# RING ENLARGEMENT OF EIGHT- AND NINE-MEMBERED CYCLIC SULFONAMIDE DERIVATIVES IN REACTIONS WITH 3-AMINO-2*H*-AZIRINES

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(Dedicated to Prof. Dr. B. Witkop on the occasion of his 80th birthday)

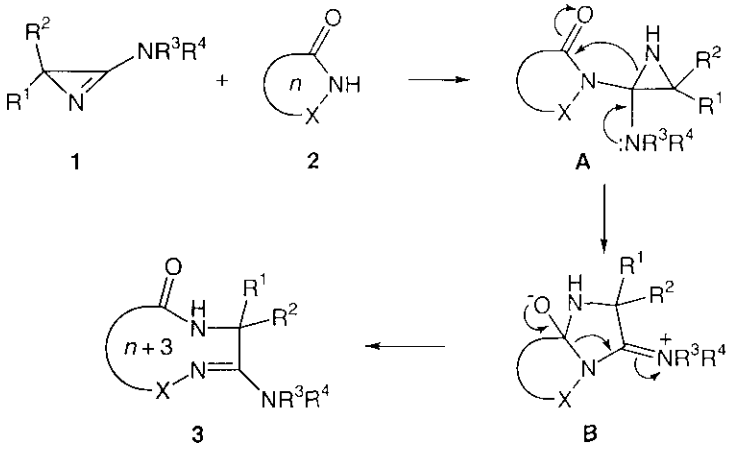
**Abstract** - The reactions of 3-dimethylamino-2*H*-azirines (**1**) with 3,4,5,6-tetrahydro-8,9-dimethoxy-2*H*-1,2-benzothiazocin-3-one 1,1-dioxide (**6a**) in acetonitrile gave the correspondingly substituted 3-dimethylamino-4,5,6,7,8,9-hexahydrobenzo-1-thia-2,5-diazacycloundecen-6-one 1,1-dioxides (**8**). In the case of the reaction of **1a** with **6a**, the 3-amino-5,6-dihydro-4*H*-benzothiazocine 1,1-dioxide derivative (**9**) was formed as a minor product. The structures of the starting material (**6a**), the unexpected 4,5-dimethoxy-2-(3-cyanopropyl)benzenesulfonyl chloride (**7**), the novel eleven-membered heterocycles (**8a**, **8c**), and that of **9** were established by X-Ray crystallography. With the nine-membered homologue 2,3,4,5,6,7-hexahydro-9,10-dimethoxy-1,2-benzothiazonin-3-one 1,1-dioxide (**6b**), only the most reactive aminoazirine yielded the ring enlarged twelve-membered heterocycle (**10**).

## INTRODUCTION

In several papers[2-6] we showed that 3-amino-2*H*-azirines (**1**) and NH-acidic heterocycles (**2**) with $pK_a < 8$ react to give ring enlarged products of type (**3**) (*Scheme 1*). All experimental data are in accord with the following reaction mechanism: protonation of the azirine and nucleophilic attack of the lactam anion lead to aziridine (**A**), which undergoes a ring enlargement to give a zwitterion of type (**B**). A second ring enlargement then yields the new heterocycle (**3**).[2] In the case of reactions with cyclic *N*-unsubstituted oxo-sulfonamides (**2**) (X = $SO_2$), the ring enlargement to seven- and eight-membered heterocycles is a smooth reaction at room temperature.[6-9] The reactions with six- and seven-membered sulfonamides of type (**2**) (X = $SO_2$), yielding nine- and ten-membered products (**3**), are more sluggish, especially with the less reactive 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirines (**1**) ($R^3$ = Me, $R^4$ =

Ph).[3-5] As it is well known that the formation of medium sized rings is most difficult, these observations follow the usual trend.

*Scheme 1*




In the present paper, we describe the results of the ring enlargements of eight- and nine-membered starting materials of type (**2**) (X = $SO_2$), together with the syntheses of the latter.

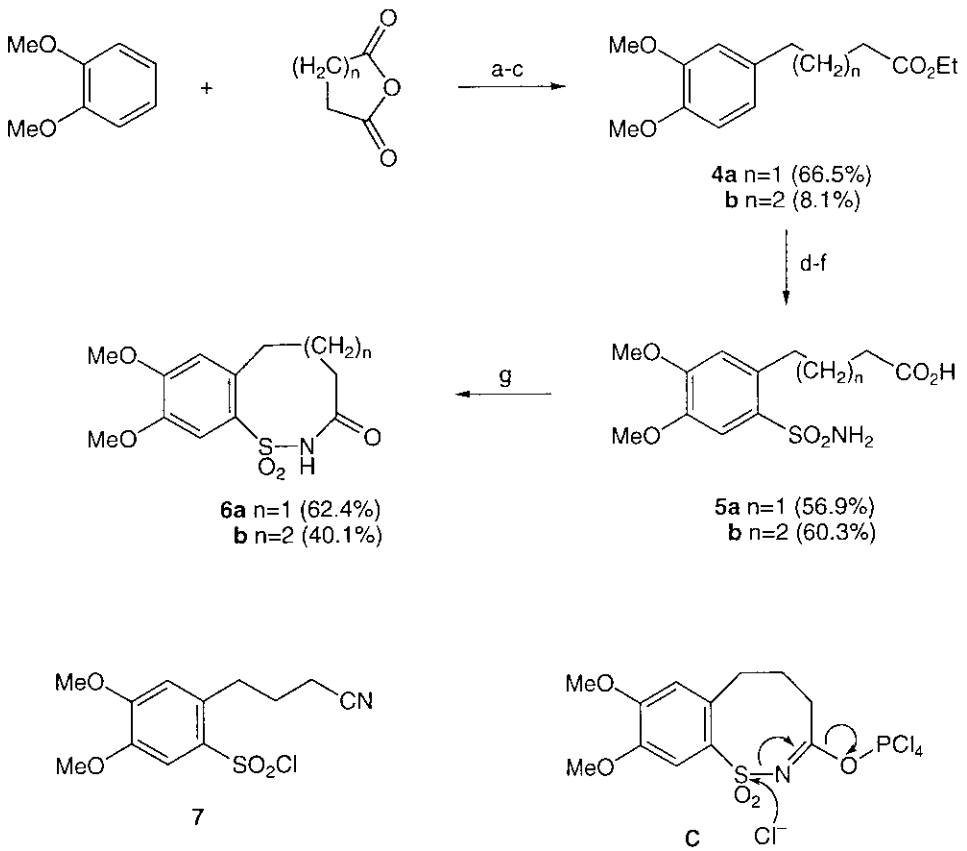
## RESULTS AND DISCUSSION

As the synthesis of the seven-membered 4,5-dihydro-7,8-dimethoxy-2*H*-1,2-benzothiazepin-3-one 1,1-dioxide has already been described,[10] we intended to prepare the eight- and nine-membered analogues following a similar protocol (*Scheme 2*). Acylation of 1,2-dimethoxybenzene with succinic and glutaric acid anhydrides in nitrobenzene,[11] followed by reduction of the aryl ketone with $Et_3SiH$ in $CF_3COOH$[11,12] and esterification, led to ethyl 4-arylbutanoate (**4a**) and 5-arylpentanoate (**4b**), respectively. By analogy to ref.,[10] chlorosulfonation of **4** at low temperature, treatment with $NH_3$ in dioxane and saponification yielded the sulfonamido acids (**5**). All attempts to cyclize **5a** *via* the corresponding acid chloride by following the described protocol,[10] *i.e.* using $PCl_5$ in anhydrous benzene at room temperature, failed.[13]

When the mixture of **5a** and $PCl_5$ in benzene was stirred at room temperature for six days and then, after changing the solvent to xylene, refluxed for 24 h, **6a** was isolated in up to 14% yield.[15] A very unexpected result was obtained using 2.8 equiv. of $PCl_5$ in ether at room temperature and then heating the mixture in xylene to 140°C for 2 h: after chromatographic workup, carbonitrile (**7**) was isolated as the only product in 43% yield. The elucidation of the structure of **7** was based on the spectral data (IR, NMR, MS) and, after growing single crystals from $CHCl_3$/hexane, it was established by an X-Ray crystal-structure determination (*Figure 1*,

a)). As a reaction mechanism for the formation of **7** we propose an intermediate formation of **6a**, followed by the reaction with a second equivalent of $PCl_5$ to give **C**. Ring opening by nucleophilic attack of $Cl^-$ and elimination of $Cl_3PO$ could then lead to the nitrile (**7**).

*Scheme 2*




a) $AlCl_3$, $C_6H_5NO_2$; b) $Et_3SiH$, $CF_3CO_2H$; c) EtOH, $H_2SO_4$; d) $HSO_3Cl$, $CCl_4$, -5→0°C; e) $NH_3$, dioxane, rt; f) KOH, MeOH, reflux; g) $(EtO)_2P(O)CN$, $EtN(i\text{-}Pr)_2$, $CH_2Cl_2$, rt.

As the cyclization of **5a** to **6** was unsuccessful or proceeded with inferior yield under the conditions described above, we tried to form the 'lactam bond' by using some reagents for peptide coupling, *e.g.* the formation of cyclic peptides. Surprisingly, sulfonamido acid (**5a**) reacted neither with DCC in DMF nor with DCC/HOBT in DMF.[17] Performing the cyclization of **5a** in a dilute $CH_2Cl_2$ solution with diethylphosphoryl cyanide (DEPC)[18] in the presence of ethyldiisopropylamine (*Hünig* base) at room temperature gave the eight-membered 1,2-benzothiazocin-3-one 1,1-dioxide (**6a**) in 62.4% yield. The higher homologue pentanoic acid (**5b**) was cyclized under the same conditions to yield nine-membered 1,2-benzothiazonin-3-one 1,1-dioxide (**6b**) (40.1% yield).

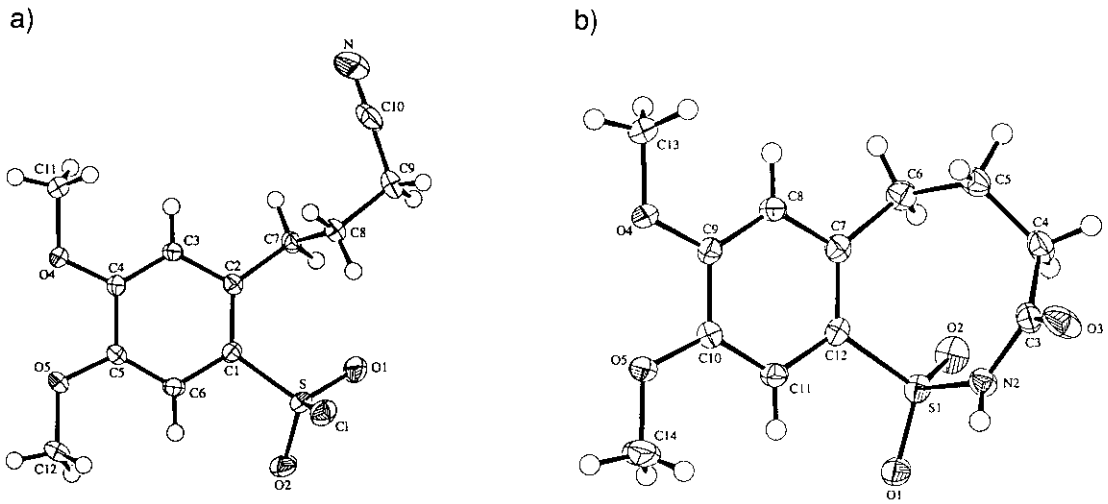
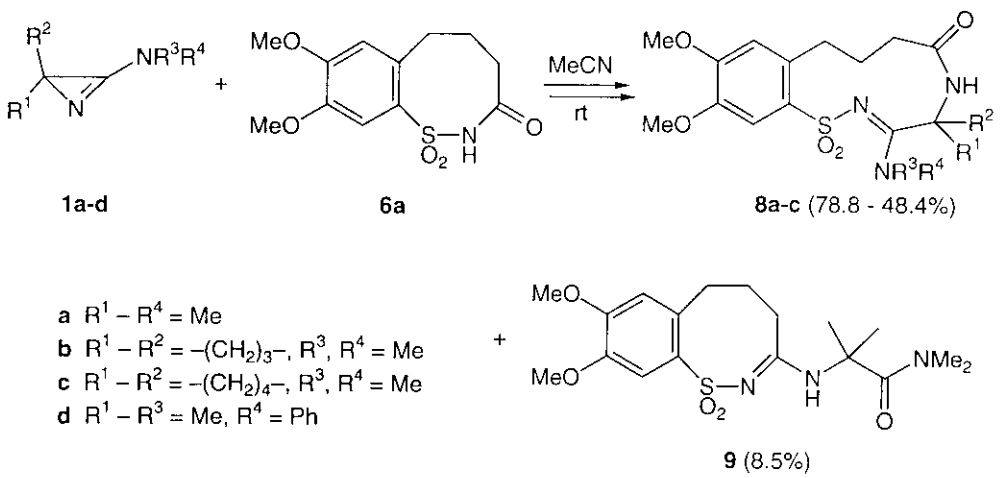



*Figure 1.* ORTEP plots[16] of the molecular structures of a) **7** and b) **6a** (displacement ellipsoids with 50% probability).

The molecular structure of **6a** was also established by an X-Ray crystal-structure determination (*Figure 1*, b)). It is worth mentioning that the eight-membered ring contains a *cis*-amide bond (torsion angles: S(1)-N(2)-C(3)-C(4) -16.8(3)°; S(1)-N(2)-C(3)-O(3) 166.3(2)°).[19] The molecules are linked into centrosymmetric dimers by intermolecular hydrogen bonds between N(2)-H and O(3) of the carbonyl group of a neighboring molecule (N···O distance 2.830(2) Å, angle N-H···O 173(2)°); graph set $R_2^2(8)$.[20]

*Scheme 3*




The reactions of the eight-membered oxo-sulfonamide (**6a**) with 3-dimethylamino-2*H*-azirines (**1a-c**) were performed in acetonitrile at room temperature. After stirring for 19-120 h, two

spots for new products were detected by TLC. In the case of the reaction with **1a**, workup by chromatography ($SiO_2$, $CH_2Cl_2$/MeOH) and crystallization from $CH_2Cl_2/Et_2O$ gave two isomeric 1:1 adducts (**8a** and **9**) in 78 and 8.5% yields,[21] respectively. Based on the spectral data and the comparison with those of the previously described ten-membered analogues (cf. [5]), structure (**8a**) (*Scheme 3*) was proposed for the main product.

The structure of **8a** was established by an X-Ray crystal-structure determination (*Figure 2*, a)). The molecule contains a *trans*-amide bond (torsion angles: C(4)-N(5)-C(6)-C(7) -163.7(2)°; C(4)-N(5)-C(6)-O(6) 17.0(3)°)[19] and a nearly planar amidine group (torsion angles: N(2)-C(3)-N(3)-C(16) -10.7(3)°, N(2)-C(3)-N(3)-C(17) 168.8(2)°). The NH group forms an intermolecular hydrogen bond with one of the methoxy O-atoms of a neighboring molecule (N···O distance 3.172(2)Å, angle N-H···O 177(2)°), thereby linking the molecules into infinite one-dimensional chains which run parallel to the y-axis; graph set: C(10).[20] A similar structure for **8c** was found by X-Ray crystallography (*Figure 2*, b)).

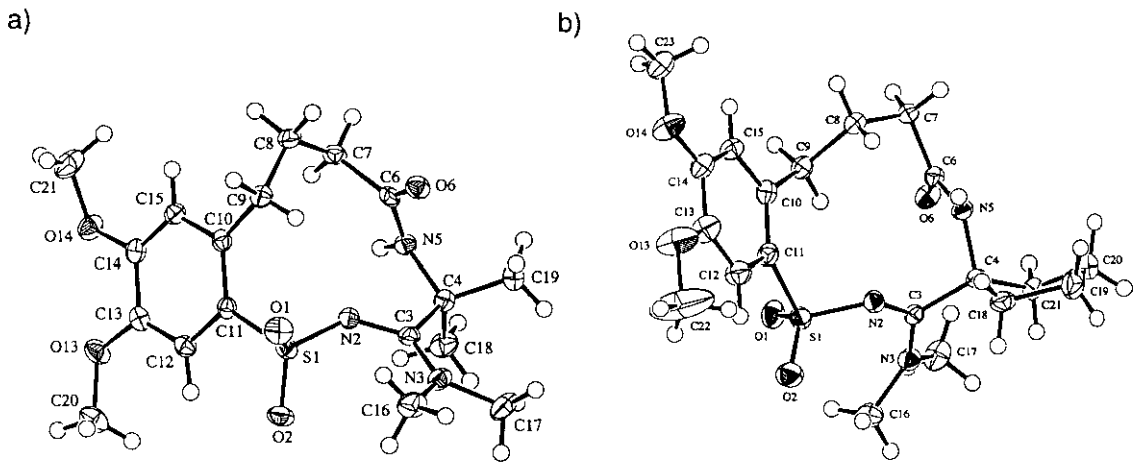



*Figure 2.* ORTEP plots[16] of the molecular structures of a) **8a** and b) one of the independent molecules of **8c** (displacement ellipsoids with 50% probability).

Although the spectral data of **8a** and **9** are very similar, there are some minor differences. *E.g.*, the IR spectrum of **8a** shows strong absorption bands at 1685, 1585, and 1575 $cm^{-1}$ for C=O and C=N, whereas the absorptions of **9** are at 1620, 1600, and 1550 $cm^{-1}$. In the NMR spectra, the most clear differences are shown by the absorptions of the $(CH_3)_2C$ groups (**8a**: 1.51/32.1 ppm; **9**: 1.42/24.9 ppm) and the $(CH_3)_2N$ groups (**8a**: 3.34/43.5 ppm; **9**: 2.51/36.6 ppm). As these data did not allow to assign with certainty a structure for the minor product (**9**), it was again determined by X-Ray crystallography (*Figure 3*). To our surprise, it was found to be an *N*-substituted α-aminoisobutyramide, *i.e.* the oxo group of **6a** has been substituted by

an amino function. By analogy to the reactions of aminoazirines (**1**) with carboxylic acids, the reaction mechanism depicted in *Scheme 4* is in accordance with the formation of **9**.[2]

Two spots for new products (TLC) were also detected in the crude mixtures of the reactions of **6a** with **1b** and **1c**, respectively, but only the main products (**8b** and **8c**) were isolated (57.1 and 48.4% yield,[21] respectively). On the other hand, no reaction was observed when a solution of **6a** and the 3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**1d**) in acetonitrile was stirred at room temperature. Even after heating to 80°C for 22 h, no product could be detected and 85.5% of **6a** were recovered.

*Scheme 4*

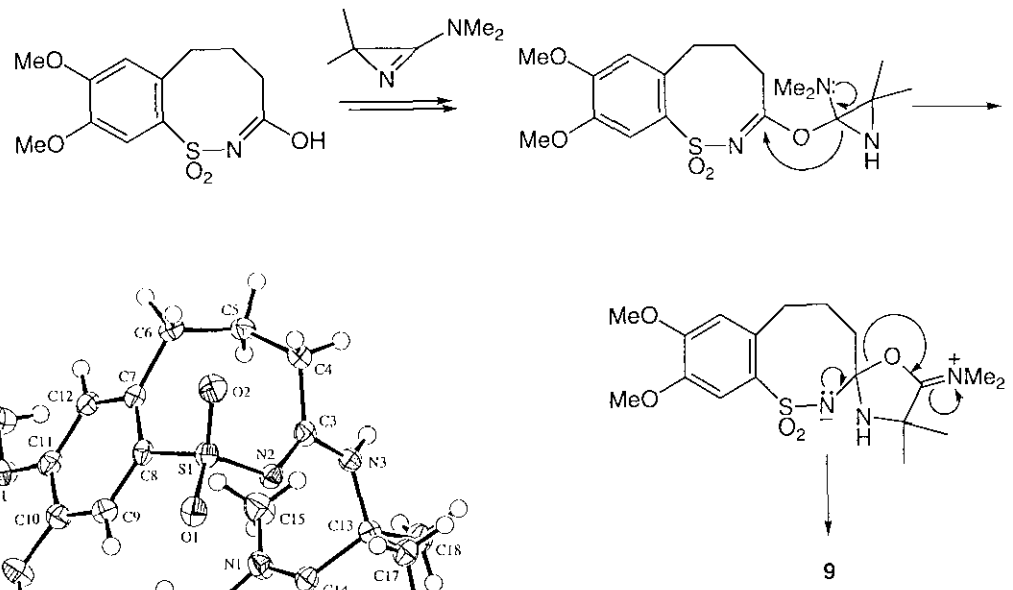


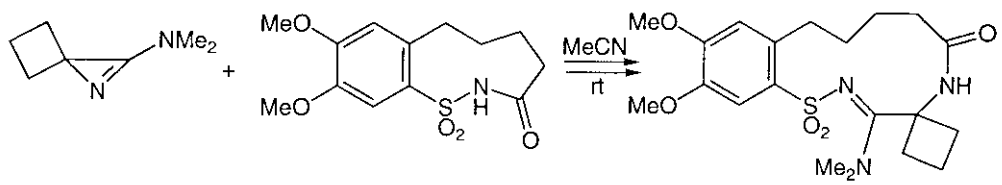




*Figure 3.* ORTEP plot[16] of the molecular structure of **9** (displacement ellipsoids with 50% probability).

The nine-membered oxo-sulfonamide (**6b**) reacted with **1a** and **1b**, respectively, in acetonitrile at room temperature, but only in the case of the most reactive azirine (**1b**) was an addition product detected. After 65 h, there were still *ca.* 80% of **6b** present, and chromatographic workup gave only one 1:1-adduct in 8.4% yield as colorless crystals. No other product could be isolated. Based on the spectral data, the structure of the twelve-membered 5,6,7,8,9,10-hexahydrobenzo-4*H*-1-thia-2,5-diazacyclododecen-6-one 1,1-dioxide (**10**) was assigned to the product (*Scheme 5*).

*Scheme 5*




**1b** **6b** **10** (8.4%)

In conclusion, the present results further generalize the ring enlargement of cyclic oxo-sulfonamides in reactions with 3-amino-2*H*-azirines, but some limitations are obvious in the case of the nine-membered starting material (**6b**).[22]

## EXPERIMENTAL

*General remarks*. See ref.[9] Melting points were determined on a *Mettler FP-5* apparatus and are uncorrected. If not otherwise stated, IR spectra were recorded on a *Perkin-Elmer-781* instrument (KBr, $cm^{-1}$), $^1$H-NMR and $^{13}$C-NMR spectra on a *Bruker-AC-300* or *ARX-300* instrument (DMSO-$d_6$, 300 and 75.5 MHz, respectively, $\delta$ in ppm, $J$ in Hz), and MS spectra on a *Finnigan-MAT-90* (70 eV; CI with $NH_3$) or *Finnigan-SSQ-700* spectrometer (ESI). Column chromatography (CC) or prep. TLC on silica gel ($SiO_2$).

*Syntheses of starting materials*. 4-(3,4-Dimethoxyphenyl)butanoic acid and 5-(3,4-dimethoxyphenyl)pentanoic acid were prepared according to refs.[11,12] but the protocol of the reduction of the carbonyl group with trifluoracetic acid (TFA) and triethylsilane had to be modified as follows: to a solution of the oxo-carboxylic acid (0.027 mol) in TFA (30 mL), cooled in an ice bath and kept under nitrogen, triethylsilane (7.0 g, 0.06 mol) was slowly added. The reaction mixture was allowed to reach rt and was stirred overnight. Then, TFA was removed under reduced pressure, the oily residue was dissolved in ether, washed with water, and extracted with saturated aq. $NaHCO_3$. The latter extract was acidified with conc. HCl and the product was extracted with $CH_2Cl_2$.

*3-(3,4-Dimethoxybenzoyl)propanoic acid*.[23] Yield 78.6%. Colorless solid, mp 161.6-162.2°C. $^1$H-NMR: 2.57 (*t*, $J$ = 6.2, 2H, $CH_2$), 3.21 (*t*, $J$ = 6.2, 2H, $CH_2$), 3.82, 3.85 (2*s*, 6H, 2 $CH_3O$), 7.07 (*d*, $J$ = 8.5, 1H, H $_{arom}$), 7.46 (*d*, $J$ = 1.6, 1H, $H_{arom}$), 7.66 (*dd*, $J$ = 8.5, 2.0, 1H, $H_{arom}$); $^{13}$C-NMR: 27.9, 32.6 (2*t*, 2 $CH_2$), 55.4, 55.6 (2*q*, 2 $CH_3O$), 110.4, 110.8, 122.4 (3*d*, 3 $C_{arom}$), 129.3, 148.5, 153.0 (3*s*, 3 $C_{arom}$), 173.8, 196.8 (2*s*, 2 C=O); IR: 3350*vs*, 2925*m*, 1735*vs*, 1660*vs*, 1595*vs*, 1590*s*, 1515*s*, 1460*s*, 1440*s*, 1415*vs*, 1390*s*, 1335*s*, 1265*vs*, 1240*s*, 1160*vs*, 1145*vs*, 1140*vs*, 1080*m*, 1020*s*, 875*s*, 795*s*, 765*s*, 605*m*; CI-MS: 239 (100, $[M+1]^+$).

*4-(3,4-Dimethoxybenzoyl)butanoic acid.*[24] Yield 10.4%. Yellowish solid, mp 145.7-146.0°C. $^1$H-NMR: 1.81-1.87 (*m*, 2H, $CH_2$), 2.31 (*t*, *J* = 7.3, 2H, $CH_2$), 3.00 (*t*, *J* = 7.3, 2H, $CH_2$), 3.82, 3.85 (2*s*, 6H, 2 $CH_3O$), 7.06 (*d*, *J* = 8.4, 1H, H arom), 7.40 (*d*, *J* = 2.0, 1H, $H_{arom}$), 7.63 (*dd*, *J* = 8.4, 2.0, 1H, $H_{arom}$); $^{13}$C-NMR: 19.6, 32.8, 36.6 (3*t*, 3 $CH_2$), 55.4, 55.7 (2*q*, 2 $CH_3O$), 110.1, 110.8, 122.5 (3*d*, 3 $C_{arom}$), 129.5, 148.5, 153.0 (3*s*, 3 $C_{arom}$), 174.2, 198.0 (2*s*, 2 C=O); IR: 3020*vs*, 2970*vs*, 2930*vs*, 2900*vs*, 1710*vs*, 1670*vs*, 1590*vs*, 1515*vs*, 1460*vs*, 1415*vs*, 1370*m*, 1345*m*, 1300*vs*, 1280*vs*, 1255*vs*, 1240*vs*, 1220*vs*, 1190*vs*, 1155*vs*, 1080*s*, 1040*s*, 1025*vs*, 910*s*, 875*vs*, 850*m*, 810*s*, 760*s*, 745*m*, 625*m*; CI-MS: 252 (24, $[M+1]^+$), 165 (100).

*4-(3,4-Dimethoxyphenyl)butanoic acid.*[23] Yield 91.2%. Colorless solid, mp 59.9-60.5°C. $^1$H-NMR ($CDCl_3$): 1.93-1.99 (*m*, 2H, $CH_2$), 2.37 (*t*, *J* = 7.4, 2H, $CH_2$), 2.62 (*t*, *J* = 7.5, 2H, $CH_2$), 3.85, 3.87 (2*s*, 6H, 2 $CH_3O$), 7.69-7.75 (*m*, 2H, $H_{arom}$), 7.79 (*d*, *J* = 8.0, 1H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 26.4, 33.3, 34.6 (3*t*, 3 $CH_2$), 55.8, 56.0 (2*s*, 2 $CH_3O$), 111.4, 111.8, 120.4 (3*d*, 3 $C_{arom}$), 133.8, 147.4, 148.9 (3*s*, 3 $C_{arom}$), 180.0 (*s*, C=O); IR: 2950*s*, 1695*vs*, 1520*vs*, 1460*m*, 1440*m*, 1425*m*, 1405*m*, 1340*m*, 1270*s*, 1260*s*, 1235*s*, 1210*s*, 1195*m*, 1160*s*, 1140*s*, 1030*s*, 850*m*, 810*m*; CI-MS: 242 (100, $[M+NH_4]^+$).

*5-(3,4-Dimethoxyphenyl)pentanoic acid.*[24] Yield 81.8%. Colorless solid, mp 77.8-78.1°C. $^1$H-NMR ($CDCl_3$): 1.60-1.70 (*m*, 4H, 2 $CH_2$), 2.35-2.41, 2.55-2.61 (2*m*, 4H, 2 $CH_2$), 3.85, 3.87 (2*s*, 2 $CH_3O$), 6.68-6.74 (*m*, 2H, $H_{arom}$), 6.76-6.82 (*m*, 1H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 24.3, 30.9, 33.9, 35.1 (4*t*, 4 $CH_2$), 55.8, 55.9 (2*q*, 2 $CH_3O$), 111.3, 111.8, 120.2 (3*d*, 3 $C_{arom}$), 134.7, 147.2, 148.9 (3*s*, 3 $C_{arom}$), 180.0 (*s*, C=O); IR: 2990*m*, 2930*s*, 2840*m*, 1705*vs*, 1690*vs*, 1590*m*, 1515*vs*, 1460*s*, 1450*m*, 1410*m*, 1335*m*, 1310*m*, 1270*s*, 1260*vs*, 1205*s*, 1190*s*, 1155*s*, 1140*vs*, 1040*m*, 1020*s*, 955*m*, 940*m*, 845*m*, 820*m*, 770*s*; EI-MS: 238 (37, $M^{+\cdot}$), 151 (100).

The sulfonamido acids (**5a** and **5b**) were prepared according to a described procedure.[10] *Ethyl 4-(3,4-dimethoxyphenyl)butanoate* (**4a**).[25] The product was purified by CC ($SiO_2$, hexane/ethyl acetate 3:1). Yield 92.8%. Colorless oil. $^1$H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.1, 3H, $CH_3$), 1.90-1.96 (*m*, 2H, $CH_2$), 2.31 (*t*, *J* = 7.5, 2H, $CH_2$), 2.60 (*t*, *J* = 7.5, 2H, $CH_2$), 3.85, 3.87 (2*s*, 6H, 2 $CH_3O$), 4.12 (*q*, *J* = 7.1, 2H, $CH_2O$), 6.68-6.74 (*m*, 2H, $H_{arom}$), 6.76-6.82 (*m*, 1H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 14.3 (*q*, $CH_3$), 26.8, 33.6, 34.7 (3*t*, 3 $CH_2$), 55.8, 55.9 (2*q*, 2 $CH_3O$), 60.2 (*t*, $CH_2O$), 111.3, 111.9, 120.4 (3*d*, 3 $C_{arom}$), 134.1, 147.7, 148.9 (3*s*, 3 $C_{arom}$), 173.5 (*s*, C=O); IR ($CHCl_3$): 3010*s*, 2960*s*, 2940*s*, 2840*m*, 1725*vs*, 1590*m*, 1515*vs*, 1470*vs*, 1455*s*, 1445*s*, 1420*s*, 1375*s*, 1380*m*, 1305*m*, 1260*vs*, 1240*vs*, 1155*vs*, 1145*vs*, 1030*vs*, 850*m*, 805*s*; CI-MS (with *i*-butane): 253 (100, $[M+1]^+$), 207 (63).

*Ethyl 5-(3,4-dimethoxyphenyl)pentanoate* (**4b**).[24] The product was purified by CC ($SiO_2$, hexane/ethyl acetate 2:1). Yield 95.6%. Colorless oil. $^1$H-NMR ($CDCl_3$): 1.34 (*t*, *J* = 7.1, 3H, $CH_3$), 1.60-1.70 (*m*, 4H, 2 $CH_2$), 2.32 (br *t*, 2H, $CH_2$), 2.57 (br *t*, 2H, $CH_2$), 3.84, 3.86 (2*s*, 6H,

2 $CH_3O$), 4.12 (*q*, *J* = 7.1, 2H, $CH_2O$), 6.68-7.74 (*m*, 2H, $H_{arom}$), 6.78 (*d*, *J* = 8.6, 1H, $H_{arom}$); $^{13}$C-NMR: ($CDCl_3$): 14.3 (*q*, $CH_3$), 24.6, 31.1, 34.2, 35.2 (4*t*, 4 $CH_2$), 55.8, 55.9 (2*q*, 2 $CH_3O$), 60.2 (*t*, $CH_2O$), 111.3, 111.8, 120.2 (3*d*, 3 $C_{arom}$), 134.9, 147.2, 148.9 (3*s*, 3 $C_{arom}$), 173.6 (*s*, C=O); IR ($CHCl_3$): 3000*s*, 2940*vs*, 2860*m*, 2840*m*, 1730*vs*, 1590*s*, 1515*vs*, 1465*vs*, 1455*vs*, 1420*s*, 1375*s*, 1265*vs*, 1215*vs*, 1155*vs*, 1145*vs*, 1095*m*, 1070*m*, 1030*vs*, 855*m*, 625*m*; EI-MS: 266 (43, $M^{+\cdot}$), 221 (13), 177 (7), 164 (29), 151 (100).

*2-(3-Ethoxycarbonylpropyl)-4,5-dimethoxybenzenesulfonyl chloride*. Isolated by CC ($SiO_2$, hexane/ethyl acetate 2:1). Yield 80%. Colorless oil. $^1$H-NMR ($CDCl_3$): 1.27 (*t*, *J* = 7.1, 3H, $CH_3$), 2.05-2.11 (*m*, 2H, $CH_2$), 2.44 (*t*, *J* = 7.3, 2H, $CH_2$), 3.08-3.14 (*m*, 2H, $CH_2$), 3.94, 3.99 (2*s*, 6H, 2 $CH_3O$), 4.16 (*q*, *J* = 7.1, 2H, $CH_2O$), 6.90, 7.49 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 14.3 (*q*, $CH_3$), 26.3, 31.8, 33.8 (3*t*, 3 $CH_2$), 56.4, 56.5 (2*q*, 2 $CH_3O$), 60.4 (*t*, $CH_2O$), 111.4, 114.0 (2*d*, 2 $C_{arom}$), 134.2, 136.4, 147.1, 154.4 (4*s*, 4 $C_{arom}$), 173.2 (*s*, C=O); IR ($CHCl_3$): 3020*s*, 2980*m*, 2940*m*, 1725*vs*, 1600*m*, 1570*m*, 1515*vs*, 1465*s*, 1440*m*, 1395*s*, 1370*vs*, 1270*vs*, 1180*vs*, 1160*vs*, 1045*vs*, 870*m*, 710*m*, 675*m*, 625*m*; ESI-MS (with NaI): 373 ($[M+Na]^+$).

*2-(4-Ethoxycarbonylbutyl)-4,5-dimethoxybenzenesulfonyl chloride*. Isolated by CC ($SiO_2$, hexane/ethyl acetate 2:1). Yield 80.8%. Colorless oil, which slowly crystallized at 4°C. $^1$H-NMR ($CDCl_3$): 1.26 (*t*, *J* = 7.1, 3H, $CH_3$), 1.72-1.80 (*m*, 4H, 2 $CH_2$), 2.38, 3.08 (2br *t*, 4H, 2 $CH_2$), 3.93, 3.99 (2*s*, 6H, 2 $CH_3O$), 4.13 (*q*, *J* = 7.1, 2H, $CH_2O$), 6.85, 7.49 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 14.3 (*q*, $CH_3$), 24.8, 30.6, 32.4, 33.9 (4*t*, 4 $CH_2$), 56.4 (*q*, 2 $CH_3O$), 111.3, 113.7 (2*d*, 2 $C_{arom}$), 134.1, 137.0, 146.9, 154.4 (4*s*, 4 $C_{arom}$), 173.4 (*s*, C=O); IR ($CHCl_3$): 3020*s*, 2970*s*, 2940*s*, 1725*vs*, 1600*s*, 1570*s*, 1510*vs*, 1465*vs*, 1440*s*, 1390*vs*, 1370*vs*, 1265*vs*,1175*vs*, 1160*vs*, 1045*vs*, 870*m*, 710*m*, 625*m*; CI-MS: 382 (100, $[M+NH_4]^+$).

*2-(3-Ethoxycarbonylpropyl)-4,5-dimethoxybenzenesulfonamide*. Yield 96.7%. Colorless solid, mp 118.0-119.2°C. $^1$H-NMR ($CDCl_3$): 1.27 (*t*, *J* = 7.1, 3H, $CH_3$); 2.00-2.06 (*m*, 2H, $CH_2$), 2.47 (*t*, *J* = 6.4, 2H, $CH_2$), 2.97-3.03 (*m*, 2H, $CH_2$), 3.88, 3.92 (2*s*, 6H, 2 $CH_3O$), 4.17 (*q*, 2H, $CH_2O$), 5.62 (*s*, 2H, $NH_2$), 6.78, 7.51 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 14.2 (*q*, $CH_3$), 26.5, 31.6, 33.3 (3*t*, 3 $CH_2$), 56.1, 56.2 (2*q*, 2 $CH_3O$), 60.9 (*t*, $CH_2O$), 111.4, 113.6 (2*d*, 2 $C_{arom}$), 132.3, 133.7, 146.6, 152.0 (4*s*, 4 $C_{arom}$), 174.4 (*s*, C=O); IR: 3370*s*, 3270*s*, 2970*m*, 2940*m*, 1720*vs*, 1600*m*, 1515*vs*, 1470*m*, 1460*m*, 1415*m*, 1420*m*, 1390*s*, 1380*m*, 1365*m*, 1330*vs*, 1270*vs*, 1220*vs*, 1185*vs*, 1150*vs*, 1050*vs*, 1045*m*, 980*m*, 870*s*, 745*m*, 690*m*, 630*m*; EI-MS: 331 (19, $M^{+\cdot}$), 250 (91), 222 (45), 206 (31), 177 (100), 164 (39).

*2-(4-Ethoxycarbonylbutyl)-3,4-dimethoxybenzenesulfonamide*. Yield 84.2%. Colorless solid, mp 136.6-137.3°C. $^1$H-NMR ($CDCl_3$): 1.24 (*t*, *J* = 7.1, 3H, $CH_3$), 1.70-1.80 (*m*, 4H, 2 $CH_2$), 2.34-2.40, 2.94-3.00 (2*m*, 4H, 2 $CH_2$), 3.87, 3.92 (2*s*, 6H, 2 $CH_3O$), 4.11 (*q*, *J* = 7.1, 2H,

$CH_2O$); 6.77 (*s*, 2H, $NH_2$), 7.28, 7.49 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 14.2 (*q*, $CH_3$), 24.8, 30.7, 32.4, 33.8 (4*t*, 4 $CH_2$), 56.1, 56.2 (2*q*, 2 $CH_3O$), 60.4 (*t*, $CH_2O$), 111.6, 113.5 (2*d*, 2 $C_{arom}$), 131.4, 134.8, 146.6, 152.1 (4*s*, 4 $C_{arom}$), 174.0 (*s*, C=O); IR: 3340*s*, 3235*vs*, 3095*m*, 2970*s*, 2930*s*, 2850*m*, 1725*vs*, 1605*s*, 1575*s*, 1510*vs*, 1465*s*, 1445*s*, 1390*s*, 1380*m*, 1365*s*, 1350*vs*, 1320*vs*, 1290*vs*, 1265*vs*, 1230*vs*, 1215*vs*, 1175*vs*, 1140*vs*, 1060*m*, 1050*vs*, 1025*s*, 995*m*, 965*s*, 895*m*, 875*vs*, 805*m*, 750*m*, 645*s*, 620*s*; CI-MS: 363 (100, $[M+NH_4]^+$), 346 (5, $[M+1]^+$).

*2-(3-Carboxypropyl)-4,5-dimethoxybenzenesulfonamide* (**5a**). Yield 73.6%. Colorless solid, mp 182.0-184.0°C. $^1$H-NMR: 1.82-1.88 (*m*, 2H, $CH_2$), 2.29 (*t*, $J$ = 7.5, 2H, $CH_2$), 2.86-2.92 (*m*, 2H, $CH_2$), 3.77, 3.82 (2*s*, 6H, 2 $CH_3O$), 6.93, 7.39 (2*s*, 2H, $H_{arom}$), 7.27 (s, 2H, $NH_2$); $^{13}$C-NMR: 26.3, 31.1, 33.4 (3*t*, 3 $CH_2$), 55.7 (*q*, 2 $CH_3O$), 111.1, 113.0 (2*d*, 2 $C_{arom}$), 133.2, 133.6, 145.8, 150.9 (4*s*, 4 $C_{arom}$), 174.5 (*s*, C=O); IR: 3370*s*, 3280*s*, 2960*m*, 2920*m*, 1720*vs*, 1600*m*, 1575*m*, 1540*m*, 1515*vs*, 1455*m*, 1445*m*, 1390*m*, 1330*vs*, 1290*s*, 1265*s*, 1210*m*, 1170*s*, 1150*vs*, 1050*s*, 870*m*, 640*m*, 630*m*; CI-MS (with *i*-butane): 304 (52, $[M+1]^+$), 286 (100), 207 (59).

*2-(4-Carboxybutyl)-4,5-dimethoxybenzenesulfonamide* (**5b**). Yield 88.7%. Colorless solid, m p 177.3-178.6°C. $^1$H-NMR: 1.55-1.65 (*m*, 4H, 2 $CH_2$), 2.25 (br *t*, 2H, $CH_2$), 2.89 (br *t*, 2H, $CH_2$), 3.77, 3.82 (2*s*, 6H, 2 $CH_3O$), 6.93, 7.39 (2*s*, 2H, $H_{arom}$), 7.27 (*s*, 2H, $NH_2$); $^{13}$C-NMR: 24.4, 30.3, 31.5, 33.5 (4*t*, 4 $CH_2$), 55.6 (*q*, 2 $CH_3O$), 111.0, 113.8 (2*d*, 2 $C_{arom}$), 133.5, 133.7, 145.6, 150.8 (4*s*, 4 $C_{arom}$), 174.4 (*s*, C=O); IR: 3320*vs*, 3210*vs*, 2950*s*, 1720*vs*, 1600*s*, 1575*s*, 1510*vs*, 1470*vs*, 1450*m*, 1440*m*, 1430*m*, 1405*s*, 1390*vs*, 1335*s*, 1310*vs*, 1265*vs*, 1210*vs*, 1195*vs*, 1165*vs*, 1135*vs*, 1045*vs*, 975*s*, 890*s*, 845*s*, 830*vs*, 730*s*, 645*s*, 635*vs*; CI-MS: 335 (26, $[M+NH_4]^+$), 298 (100).

The cyclization of the sulfonamides (**5**), affording the heterocycles (**6**), was realized by using diethylphosphoryl cyanide (DEPC) as a coupling reagent in diluted reaction mixtures in the presence of a base:[18] To a solution of **8** (0.5 mmol) in $CH_2Cl_2$ (50 mL), $EtN(i\text{-}Pr)_2$ (161.5 mg, 1.25 mmol) and then DEPC (81.6 mg, 0.5 mmol) in $CH_2Cl_2$ (2 mL) were added. The mixture was stirred at rt for 20 h, then, the solvent was removed under reduced pressure and the products were isolated after CC ($SiO_2$, $CH_2Cl_2$/MeOH 30:1).

*3,4,5,6-Tetrahydro-8,9-dimethoxy-2H-1,2-benzothiazocin-3-one 1,1-dioxide* (**6a**). Yield 62.4%. Colorless solid, mp 201.9-203.1°C ($CH_2Cl_2$/hexane). $^1$H-NMR: 1.90, 2.85, 3.25 (3br *s*, 6H, 3 $CH_2$); 3.81, 3.85 (2*s*, 6H, 2 $CH_3O$), 7.04, 7.35 (2*s*, 2H, $H_{arom}$); NH is seen in the spectrum in $CDCl_3$ at 8.11 ppm; $^{13}$C-NMR: 25.3, 33.0, 35.5 (3*t*, 3 $CH_2$), 55.8, 55.9 (2*q*, 2 $CH_3O$), 110.6, 115.9 (2*d*, 2 $C_{arom}$), 130.2, 133.5, 146.8, 152.4 (4s, 4 $C_{arom}$), 173.7 (s, C=O); IR: 3110*s*, 3030*s*, 2940*s*, 2840*s*, 1680*vs*, 1600*s*, 1570*s*, 1515*vs*, 1455*s*, 1430*vs*, 1390*m*, 1360*vs*, 1340*vs*, 1320*s*, 1270*vs*, 1250*s*, 1215*vs*, 1180*vs*, 1155*vs*, 1135*vs*, 1060*s*, 1045*vs*, 960*s*, 875*s*,

815*m*, 770*m*, 705*m*, 680*s*, 630*vs*; EI-MS: 285 (100, $M^{+\cdot}$), 221 (40), 206 (13), 193 (19), 177 (31), 169 (18), 150 (21), 106, (20), 91 (38). Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.45; H, 5.32; N, 4.79. Suitable crystals for an X-Ray crystal structure determination were obtained from $CH_2Cl_2$/$CH_3CN$/hexane.

*2,3,4,5,6,7-Hexahydro-9,10-dimethoxy-1,2-benzothiazonin-3-one 1,1-dioxide* (**6b**). Yield 40.1%. Colorless solid, mp 191.5-193.5°C ($CH_2Cl_2$/hexane). $^1$H-NMR: 1.50, 1.85, 2.40, 3.05 (4br *s*, 8H, 4 $CH_2$), 3.80. 3.84 (2*s*, 6H, 2 $CH_3O$); 7.02, 7.34 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR: 23.0, 27.9, 29.2, 35.7 (4*t*, 4 $CH_2$); 55.7, 55.8 (2*q*, 2 $CH_3O$), 111.3, 114.3 (2*d*, 2 $C_{arom}$), 131.1, 134.2, 146.0, 152.4 (4*s*, 4 $C_{arom}$), 174.2 (*s*, C=O); IR: 3230*vs*, 2940*m*, 1715*vs*, 1605*m*, 1570*m*, 1515*s*, 1470*m*, 1460*m*, 1435*s*, 1420*s*, 1390*m*, 1360*s*, 1340*s*, 1270*vs*, 1240*m*, 1220*m*, 1210*m*, 1180*s*, 1155*vs*, 1125*s*, 1045*s*, 1000*s*, 895*m*, 875*m*, 775*m*, 690*m*; CI-MS: 317 (100, $[M+NH_4]^+$), 300 (6, $[M+1]^+$), 253 (30), 236 (32), 210 (8). Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68. Found: C, 52.30; H, 5.87; N, 4.51.

*4,5-Dimethoxy-2-(3-cyanopropyl)benzenesulfonyl chloride* (**7**). To a suspension of **5a** (303 mg, 1 mmol) in dry $Et_2O$ (15 mL) kept under nitrogen at rt, $PCl_5$ (580 mg, 2.8 mmol) was added and the reaction mixture was stirred overnight. Then, the solvent was removed under reduced pressure, xylene (15 mL) was added, and the suspension was refluxed for 3 h. The solvent was evaporated and after CC ($SiO_2$, hexane/EtOAc 3:2) **7** was obtained in 43% yield (130.6 g). Colorless solid, mp 106.5-107.6°C ($CHCl_3$/hexane). $^1$H-NMR ($CDCl_3$): 2.06-2.12 (*m*, 2H, $CH_2$), 2.18-2.24 (*m*, 2H, $CH_2$), 2.47 (*t*, *J* = 7.0, 2H, $CH_2$), 3.95, 4.00 (2*s*, 6H, 2 $CH_3O$), 6.86, 7.51 (2*s*, 2H, $H_{arom}$); $^{13}$C-NMR ($CDCl_3$): 17.0, 26.9, 31.8 (3*t*, 3 $CH_2$), 55.5, 56.5 (2*q*, 2 $CH_3O$), 111.6, 114.0 (2*d*, 2 $C_{arom}$), 119.3, 134.3, 134.5, 147.5, 154.5 (5*s*, 4 $C_{arom}$, CN); IR: 2940*m*, 2240*m*, 1600*m*, 1560*m*, 1515*vs*, 1465*m*, 1450*m*, 1415*m*, 1395*s*, 1365*vs*, 1270*vs*, 1235*s*, 1215*s*, 1180*s*, 1165*vs*, 1085*vs*, 975*m*, 880*m*, 850*m*, 645*m*, 635*s*; CI-MS: 321 (35, $[M+NH_4]^+$), 268 (100). Anal. Calcd for $C_{12}H_{14}NO_4ClS$: C, 47.45; H, 4.65; N, 4.61; Cl, 11.68; S, 10.56. Found: C, 47.48; H, 4.72; N, 4.63; Cl, 11.36; S, 10.31. Suitable crystals for an X-Ray analysis were grown from $CHCl_3$/hexane.

*Reactions of 3-amino-2*H*-azirines* (**1a-d**) *with* **6a** *and* **6b**. *General procedure*: To a solution of **6** in dry MeCN, kept under nitrogen, 1.1-1.5 equiv. of **1** in MeCN were added. The mixture was stirred at rt until **1** had disappeared (TLC), the solvent was removed under reduced pressure and the products were isolated by means of CC ($SiO_2$, $CH_2Cl_2$/MeOH). The yields given in brackets refer to consumed **6** and are calculated after recovering **6a** from the reaction mixtures.

*Reaction of 3-dimethylamino-2,2-dimethyl-2*H*-azirine* (**1a**) *with* **6a**. To a solution of **6a** (114 mg, 0.4 mmol) in MeCN (5 mL), **1a** (49 mg, 0.44 mmol) in MeCN (1.5 mL) was added; reaction time 120 h. CC with $CH_2Cl_2$/MeOH 40:1 and 30:1 gave two products (**8a** and **9**): *3*-

*Dimethylamino-4,5,6,7,8,9-hexahydro-11,12-dimethoxy-4,4-dimethylbenzo-1-thia-2,5-diaza-cycloundecen-6-one 1,1-dioxide* (**8a**). Yield 35.2(78.8)%. Colorless solid, mp 221.5-222.1°C ($CH_2Cl_2$/hexane). $^1$H-NMR (600 MHz, 345 K): 1.51 (*s*, 6H, 2 $CH_3$), 1.98 (br *s*, 4H, 2 $CH_2$), 3.00 (br *s*, 2H, $CH_2$), 3.34 (*s*, 6H, $(CH_3)_2N$), 3.75, 3.81 (2*s*, 2 $CH_3O$), 6.94, 7.39 (2*s*, 2H, $H_{arom}$), 7.18 (*s*, 1H, NH); $^{13}$C-NMR (150.9 MHz, 345 K): 24.4, 26.7, 26.8 (3*t*, 3 $CH_2$), 32.1 (*q*, 2 $CH_3$), 43.5 (*q*, $(CH_3)_2N$), 55.5, 55.6 (2*q*, 2 $CH_3O$), 59.4 (*s*, C(4)), 110.4, 112.7 (2*d*, 2 $C_{arom}$), 132.4, 137.0, 145.3, 150.6 (4*s*, 4 $C_{arom}$), 168.2, 173.2 (2*s*, C(3), C=O); IR: 3390*s*, 2940*m*, 1685*vs*, 1585*vs*, 1575*vs*, 1515*vs*, 1505*vs*, 1470*vs*, 1455*vs*, 1445*vs*, 1430*vs*, 1420*vs*, 1390*m*, 1375*m*, 1360*m*, 1345*m*, 1320*m*, 1270*vs*, 1260*vs*, 1215*s*, 1135*vs*, 1115*vs*, 1045*vs*, 1010*m*, 980*m*, 960*m*, 895*m*, 880*s*, 845*s*, 810*m*, 660*m*, 640*s*; ESI-MS: 398 ([*M*+1]$^+$). Anal. Calcd for $C_{18}H_{27}N_3O_5S$: C, 54.39; H, 6.85; N, 10.57. Found: C, 54.39; H, 6.75; N, 10.44. Suitable crystals for an X-Ray crystal structure determination were grown from $CH_2Cl_2$/hexane. *3-[*N*-(2-Dimethylcarbamoyl-2-methylethyl)amino]-5,6-dihydro-8,9-dimethoxy-4*H*-benzothiazocine 1,1-dioxide* (**9**). Yield 3.8(8.5)%. Colorless solid, mp 185.6-186.0°C ($CH_2Cl_2$/$Et_2O$). $^1$H-NMR (368 K): 1.42 (*s*, 6H, 2 $CH_3$), 1.80-1.90 (*m*, 2H, $CH_2$), 2.45-2.55 (*m*, 2H, $CH_2$), 2.51 (*s*, 6H, $(CH_3)_2N$), 3.10-3.20 (*m*, 2H, $CH_2$), 3.80, 3.84 (2*s*, 2 $CH_3O$), 6.87, 7.42 (2*s*, 2H, $H_{arom}$), 8.26 (br *s*, 1H, NH); $^{13}$C-NMR (368 K): 24.9 (*q*, 2 $CH_3$), 26.4, 29.5, 31.0 (3*t*, 3 $CH_2$), 36.6 (*q*, $(CH_3)_2N$), 55.7, 55.8 (2*q*, 2 $CH_3O$), 57.0 (*s*, C(3)), 112.2, 115.2 (2*d*, 2 $C_{arom}$), 131.1, 135.4, 146.5, 151.3 (4*s*, 4 $C_{arom}$), 162.7, 171.1 (2*s*, C(4), C=O); IR: 3450*s*, 3250*m*, 3080*m*, 2940*m*, 1620*vs*,1600*s*, 1550*s*, 1535*vs*, 1505*vs*, 1465*m*, 1440*m*, 1400*m*, 1390*m*, 1335*m*, 1280*vs*, 1265*vs*, 1240*s*, 1215*s*, 1130*vs*, 1070*s*, 1045*m*, 1010*m*, 980*m*, 760*m*, 710*m*, 690*s*, 635*s*; ESI-MS (with NaI): 420 ([*M*+Na]$^+$). Suitable crystals for an X-Ray crystal structure determination were obtained from $CH_2Cl_2$/$Et_2O$.

*Reaction of 2-dimethylamino-1-azaspiro[2.3]hex-1-ene* (**1b**) *with* **6a**. To a solution of **6a** (57 mg, 0.2 mmol) in MeCN (4 mL), **1b** (37mg, 0.3 mmol) in MeCN (1 mL) was added; reaction time 19 h. CC with $CH_2Cl_2$/MeOH 40:1 and MPLC with the same solvent mixture gave *3-dimethylamino-4,5,6,7,8,9-hexahydro-11,12-dimethoxyspiro[benzo-1-thia-2,5-diazacycloun-decene-4,1'-cyclobutan]-6-one 1,1-dioxide* (**8b**) in 48.8(57.1)% yield.[26] Colorless solid, mp 129.3-130.3°C ($CH_2Cl_2$/$Et_2O$). $^1$H-NMR (355 K)[27]: 1.71-1.77 (*m*, 1H, $CH_2$), 1.99-2.05 (*m*, 1H, $CH_2$), 2.12-2.18 (*m*, 2H, $CH_2$), 2.23-2.40 (*m*, 4H, 2 $CH_2$), 2.55-2.65 (*m*, 2H, $CH_2$), 2.85 (*t*, $J$ = 7.1, 2H, $CH_2$), 3.89, 3.94 (2*s*, 6H, 2 $CH_3O$), 7.02, 7.57 (2*s*, 2H, $H_{arom}$), 7.80 (*s*, 1H, NH); $^{13}$C-NMR (355 K): 15.2, 25.7, 27.1, 33.6, 33.7 (5*t*, 6 $CH_2$), 42.3 (*q*, $(CH_3)_2N$), 55.6, 55.7 (2*q*, 2 $CH_3O$), 61.5 (*s*, C(4)), 111.7, 113.3 (2*d*, 2 $C_{arom}$), 132.8, 136.0, 145.6, 136.0 (4*s*, 4 $C_{arom}$), 152.0 (br. *s*, C(3)),[28] 173.9 (*s*, C=O); IR: 3240*s*, 3060*m*, 3000*m*, 2940*m*, 1655*vs*, 1645*vs*, 1570*vs*, 1550*vs*, 1510*vs*, 1460*vs*, 1440*s*, 1415*vs*, 1345*m*, 1270*vs*, 1220*vs*, 1190*m*, 1125*vs*, 1105*vs*, 1050*vs*, 1025*m*, 975*m*, 875*m*, 845*s*, 810*m*, 775*m*, 740*m*, 730*m*, 685*m*, 655*m*, 640*s*; CI-MS: 410 (100, [*M*+1]$^+$). Anal. Calcd for $C_{19}H_{27}N_3O_5S$: C, 55.73; H, 6.65; N, 10.26. Found: C, 55.51; H, 6.57; N, 9.99.

*Reaction of 2-dimethylamino-1-azaspiro[2.4]hept-1-ene* (**1c**) *with* **6a**. To a solution of **6a** (57 mg, 0.2 mmol) in MeCN (4 mL), **1c** (30 mg, 0.22 mmol) in MeCN (1.5 mL) was added; reaction time 70 h. CC with $CH_2Cl_2$/ MeOH 40:1 and MPLC with the same solvent mixture gave *3-dimethylamino-4,5,6,7,8,9-hexahydro-11,12-dimethoxyspiro[benzo-1-thia-2,5-diazacycloundecen-4,1'-cyclopentan]-6-one 1,1-dioxide* (**8c**) in 27.2(48.4)% yield. Colorless crystals, mp 198.2-199.3°C ($CH_2Cl_2$/$Et_2O$). $^1$H-NMR (365 K): 2.40-2.60 (*m*, 4H, 2 $CH_2$), 1.90-2.20 (*m*, 2H, $CH_2$), 2.20-2.45 (*m*, 4H, 2 $CH_2$), 2.55-2.75 (*m*, 2H, $CH_2$), 2.89 (br *t*, 2H, $CH_2$), 3.38 (*s*, 6H, $(CH_3)_2N$), 3.79, 3.84 (2*s*, 6H, 2 $CH_3O$), 6.94, 7.48 (2*s*, 2H, $H_{arom}$), 7.21 (*s*, 1H, NH); $^{13}$C-NMR (365 K): 22.0, 25.4, 26.8, 33.0, 38.0 (5*t*, 7 $CH_2$), 43.6 (*q*, $(CH_3)_2N$), 55.9, 56.0 (2*q*, 2 $CH_3O$), 69.9 (*s*, C(4)), 112.1, 113.3 (2*d*, 2 $C_{arom}$), 133.2, 136.8, 145.9, 151.2 (4*s*, 4 $C_{arom}$), 171.7,[29] 173.6 (2*s*, C(3), C=O); IR: 3260*m*, 3060*m*, 2960*m*, 2930*m*, 1640*s*, 1560*vs*, 1510*s*, 1465*s*, 1420*m*, 1415*s*, 1390*m*, 1215*s*, 1220*s*, 1150*m*, 1130*m*, 1115*s*, 1050*s*, 850*m*, 805*m*, 730*m*, 630*m*; CI-MS: 424 (100, $[M+1]^+$), 285 (17), 139 (22). Anal. Calcd for $C_{20}H_{29}N_3O_5S \cdot 0.5\ CH_2Cl_2$: C, 52.84; H, 6.49; N, 9.02. Found: C, 52.95; H, 6.35; N, 9.05. Suitable crystals for an X-Ray analysis were grown from $CH_2Cl_2$/$Et_2O$.

*Reaction of 2,2-dimethyl-3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine* (**1d**) with **6a**. To a solution of **6a** (62 mg, 0.22 mmol) in MeCN (4 mL), a solution of **1d** (42 mg, 0.24 mmol) in MeCN (1.5 mL) was added. After stirring for 24 h at rt and 22 h at 80°C, only starting material (**6a**) could be detected (TLC). By CC with $CH_2Cl_2$/MeOH 40:1, only **6a** (85.5%) was isolated.

*Reaction of* **1b** *with* **6b**. To a solution of **6b** (93 mg, 0.31 mmol) in MeCN (5 mL), **1b** (58 mg, 0.46 mmol) in MeCN (0.5 mL) was added; reaction time 65 h. CC with $CH_2Cl_2$/MeOH 40:1 and a second one with $CH_2Cl_2$/MeOH/25%$NH_3$ 20:1:0.2 gave *5-dimethylamino-5,6,7,8,9,10-hexahydro-12,13-dimethoxy-4*H*-spiro[benzo-1-thia-2,6-diazacyclododecene-4,1'-cyclobutan]-6-one 1,1-dioxide* (**10**). Yield 8.4%. Colorless solid, mp 244.7-255.1°C ($CH_2Cl_2$/$Et_2O$). $^1$H-NMR (350K): 1.55-1.80 (*m*, 5H of 3 $CH_2$), 1.95-2.20 (*m*, 1H of $CH_2$), 2.40-2.48 (*m*, 2H, $CH_2$), 2.50-2.70 (*m*, 4H, 2 $CH_2$), 2.75-2.85 (*m*, 2H, $CH_2$), 3.13 (*s*, 6H, $(CH_3)_2N$), 3.76, 3.80 (2*s*, 6H, $CH_3O$), 6.85, 7.43 (2*s*, 2H, $H_{arom}$), 8.11 (*s*, 1H, NH); $^{13}$C-NMR ($CDCl_3$): 16.3, 26.1, 30.2, 31.8, 36.5 (5*t*, 7 $CH_2$),[30] 41.4 (br *q*, $(CH_3)_2N$),[31] 56.0, 56.2 (2*q*, 2 $CH_3O$), 59.9 (*s*, C(4)), 110.4, 114.0 (2*d*, 2 $C_{arom}$), 133.3, 135.3, 146.3, 150.9 (4*s*, 4 $C_{arom}$), 165.0, 176.1 (2*s*, C(3), C=O); IR 3360*m*, 2950*m*, 1680*s*, 1600*m*, 1565*s*, 1505*s*, 1490*s*, 1445*m*, 1400*m*, 1340*m*, 1265*vs*, 1225*s*, 1120*s*, 1105*s*, 1050*s*, 870*s*, 725*m*, 650*m*, 605*m*; CI-MS: 424 (100, $[M+1]^+$). Anal. Calcd for $C_{20}H_{29}N_3O_5S \cdot CH_2Cl_2$: C, 49.60; H, 6.14; N, 8.26. Found: C, 49.56; H, 5.93, N, 8.07.

*Crystal Structure Determination of* **6a**, **7**, **8a**, **8c**, *and* **9** (see *Tables 1* and *2* and *Figures 1-3*).[32] The intensities were collected on a *Rigaku AFC5R* diffractometer in the $\omega/2\theta$-scan mode using graphite-monochromated Mo$K_\alpha$ radiation ($\lambda$ = 0.71069 Å) and a 12 kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, and in the case

of **7** an empirical absorption correction based on $\psi$-scans was applied.[33] Data collection and refinement parameters are listed in *Tables 1* and *2*, views of the molecules are shown in *Figures 1-3*. The structures of **6a**, **8a**, **8c**, and **9** were solved by direct methods using *SHELXS86* ,[34] which revealed the positions of all non-H atoms. In the case of **7**, the structure was solved by *Patterson* methods using *SHELXS86*, which revealed the positions of the S and Cl atoms. All remaining non-H atoms were located in a *Fourier* expansion of the *Patterson* solution. The non-H atoms were refined anisotropically. All of the H-atoms of **6a**, **7**, **8a**, and **9** and the NH-atom of **8c** were located in difference electron density maps, and their positions were allowed to refine together with individual isotropic displacement factors. The remaining H-atoms of **8c** were fixed in geometrically calculated positions [$d$(C-H) = 0.95 Å] and they were assigned fixed isotropic displacement parameters with a value equal to $1.2U_{eq}$ of the atom to which each was bonded. Refinements of the structures were carried out on $F$ using full-matrix least-squares procedures. Corrections for secondary extinction were applied, except for **6a**. Neutral atom scattering factors for non-H atoms were taken from ref.[35a] and the scattering factors for H-atoms from ref.[36] Anomalous dispersion effects were included in $F_{calc}$;[37] the values for $f'$ and $f''$ were those of ref.[35b] All calculations were performed using the TEXSAN crystallographic software package.[38]

For **8c**, the asymmetric unit contains two symmetry independent molecules of **8c** plus one molecule of $CH_2Cl_2$. The two independent molecules are mirror images of one another. Although the compound is achiral, it crystallizes in a polar space group. Refinement of the absolute structure parameter yielded a value of 0.0(1), which suggests that the direction of the polar axis has been correctly chosen. The amide group of each symmetry independent molecule acts as a donor for intermolecular H-bonds. In each case, the corresponding acceptor atom is the amide O-atom from a neighboring molecule of the other type. These interactions link the molecules into infinite one-dimensional ···A···B···A···B··· chains which run parallel to the $y$-axis and have the binary graph set motif[20] of $C_2^2(8)$.

Compound (**9**) forms a 1:1 solvate with $H_2O$. The NH group of the molecule forms an intermolecular H-bond with the O-atom of the $H_2O$ molecule, which in turn forms two intermolecular H-bonds with the amide O-atom and one of the sulfonyl O-atoms of the same neighboring molecule. The combined interactions link the $H_2O$ and organic molecules into infinite one-dimensional chains running parallel to the $z$-axis. Two binary graph set motifs[20] can be defined: $C_2^2(7)$ is for the interactions involving the amide O-atoms, while $C_2^2(8)$ is for those involving the sulfonyl O-atom.

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Table 1. *Crystallographic Data for Compounds* (**6a**, **7**, *and* **8a**)

| | | **6a** | **7** | **8a** |
|---|---|---|---|---|
| Crystallised from | | $CH_2Cl_2/CH_3CN$/ hexane | $CH_2Cl_2$/hexane | $CHCl_3$/hexane |
| Empirical formula | | $C_{12}H_{15}NO_5S$ | $C_{12}H_{14}NO_4ClS$ | $C_{18}H_{27}N_3O_5S$ |
| Formula weight | | 285.31 | 303.76 | 397.49 |
| Crystal color, habit | | colorless, plate | colorless, prism | colorless, prism |
| Crystal dimensions [mm] | | 0.12x0.30x0.38 | 0.17x0.38x0.40 | 0.15x0.35x0.43 |
| Temperature [K] | | 173 (1) | 173 (1) | 173(1) |
| Crystal system | | triclinic | triclinic | monoclinic |
| Space group | | *P*1 | *P*1 | $P2_1/c$ |
| *Z* | | 2 | 2 | 4 |
| Reflections for cell determination | | 25 | 25 | 25 |
| 2$\theta$ range for cell determination [°] | | 39 – 40 | 39 – 40 | 37 – 40 |
| Unit cell parameters | *a* [Å] | 9.292 (1) | 9.376 (2) | 9.005 (2) |
| | *b* [Å] | 9.947 (2) | 9.400 (2) | 9.686 (3) |
| | *c* [Å] | 8.3587 (9) | 9.202 (2) | 22.689 (3) |
| | $\alpha$ [°] | 104.79 (1) | 113.03 (2) | 90 |
| | $\beta$ [°] | 106.34 (1) | 101.76 (2) | 90.15 (2) |
| | $\gamma$ [°] | 64.86 (1) | 65.90 (1) | 90 |
| | *V* [Å$^3$] | 662.8 (2) | 680.4 (3) | 1978.8 (7) |
| $D_x$ [g cm$^{-3}$] | | 1.429 | 1.483 | 1.334 |
| $\mu$(Mo$K_\alpha$) [mm$^{-1}$] | | 0.260 | 0.442 | 0.197 |
| $2\theta_{(max)}$ [°] | | 55 | 55 | 60 |
| Total reflections measured | | 3229 | 3320 | 6224 |
| Symmetry independent reflections | | 3042 | 3129 | 5868 |
| Reflections used [$I > 2\sigma(I)$] | | 2445 | 2787 | 4128 |
| Parameters refined | | 232 | 229 | 353 |
| Final *R* | | 0.0366 | 0.0315 | 0.0435 |
| *wR* | | 0.0356 | 0.0383 | 0.0411 |
| Weights: *p* in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$ | | 0.005 | 0.0075 | 0.005 |
| Goodness of fit | | 1.751 | 2.108 | 1.567 |
| Secondary extinction coefficient | | - | 7.0(4) x 10$^{-6}$ | 2.6(4) x 10$^{-7}$ |
| Final $\Delta_{max}/\sigma$ | | 0.0002 | 0.0004 | 0.0003 |
| $\Delta\rho$ (max; min) [e Å$^{-3}$] | | 0.26; -0.33 | 0.39; -0.36 | 0.33; -0.41 |
| $\sigma(d_{(C-C)})$ [Å] | | 0.003 | 0.002 – 0.003 | 0.003 |

Table 2. *Crystallographic Data for Compounds* (**8c** *and* **9**)

| | | **8c** | **9** |
|---|---|---|---|
| Crystallised from | | $CH_2Cl_2/Et_2O$ | $CH_2Cl_2/Et_2O$ |
| Empirical formula | | $C_{20}H_{29}N_3O_5S \cdot 1/2\ CH_2Cl_2$ | $C_{18}H_{27}N_3O_5S \cdot H_2O$ |
| Formula weight | | 465.99 | 415.50 |
| Crystal color, habit | | colorless, prism | colorless, prism |
| Crystal dimensions [mm] | | 0.38x0.40x0.50 | 0.27x0.40x0.48 |
| Temperature [K] | | 173 (1) | 173(1) |
| Crystal system | | monoclinic | orthorhombic |
| Space group | | $P2_1$ | *Pbca* |
| $Z$ | | 4 | 8 |
| Reflections for cell determination | | 25 | 25 |
| $2\theta$ range for cell determination [°] | | 39 – 40 | 36 – 39 |
| Unit cell parameters | $a$ [Å] | 12.332 (3) | 19.622 (2) |
| | $b$ [Å] | 16.376 (3) | 14.998 (2) |
| | $c$ [Å] | 12.371 (3) | 14.130 (2) |
| | $\beta$ [°] | 113.97 (2) | 90 |
| | $V$ [Å$^3$] | 2283(1) | 4158.3 (8) |
| $D_x$ [g cm$^{-3}$] | | 1.356 | 1.327 |
| $\mu(MoK_\alpha)$ [mm$^{-1}$] | | 0.295 | 0.194 |
| $2\theta_{(max)}$ [°] | | 60 | 55 |
| Total reflections measured | | 7158 | 6016 |
| Symmetry independent reflections | | 6870 | 4765 |
| Reflections used [$I > 2\sigma(I)$] | | 6037 | 3457 |
| Parameters refined | | 558 | 370 |
| Final $R$ | | 0.0411 | 0.0421 |
| $wR$ | | 0.0399 | 0.0388 |
| Weights: $p$ in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$ | | 0.005 | 0.005 |
| Goodness of fit | | 1.933 | 1.888 |
| Secondary extinction coefficient | | 6.5(7) x 10$^{-7}$ | 5(1) x 10$^{-8}$ |
| Final $\Delta_{max}/\sigma$ | | 0.0006 | 0.0003 |
| $\Delta\rho$ (max; min) [e Å$^{-3}$] | | 0.53; -0.44 | 0.29; -0.43 |
| $\sigma(d_{(C-C)})$ [Å] | | 0.004 – 0.006 | 0.003 |

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