Ring-Enlargement and Ring-Opening Reactions of 1,2-Thiazetidin-3-one 1,1-Dioxides with Ammonia and Primary Amines as Nucleophiles

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The *N*-benzyl- and *N*-alkyl-substituted 1,2-thiazetidin-3-one 1,1-dioxides **1b**–**d** reacted readily with NH_3 and primary amines *via* ring opening. The reaction with NH_3 proceeded at $-78° \rightarrow$ room temperature yielding ring-opened adducts *via* nucleophilic attack of NH_3 at the sulfonyl group, whereas the reactions with amines at room temperature yielded products *via* attack at the carbonyl group. The *N*-unsubstituted analogue **1a**, when reacted with benzylamine in refluxing EtOH, also gave a product of ring opening *via* nucleophilic attack at the carbonyl group of **1a**. The transamidation-like reactions of the 2-(aminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxides **19a**–**d** proceeded *via* six-, seven-, and eight-membered intermediates, giving the ring-enlarged eight-, nine-, and ten-membered products **21**–**24** (*Schemes 8* and *9*), respectively, in 42–87% yields. The products resulted from the nucleophilic attack of the amino group of the side chain at the carbonyl C-atom. The structure of the eight-membered product **24** with an asymmetrically situated methyl substituent was established by X-ray crystallography.

1. Introduction. – Several studies established that 1,2-thiazetidin-3-one 1,1-dioxides (oxosultams, **1**) are highly reactive compounds. Due to their various functionalities and the ring strain, they readily undergo reactions with nucleophiles. Because of the presence of two electrophilic centers in the molecule, two alternative nucleophilic attacks are possible, either at the carbonyl or at the sulfonyl group.

In a previous paper [1], we have shown that *N*-unsubstituted 4,4-dialkyl-1,2-thiazetidin-3-one 1,1-dioxides **1a** react with 3-amino-2*H*-azirines **2** to give ring-enlargement products **3** (*Scheme 1*). All these reactions proceed in a regioselective way *via* formation of aziridine **A** as an intermediate, in which the nucleophilic attack of the former azirine N(1) atom occurs at the carbonyl group of the 1,2-thiazetidin-3-one 1,1-dioxide.

Other authors [2][3] have shown that 1,2-thiazetidin-3-one 1,1-dioxides undergo ring-opening and ring-enlargement reactions with various nucleophiles. The reported transformations include reactions in which a cleavage of the N–C (type a)) or/and N–S bond (type b)) was observed, *i.e.* the nucleophilic attack occurred at the carbonyl and sulfonyl group, respectively. The results are summarized in *Scheme 2*. Heating of **1** (R = H) with anhydrous hydrazine in EtOH led to hydrazide **4** *via* selective attack at the carbonyl group. Hydrolysis of the same compound with diluted HCl solution yielded 2-carbamoylpropane-2-sulfonic acid (**5**) *via* attack at the sulfonyl group, as well as 2-sulfamoyl-2-methylpropanoic acid (**6**) *via* attack at the carbonyl group. Reduction with $LiAlH_4$ gave the open-chained product **7**, *i.e.*, the former N–C bond has been

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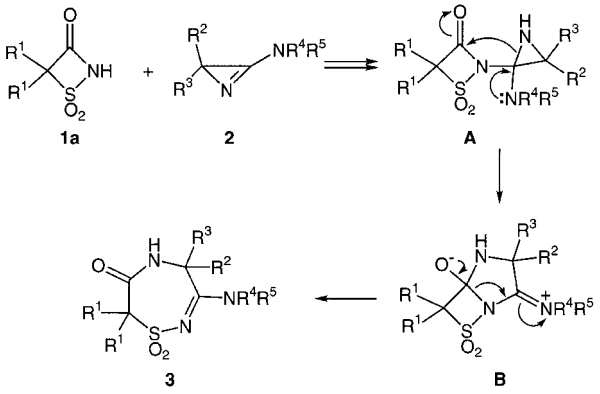
Scheme 1



cleaved [2]. In the case of the *N*-substituted derivative **1** (R = Me), the hydrolysis under acidic conditions led to the sulfonic acid **8**, *i.e.*, the nucleophilic attack occurred at the SO_2 group [2].

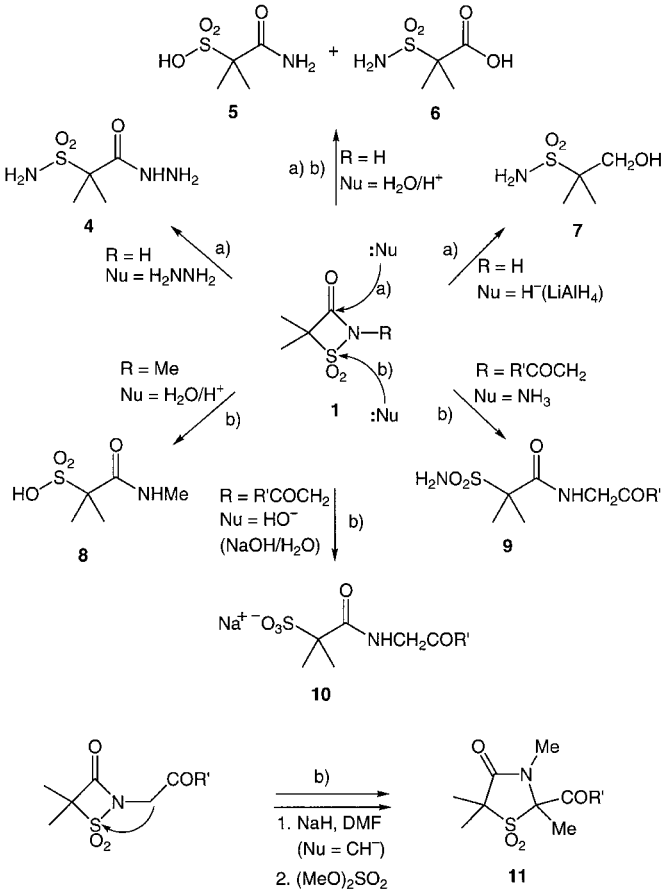
Recently, *Glasl et al.* [3] prepared some 2-(acylmethyl)-4,4-dialkyl-1,2-thiazetidin-3-one 1,1-dioxides **1** (R = R′$COCH_2$). These derivatives, when treated with NH_3 at $-78°$ or refluxed in aqueous NaOH, gave products **9** and **10**, respectively, *via* cleavage of the N–S bond, *i.e.*, *via* nucleophilic attack at the SO_2 group (*Scheme 2*). The reaction with NaH in DMF at $-20°$, followed by treatment with dimethyl sulfate, yielded ring-enlarged products of type **11** *via* intramolecular attack of the deprotonated methylene group at the S-atom.

In the cited papers [2][3], no explanation for the observed selectivity was given. Even though, from the results listed above, it could be concluded that *N*-substituted 1,2-thiazetidin-3-one 1,1-dioxides undergo reactions proceeding mainly *via* nucleophilic attack at the sulfonyl group. But this conclusion is not in accord with the results of the ring enlargements performed by using 3-amino-2*H*-azirines **2** as nucleophiles [1].

With the aim of obtaining further insight into the reactivity of 1,2-thiazetidin-3-one 1,1-dioxides towards nucleophiles, we planned two series of experiments. In the first series, NH_3 and primary amines were reacted with *N*-substituted and *N*-unsubstituted derivatives **1**, respectively, the resulting transformations being ring-opening reactions. In the second series, the nucleophilic NH_2 group was attached to the aliphatic substituent at the N-atom of the thiazetidine molecule (**1**, R = $NH_2(CH_2)_n$), and the transformations were expected to proceed *via* intramolecular ring enlargement.

2. Results and Discussion. – 2.1. *Ring-Opening Reactions with Ammonia and Amines.* Following the procedure described in [2], 2-benzyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide (**1b**) was prepared and its structure confirmed by X-ray crystallography (*Fig. 1*). The 2-cyclohexyl- and 2-isobutyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxides (**1c** and **1d**, resp.) were synthesized following the protocol described in [4][5], and the *N*-unsubstituted derivative **1e** was prepared according to [2].

Scheme 2



a) b) See text.

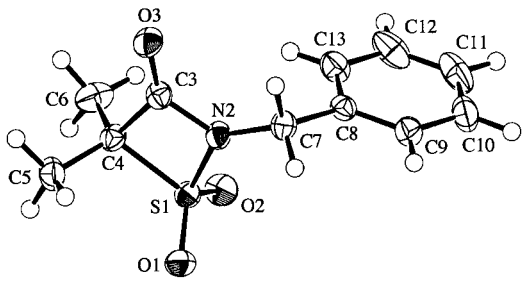
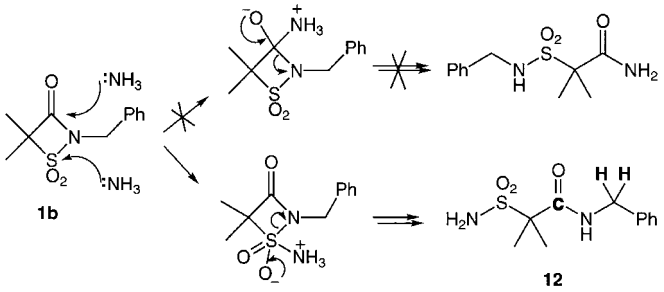


Fig. 1. *ORTEP Plot* [6] *of the molecular structure of* **1b** (displacement ellipsoids with 50% probability)

The reaction of **1b** with NH_3 was performed at $-78°$ in liquid NH_3 as the solvent. The mixture was then allowed to reach room temperature, the NH_3 was evaporated, and the oily residue was treated with Et_2O yielding 91% of *N*-benzyl-2-methyl-2-sulfamoylpropanamide (**12**) as a colorless solid. Obviously, the substance was formed *via* nucleophilic attack of NH_3 at the sulfonyl group of **1b** (*Scheme 3*). The structure of **12** was elucidated from the MS, IR, and NMR data.

Scheme 3

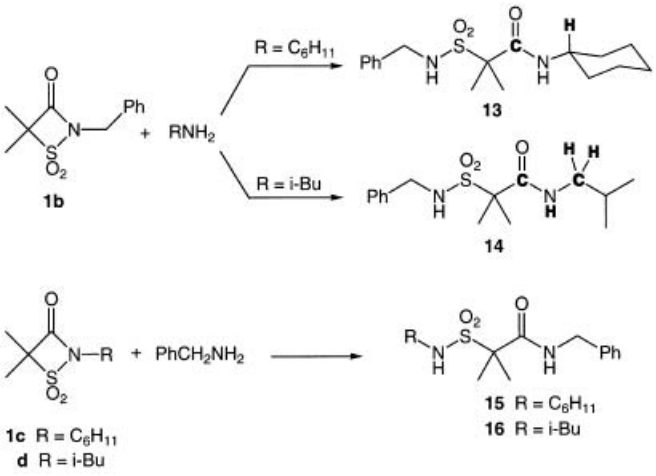


Characteristic differences between the starting material **1b** and the product **12** arose from the opening of the four-membered ring: in the ^{1}H-NMR spectrum, the signal of the H-atoms of the Me groups moved from 1.66 (for **1b**) to 1.53 ppm (for **12**), and in the ^{13}C-NMR spectrum, the signal of the quaternary C-atom was shifted from 83.1 to 65.7 ppm. The direction of the nucleophilic attack was determined by an NMR experiment (HMBC), in which the long-range C,H correlations were measured. A cross-peak between the carbonyl C-atom (*s* at 168.3 ppm) and the H-atoms of the CH_2 group of the benzyl substituent (*d* at 4.33 ppm) was unambiguously detected (the correlating atoms are indicated by bold letters in *Scheme 3*). This result proved the attack of NH_3 at the S-atom followed by cleavage of the S–N bond, *i.e.*, the benzyl group remained close to the carbonyl group.

The reactions of **1b** with cyclohexylamine and isobutylamine were performed first in absolute EtOH with equimolar amounts of reagents. In both cases, after heating to reflux for 2–2.5 h, the only product isolated was the hydrolyzed starting material, formed by the reaction of **1b** and traces of H_2O in the reaction media (*cf.* below, *Scheme 5*). When the amines were taken as solvents and any moisture was excluded carefully, 1:1 adducts of the starting materials were obtained. On the basis of their MS, IR, and NMR data, the structures of the products were determined as 2-(benzylsulfamoyl)-*N*-cyclohexyl-2-methylpropanamide (**13**) and 2-(benzylsulfamoyl)-*N*-isobutyl-2-methylpropanamide (**14**), respectively (*Scheme 4*). The ring opening was proven again by the characteristic signals of the products in the NMR spectra compared with those of **1b**.

In the IR spectra, the absorption band for the carbonyl group moved to longer wavelengths, *i.e.*, from 1770 cm^{-1} (**1b**) to 1645 and 1650 cm^{-1} for **13** and **14**, respectively. The positions of the cyclohexyl and isobutyl substituent were established by NMR experiments (HMBC). Although the signal for the tertiary H-atom of the cyclohexyl group was broadened in the spectrum of **13**, a cross-peak between this H-atom (*m* at *ca.* 3.6 ppm) and the carbonyl C-atom (*s* at 166.7 ppm) was present. In the HMBC spectrum of **14**, the corresponding correlation between the H-atoms of the CH_2 group of the isobutyl substituent (*t* at 2.94 ppm) and the carbonyl C-atom (*s* at 167.5 ppm) was shown. In addition, another NMR experiment (HSQC) was performed in which cross-peaks showed the direct C,H correlations in **14**. This experiment allowed us to distinguish between the signals of the CH_2 C-atoms of the benzyl (*t* at 47.1 ppm) and the isobutyl group (*t* at 46.8 ppm). The H-atoms of the CH_2 group of the benzyl group resonated at lower field (br. *s* at 4.17 ppm) than the H-atoms of the CH_2 group of the

Scheme 4



isobutyl group (*t* at 2.94 ppm). Furthermore, in the long-range HMBC spectrum, the CH_2 C-atom of the isobutyl group showed a cross-peak with the NH proton (*t* at 7.69 ppm), which correlated also with the carbonyl C-atom (the correlating atoms are indicated by bold letters in *Scheme 4*). As a result of the NMR analyses, the sequence $CO-NH-CH_2-CHMe_2$ was confirmed.

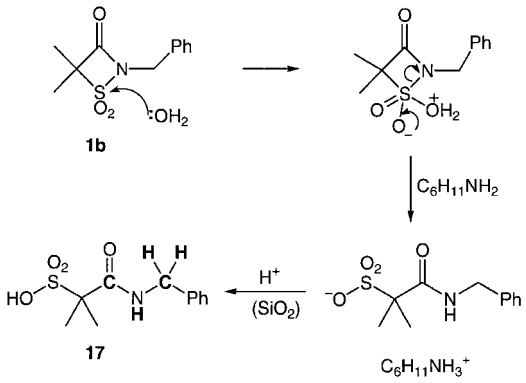
The reactions of 2-cyclohexyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide (**1c**) and 2-isobutyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide (**1d**) with benzylamine (*Scheme 4*) were performed with the aim of obtaining isomers of **13** and **14** with an *N*-benzylamide structure. The formation of these products should establish once more the nucleophilic attack of the amine at the carbonyl group of **1**. Both reactions were carried out at room temperature in benzylamine as the solvent. The isolated products were *N*-benzyl-2-(cyclohexylsulfamoyl)-2-methylpropanamide (**15**) and *N*-benzyl-2-(isobutylsulfamoyl)-2-methylpropanamide (**16**).

The results of the experiments performed with the 1,2-thiazetidin-3-one 1,1-dioxides **1b**–**d** can be summarized as follows: the reaction with NH_3 yields ring-opened adducts *via* nucleophilic attack of the NH_3 at the sulfonyl group, whereas the reaction with primary amines yields products of ring opening *via* attack at the carbonyl group.

As already mentioned, **1b** was easily hydrolyzed, even with only traces of H_2O. Heating an equimolar mixture of **1b** and cyclohexylamine in refluxing 'absolute' EtOH[3]) for 2 h and removing the solvent under reduced pressure yielded a crude reaction mixture, which, according to the NMR spectra, consisted of only one single product with an open-chain structure: the signal for the Me_2C atom was shifted towards high field (from 83.1 ppm for **1b** to 61.1 ppm). In the mass spectra, peaks corresponding to a 1:1 adduct between **1b** and H_2O appeared. After column chromatography (SiO_2, CH_2Cl_2/MeOH/25% NH_4OH solution), a single product was isolated, which turned out to be 2-(Benzylamino)-1,1-dimethyl-2-oxoethanesulfonic acid (**17**; *Scheme 5*). Obvi-

[3]) The used abs. EtOH was stored over molecular sieves (4 Å), and the cyclohexylamine was distilled and kept over KOH.

Scheme 5



ously, an ammonium salt of cyclohexylamine and **17** was formed first which on silica gel was protonated to give **17**.

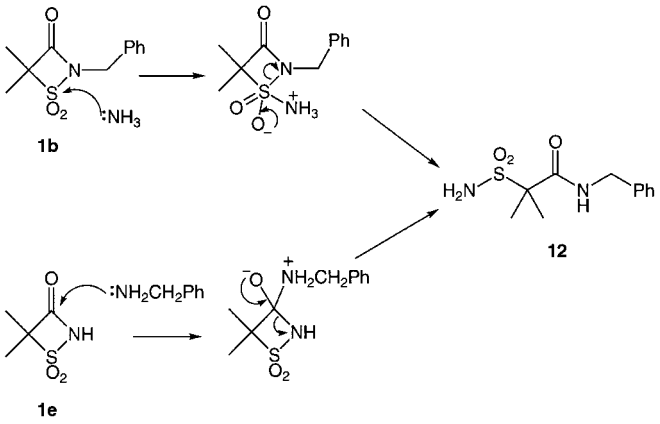
The structure of **17** was established from its spectral data. The position of the benzyl substituent was determined again by an HMBC-NMR experiment, which confirmed the sequence CO–NH–CH_2Ph. Therefore, the hydrolysis occurred *via* nucleophilic attack of H_2O at the sulfonyl group, followed by the opening of the ring *via* cleavage of the S–N bond. This is the ring opening analogous to that observed in the reaction of **1b** with NH_3 (*Scheme 3*) and opposite to that in the reactions of **1b**–**d** with amines (*Scheme 4*). The reaction of **1b** with H_2O is in accord with the results described in earlier studies in which the hydrolyses of *N*-substituted 1,2-thiazetidin-3-one 1,1-dioxides under acidic [2] and under basic conditions [3] afforded sulfonic acids or their salts. In our case, the reaction can be classified as a hydrolysis under basic conditions because of the presence of the amine. Benzylamine, when taken in a ratio of 1:1 with **1b**, obviously did not compete with H_2O as a nucleophile. As a control experiment, **1b** was heated for 2.5 h in refluxing EtOH in the absence of any other reagent. Under these conditions, no reaction was observed, and **1b** was recovered quantitatively. This experiment showed that EtOH, taken as a solvent, did not influence the reaction course.

The only two published examples of ring-opening reactions of *N*-unsubstituted 1,2-thiazetidin-3-one 1,1-dioxides in which the direction of the nucleophilic attack could be determined, are the reactions of **1e** (R = H) with H_2O under acidic conditions and with hydrazine [2] (*Scheme 2*). A further example of a nucleophilic ring opening of **1a** was the reaction with NH_3 under high pressure [7]. However, this example gave no information about the mechanism as the nucleophilic attack at the carbonyl group and at the sulfonyl group leads to the same product.

We decided to perform analogous reactions with the *N*-unsubstituted **1e**. A solution of **1e** in benzylamine as the solvent was stirred at room temperature for 24 h. After removing the excess benzylamine, the ^{13}C-NMR spectrum of the crude reaction mixture clearly showed that the four-membered ring had not been opened, as the resonance of the quaternary sp^3-C-atom of the geminal dimethyl moiety did not show the characteristic upfield shift observed in products with an open-chain structure. The

only product was the salt between **1e** and benzylamine. After dissolving this salt in H_2O, addition of conc. HCl solution, and extraction with CH_2Cl_2, the starting material **1e** was recovered. In contrast, heating a mixture of **1e** and five equiv. of benzylamine in refluxing EtOH for 20 h yielded a 1:1 adduct of the starting materials as the only product. It turned out that this product was identical with **12**, resulting from the reaction of 2-benzyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide (**1b**) with NH_3, which proceeded *via* nucleophilic attack of NH_3 at the sulfonyl function of **1b** (*Scheme 6*). In the case of the reaction between **1e** and benzylamine, **12** was formed *via* the alternative ring opening of the cyclic oxosulfonamide, *i.e.* the nucleophilic attack of the benzylamine took place at the carbonyl group of **1e**.

Scheme 6



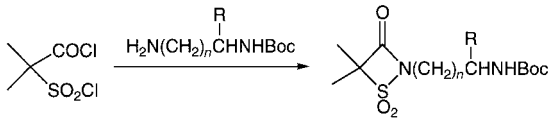
In conclusion, the reactions of amines with **1e** (*N*-unsubstituted oxosulfonamide) and with **1b**–**d** (*N*-benzyl- or *N*-alkyl-substituted derivatives) all proceed *via* nucleophilic attack at the carbonyl function, but in the case of **1e**, a higher temperature was required. This is most probably a consequence of the primary formation of an ammonium salt of **1e**, in which the electrophilicity of the carbonyl C-atom is decreased.

2.2. *Ring Enlargements by Intramolecular Reactions of 2-(Aminoalkyl)-1,2-thiazetidin-3-one 1,1-Dioxides.* It is well known that lactams bearing an aminoalkyl substituent at the N-atom undergo intramolecular transamidation reactions leading to ring-expanded lactams. Generally, a strong base is used to deprotonate the amino group, which then acts as the nucleophile. The reactions proceed *via* bicyclic intermediates in which the size of the newly formed ring plays an important role. This reaction type has been largely investigated by *Schmid*, *Hesse*, and co-workers [8–13] (*cf.* also [14]). In most cases, potassium (3-aminopropyl)amide (KAPA reagent) was used as a base. The size of the lactam ring of the starting materials varied between seven- and eighteen-membered, but only aminoethyl and aminopropyl substituents at the N-atom led to ring-enlarged products, *i.e.*, the transamidation reactions proceeded only *via* five- or six-membered intermediates. In several cases, base-induced transamidations *via* a seven-membered cyclic intermediate have been investigated, but the results were mainly negative [13][15].

Begley et al. [16] reported on transamidation reactions with *N*-(aminoalkyl)-substituted β-lactams, substances with a structure similar to that of the compounds we were interested in. The reactions occurred smoothly *via* five- or six-membered intermediate. In the case of the energetically less favorable seven-membered intermediate state, the reaction temperature had to be increased to 55–65°. Furthermore, the authors failed to obtain a ring-enlarged product *via* an eight-membered intermediate.

Our investigations of the transamidation-like reactions of 2-(aminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxides were carried out in order to answer the following questions: *a*) is this reaction applicable to this class of compounds, and if so, what is the largest ring that could be synthesized, and *b*) which of the two electrophilic centers of the molecule is the site of the intramolecular nucleophilic attack. For this series of experiments, *N*-(aminoalkyl)-substituted 1,2-thiazetidin-3-one 1,1-dioxides **19a–d** with a Boc-protected amino group (*Scheme 7*) were prepared from **18** by following the general procedure described in [4][5]. For this purpose, several mono-Boc-protected diamines were synthesized [17–20].

Scheme 7



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19a $n = 2$, R = H
b $n = 3$, R = H
c $n = 4$, R = H
d $n = 2$, R = Me

The first compound examined was the Boc-protected 2-(3-aminopropyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide **19a**. The Boc group was removed by stirring **19a** in trifluoroacetic acid (CF_3COOH) for 2 h at room temperature. A diluted solution of the resulting ammonium trifluoroacetate **20a** in MeCN was treated with (piperidinomethyl)polystyrene in *ca.* 15-fold molar excess at room temperature for 63 h[4]). The expected eight-membered product **21** was obtained in 87% yield (*Scheme 8*). The structure of **21** was elucidated from its spectral data.

At room temperature, the ^{1}H-NMR spectrum ((D$_6$)DMSO) of **21** showed only a few broad signals at high field, and no signals could be observed in the ^{13}C-NMR spectrum. After increasing the temperature to 380 K, interpretable spectra were obtained. This temperature dependence reflects the rigid structure of the eight-membered ring. Obviously, at room temperature the molecule exists in several conformations, which interconvert only slowly. With increasing temperature, the conformers are in a rapid equilibrium, and the resonances observed are those for an average structure. In the ^{13}C-NMR spectra, the characteristic high-field shift of the signal for the C-atom bearing the two Me groups was observed at 67.6 ppm, while for **20a**, the value was 83.2 ppm. On the other hand, the carbonyl C-atom showed a down-field shift from 164.5 in **20a** to 171.2 ppm in **21**. In accordance with expectation, the IR spectrum of the eight-membered ring **21** showed the absorption of the C=O group at lower wavenumbers (1650 cm^{-1}) than the starting material **20a** (1770 cm^{-1}).

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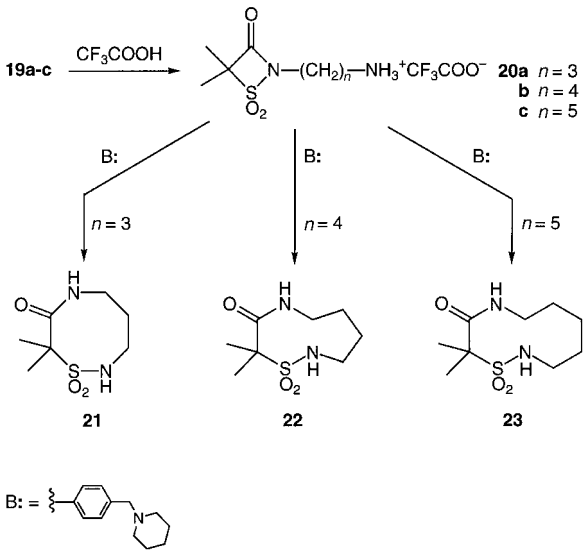
4) The use of this polymer-bound base was very convenient with respect to the workup of the reaction mixture; the resulting piperidinium trifluoroacetate attached to the polymer was removed by filtration.

Scheme 8



Finally, the structure of **21** was established by means of X-ray crystallography (*Fig. 2*). The eight-membered ring contains a *trans*-configured amide bond (H and O *trans*). Intermolecular H-bonds between the amide NH and a sulfonyl O-atom of a neighboring molecule, as well as between the sulfonamide NH and the amide O-atom of a different neighboring molecule, link the molecules into an infinite two-dimensional network which lies parallel to the *xz*-plane. Independently, each type of H-bond links the molecules into infinite one-dimensional chains, each of which has a graph set C(6) [21].

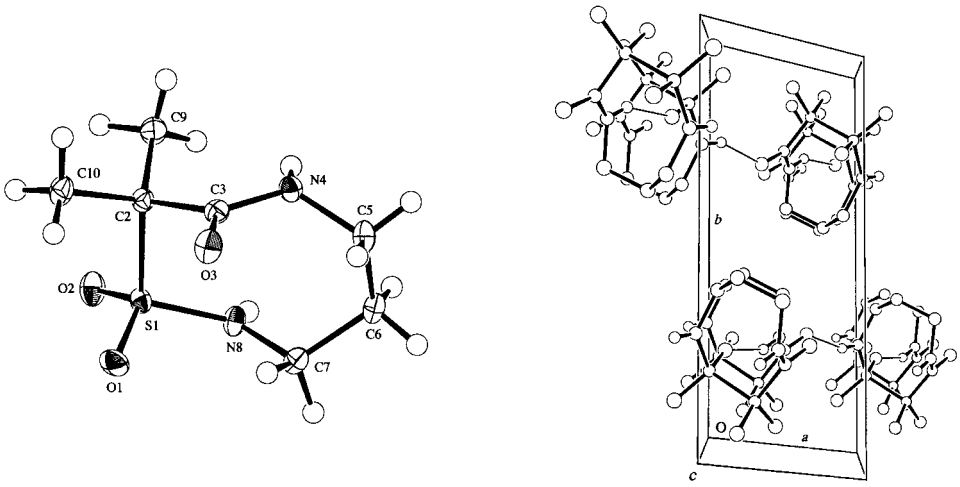


Fig. 2. *ORTEP Plot* [6] *of the molecular structure of* **21** (displacement ellipsoids with 50% probability) *and packing diagram of* **21**

An analogous transamidation was performed with the Boc-protected 2-(4-aminobutyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide **19b**. After deprotection with CF_3COOH, the salt **20b** in diluted MeCN solution at room temperature was treated with a large excess of (piperidinomethyl)polystyrene. The nine-membered product **22** was obtained in 68% yield (*Scheme 8*)[5]. The structure of **22** was determined by comparing its NMR, IR, and MS data with those of **21**.

Similarly, the Boc-protected 2-(5-aminopentyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide **19c** was deprotected with CF_3COOH; the resulting trifluoroacetate **20c** was dissolved in MeCN and, after addition of (piperidinomethyl)polystyrene, the suspension was stirred at room temperature for 120 h. Then, the reaction mixture was divided in two equal parts. The only substance obtained from the filtrate of the first part, after evaporation and recrystallization, was the starting material **20c**. The second part of the reaction mixture was heated under reflux (80°) for 45 h, the resin removed by filtration, and the ten-membered product **23** isolated from the filtrate in 42% yield as the only product (*Scheme 8*). In this reaction, proceeding *via* an eight-membered intermediate, a higher energy barrier had to be overcome; the necessary energy could not be supplied just by opening of the four-membered oxosulfonamide ring. It is worth mentioning that the analogous transamidation with a β-lactam could not be performed even at higher temperature [16]. The spectral data of **23** fully supported the ten-membered structure. Surprisingly, NMR spectra with good resolution were obtained at room temperature.

In the ^{1}H-NMR spectrum of **23**, two *t* for two NH groups were observed, and in the ^{13}C-NMR spectrum, the signal for the Me_2 *C* atom was shifted from 83.1 ppm for **20c** to 66.9 ppm for **23**. The shift of the carbonyl C-atom was small, but it followed the trend observed in the spectra of the lower homologues (from 164.5 ppm for **20c** to 167.4 ppm for **23**). The C=O absorption in the IR spectrum was also shifted from 1770 cm^{-1} for **20c** to 1650 cm^{-1} for **23**.

From the experiments performed with **19a – c**, no conclusion concerning the site of the nucleophilic attack could be drawn, as all substituents at N(2) were symmetric and, therefore, the attack of the amine at the carbonyl or at the sulfonyl group led to the same product. To test the hypothesis that the transamidation reactions of **19a – c** proceed *via* nucleophilic attack of the amino function at the carbonyl group, we prepared the Boc-protected *N*-(3-amino-3-methylpropyl) derivative **19d** with an asymmetric side chain. After removing the Boc-protecting group and stirring the resulting salt **20d** in MeCN, the transamidation reaction was performed in the presence of a large excess of (piperidinomethyl)polystyrene. After 48 h at room temperature, a single product was obtained in 74% yield. The choice between the anticipated product **24** or **25** (*Scheme 9*) by ^{1}H-NMR experiments was difficult to make.

The structure **24** or **25** should be established by the determination of the couplings between the H-atoms and C-atoms in an HMBC-NMR experiment (the expected correlations are shown in *Scheme 9* by indicating the correlating atoms with bold letters). Unfortunately, no NMR spectra with reasonable resolution were obtained either at higher temperature in (D_6)DMSO nor at lower temperature in CD_3OD. In (D_6)DMSO at 380 K, the

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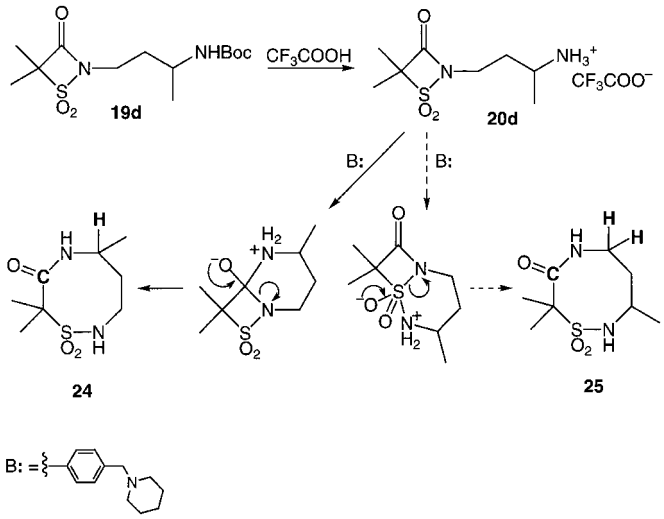
[5]) Compared with the reaction of the corresponding β-lactam (*cf.* [16]), the reaction of **19b** proceeded under milder conditions (room temperature, atmospheric pressure). Presumably, the presence of the sulfonyl group in the four-membered ring additionally increases the ring strain, making the ring opening energetically more favorable.

Scheme 9



signals of the H-atoms of the CH and NH groups were too broad, and no correlations could be detected. In addition, none of the H-atoms of the CH_2 group (in spite of sharp signals) showed any correlation with the carbonyl C-atom. At low temperature in CD_3OD, several conformers could be recognized, but none of their correlations in the HMBC spectrum gave a basis upon which to draw a conclusion. Additionally, the NH protons did not show any signal because of the fast exchange with the solvent. Spectra were then measured in $CDCl_3$ at 225 K; although the substance was very poorly soluble, especially at low temperature, the solvent was choosen in order to be able to recognize the H signals for the NH groups. Again, several conformers of the substance were recognized. The main conformer was present to more than 50%, and in the ^{1}H-NMR spectrum, the main signals corresponding to that conformer could be identified by considering the integrals and the chemical shifts. A further problem arose from the fact that it was not possible to measure a ^{13}C-NMR spectrum within reasonable time as the amount of dissolved material was very small and the compound existed in several conformations. This problem was solved taking the ^{13}C-NMR spectrum as inside projection from the two-dimensional HMBC spectrum. The C-resonances and the remaining H-signals of the main conformer could be assigned from an HSQC-NMR spectrum (direct C,H correlations). Combining the information of the long-range C,H correlations (HMBC) and the H,H correlations (DQF-COSY), the structure **24** was established with a very high probability. In the HMBC spectrum, a correlation between NH at 6.06 ppm (*d*) and the carbonyl C-atom (*s* at 171.9 ppm) was observed. In the DQF-COSY spectrum, the same NH showed a cross-peak with CH (*m* at *ca.* 4.10 ppm). These two correlations proved the sequence CO–NH–CH(Me).

Fortunately, suitable crystals for an X-ray crystal-structure determination were grown, and the experiment confirmed structure **24** (*Fig. 3*). The additional Me substituent in the α-position to the amide group in **24** has a remarkable influence on the conformation of the eight-membered ring of **24** compared with that of **21**. In the case of **24**, the amide bond has a *cis*-configuration (H and O *cis*), whereas in **21**, the amide bond is *trans*-configured. Each NH group of **24** acts as a donor for intermolecular H-bonds: the amide NH interacts with one of the sulfonyl O-atoms of a neighboring molecule, while the other NH interacts with the amide O-atom of a different neighboring molecule. Independently, the two H-bonds link the molecules into infinite one-dimensional chains, each with a graph set of C(6) [21]. The combination of both interactions links the molecules into a three-dimensional network.

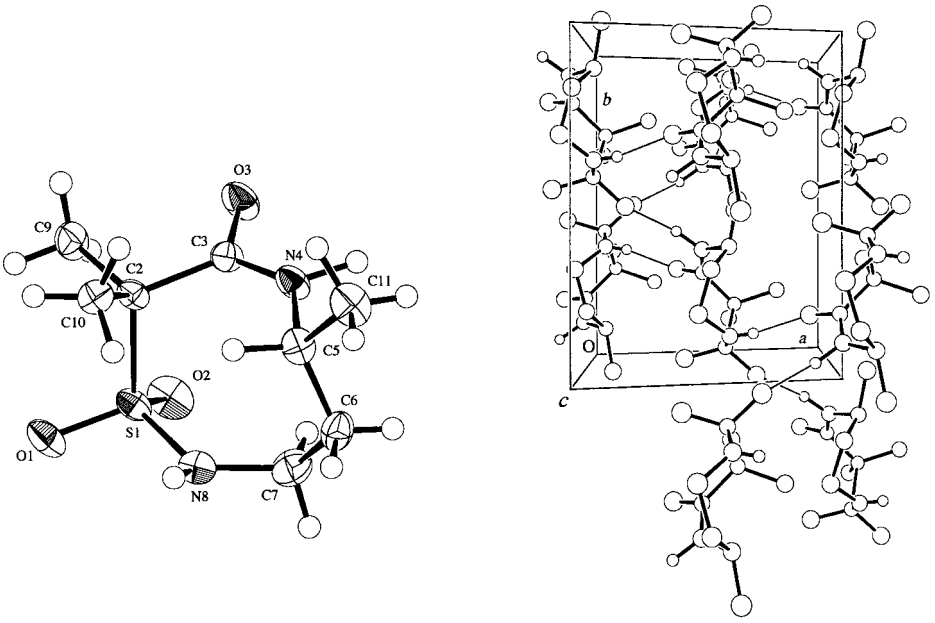


Fig. 3. *ORTEP Plot* [6] *of the molecular structure of* **24** (displacement ellipsoids with 50% probability) *and packing diagram of* **24**

3. Conclusions. – In the present work, we investigated additional reactions of nucleophiles with oxosultams of type **1** and **19** with the aim to deduce the factors responsible for the direction of the nucleophilic attack at the SO_2 or at the CO group. We performed two types of reactions, leading either to ring opening or to ring enlargement. In conclusion, *N*-benzyl-substituted oxosultam **1b** underwent ring opening reactions with H_2O and NH_3 *via* attack at the SO_2 group of the four-membered ring. On the other hand, the reactions of **1b**–**d** with amines proceeded *via* nucleophilic attack at the carbonyl C-atom. In the case of *N*-unsubstituted **1e**, we expected decreased electrophilicity of the carbonyl C-atom because of the amide tautomerism. This should favor the alternative reaction *via* attack of the nucleophile at the SO_2 group. Unexpectedly, the experiment did not support this proposal, as 4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide (**1e**) reacted with benzylamine giving only one product, resulting from ring opening *via* attack at the carbonyl C-atom. Compared with the analogous reactions of *N*-substituted compounds **1b**–**d**, the only difference was the higher reaction temperature needed.

In the case of *N*-(aminoalkyl)-substituted 1,2-thiazetidin-3-one 1,1-dioxides **19a**–**d**, ring enlargement (transamidation) reactions were realized. The products obtained resulted from the intramolecular nucleophilic attack of the amino group attached to the side chain at the carbonyl C-atom. The transamidation reactions proceeded readily at room temperature giving eight- and nine-membered products **21**, **22**, and **24** in satisfactory yields (68–87%). The ten-membered analogue **23** was obtained when the temperature was increased to 80°. The transformation to give the nine-membered **22** proceeded *via* a seven-membered intermediate, and product **23** was formed *via* an

eight-membered intermediate. No base was necessary for deprotonation of the NH_2 group. These observations are remarkable, as similar reactions with β- and larger lactams were unsuccessful. Although two electrophilic centers are available in **19**, products were formed exclusively *via* nucleophilic attack of the NH_2 group at the carbonyl C-atom. Some limitations of the transamidation reaction of cyclic, four-membered oxosulfonamides became obvious as the number of CH_2 groups of the side chain at N(2) was increased, with a corresponding increase in the ring size of the bicyclic intermediate. Whereas reactions *via* six- and seven-membered intermediates proceeded smoothly at room temperature, the ring enlargement *via* an eight-membered intermediate needed a higher temperature.

Unfortunately, the available experimental data did not allow any conclusion to be drawn about the factors which determine the direction of the nucleophilic attack. This problem still remains as a field for further investigations.

We thank the analytical units of our institute for spectra and analyses, and the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *General*. See [22]. The used amines were distilled and stored over KOH. Moreover, if not otherwise stated: TLC: detection under UV light of 254 nm. IR Spectra: in KBr. NMR Spectra: in (D_6)DMSO at 300 (^{1}H) and 50.4 (^{13}C) MHz. CI-MS: with NH_3.

2. *Ring-Opening Reactions of 1,2-Thiazetidin-3-one 1,1-Dioxides with NH_3 and Amines*. 2.1. *Starting Materials. 2-Benzyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide* (**1b**) and *4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide* (**1e**) were prepared according to [2] (*cf.* [1]); *2-cyclohexyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide* (**1c**) and *2-isobutyl-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-dioxide* (**1d**) were prepared according to [4][5].

2.2. N-*Benzyl-2-methyl-2-sulfamoylpropanamide* (**12**). To **1b** (36 mg, 0.15 mmol) at $-78°$, liquid NH_3 (10 ml) was added dropwise. The soln. was stirred without cooling until reaching r.t. The remaining colorless oil was treated with Et_2O and the resulting solid material recrystallized from Et_2O: 35 mg (91%) of **12**. Colorless solid. M.p. 103–106°. IR: 3415v*s*, 3265*s*, 1653v*s*, 1536v*s*, 1496*w*, 1476*m*, 1451*m*, 1428*s*, 1365*m*, 1326v*s*, 1166*m*, 1128v*s*, 731v*s*, 687*s*, 635*m*. ^{1}H-NMR: 8.22 (*t*, $J = 5.9$, NH); 7.35–7.15 (*m*, 5 arom. H); 6.98 (*s*, NH_2); 4.33 (br. *d*, PhCH_2); 1.52 (*s*, Me_2C). ^{13}C-NMR: 168.3 (*s*, CO); 139.2 (*s*, 1 arom. C); 128.1, 126.7, 126.5 (3*d*, 5 arom. C); 65.7 (*s*, Me_2C); 42.7 (*t*, PhCH$_2$); 21.2 (*q*, *Me*$_2$C); a long-range coupling between PhCH_2 and *C*O was established ($CDCl_3$, 298 K, coloc pulse program). CI-MS: 274 (100, $[M + NH_4]^+$), 257 (30, $[M + 1]^+$), 176(12). Anal. calc. for $C_{11}H_{16}N_2O_3S$ (256.23): C 51.56, H 6.29, N 10.93; found: C 51.16, H 6.02, N 10.93.

2.3. *2-(Benzylsulfamoyl)*-N-*cyclohexyl-2-methylpropanamide* (**13**). A soln. of **1b** (36 mg, 0.15 mmol) in cyclohexylamine (1.5 ml) was stirred at r.t. for 16 h (until **1b** was consumed). Cyclohexylamine was removed at r.t./10^{-2} mbar, and workup by CC (CH_2Cl_2/MeOH 40:1) gave crude **13**: 35 mg (68.6%). Colorless solid. M.p. 117.5–119.5° (CH_2Cl_2/hexane). IR: 3370*s*, 3200*s*, 2920*s*, 2850*s*, 1645v*s*, 1535*s*, 1470*m*, 1450*s*, 1435*m*, 1350*m*, 1325*s*, 1310v*s*, 1165*m*, 1125v*s*, 1085*m*, 1070*s*, 905*m*, 890*m*, 745*s*, 700*s*, 635*s*. ^{1}H-NMR: 7.79 (*s*, NH); 7.4–7.25 (*m*, NH, 5 arom. H); 4.17 (*s*, PhCH_2); 3.55–3.45 (br. *m*, CH); 1.75–1.0 (*m*, 5 CH_2); 1.50 (*s*, Me_2C). ^{13}C-NMR: 166.7 (*s*, CO); 139.1 (*s*, 1 arom. C); 128.2, 127.2, 127.0 (3*d*, 5 arom. C); 66.6 (*s*, Me_2C); 48.3 (*d*, CH); 47.2 (*t*, PhCH$_2$); 31.7, 25.1, 24.5 (3*t*, 5 CH_2); 21.2 (*q*, *Me*$_2$C). HMBC: long-range coupling between C*H* of the cyclohexyl group and *C*O. ESI-MS (with NaI): 361 ($[M + Na]^+$).

2.4. *2-(Benzylsulfamoyl)*-N-*isobutyl-2-methylpropanamide* (**14**). A soln. of **1b** (36 mg, 1.5 mmol) in isobutylamine (1.5 ml) was stirred at r.t. for 64 h (until **1b** was consumed). The excess of the amine was removed at r.t./10^{-2} mbar and the residue purified by CC (hexane/AcOEt 1:1): 42 mg (89.3%) of **14**. Colorless solid. M.p. 93.5–94° (CH_2Cl_2/hexane). IR: 3380*s*, 3260*m*, 2945*m*, 2860*m*, 1650*s*, 1550*m*, 1540*m*, 1470*w*, 1450*m*, 1435*m*, 1310*s*, 1275*w*, 1165*m*, 1125*s*, 1065*m*, 820*w*, 750*m*, 700*m*. ^{1}H-NMR: 7.79 (br. *s*, NH); 7.69 (br. *t*, NH); 7.35–7.25 (*m*, 5 arom. H); 4.17 (br. *s*, PhCH_2); 2.94 (*t*, $J = 6.4$, CH_2 of i-Bu); 1.85–1.7 (*m*, $J = 6.4$, CH); 1.51 (*s*, Me_2C); 0.83 (*d*, $J = 6.5$, *Me*$_2$CH). ^{13}C-NMR: 167.6 (*s*, CO); 139.2 (*s*, 1 arom. C); 128.2, 127.2, 127.0 (3*d*, 5 arom. C); 66.6 (*s*, Me_2C); 47.2 (*t*, PhCH$_2$); 46.8 (*t*, CH_2 of i-Bu); 27.6 (*d*, CH); 21.2 (*q*, *Me*$_2$C); 20.0 (*q*, *Me*$_2$CH). HMBC and

HSQC: long-range coupling between CH_2 of the i-Bu group and *CO*. CI-MS: 330 (18, $[M+NH_4]^+$), 313 (100, $[M+1]^+$). Anal. calc. for $C_{15}H_{24}N_2O_3S$ (312.44): C 57.66, H 7.74, N 8.97; found: C 57.90, H 7.44, N 9.03.

2.5. N-*Benzyl-2-(cyclohexylsulfamoyl)-2-methylpropanamide* (**15**). A soln. of **1c** (46 mg, 0.2 mmol) in benzylamine (2 ml) was stirred at r.t. for 15 h (until **1c** was consumed), excess amine was removed at r.t./10^{-2} mbar, and the product isolated by CC (CH_2Cl_2/MeOH 60:1): 49 mg (72.3%) of **15**. Colorless solid. M.p. 118.2–119° (CH_2Cl_2/hexane). IR: 3400*s*, 3290v*s*, 2940*s*, 2850*m*, 1665v*s*, 1520*s*, 1450*s*, 1440*s*, 1305v*s*, 1295v*s*, 1275*m*, 1240*m*, 1130v*s*, 1090*s*, 1005*w*, 925*w*, 910*m*, 890*m*, 740*m*. ^{1}H-NMR: 8.23 (br. *t*, BnN*H*); 7.35–7.25 (*m*, 5 arom. H); 7.13 (br. *d*, $C_6H_{11}NH$); 4.31 (*d*, $J=5.9$, PhCH_2); 3.0–2.9 (br. *m*, CH); 1.8–1.75 (br. *m*, CH_2); 1.6–1.55 (br. *m*, CH_2); 1.50 (*s*, Me_2C); 1.15–1.0 (*m*, 2 CH_2). ^{13}C-NMR: 167.8 (*s*, CO); 139.2 (*s*, 1 arom. C); 128.0, 126.9, 126.5 (3*d*, 5 arom. C); 66.3 (*s*, Me_2C); 53.4 (*d*, CH); 42.7 (*t*, PhCH_2); 34.2, 24.8, 24.7 (3*t*, 5 CH_2); 21.2 (*q*, Me_2C). CI-MS: 356 (100, $[M+NH_4]^+$), 339 (58, $[M+1]^+$). Anal. calc. for $C_{17}H_{26}N_2O_3S$ (338.45): C 60.32, H 7.74, N 8.28, S 9.47; found: C 59.97, H 7.75, N 8.30, S 9.19.

2.6. N-*Benzyl-2-(isobutylsulfamoyl)-2-methylpropanamide* (**16**). A soln. of **1d** (41 mg, 0.2 mmol) in benzylamine (2 ml) was stirred at r.t. for 15 h (until **1d** was consumed). Excess amine was removed at r.t./10^{-2} mbar and the solid residue purified by CC (CH_2Cl_2/MeOH 40:1): 55 mg (88.7%) of **16**. Colorless solid. M.p. 115–115.5° (CH_2Cl_2/hexane). IR: 3400*s*, 3310*s*, 2960*m*, 1670*s*, 1520*s*, 1470*m*, 1465*m*, 1430*m*, 1305v*s*, 1245*w*, 1170*m*, 1125*s*, 1075*m*, 850*w*, 750*m*, 700*s*. ^{1}H-NMR (600 MHz): 8.27 (br. *t*, NH); 7.29–7.27 (*m*, 3 arom. H); 7.21–7.20 (*m*, 2 arom. H); 4.30 (*d*, $J=6.0$, PhCH_2); 2.67 (*t*, $J=6.3$, CH_2 of i-Bu); 1.59–1.57 (*m*, CH); 1.51 (*s*, Me_2C); 1.78 (*d*, $J=6.7$, Me_2CH). ^{13}C-NMR (150 MHz): 167.8 (*s*, CO); 139.2 (*s*, 1 arom. H); 128.0, 127.0, 126.5 (3*d*, 5 arom. C); 66.5 (*s*, Me_2C); 51.3 (*t*, CH_2 of i-Bu); 42.8 (*t*, PhCH_2); 29.0 (*d*, CH); 21.3 (*q*, Me_2C); 19.7 (*q*, Me_2CH). HSQC and HMBC: long-range coupling between PhCH_2 and *CO*. CI-MS: 330 (92, $[M+NH_4]^+$), 313 (100, $[M+1]^+$).

2.7. *2-(Benzylamino)-1,1-dimethyl-2-oxoethanesulfonic Acid* (**17**). A soln. of **1b** (36 mg, 0.15 mmol) and cyclohexylamine (15 mg, 0.15 mmol) in abs. EtOH (3 ml) was heated to reflux for 2 h. Then, the mixture was cooled to r.t. and evaporated. The solid residue contained **17** as the major product which was isolated by CC (CH_2Cl_2/MeOH/25% NH_4OH 12:2:0.2): 25 mg (64.7%). Colorless solid. M.p. 204.4–213.2°. IR: 3336v*s*, 3065v*s*, 1642v*s*, 1537v*s*, 1497*s*, 1453v*s*, 1420v*s*, 1365*s*, 1290*s*, 1261*s*, 1174v*s*, 1032v*s*, 1001*s*, 712v*s*, 693*s*, 643*s*, 620*m*, 597*m*, 569*m*, 532*m*. ^{1}H-NMR: 8.60 (br. *t*, NH); 7.3–7.25 (*m*, 5 arom. H); 7.10 (br. *s*, OH); 4.31 (*d*, $J=5.9$, PhCH_2); 1.35 (*s*, Me_2C). ^{13}C-NMR: 172.4 (*s*, CO); 139.4 (*s*, 1 arom. C); 128.1, 126.7, 126.4 (3*d*, 5 arom. C); 61.1 (*s*, Me_2C); 42.1 (*t*, PhCH_2); 22.9 (*q*, Me_2C). HMBC: long-range coupling between PhCH_2 and *CO*. ESI-MS (with NaI): 280 ($[M+Na]^+$), 258 ($[M+1]^+$). CI-MS: 275 ($[M+NH_4]^+$).

2.8. *Control Experiment with* **1b** *in Refluxing EtOH*. A soln. of **1b** (18 mg, 0.075 mmol) in abs. EtOH (1.5 ml) was refluxed for 2.5 h. The solvent was evaporated, and the NMR spectra of the crude solid were measured: only almost pure **1b**.

2.9. *Reactions of* **1e** *with Benzylamine*. A soln. of **1e** (50 mg, 0.33 mmol) in benzylamine (2 ml) was stirred at r.t. for 24 h. The excess of benzylamine was evaporated, the solid residue dissolved in H_2O (5 ml), acidified with 10% aq. HCl, and extracted with CH_2Cl_2: 42 mg (84%) of **1e**.

A soln. of **1e** (104 mg, 0.7 mmol) and benzylamine (380 mg, 3.5 mmol) in abs. EtOH (10 ml) was refluxed for 20 h. After evaporation, the residue was dissolved in H_2O (25 ml) and extracted with CH_2Cl_2 (3 × 30 ml). Purification on a short column (CH_2Cl_2/MeOH 30:1) gave 63 mg (50.1%) of **12**.

3. *Intramolecular Ring-Enlargement Reactions of 2-(Aminoalkyl)-1,2-thiazetidin-3-one 1,1-Dioxides.*

3.1. *Starting Materials.* 3.1.1. *Boc-Protected 2-(Aminoalkyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-Dioxides* (**19a–d**) were prepared according to [4][5]. The mono-Boc-protected aliphatic diamines were prepared according to [17–20].

*2-(3-{[(*tert*-Butoxy)carbonyl]amino}propyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-Dioxide* (**19a**). Yield: 65.3%. Colorless solid. M.p. 101.4–102.6° (Et_2O). IR ($CHCl_3$): 3450*s*, 2980v*s*, 2940*s*, 1770v*s*, 1705v*s*, 1695v*s*, 1670*m*, 1505v*s*, 1455*m*, 1390*m*, 1370*s*, 1335v*s*, 1245v*s*, 1170v*s*, 1120v*s*, 1040*s*. ^{1}H-NMR: 6.84 (br. *t*, BocN*H*); 3.44 (*t*, $J=7.2$, CH_2); 2.99 (*q*, $J=6.4$, CH_2); 1.75–1.7 (*m*, $J=7.1$, CH_2); 1.64 (*s*, Me_2C(4)); 1.38 (*s*, *t*-Bu). ^{13}C-NMR: 164.4, 155.5 (2*s*, CO, NHCO); 83.1 (*s*, C(4)); 77.5 (*s*, Me_3C); 37.9, 37.1, 27.7 (3*t*, 3 CH_2); 28.1 (*q*, Me_3C); 17.7 (*q*, Me_2C(4)). ESI-MS (with NaI): 329 ($[M+Na]^+$). Anal. calc. for $C_{12}H_{22}N_2O_5S$ (306.39): C 47.04, H 7.24, N 9.14; found: C 47.41, H 6.99, N 9.14.

*2-(4-{[(*tert*-Butoxy)carbonyl]amino}butyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-Dioxide* (**19b**). Yield: 86.4%. Colorless solid. M.p. 121.7–122.1° (Et_2O). IR: 3330v*s*, 2980*s*, 2940*m*, 2860*w*, 1770v*s*, 1705*s*, 1690v*s*, 1680v*s*, 1535v*s*, 1465*m*, 1455*s*, 1390*s*, 1365*s*, 1380v*s*, 1275v*s*, 1250*s*, 1175v*s*, 1165v*s*, 1140*s*, 1120v*s*, 1010*w*, 1000*w*, 950*m*, 670*w*, 635*w*. ^{1}H-NMR: 6.80 (br. *t*, BocN*H*); 3.43 (*t*, $J=6.8$, CH_2); 2.92 (*q*, $J=6.4$, CH_2); 1.64 (*s*, Me_2C(4)); 1.65–1.55 (*m*, CH_2); 1.45–1.35 (*m*, CH_2); 1.37 (*s*, *t*-Bu). ^{13}C-NMR: 164.5, 155.5 (2*s*, CO, NHCO); 83.0

(*s*, C(4)); 77.3 (*s*, Me_3C); 39.9, 38.9, 26.5, 24.7 (4*t*, 4 CH_2); 28.2 (*q*, *Me*$_3$C); 17.7 (*q*, *Me*$_2$C(4)). CI-MS: 338 (6, $[M+NH_4]^+$), 282 (100), 221 (29). Anal. calc. for $C_{13}H_{24}N_2O_5S$ (320.42): C 48.73, H 7.55, N 8.74; found: C 48.42, H 7.22, N 8.71.

*2-(5-{[(*tert*-Butoxy)carbonyl]amino}pentyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-Dioxide* (**19c**). Yield: 61.1%. Colorless solid. M.p. 60.6–73.7° (CH_2Cl_2/hexane). IR: 3450*m*, 2980*m*, 2930*m*, 2860*w*, 1760v*s*, 1690v*s*, 1535*s*, 1450*w*, 1390*m*, 1330*s*, 1275*m*, 1250*m*, 1170*s*, 1125*s*. ^{1}H-NMR: 6.74 (br. *t*, BocN*H*); 3.41 (*t*, *J* = 6.9, CH_2); 2.89 (*q*, *J* = 6.3, CH_2); 1.64 (*s*, Me_2C(4)); 1.65–1.55 (*m*, CH_2); 1.4–1.25 (*m*, 2 CH_2); 1.37 (*s*, *t*-Bu). ^{13}C-NMR: 164.5, 155.5 (2*s*, CO, NHCO); 83.1 (*s*, C(4)); 77.2 (*s*, Me_3C); 40.0, 39.5, 28.6, 26.9, 23.2 (5*t*, 5 CH_2); 18.2 (*q*, *Me*$_3$C); 17.7 (*q*, *Me*$_2$C(4)). CI-MS: 352 (3, $[M+NH_4]^+$), 296 (100, $[(M-t\text{-Bu})+H+NH_4]^+$), 135 (40, $[(M-Boc)+H+1]^+$). Anal. calc. for $C_{14}H_{26}N_2O_5S$ (334.44): C 50.27, H 7.84, N 8.38; found: C 50.49, H 7.56, N 8.38.

*2-(3-{[(*tert*-Butoxy)carbonyl]amino}butyl)-4,4-dimethyl-1,2-thiazetidin-3-one 1,1-Dioxide* (**19d**). Yield: 49.3%. Colorless solid. M.p. 124.8–135.1° (hexane/AcOEt). IR: 3330v*s*, 2980*m*, 2940*m*, 1770v*s*, 1680v*s*, 1530v*s*, 1450*m*, 1390*s*, 1365*s*, 1330v*s*, 1310*s*, 1270v*s*, 1250*s*, 1180v*s*, 1125v*s*, 1080*s*, 990*m*, 915*m*, 680*m*, 635*m*. ^{1}H-NMR: *ca*. 6.75 (br. *d*, BocN*H*); *ca*. 3.55 (br. *m*, CH); 3.45–3.35 (*m*, CH_2N); 1.75–1.65 (*m*, C*H*$_2$CH); 1.64, 1.63 (2*s*, Me_2C(4)); 1.37 (*s*, *t*-Bu); 1.03 (*d*, *J* = 6.6, *Me*CH). ^{13}C-NMR: 164.1, 154.9 (2*s*, CO, NHCO); 83.1 (*s*, C(4)); 77.4 (*s*, Me_3C); 43.3 (*d*, CH); 37.5, 33.8 (2*t*, 2 CH_2); 28.1 (*q*, *Me*$_3$C); 20.6 (*q*, *Me*CH); 17.7, 17.6 (2*q*, *Me*$_2$C(4)). ESI-MS (with NaI): 375 ($[M+Na+MeOH]^+$), 343 ($[M+Na]^+$).

3.1.2. *Trifluoroacetates of 2-(Aminoalkyl)-1,2-thiazetidin-3-one 1,1-Dioxides* (**20a–d**). *General Procedure*. The soln. of the Boc-protected 2-(aminoalkyl)-1,2-thiazetidin-3-one 1,1-dioxide **19** in CF_3COOH was stirred for 2 h at r.t. Then, CF_3COOH was evaporated, the resulting oily residue treated with Et_2O, and the precipitation filtered.

3-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)propylammonium Trifluoroacetate (**20a**). From 320 mg (1.04 mmol) of **19a** in 10 ml of CF_3COOH: 334 mg (99.8%). Colorless solid. M.p. 152–155.5°. IR: 3430*m*, 3050*s*, 1770v*s*, 1695v*s*, 1685v*s*, 1645*m*, 1535*m*, 1325v*s*, 1315v*s*, 1205v*s*, 1190v*s*, 1135v*s*, 1120v*s*, 930*m*, 845*m*, 800*m*, 720*m*. ^{1}H-NMR: 7.93 (br. *s*, NH_3^+); 3.56 (*t*, *J* = 7.1, CH_2); 2.88 (*t*, *J* = 7.6, CH_2); 1.95–1.85 (*m*, *J* = 7.6, CH_2); 1.66 (*s*, Me_2C). ^{13}C-NMR: 164.6 (*s*, CO); 158.4 (*q*, ^2J(C,F) = 31, CF_3COO^-); 117.0 (*q*, ^1J(C,F) = 299, CF_3); 83.3 (*s*, Me_2C); 37.5, 36.5, 25.7 (3*t*, 3 CH_2); 17.7 (*q*, *Me*$_2$C). ESI-MS (with NaI): 239 ($[M_{cation}+MeOH]^+$), 207 ($[M_{cation}]^+$).

4-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)butylammonium Trifluoroacetate (**20b**). From 160 mg (0.5 mmol) of **19b** in 5 ml of CF_3COOH: 160 mg (95.8%). Colorless solid. M.p. 169.2–171.1°. IR: 3420*m*, 3050*s*, 2940*s*, 1770v*s*, 1690v*s*, 1680v*s*, 1645*m*, 1605*m*, 1505*m*, 1430*m*, 1330v*s*, 1310*s*, 1210v*s*, 1190v*s*, 1170v*s*, 1150*s*, 1125v*s*, 945*w*, 850*w*, 830*m*, 795*m*, 720*m*, 630*m*. ^{1}H-NMR: 7.84 (br. *s*, NH_3^+); 3.48 (*t*, *J* = 6.5, CH_2); 2.85–2.8 (br. *m*, CH_2); 1.7–1.6 (*m*, 2 CH_2); 1.66 (*s*, Me_2C). ^{13}C-NMR: 164.6 (*s*, CO): 158.1 (*q*, ^2J(C,F) = 31, CF_3COO^-); 117.1 (*q*, ^1J(C,F) = 299, CF_3); 83.2 (*s*, Me_2C); 39.6, 38.1, 24.4, 24.2 (4*t*, 4 CH_2); 17.7 (*q*, *Me*$_2$C). ESI-MS: 253 ($[M_{cation}+MeOH]^+$), 221 ($[M_{cation}]^+$).

5-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)pentylammonium Trifluoroacetate (**20c**). From 175 mg (0.52 mmol) of **19c** in 5 ml of CF_3COOH: 180 mg (99.4%). Colorless solid. M.p. 154.2–154.8°. IR: 3050*s*, 2980*s*, 1770v*s*, 1675v*s*, 1430*m*, 1390*m*, 1330v*s*, 1205v*s*, 1175v*s*, 1135v*s*, 1120v*s*, 965*w*, 835*m*, 795*m*, 720*m*. ^{1}H-NMR: 7.88 (br. *s*, NH_3^+); 3.44 (*t*, *J* = 6.9, CH_2); 2.78 (br. *q*, CH_2); 1.65 (*s*, Me_2C); 1.65–1.55 (*m*, 2 CH_2); 1.4–1.3 (*m*, CH_2). ^{13}C-NMR: 164.5 (*s*, CO); 158.0 (*q*, ^2J(C,F) = 31, CF_3COO^-); 117.1 (*q*, ^1J(C,F) = 300, CF_3); 83.1 (*s*, Me_2C); 39.8, 38.4, 26.6, 26.1, 22.8 (5*t*, 5 CH_2); 17.7 (*q*, *Me*$_2$C). ESI-MS: 267 ($[M_{cation}+MeOH]^+$), 235 ($[M_{cation}]^+$).

3-(4,4-Dimethyl-1,1-dioxido-3-oxo-1,2-thiazetidin-2-yl)-1-methylpropylammonium Trifluoroacetate (**20d**). From 100 mg (0.31 mmol) of **19d** in 4 ml of CF_3COOH: 98 mg (94.6%). Colorless solid. M.p. 137.9–139.0°. IR: 3420*m*, 3050*s*, 2980*s*, 1775v*s*, 1670v*s*, 1520*m*, 1440*m*, 1390*m*, 1325v*s*, 1310*s*, 1205v*s*, 1185v*s*, 1125v*s*, 835*m*, 800*m*, 720*m*, 635*m*. ^{1}H-NMR: 7.98 (br. *s*, NH_3^+); 3.6–3.55 (*m*, CH_2N); *ca*. 3.25 (br. *s*, CH); 2.05–1.95 (*m*, 1 H, C*H*$_2$CH); 1.85–1.75 (*m*, 1 H, C*H*$_2$CH); 1.66 (*s*, Me_2C); 1.21 (*d*, *J* = 6.6, *Me*CH). ^{13}C-NMR: 164.4 (*s*, CO); 158.1 (*q*, ^2J(C,F) = 31, CF_3COO^-); 117.1 (*q*, ^1J(C,F) = 299, CF_3); 83.2 (*s*, Me_2C); 44.5 (*d*, CH); 36.7, 32.1 (2*t*, 2 CH_2); 17.6, 17.5 (2*q*, *Me*$_2$C, *Me*CH). ESI-MS: 253 ($[M_{cation}+MeOH]^+$), 221 ($[M_{cation}]^+$).

3.2. *Ring-Enlargement Products of* **20a–d**. 3.2.1. *3,4,5,6-Tetrahydro-8,8-dimethyl-2*H*-1,2,6-thiadiazocin-7(8*H*)-one 1,1-Dioxide* (**21**). To a stirred soln. of **20a** (34 mg, 0.11 mmol) in dry MeCN (25 ml), (piperidinomethyl)polystyrene (0.6 g, 2.6–2.8 mmol base/g resin) was added. The mixture was stirred at r.t. for 63 h, the resin removed by filtration, and the filtrate evaporated. Recrystallization from MeCN afforded 20 mg (86.9%) of **21**. Colorless solid. M.p. 198.5–200.5°. IR: 3400v*s*, 3250v*s*, 2940*s*, 1650v*s*, 1530v*s*, 1475*s*, 1450*s*, 1420*s*, 1395*s*, 1315v*s*, 1290*s*, 1270*s*, 1200*s*, 1160v*s*, 1130*s*, 1110v*s*, 1080*s*, 1060*s*, 995*m*, 870*m*, 820*m*, 775*m*, 705*s*, 655*m*, 610*m*. ^{1}H-NMR (380 K): 6.66 (br. *s*, NH); *ca*. 6.5–6.0 (very br. signal, NH); 3.4–3.35, 3.15–3.1, 1.65–1.6

(3*m*, 3 CH_2); 1.51 (*s*, Me_2C). ^{13}C-NMR (380 K): 171.2 (*s*, CO); 68.5 (*s*, Me_2C); 40.9, 40.0, 26.3 (3*t*, 3 CH_2); 20.8 (*q*, Me_2C). CI-MS: 224 (100, $[M+NH_4]^+$), 207 (37, $[M+1]^+$). Anal. calc. for $C_7H_{14}N_2O_3S$ (206.27): C 40.76, H 6.84, N 13.58; found: C 40.96, H 6.66, N 13.48.

Suitable crystals for an X-ray crystal-structure determination were grown from MeCN/CH_2Cl_2.

3.2.2. *2,3,4,5,6,7-Hexahydro-9,9-dimethyl-1,2,7-thiadiazonin-8(9*H*)-one 1,1-Dioxide* (**22**). To a stirred soln. of **20b** (100 mg, 0.3 mmol) in dry MeCN (60 ml), (piperidinomethyl)polystyrene (1.9 g, 2.6–2.8 mmol base/g resin) was added. The mixture was stirred at r.t. for 90 h, the resin removed by filtration, and the filtrate evaporated. Recrystallization from MeCN afforded 45 mg (68.1%) of **22**. Colorless solid. M.p. 173.5–175°. IR: 2860*m*, 1650v*s*, 1550*s*, 1540*s*, 1450*m*, 1315v*s*, 1290*s*, 1210*w*, 1160*m*, 1120v*s*, 1095*m*, 1035*m*, 945*m*, 835*m*, 735*m*, 625*m*. ^{1}H-NMR (360 K): 7.3–7.15 (br. *s*, NH)[6]); 6.35–6.15 (br. *m*, NH)[7]); 3.22 (*q*, *J* = 5.7, CH_2); 3.2–3.15 (*m*, CH_2); 1.7–1.6 (*m*, CH_2); 1.55–1.45 (*m*, 2 CH_2); 1.48 (*s*, Me_2C). ^{13}C-NMR (360 K): 168.3 (*s*, CO); 67.7 (*s*, Me_2C); 44.8, 28.1, 26.4 (3*t*, 4 CH_2); 19.7 (*q*, Me_2C). CI-MS: 238 (100, $[M+NH_4]^+$), 221 (41, $[M+1]^+$).

3.2.3. *3,4,5,6,7,8-Hexahydro-10,10-dimethyl-2*H*-1,2,8-thiadiazecin-9(10*H*)-one 1,1-Dioxide* (**23**). To a stirred soln. of **20c** (150 mg, 0.43 mmol) in dry MeCN (120 ml), (piperidinomethyl)polystyrene (3.2 g, 2.6–2.8 mmol base/g resin) was added. The mixture was stirred at r.t. for 120 h. Then, it was divided in two equal parts. From the first part, after removal of the resin by filtration, evaporation of the filtrate, and recrystallization of the residue from MeCN, the starting material **20c** (52 mg) was isolated. The second part was heated under reflux for 45 h, the mixture filtered, and the filtrate evaporated. Product **23** was isolated by CC (CH_2Cl_2/MeOH/25% NH_4OH 40 : 3 : 0.6): 21 mg (41.9%). Colorless solid. M.p. 183.3–193.4° (MeCN). IR: 3410*s*, 3160*m*, 2930*m*, 1650v*s*, 1535*s*, 1470*m*, 1450*m*, 1310v*s*, 1245*m*, 1165*m*, 1125*s*. ^{1}H-NMR: 7.71 (*t*, *J* = 5.5, NH); 7.11 (*t*, *J* = 5.5, NH); 3.16 (*q*, *J* = 5.5, CH_2); 3.0 (br. *m*, CH_2); 1.55–1.5 (br. *m*, CH_2); 1.45–1.4 (br. *m*, 2 CH_2); 1.45 (*s*, Me_2C). ^{13}C-NMR: 167.4 (*s*, CO); 66.9 (*s*, Me_2C); 40.0, 38.4, 26.9, 23.6, 19.8 (5*t*, 5 CH_2); 20.7 (*q*, Me_2C). ESI-MS: 491 ($[2M+Na]^+$), 273 ($[M+K]^+$), 257 ($[M+Na]^+$), 235 ($[M+1]^+$).

3.2.4. *3,4,5,6-Tetrahydro-5,8,8-trimethyl-2*H*-1,2,6-thiadiazocin-7(8*H*)-one 1,1-Dioxide* (**24**). To a stirred soln. of **20d** (70 mg, 0.21 mmol) in dry MeCN (60 ml), (piperidinomethyl)polystyrene (1.6 g, 2.6–2.8 mmol base/g resin) was added. The mixture was stirred at r.t. for 48 h, the resin removed by filtration, and the filtrate evaporated. Recrystallization from MeCN yielded 34 mg (73.9%) of **24**. Colorless solid. M.p. 171.0–174.1°. IR: 3380*s*, 3270*s*, 2980*m*, 1645v*s*, 1525*s*, 1420*m*, 1325v*s*, 1280*m*, 1195*m*, 1190*m*, 1160*s*, 1140*m*, 1125*s*, 1100*m*, 1055*w*, 995*w*, 900*w*, 870*w*, 835*w*, 710*w*, 655*m*, 625*s*. ^{1}H-NMR (380 K): 6.70 (br. *s*, NH); 6.36 (br. *s*, NH); 4.01 (br. *s*, CH); 3.21 (*dq*, *J* = 7.6, 2.8, 1 H, CH_2NH); 3.06 (*dq*, *J* = 7.8, 2.6, 1 H, CH_2NH); 1.8–1.7 (*m*, 1 H, CH_2CH); 1.55–1.45 (*m*, 1 H, CH_2CH); 1.54, 1.51 (2*s*, Me_2C); 1.20 (*d*, *J* = 6.7, *Me*CH). ^{1}H-NMR[8]) ($CDCl_3$, 600 MHz, 225 K): 6.06 (*d*, *J* = 8.5, NH); 4.86 (br. *s*, NH); 4.10 (*m*, *J* = 7.1, CH); 3.4–3.3 (*m*, 1 H, CH_2NH); 3.26–3.23 (*m*, 1 H, CH_2NH); 2.27–2.22 (*m*, 1 H, CH_2CH); 1.64, 1.48 (2*s*, Me_2C); 1.30 (*dd*, *J* = 15.1, 4.5, 1 H, CH_2CH); 1.19 (*d*, *J* = 6.9, *Me*CH). ^{13}C-NMR[9]) ($CDCl_3$, 600 MHz, 225 K): 171.9 (*s*, CO); 70.2 or 68.6 (*s*, Me_2C) 44.6 (*d*, CH); 38.6 (*t*, CH_2NH); 29.8 (*t*, CH_2CH); 21.0 (*q*, Me_2C); 19.8 (*q*, *Me*CH). ESI-MS: 463 ($[2M+Na]^+$), 259 ($[M+K]^+$), 243 ($[M+Na]^+$), 221 ($[M+1]^+$).

Suitable crystals for an X-ray crystal-structure determination were grown from MeCN.

4. *Crystal-Structure Determination of* **1b**, **21**, *and* **24** (see *Table* and *Figs. 1–3*)[10]). All measurements were made on a *Rigaku-AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The $\omega/2\theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given in the *Table*, views of the molecules are shown in *Figs. 1–3*. The structures were solved by direct methods using 'SHELXS86' [23], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were located in difference electron density maps, and their

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[6]) At r.t., this signal is a sharp *s* at 7.57 ppm, but under these conditions, the other signals were difficult to recognize.

[7]) At r.t., this signal is a sharp *s* at 7.10 ppm.

[8]) The spectrum of the main conformer is described.

[9]) Spectrum of the main conformer, inside projection from HMBC.

[10]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-112649, 112650, and 112651 for **1b**, **21**, and **24**, respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

Table 1. *Crystallographic Data of Compounds* **1b**, **21** *and* **24**

	1b	**21**	**24**
Crystallized from	sublimation	$MeCN/CH_2Cl_2$	MeCN
Empirical formula	$C_{11}H_{13}NO_3S$	$C_7H_{14}N_2O_3S$	$C_8H_{16}N_2O_3S$
Formula weight [g·mol^{-1}]	239.29	206.26	220.28
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.33 \times 0.38 \times 0.48$	$0.30 \times 0.35 \times 0.40$	$0.20 \times 0.20 \times 0.50$
Temperature [K]	173(1)	173(1)	173(1)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P\bar{1}$	Cc
Z	4	2	4
Reflections for cell determination	25	25	25
2θ Range for cell determination [°]	39 – 40	39 – 40	38 – 40
Unit cell parameters a [Å]	10.201(2)	6.166(1)	9.077(5)
b [Å]	11.712(2)	14.282(2)	11.291(3)
c [Å]	9.643(2)	5.890(1)	10.894(3)
α [°]	90	95.54(2)	90
β [°]	94.37(2)	116.44(2)	106.72(3)
γ [°]	90	96.45(2)	90
V [Å^3]	1148.8(3)	455.2(2)	1069.3(7)
D_x [g cm^{-3}]	1.383	1.505	1.368
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.273	0.333	0.288
$2\theta_{(\max)}$ [°]	60	60	60
Total reflections measured	3699	2879	1724
Symmetry-independent reflections	3358	2651	1646
Reflections used ($I > 2\sigma(I)$)	2786	2421	1544
Parameters refined	198	175	189
Final R	0.0367	0.0312	0.0362
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0391	0.0367	0.0357
Goodness of fit	2.192	2.558	2.434
Secondary extinction coefficient	$1.6(2) \cdot 10^{-6}$	$1.4(5) \cdot 10^{-6}$	–
Final $\Delta_{\max}/\sigma$	0.0002	0.0002	0.0003
$\Delta\rho$ (max; min) [e·Å^{-3}]	0.30; −0.32	0.41; −0.41	0.34; −0.32

positions were allowed to refine together with individual isotropic displacement parameters. Refinement of the structures was carried out on F using full-matrix least-squares procedures, which minimized the function $\sum w (|F_o| - |F_c|)^2$. Corrections for secondary extinction were applied for **1b** and **21**. Neutral-atom scattering factors for non-H-atoms were taken from [24a] and the scattering factors for H-atoms from [25]. Anomalous dispersion effects were included in F_{calc} [26]; the values for f' and f'' were those of [24b]. All calculations were performed using the 'TEXSAN' crystallographic software package [27].

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