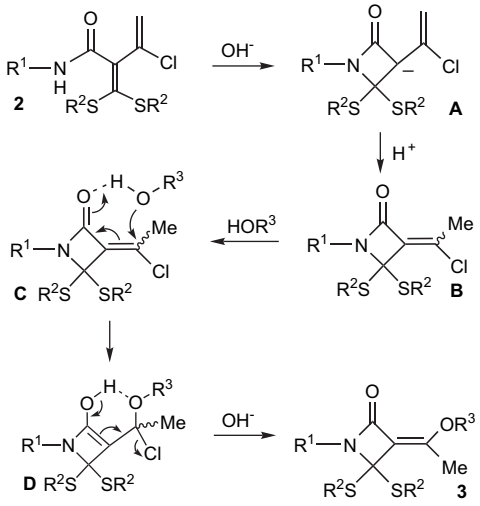
2 **3**

Entry	2	R^1	R^2	R^3	Time [h]	3	Yield[a] [%]
1	**2a**	C_6H_5	Me	Et	12	**3a**	69 (23)
2	**2b**	C_6H_5	Et	Et	21	**3b**	61
3	**2c**	4-MeC_6H_4	Me	Et	15	**3c**	80
4	**2d**	4-MeC_6H_4	Et	Et	18	**3d**	76
5	**2e**	4-$MeOC_6H_4$	Me	Et	19	**3e**	88
6	**2f**	4-$MeOC_6H_4$	Et	Et	26	**3f**	68
7	**2g**	4-ClC_6H_4	Me	Et	11	**3g**	94
8	**2h**	4-ClC_6H_4	Et	Et	48	**3h**	67
9	**2i**	2,4-$Me_2C_6H_3$	Me	Et	44	**3i**	64
10	**2j**	2,4-$Me_2C_6H_3$	Et	Et	42	**3j**	77
11	**2k**	Me	Me	Et	56	**3k**	43 (18)
12	**2l**	Me	Et	Et	50	**3l**	52 (21)
13	**2a**	C_6H_5	Me	Me	36	**3m**	78
14	**2b**	C_6H_5	Et	Me	42	**3n**	56
15	**2c**	4-MeC_6H_4	Me	Me	38	**3o**	57
16	**2d**	4-MeC_6H_4	Et	Me	48	**3p**	59
17	**2e**	4-$MeOC_6H_4$	Me	Me	40	**3q**	84
18	**2f**	4-$MeOC_6H_4$	Et	Me	58	**3r**	60
19	**2g**	4-ClC_6H_4	Me	Me	34	**3s**	87
20	**2h**	4-ClC_6H_4	Et	Me	48	**3t**	63
21	**2i**	2,4-$Me_2C_6H_3$	Me	Me	56	**3u**	60
22	**2j**	2,4-$Me_2C_6H_3$	Et	Me	32	**3v**	54
23	**2k**	Me	Me	Me	56	**3w**	41 (16)
24	**2l**	Me	Et	Me	60	**3x**	47
25	**2a**	C_6H_5	Me	*i*-Pr	32	**3y**	45
26	**2a**	C_6H_5	Me	*t*-Bu	48	**3z**	No reaction

[a] Isolated yields for **(*E*)-3** and the data in parentheses for **(*Z*)-3**.

group of the alkoxide nucleophile. Nevertheless, we provided an alternative access to α-alkylidene-β-lactams **3** via aqueous base-induced cyclization of α-carbamoyl ketene-*S*,*S*-acetals **2** in the presence of alcoholic co-solvent. It should be noted that the richness of the functionality of substituted α-alkylidene-β-lactams **3** may render them versatile as synthons in further synthetic transformations, for example, upon hydrogenation or Michael addition reaction to produce the corresponding substituted β-lactams analogues bearing two chiral carbon atoms.

Pak and co-workers had ever reported the synthesis of 2-quinolinones through thermal cyclization of α-carbamoyl ketene-*S*,*S*-acetals **1** in NaH/DMF.[22] Recently, they corrected the structure of the product as substituted 4-quinolinone, and proposed an aza-Michael addition mechanism and trapped the unstable 2-azetidinone intermediates by the use of alkylhalides.[23] On the basis of our results obtained together with the reported literatures,[23,24] a plausible mechanism for the cyclization reaction of amides **2** is presented in Scheme 3. The transformation commences from an intramolecular aza-Michael addition of the nitrogen atom to the unsaturated β-carbon of **2** under basic conditions, generating a carboanionic intermediate **A**. Clearly, anionic **A** is stabilized via delocalization of negative charge to the adjacent vinyl and amide groups, and can be regarded as a 1,3-nucleophilic 3-carbon species, which subsequently undergoes protonation reaction in alcoholic aqueous media to afford intermediate **B**. Finally, the displacement of chloride of **B** by alkoxide via a nucleophilic vinylic substitution (S_NV)[25] reaction gives rise to 2-azetidinone **3**. During the S_NV reaction, the hydrogen bonding interaction between intermediate **B** and alcohol leads to the formation of intermediates **C** and **D**, and hence results in the high stereoselectivity of products **3**. On the other hand, alkylthio groups might be distorted by bulkier substituents on the nitrogen atom, and this protects the attack of



Scheme 3. Plausible mechanism for the cyclization of **2** in aqueous media.

alkoxide from the side of alkylthio groups. Thus, when methyl group is attached to the nitrogen atom, alkoxide may attack from the side of alkylthio groups. Actually, substituents on the sulfur of **2** and the nucleophilicity of alkoxide also affect the stereochemistry.

3. Conclusion

In summary, we have described a facile and efficient synthesis of substituted α-alkylidene-β-lactams of type **3** via NaOH-promoted intramolecular cyclization reaction of α-carbamoyl, α-(1-chlorovinyl) ketene-*S*,*S*-acetals **2** in alcoholic aqueous media. The key cyclization involves intramolecular aza-Michael addition of **2** and subsequent S_NV reaction with alcohol under basic conditions. The simplicity of execution, ready availability of substrates, and important synthetic potential of products make this synthetic strategy attractive and practical. Further studies on the expansion of the scope and synthetic utility of this protocol are in progress.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400–4000 cm^{-1}.

4.2. Typical for the synthesis of 2a–l (2a as an example)

The Vilsmeier reagent was prepared by adding $POCl_3$ (10 mmol) dropwise to ice cold dry DMF (5 mL) under stirring. The mixture was then stirred for 10–15 min at 0 °C. To the above Vilsmeier reagent was added 2-[bis(methylthio)methylene]-3-oxo-*N*-phenylbutanamide **1a** (10 mmol) as a solution in DMF (20 mL). Then the mixture was allowed to warm to room temperature and then stirred for 12 h. After the starting material was consumed (monitored by TLC), the reaction mixture was poured into saturated aqueous NaCl (50 mL). The mixture was extracted with dichloromethane (3×30 mL), the combined organic phase was washed with water (2×30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/diethyl ether 12:1) to give **2a** (2.55 g, 85%) as a white solid.

4.3. Selected data for 2a–l

*4.3.1. 2-(Bis(methylthio)methylene)-3-chloro-N-phenylbut-3-enamide (**2a**)*

White solid; mp 129–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.44 (d, J=3.0 Hz, 6H), 5.58 (s, 1H), 5.76 (s, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.34 (t, J=8.0 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.7, 120.1, 120.8, 124.9, 129.3, 134.9, 135.2, 137.8, 150.2, 162.9; IR (KBr, neat): ν=3291, 1699, 1650, 1620, 1597, 1539, 1436, 1396, 905, 757 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClNOS_2$: C, 52.07; H, 4.71; N, 4.67. Found: C, 52.20; H, 4.87; N, 4.82.

Crystal data for **2a**: $C_{13}H_{14}ClNOS_2$, M_r=299.82, approximate dimensions of crystal fragment 0.34×0.31×0.27 mm^3, orthorhombic, space group *Pna*2 (1), a=9.868(2), b=17.237(4), c=8.728(2) Å, V=1881.2(5) Å^3, T=293(2) K, Z=4, ρ_{calcd}=1.342 Mg m^{-3}, $2\theta_{max}$=56.80°, Mo Kα radiation (λ=0.71073 Å), $R1$=0.0584 (for 10,386 reflections with $I>2\sigma(I)$), wR_2=0.1227, and S=1.025 for 163 parameters and 3285 unique reflections. Minimum/maximum residual electron density −0.370/0.345 e Å^{-3}.

*4.3.2. 2-(Bis(ethylthio)methylene)-3-chloro-N-phenylbut-3-enamide (**2b**)*

White solid; mp 93–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.28–1.32 (m, 6H), 2.88–2.94 (m, 4H), 5.56 (s, 1H), 5.73 (s, 1H), 7.13 (t, J=7.0 Hz, 1H), 7.34 (t, J=8.0 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.0, 15.1, 29.3, 29.6, 120.1, 120.6, 124.9, 129.3, 134.7, 137.9, 138.2, 145.8, 163.0; IR (KBr, neat): ν=3272, 2968, 1649, 1600, 1540, 1440, 1323, 1260, 971, 757 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNOS_2$: C, 54.94; H, 5.53; N, 4.27. Found: C, 54.81; H, 5.63; N, 4.39.

*4.3.3. 2-(Bis(methylthio)methylene)-3-chloro-N-p-tolylbut-3-enamide (**2c**)*

White solid; mp 103–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.32 (s, 3H), 2.43 (d, J=3.0 Hz, 6H), 5.57 (s, 1H), 5.74 (s, 1H), 7.13 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.0 Hz, 2H), 7.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.6, 21.2, 120.2, 120.7, 129.8, 134.6, 134.9, 135.3, 135.4, 149.8, 162.8; IR (KBr, neat): ν=3281, 2923, 2854, 1649, 1539, 1512, 1456, 672 cm^{-1}. Anal. Calcd for $C_{14}H_{16}ClNOS_2$: C, 53.57; H, 5.14; N, 4.46. Found: C, 53.71; H, 5.02; N, 4.39.

*4.3.4. 2-(Bis(ethylthio)methylene)-3-chloro-N-p-tolylbut-3-enamide (**2d**)*

White solid; mp 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.28–1.33 (m, 6H), 2.33 (s, 3H), 2.88–2.94 (m, 4H), 5.56 (s, 1H), 5.73 (s, 1H), 7.15 (d, J=8.0 Hz, 2H), 7.47 (d, J=8.0 Hz, 2H), 7.58 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.0, 15.2, 21.2, 29.3, 29.5, 120.1, 120.5, 129.8, 134.5, 134.7, 135.3, 138.3, 145.5, 162.9; IR (KBr, neat): ν=3278, 2923, 1649, 1539, 1556, 1512, 1456, 1399, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClNOS_2$: C, 56.20; H, 5.90; N, 4.10. Found: C, 56.31; H, 6.03; N, 4.25.

*4.3.5. 2-(Bis(methylthio)methylene)-3-chloro-N-(4-methoxyphenyl)but-3-enamide (**2e**)*

White solid; mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.44 (s, 6H), 3.80 (s, 3H), 5.57 (s, 1H), 5.75 (s, 1H), 6.87 (d, J=8.0 Hz, 2H), 7.49 (d, J=8.0 Hz, 2H), 7.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.6, 18.7, 55.8, 114.4, 120.7, 122.0, 130.9, 134.9, 135.3, 149.7, 156.9, 162.8; IR (KBr, neat): ν=3267, 1699, 1648, 1540, 1507, 1457, 1414, 1316, 1277, 1172, 1109, 1023, 827, 762 cm^{-1}. Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.98; H, 4.89; N, 4.25. Found: C, 50.85; H, 4.80; N, 4.37.

*4.3.6. 2-(Bis(ethylthio)methylene)-3-chloro-N-(4-methoxyphenyl)but-3-enamide (**2f**)*

White solid; mp 89–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.27–1.32 (m, 6H), 2.87–2.94 (m, 4H), 3.80 (s, 3H), 5.55 (s, 1H), 5.72 (s, 1H), 6.87 (d, J=9.0 Hz, 2H), 7.49 (d, J=9.0 Hz, 2H), 7.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.0, 15.2, 29.3, 29.5, 55.8, 114.4, 120.5, 121.9, 130.9, 134.7, 138.3, 145.3, 156.9, 162.9; IR (KBr, neat): ν=3239, 2932, 1602, 1541, 1513, 1454, 1252, 831, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClNO_2S_2$: C, 53.69; H, 5.63; N, 3.91. Found: C, 53.81; H, 5.72; N, 3.85.

*4.3.7. 2-(Bis(methylthio)methylene)-3-chloro-N-(4-chlorophenyl)but-3-enamide (**2g**)*

White solid; mp 133–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.44 (s, 6H), 5.57 (s, 1H), 5.76 (s, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.53 (d, J=8.0 Hz, 2H), 7.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.7, 121.0, 121.4, 129.3, 129.9, 134.7, 134.8, 136.4, 151.2, 162.8; IR (KBr, neat): ν=3294, 1649, 1599, 1539, 1491, 1396, 1320, 1261, 831, 737 cm^{-1}. Anal. Calcd for $C_{13}H_{13}Cl_2NOS_2$: C, 46.71; H, 3.92; N, 4.19. Found: C, 46.57; H, 3.80; N, 4.31.

*4.3.8. 2-(Bis(ethylthio)methylene)-3-chloro-N-(4-chlorophenyl)but-3-enamide (**2h**)*

White solid; mp 110–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.27–1.32 (m, 6H), 2.88–2.94 (m, 4H), 5.55 (s, 1H), 5.74 (s, 1H), 7.30 (d, J=8.5 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 7.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.7, 14.9, 29.2, 29.3, 120.6, 121.0, 129.0, 129.5, 134.3, 136.1, 137.3, 146.5, 162.7; IR (KBr, neat): ν=3290, 1699, 1651, 1598, 1532, 1437, 1396, 1255, 830, 734 cm^{-1}. Anal. Calcd for $C_{15}H_{17}Cl_2NOS_2$: C, 49.72; H, 4.73; N, 3.87. Found: C, 49.65; H, 4.57; N, 3.96.

*4.3.9. 2-(Bis(methylthio)methylene)-3-chloro-N-(2,4-dimethylphenyl)but-3-enamide (**2i**)*

White solid; mp 93–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.25 (s, 3H), 2.29 (s, 3H), 2.45 (d, J=7.0 Hz, 6H), 5.58 (s, 1H), 5.76 (s, 1H), 7.00 (s, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.45 (s, 1H), 7.80 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.6, 17.3, 17.4, 19.9, 119.2, 121.7, 126.3, 128.0, 130.1, 131.8, 134.0, 148.7, 161.5; IR (KBr, neat): ν=3197, 2996, 1699, 1639, 1556, 1512, 1456, 1372, 899, 741 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNOS_2$: C, 54.94; H, 5.53; N, 4.27. Found: C, 54.86; H, 5.69; N, 4.15.

*4.3.10. 2-(Bis(ethylthio)methylene)-3-chloro-N-(2,4-dimethylphenyl)but-3-enamide (**2j**)*

White solid; mp 119–120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.28–1.33 (m, 6H), 2.26 (s, 3H), 2.29 (s, 3H), 2.90–2.94 (m, 4H), 5.57 (s, 1H), 5.74 (s, 1H), 7.00 (s, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.43 (s, 1H), 7.80 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6, 14.9, 17.7, 20.9, 29.1, 29.2, 120.1, 122.7, 127.3, 129.1, 131.1, 132.8, 134.7, 134.9, 138.1, 145.4, 162.6; IR (KBr, neat): ν=3197, 2966, 2925, 1638, 1539, 1523, 1455, 1263, 899, 741 cm^{-1}. Anal. Calcd for $C_{17}H_{22}ClNOS_2$: C, 57.36; H, 6.23; N, 3.94. Found: C, 57.43; H, 6.35; N, 4.07.

*4.3.11. 2-(Bis(methylthio)methylene)-3-chloro-N-methylbut-3-enamide (**2k**)*

White solid; mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.40 (d, J=7.0 Hz, 6H), 2.91 (d, J=5.0 Hz, 3H), 5.48 (s, 1H), 5.67 (s, 1H), 5.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=15.7, 15.8, 24.4, 117.5, 132.3, 133.4, 145.3, 163.2; IR (KBr, neat): ν=3230, 2921, 1632, 1557, 1524, 1402, 1306, 1198, 801, 734 cm^{-1}. Anal. Calcd for $C_8H_{12}ClNOS_2$: C, 40.41; H, 5.09; N, 5.89. Found: C, 40.54; H, 4.97; N, 5.97.

*4.3.12. 2-(Bis(ethylthio)methylene)-3-chloro-N-methylbut-3-enamide (**2l**)*

White solid; mp 69–70 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.26–1.29 (m, 6H), 2.84–2.92 (m, 4H), 2.97 (d, J=5.0 Hz, 3H), 5.47 (s, 1H), 5.65 (s, 1H), 5.88 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.6, 14.8, 26.6, 28.6, 28.7, 119.7, 134.2, 138.6, 143.3, 165.5; IR (KBr, neat):

ν=3236, 2927, 1632, 1541, 1452, 1403, 1179, 1084, 903, 788 cm^{-1}. Anal. Calcd for $C_{10}H_{16}ClNOS_2$: C, 45.18; H, 6.07; N, 5.27. Found: C, 45.26; H, 6.21; N, 5.15.

4.4. Typical for the synthesis of 3a–y (3a as an example)

To a 50 mL round-flask was added **2a** (2.00 mmol, 0.60 g), EtOH (25 mL), and a solution of NaOH (10.0 mmol, 0.40 g) in water (10 mL). The mixture was stirred at room temperature for 12 h. After the starting material was consumed (monitored by TLC), the reaction mixture was poured into saturated aqueous NaCl (50 mL). The mixture was extracted with dichloromethane (3×20 mL), the combined organic phase was washed with water (2×30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/diethyl ether 15:1) to give **(*E*)-3a** (0.41 g, 69%) and **(*Z*)-3a** (0.14 g, 23%), respectively.

4.5. Selected data for 3a–y

*4.5.1. (E)-3-(1-Ethoxyethylidene)-4,4-bis(methylthio)-1-phenylazetidin-2-one ((**E**)-3a)*

White solid; mp 92–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.39 (t, J=7.0 Hz, 3H), 1.97 (s, 6H), 2.14 (s, 3H), 4.49–4.54 (m, 2H), 7.12 (t, J=7.5 Hz, 1H), 7.36 (t, J=8.0 Hz, 2H), 7.94 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 15.2, 17.7, 69.8, 79.9, 109.7, 117.6, 124.2, 129.1, 136.9, 157.7, 157.8; IR (KBr, neat): ν=2921, 1732, 1652, 1591, 1504, 1456, 1396, 1354, 1310, 883, 786 cm^{-1}; MS: calcd m/z 309.1, found 310.0 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.31; H, 6.07; N, 4.65.

Crystal data for **(*E*)-3a**: $C_{15}H_{19}NO_2S_2$, M_r=309.43, approximate dimensions of crystal fragment 0.43×0.28×0.15 mm^3, monoclinic, space group $P2(1)/c$, a=16.476(3), b=14.837(3), c=14.834(3) Å, β=116.56(3)°, V=3243.5(11) $Å^3$, T=293(2) K, Z=8, ρ_{calcd}=1.267 Mg m^{-3}, $2\theta_{max}$=50.00°, Mo Kα radiation (λ=0.71073 Å), $R1$=0.0505 (for 24,449 reflections with $I>2\sigma(I)$), wR_2=0.1362, and S=1.102 for 369 parameters and 5771 unique reflections. Minimum/maximum residual electron density −0.180/0.264 e $Å^{-3}$.

*4.5.2. (Z)-3-(1-Ethoxyethylidene)-4,4-bis(methylthio)-1-phenylazetidin-2-one ((**Z**)-3a)*

White solid; mp 85–87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.35 (t, J=7.0 Hz, 3H), 2.04 (s, 6H), 2.36 (s, 3H), 4.43 (q, J=7.0 Hz, 2H), 7.09 (t, J=7.0 Hz, 1H), 7.32 (t, J=8.0 Hz, 2H), 7.88 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.3, 15.7, 17.0, 66.4, 80.9, 112.1, 117.4, 123.9, 129.1, 137.1, 157.2, 161.7; IR (KBr, neat): 2920, 1739, 1654, 1540, 1493, 1352, 1281, 753 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.33; H, 6.10; N, 4.64.

*4.5.3. (E)-3-(1-Ethoxyethylidene)-4,4-bis(ethylthio)-1-phenylazetidin-2-one ((**E**)-3b)*

White solid; mp 79–81 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 1.38 (t, J=7.0 Hz, 3H), 2.16 (s, 3H), 2.43–2.53 (m, 4H), 4.49–4.53 (m, 2H), 7.11 (t, J=7.5 Hz, 1H), 7.35 (t, J=7.5 Hz, 2H), 7.95 (d, J=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.0, 14.2, 17.0, 23.1, 68.7, 79.2, 110.6, 116.8, 123.0, 128.0, 136.0, 156.4, 156.8; IR (KBr, neat): ν=2921, 2850, 1738, 1652, 1593, 1456, 1352, 1285, 843, 752 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2S_2$: C, 60.50; H, 6.87; N, 4.15. Found: C, 60.63; H, 6.72; N, 4.26.

*4.5.4. (E)-3-(1-Ethoxyethylidene)-4,4-bis(methylthio)-1-p-tolylazetidin-2-one ((**E**)-3c)*

White solid; mp 66–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.38 (t, J=7.0 Hz, 3H), 1.96 (s, 3H), 2.13 (s, 3H), 2.33 (s, 3H), 4.49–4.53 (m, 2H), 7.16 (d, J=8.0 Hz, 2H), 7.83 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 15.2, 17.7, 21.3, 69.8, 79.9, 109.7, 117.6, 129.7, 133.9, 134.4, 157.3, 157.7; IR (KBr, neat): ν=2924, 2854, 1738, 1659, 1513, 1461, 1349, 1287, 1049, 844 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2S_2$: C, 61.50; H, 7.17; N, 3.98. Found: C, 61.38; H, 7.27; N, 4.12.

*4.5.5. (E)-3-(1-Ethoxyethylidene)-4,4-bis(ethylthio)-1-p-tolylazetidin-2-one ((**E**)-3d)*

White solid; mp 77–79 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.13 (t, J=7.0 Hz, 6H), 1.38 (t, J=7.0 Hz, 3H), 2.15 (s, 3H), 2.33 (s, 3H), 2.43–2.54 (m, 4H), 4.47–4.52 (m, 2H), 7.16 (d, J=8.0 Hz, 2H), 7.84 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.7, 14.9, 17.6, 20.9, 23.7, 69.3, 79.8, 111.4, 117.5, 129.3, 129.7, 133.4, 134.1, 156.7, 157.4; IR (KBr, neat): ν=2966, 2861, 2361, 1739, 1659, 1513, 1441, 1355, 1280, 1115, 844 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2S_2$: C, 61.50; H, 7.17; N, 3.98. Found: C, 61.39; H, 7.31; N, 4.11.

*4.5.6. (E)-3-(1-Ethoxyethylidene)-1-(4-methoxyphenyl)-4,4-bis(methylthio)azetidin-2-one ((**E**)-3e)*

White solid; mp 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.38 (t, J=7.0 Hz, 3H), 1.97 (s, 6H), 2.13 (s, 3H), 3.80 (s, 3H), 4.48–4.52 (m, 2H), 6.90 (d, J=8.0 Hz, 2H), 7.88 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 15.2, 17.6, 55.7, 69.7, 80.0, 109.7, 114.4, 119.2, 130.3, 156.4, 157.0, 157.6; IR (KBr, neat): ν=2923, 2853, 2361, 1735, 1665, 1509, 1463, 1361, 1284, 1179, 1052, 835 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_3S_2$: C, 56.61; H, 6.24; N, 4.13. Found: C, 56.48; H, 6.11; N, 4.24.

*4.5.7. (E)-3-(1-Ethoxyethylidene)-4,4-bis(ethylthio)-1-(4-methoxyphenyl)azetidin-2-one ((**E**)-3f)*

White solid; mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 1.38 (t, J=7.0 Hz, 3H), 2.15 (s, 3H), 2.43–2.53 (m, 4H), 3.81 (s, 3H), 4.47–4.51 (m, 2H), 6.90 (d, J=9.0 Hz, 2H), 7.88 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0, 15.2, 17.9, 24.4, 55.6, 69.6, 80.3, 111.7, 114.3, 119.4, 130.4, 156.2, 156.7, 157.5; IR (KBr, neat): ν=2926, 2852, 2362, 1729, 1662, 1509, 1450, 1356, 1287, 1181, 1050, 839 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_3S_2$: C, 58.82; H, 6.86; N, 3.81. Found: C, 58.95; H, 6.75; N, 3.93.

*4.5.8. (E)-1-(4-Chlorophenyl)-3-(1-ethoxyethylidene)-4,4-bis(methylthio)azetidin-2-one ((**E**)-3g)*

White solid; mp 67–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.38 (t, J=7.0 Hz, 3H), 1.94 (s, 6H), 2.13 (s, 3H), 4.47–4.52 (m, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.89 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 15.2, 17.7, 69.9, 80.0, 109.4, 118.8, 129.2, 129.3, 135.3, 157.6, 158.2; IR (KBr, neat): ν=2919, 1732, 1654, 1492, 1354, 1292, 1180, 1050, 839, 791 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ClNO_2S_2$: C, 52.39; H, 5.28; N, 4.07. Found: C, 52.54; H, 5.39; N, 4.14.

*4.5.9. (E)-1-(4-Chlorophenyl)-3-(1-ethoxyethylidene)-4,4-bis(ethylthio)azetidin-2-one ((**E**)-3h)*

White solid; mp 76–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 1.38 (t, J=7.0 Hz, 3H), 2.16 (s, 3H), 2.39–2.53 (m, 4H), 4.47–4.51 (m, 2H), 7.31 (d, J=8.5 Hz, 2H), 7.90 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.7, 14.9, 17.7, 23.8, 69.5, 80.0, 111.1, 118.7, 128.9, 135.1, 157.4, 157.7; IR (KBr, neat): ν=1740, 1659, 1494, 1353, 1290, 1120, 847, 826 cm^{-1}. Anal. Calcd for $C_{17}H_{22}ClNO_2S_2$: C, 54.90; H, 5.96; N, 3.77. Found: C, 54.79; H, 5.83; N, 3.65.

*4.5.10. (E)-1-(2,4-Dimethylphenyl)-3-(1-ethoxyethylidene)-4,4-bis(methylthio)azetidin-2-one ((**E**)-3i)*

White solid; mp 88–90 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.36 (t, J=7.0 Hz, 3H), 2.07 (s, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 2.38 (s, 3H), 4.47–4.51 (m, 2H), 7.00 (d, J=7.5 Hz, 1H), 7.07 (s, 1H), 7.45 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.9, 13.9, 16.9, 18.6, 20.0, 68.4, 79.8, 109.6, 123.7, 126.0, 130.3, 131.0, 134.6, 136.6, 155.2, 157.1; IR (KBr, neat): ν=2924, 2853, 1749, 1490, 1455, 1361, 1148,

1060, 765 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2S_2$: C, 60.50; H, 6.87; N, 4.15. Found: C, 60.64; H, 6.98; N, 4.31.

*4.5.11. (E)-1-(2,4-Dimethylphenyl)-3-(1-ethoxyethylidene)-4,4-bis(ethylthio)azetidin-2-one (**(E)-3j**)*

White solid; mp 75–77 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.16 (t, J=7.5 Hz, 6H), 1.36 (t, J=7.0 Hz, 3H), 2.15 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.53–2.65 (m, 4H), 4.46–4.50 (q, J=7.5 Hz, 2H), 7.01 (d, J=8.0 Hz, 1H), 7.07 (s, 1H), 7.42 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.8, 14.9, 18.2, 19.5, 21.1, 24.2, 69.3, 81.2, 112.4, 125.2, 126.9, 131.3, 131.9, 135.8, 137.6, 156.0, 158.2; IR (KBr, neat): ν=2924, 2855, 2361, 1739, 1664, 1498, 1348, 1280, 881, 772 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_2S_2$: C, 62.43; H, 7.44; N, 3.83. Found: C, 62.54; H, 7.31; N, 3.95.

*4.5.12. (E)-3-(1-Ethoxyethylidene)-1-methyl-4,4-bis(methylthio)azetidin-2-one (**(E)-3k**)*

White solid; mp 39–41 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.33 (t, J=7.0 Hz, 3H), 1.97 (s, 6H), 2.03 (s, 3H), 2.81 (s, 3H), 4.37–4.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$); δ=12.0, 14.8, 17.0, 23.1, 69.0, 79.5, 110.0, 154.5, 159.9; IR (KBr, neat): ν=2924, 2854, 2337, 1741, 1667, 1459, 1279 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2S_2$: C, 48.55; H, 6.93; N, 5.66. Found: C, 48.67; H, 7.01; N, 5.49.

*4.5.13. (Z)-3-(1-Ethoxyethylidene)-1-methyl-4,4-bis(methylthio)azetidin-2-one (**(Z)-3k**)*

Colorless liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=1.30 (t, J=7.0 Hz, 3H), 2.05 (s, 6H), 2.24 (s, 3H), 2.76 (s, 3H), 4.39–4.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.7, 15.3, 16.9, 23.2, 66.2, 80.8, 111.7, 154.5, 163.6; IR (KBr, neat): ν=2922, 2337, 1744, 1671, 1411, 1363, 1277, 955 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_2S_2$: C, 48.55; H, 6.93; N, 5.66. Found: C, 48.62; H, 7.05; N, 5.54.

*4.5.14. (E)-3-(1-Ethoxyethylidene)-4,4-bis(ethylthio)-1-methylazetidin-2-one (**(E)-3l**)*

Colorless liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=1.21 (t, J=7.0 Hz, 6H), 1.34 (t, J=7.0 Hz, 3H), 2.05 (s, 3H), 2.43–2.50 (m, 4H), 2.82 (s, 3H), 4.36–4.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.1, 14.7, 17.2, 23.0, 23.5, 68.9, 79.8, 117.7, 154.3, 159.9; IR (KBr, neat): ν=2927, 1746, 1675, 1361, 1282, 968, 841 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2S_2$: C, 52.33; H, 7.68; N, 5.09. Found: C, 52.45; H, 7.82; N, 4.95.

*4.5.15. (Z)-3-(1-Ethoxyethylidene)-4,4-bis(ethylthio)-1-methylazetidin-2-one (**(Z)-3l**)*

Colorless liquid; ^1H NMR (500 MHz, $CDCl_3$): δ=1.23 (t, J=7.5 Hz, 6H), 1.32 (t, J=7.0 Hz, 3H), 2.23 (s, 3H), 2.51–2.61 (m, 4H), 2.77 (s, 3H), 4.45–4.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.3, 15.7, 17.2, 23.0, 23.5, 66.4, 81.2, 113.5, 154.3, 164.0; IR (KBr, neat): ν=2927, 1746, 1675, 1361, 1282, 968, 841 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2S_2$: C, 52.33; H, 7.68; N, 5.09. Found: C, 52.44; H, 7.76; N, 5.01.

*4.5.16. (E)-3-(1-Methoxyethylidene)-4,4-bis(methylthio)-1-phenylazetidin-2-one (**(E)-3m**)*

White solid; mp 62–64 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.98 (s, 6H), 2.15 (s, 3H), 4.18 (s, 3H), 7.13 (t, J=7.5 Hz, 1H), 7.37 (t, J=8.0 Hz, 2H), 7.95 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.5, 16.4, 60.6, 78.8, 109.0, 116.6, 123.3, 128.1, 135.9, 156.7, 157.7; IR (KBr, neat): 2982, 2358, 1731, 1664, 1592, 1492, 1354, 1284, 844, 755 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74. Found: C, 56.84; H, 5.68; N, 4.83.

*4.5.17. (E)-4,4-Bis(ethylthio)-3-(1-methoxyethylidene)-1-phenylazetidin-2-one (**(E)-3n**)*

White solid; mp 60–63 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 2.16 (s, 3H), 2.44–2.54 (m, 4H), 4.16 (s, 3H), 7.11 (t, J=7.5 Hz, 1H), 7.35 (t, J=8.0 Hz, 2H), 7.95 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.7, 16.4, 22.8, 60.2, 78.8, 110.7, 116.6, 122.8, 127.8, 135.6, 156.4, 157.1; IR (KBr, neat): ν=2920, 2852, 2359, 1739, 1683, 1593, 1471, 1375, 1283, 842, 753 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.53; H, 6.61; N, 4.41.

*4.5.18. (E)-3-(1-Methoxyethylidene)-4,4-bis(methylthio)-1-p-tolylazetidin-2-one (**(E)-3o**)*

White solid; mp 104–106 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.97 (s, 6H), 2.13 (s, 3H), 2.33 (s, 3H), 4.16 (s, 3H), 7.17 (d, J=8.0 Hz, 2H), 7.84 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 17.3, 21.3, 61.6, 79.7, 110.1, 117.7, 129.7, 134.4, 140.0, 157.6, 158.3; IR (KBr, neat): ν=2924, 2853, 2362, 1733, 1671, 1512, 1454, 1352, 1284, 1047, 837 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2S_2$: C, 58.22; H, 6.19; N, 4.53. Found: C, 58.34; H, 6.11; N, 4.45.

*4.5.19. (E)-4,4-Bis(ethylthio)-3-(1-methoxyethylidene)-1-p-tolylazetidin-2-one (**(E)-3p**)*

White solid; mp 67–69 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.0 Hz, 6H), 2.15 (s, 3H), 2.33 (s, 3H), 2.43–2.53 (m, 4H), 4.16 (s, 3H), 7.16 (d, J=7.5 Hz, 2H), 7.84 (d, J=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0, 17.6, 21.3, 24.1, 61.5, 80.0, 112.1, 117.8, 129.6, 133.8, 134.4, 157.6, 158.0; IR (KBr, neat): ν=2924, 2853, 1733, 1664, 1509, 1454, 1349 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2S_2$: C, 60.50; H, 6.87; N, 4.15. Found: C, 60.42; H, 7.01; N, 4.33.

*4.5.20. (E)-3-(1-Methoxyethylidene)-1-(4-methoxyphenyl)-4,4-bis(methylthio)azetidin-2-one (**(E)-3q**)*

White solid; mp 60–62 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.97 (s, 3H), 2.13 (s, 3H), 3.81 (s, 3H), 4.16 (s, 3H), 6.91 (d, J=8.5 Hz, 2H), 7.88 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.5, 17.3, 55.7, 61.5, 79.9, 110.1, 114.4, 119.2, 130.2, 156.4, 157.4, 158.0; IR (KBr, neat): ν=2923, 2853, 1736, 1669, 1509, 1457, 1360, 1286, 1115, 673 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3S_2$: C, 55.36; H, 5.88; N, 4.30. Found: C, 55.25; H, 5.71; N, 4.42.

*4.5.21. (E)-4,4-Bis(ethylthio)-3-(1-methoxyethylidene)-1-(4-methoxyphenyl)azetidin-2-one (**(E)-3r**)*

White solid; mp 42–44 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 2.14 (s, 3H), 2.43–2.55 (m, 4H), 3.81 (s, 3H), 4.15 (s, 3H), 6.90 (d, J=9.0 Hz, 2H), 7.88 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0, 17.6, 23.0, 24.0, 55.6, 61.5, 80.2, 111.4, 114.3, 119.4, 130.3, 156.3, 157.4, 157.7; IR (KBr, neat): ν=2925, 2854, 1730, 1662, 1509, 1452, 1355, 1243, 1152, 1050, 839 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3S_2$: C, 57.76; H, 6.56; N, 3.96. Found: C, 57.92; H, 6.77; N, 4.14.

*4.5.22. (E)-1-(4-Chlorophenyl)-3-(1-methoxyethylidene)-4,4-bis(methylthio)azetidin-2-one (**(E)-3s**)*

White solid; mp 71–73 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.95 (s, 6H), 2.12 (s, 3H), 4.16 (s, 3H), 7.31 (d, J=8.0 Hz, 2H), 7.89 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.2, 16.1, 60.3, 78.6, 108.5, 117.5, 128.0, 128.1, 134.0, 156.3, 158.0; IR (KBr, neat): ν=2919, 1734, 1664, 1593, 1491, 1452, 1359, 1291, 1150, 1057, 878 cm^{-1}. Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.98; H, 4.89; N, 4.25. Found: C, 50.86; H, 4.98; N, 4.34.

*4.5.23. (E)-1-(4-Chlorophenyl)-4,4-bis(ethylthio)-3-(1-methoxyethylidene)azetidin-2-one (**(E)-3t**)*

White solid; mp 101–103 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=1.12 (t, J=7.5 Hz, 6H), 2.16 (s, 3H), 2.41–2.52 (m, 4H), 4.15 (s, 3H), 7.32 (d, J=8.5 Hz, 2H), 7.90 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=9.3, 12.9, 19.3, 56.8, 75.4, 107.0, 114.3, 124.4, 130.6, 152.8, 154.2; IR (KBr, neat): ν=2966, 2924, 1737, 1658, 1491, 1348, 1292, 1153, 1086, 884 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClNO_2S_2$: C, 53.69; H, 5.63; N, 3.91. Found: C, 53.75; H, 5.54; N, 4.05.

*4.5.24. (E)-1-(2,4-Dimethylphenyl)-3-(1-methoxyethylidene)-4,4-bis(methylthio)azetidin-2-one (**(E)-3u**)*

White solid; mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.08 (s, 6H), 2.11 (s, 3H), 2.32 (s, 3H), 2.39 (s, 3H), 4.14 (s, 3H), 7.00 (d, J=8.0 Hz, 1H), 7.08 (s, 1H), 7.44 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=10.7, 15.3, 17.3, 18.8, 59.0, 78.4, 108.8, 122.5, 124.7, 129.0, 129.7, 133.3, 135.4, 155.0, 155.7; IR (KBr, neat): ν=2920, 1667, 1375, 1341, 1277, 1054, 854 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.58; H, 6.39; N, 4.21.

*4.5.25. (E)-1-(2,4-Dimethylphenyl)-4,4-bis(ethylthio)-3-(1-methoxyethylidene)azetidin-2-one (**(E)-3v**)*

White solid; mp 75–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.50 (t, J=7.5 Hz, 6H), 2.14 (s, 3H), 2.31 (s, 3H), 2.38 (s, 3H), 2.52–2.65 (m, 4H), 4.13 (s, 3H), 7.00 (d, J=8.0 Hz, 1H), 7.07 (s, 1H), 7.41 (d, J=8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.8, 17.9, 19.5, 21.1, 24.2, 61.2, 81.1, 112.7, 125.3, 126.9, 131.3, 131.9, 135.9, 137.6, 157.0, 158.1; IR (KBr, neat): ν=2921, 1734, 1661, 1488, 1348, 1297, 1131, 1054, 854, 751 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_2S_2$: C, 61.50; H, 7.17; N, 3.98. Found: C, 61.42; H, 7.31; N, 4.16.

*4.5.26. (E)-3-(1-Methoxyethylidene)-1-methyl-4,4-bis(methylthio)azetidin-2-one (**(E)-3w**)*

White solid; mp 43–45 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.97 (s, 6H), 2.03 (s, 3H), 2.83 (s, 3H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.0, 16.6, 23.0, 60.9, 79.3, 110.2, 155.5, 159.7; IR (KBr, neat): ν=2922, 2362, 1744, 1675, 1455, 1416, 1363, 1280, 1047, 957, 833 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2S_2$: C, 46.32; H, 6.48; N, 6.00. Found: C, 46.45; H, 6.34; N, 6.12.

*4.5.27. (Z)-3-(1-Methoxyethylidene)-1-methyl-4,4-bis(methylthio)azetidin-2-one (**(Z)-3w**)*

Colorless liquid; yield: 16%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.07 (s, 6H), 2.25 (s, 3H), 2.78 (s, 3H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.6, 16.4, 23.2, 57.8, 80.6, 111.5, 155.0, 163.4; IR (KBr, neat): ν=2922, 2852, 2337, 1746, 1674, 1411, 1362, 1280, 845 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2S_2$: C, 46.32; H, 6.48; N, 6.00. Found: C, 46.22; H, 6.54; N, 6.10.

*4.5.28. (E)-4,4-Bis(ethylthio)-3-(1-methoxyethylidene)-1-methylazetidin-2-one (**(E)-3x**)*

Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.21 (t, J=7.0 Hz, 6H), 2.05 (s, 3H), 2.23 (s, 3H), 2.44–2.50 (m, 4H), 2.83 (s, 3H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.5, 17.3, 22.9, 23.4, 61.2, 80.0, 112.4, 155.6, 160.1; IR (KBr, neat): 2924, 2361, 1739, 1671, 1363, 1277, 841 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_2S_2$: C, 50.54; H, 7.33; N, 5.36. Found: C, 50.67; H, 7.55; N, 5.24.

*4.5.29. (E)-3-(1-Isopropoxyethylidene)-4,4-bis(methylthio)-1-phenylazetidin-2-one (**(E)-3y**)*

White solid; mp 93–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.33 (d, J=6.0 Hz, 6H), 1.96 (s, 6H), 2.17 (s, 3H), 5.36 (m, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.35 (t, J=7.5 Hz, 2H), 7.94 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.3, 21.2, 28.6, 74.3, 78.8, 107.7, 116.2, 122.8, 127.8, 127.9, 135.7, 155.4, 156.5; IR (KBr, neat): ν=2920, 2359, 1731, 1664, 1592, 1491, 1354, 1284, 1115, 879, 754 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.54; H, 6.42; N, 4.41.

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