

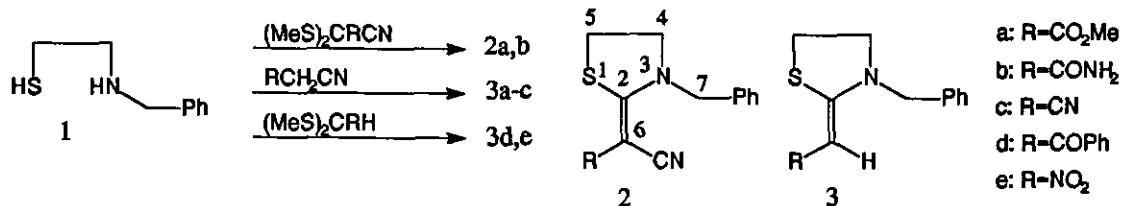
**SYNTHESIS AND STRUCTURAL INVESTIGATION OF SOME
CYCLIC KETENE ACETALS. DETECTION OF AN UNEXPECTED
PROTON TRANSFER IN (3-BENZYLTHIAZOLIDIN-2-
YLIDENE)ACETAMIDE**

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Abstract - The thiazolidines (2) and (3) were synthesized. Some of these compounds exhibit unexpected chemical behavior; e.g. in the case of (3-benzylthiazolidin-2-ylidene)acetamide (3b), NMR investigations revealed the presence of chemical exchange involving C(6)-H and the NH₂ protons.

With a view to investigating their potential gastrocytoprotective effect, several thiazolidine derivatives have been synthesized.¹ As a part of this work we allowed *N*-benzylcysteamine (1) to react with *S,S*-dimethyl dithioketals as well as cyanoacetic acid derivatives,^{1b} and this process yielded compounds (2-3).



The structures of 2-3, particularly in respect of the question of *Z/E* isomerism, were investigated by NMR technique. In each case only one set of ¹H and ¹³C signals was observed. In compounds (2) proof of the depicted configuration of the C(2)=C(6) unit came from ¹³C{¹H} nOe measurements which gave nOe from H₂-7 into the CN carbon. For compounds (3) the presence of a strong nOe connection between H-6 and the H₂-7 protons verified the *Z* configuration of the C(2)=C(6) unit. (Similarly, in the case of 3-methyl-2-nitromethylene-thiazolidine (cf. 3e) only the *Z* isomer had been detected by NMR).²

Compounds (2) and (3) are polarized *N,S*-acetals³ possessing electron-donating groups on one side of the C(2)=C(6) unit and electron-withdrawing functions on the other. The static and dynamic stereochemistry of push-pull ethylenes was reviewed by Sandström.⁴ Carbonyl conjugated ketene *N,S*-acetals exhibit low energy barriers to rotation about the C=C bond; e.g. the coalescence temperature of dimethyl (3-methylthiazolidin-2-ylidene)malonate was reported to be well below room temperature (<137 K).⁵ The observed homogeneous *Z* configuration in 2 and 3 can therefore be plausibly assumed to arise through free rotation. The dominance of the *Z* isomer can plausibly be assumed to stem from repulsive steric interactions and/or an attractive interaction between the sulfur atom and the carbonyl group (see below). Quite surprisingly, in the case of 3b the nOe difference spectra gave saturation transfer effects connecting the olefinic H-6 and the CONH₂ protons (Figure 1). H-6 and the NH₂ protons must therefore be related through proton transfer with a chemical exchange rate that is slow on the δ timescale, but fast on the relaxation timescale. Further investigation of the phenomenon gave the following results:

Upon considerable dilution of the sample, the NH₂ signal fell close to the H-6 resonance (Figure 2) and selective irradiation of either of these signals became difficult. However, saturation of the distant

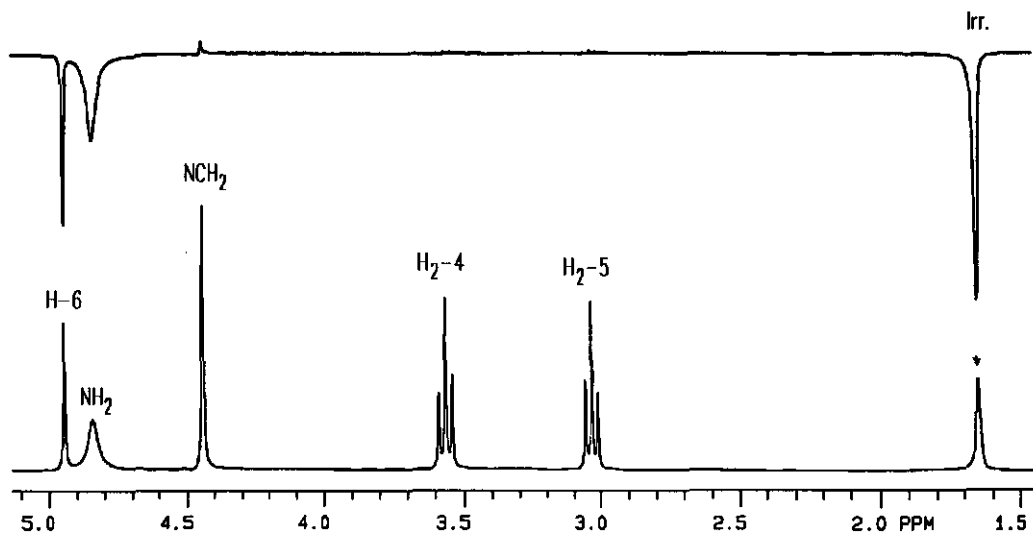


Figure 1. Upfield region of an nOe difference spectrum of **3b** (slightly acidic CDCl_3 , concentrated sample).

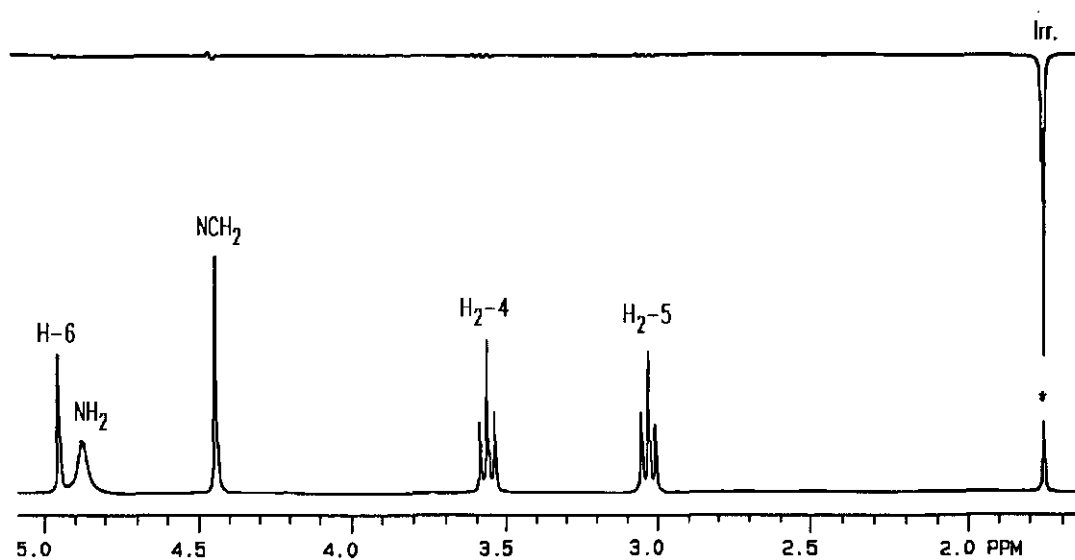


Fig. 2. Upfield region of an nOe difference spectrum of **3b** (slightly acidic CDCl_3 , dilute sample).

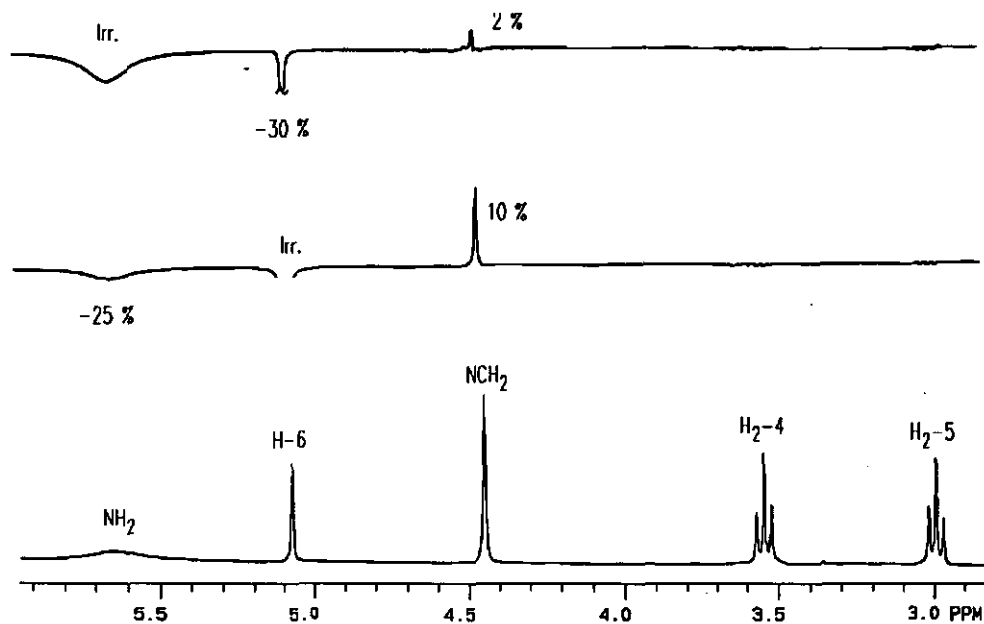


Figure 3. Upfield region of the nOe difference spectra of **3b** (acid-free CDCl_3 , 28°C , dilute sample).

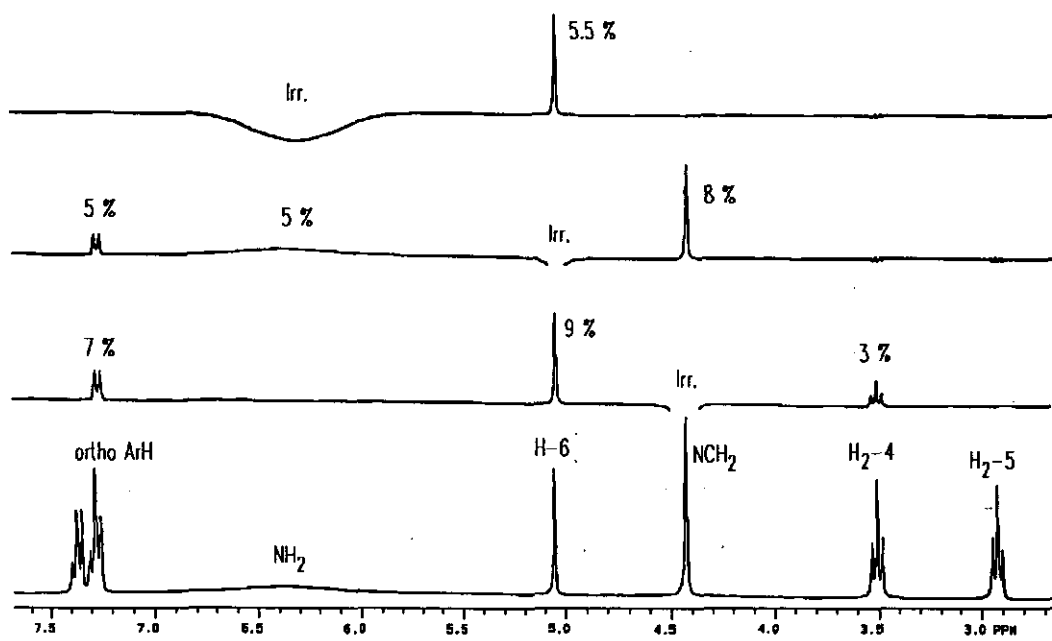


Figure 4. NOe difference spectra of **3b** (DMSO-d_6 , 28°C).

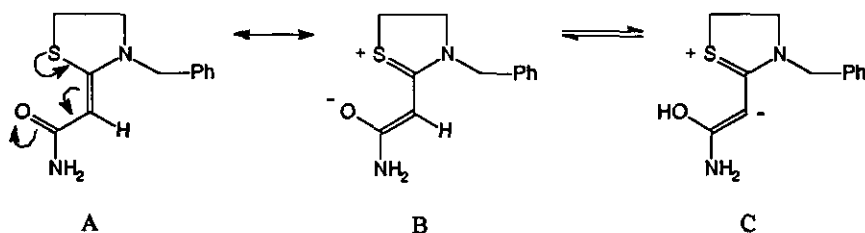
resonance due to H₂O contamination gave saturation transfer effects on both H-6 and NH₂. This experiment confirms the exchangeable nature of H-6.

In acid-free CDCl₃ the effect disappeared (Figure 3), indicating that the process is promoted or induced by protonation. (In this solvent the H-6 and NH₂ signals are very closely spaced at all workable concentrations). On adding a drop of trifluoroacetic acid, the NH₂ and H-6 resonances showed coalescence at room temperature.

In DMSO-d₆ solution the saturation transfer effects were again absent. The NH₂ and H-6 signals were conveniently separated for nOe measurements, and cross-relaxation effects were not masked by magnetization transfers (Figure 4). In this case the presence of a medium-intensity H-6—NH₂ nOe connection indicated the significant population of such a coplanar arrangement of the C(2)=C(6)-CONH₂ moiety in which the C=O oxygen becomes spatially close to the S atom.

In line with the above observations, H-6 in compound (3b) could be quickly exchanged with D by adding D₂O to the solvent. Similarly, H-6 was also exchangeable with D in compounds (3a) and (3c-e), but in these cases the process was considerably slower than in 3b. (As expected, the exchange process was absent in the relatively close analogs acrylamide and acrylonitrile).

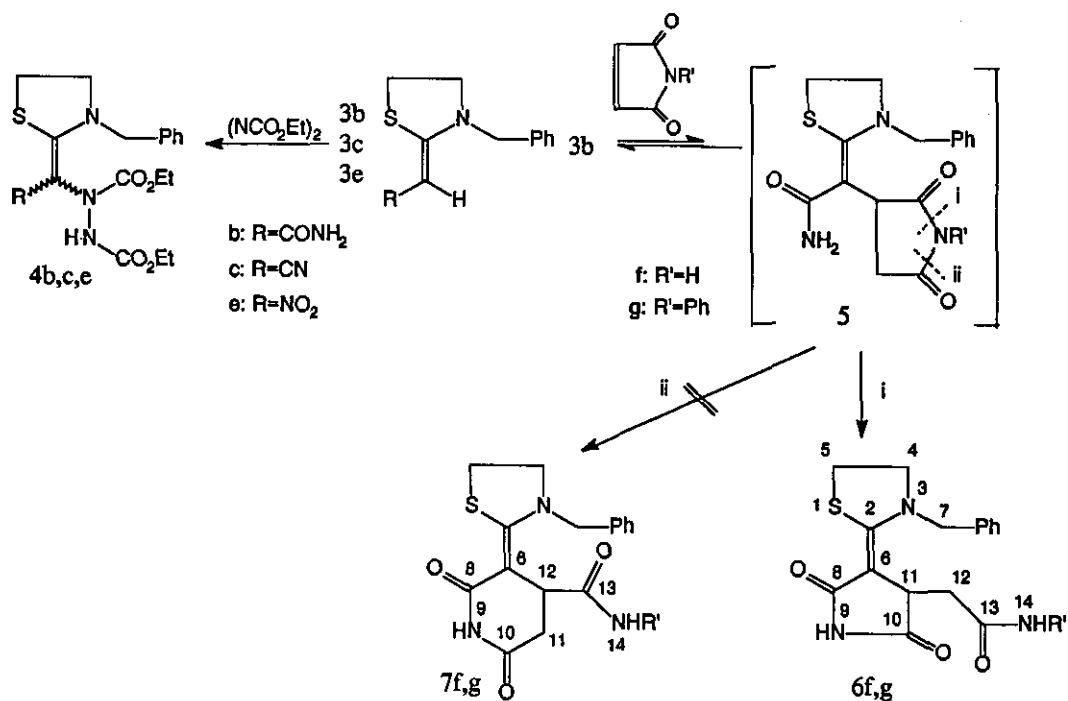
Several scenarios may be envisaged in rationalizing the exchangeable nature of H-6 in compounds (3). According to one plausible possibility, protonation of any of the heteroatoms, most likely that of the cyclic nitrogen, may occur, thus increasing the polarity of the C(6)—H bond and leading to the observed mobility of H-6. In this regard it is noted that 3a-d, unlike 3e and compounds (2), could be titrated by perchloric acid in acetic acid. In respect of 3b exhibiting the greatest mobility of H-6 within the series,



we may also consider the mesomeric forms "A" and "B", and the tautomeric structure "C", as facilitating exchange to occur between the OH and NH₂ protons. Form "B" indicates that an attractive dipolar interaction may exist between the CO oxygen and the S atom, thus possibly stabilizing the depicted and above-noted coplanar arrangement of the C(2)=C(6)-CONH₂ unit.

These results and considerations suggest that the above system may show further interesting chemical behavior. In order to explore this possibility we made attempts at bringing the system into cycloaddition reactions. However, **3b**, **3c** and **3e** all gave simple addition products (**4b,c,e**) with azodicarboxylic acid diethyl ester. This result indicates that, as opposed to their "common" behavior, the α position of the acrylic unit in the above thiazolidine compounds becomes nucleophilic.

A different behavior was observed with carbon-carbon dienophiles. While acetylenedicarboxylic acid esters and acrylic acid derivatives gave no reaction, maleimide and *N*-phenyl maleimide gave a reaction only with **3b**, yielding **6f,g**. The formation of **6** could be rationalized through ring-transformation of the simple addition product (**5**).



During the structure elucidation of **6** three possible structural isomers (**5**, **6** and **7**) had to be considered. Distinction between **5**, **6** and **7** is not trivial either by ^1H or ^{13}C NMR. In fact we first expected the formation of the simple adduct (**5**) in this reaction, and the routine ^1H and ^{13}C NMR spectra, when analyzed at a level needed for simple structural verification, did not seem to contradict this structure. However, the product obtained in the reaction of *N*-phenylmaleimide and **3b** could be titrated with AgNO_3 , indicating the presence of a cyclic imide function which is inconsistent with **5g**. This led to the consideration of the ring-transformed products (**6**) and (**7**). By using a more detailed nmr approach, distinction between the above isomers could be conveniently and unambiguously achieved *via* a combination of $^1\text{H}\{^1\text{H}\}$ and $^{13}\text{C}\{^1\text{H}\}$ nOe difference experiments. For example the ^1H NMR spectrum of **6g** exhibits two separate NH signals. Preliminary $^1\text{H}\{^1\text{H}\}$ nOe difference experiments showed that chemical exchange between these two NH protons is slow on the relaxation timescale, and therefore saturation transfer effects did not complicate the interpretation of the measured nOe enhancements. Structure (**5**) could then be ruled out on the basis that a) none of the NH protons gave nOe into the NPh *ortho* protons; b) in **5** both NH_2 protons should give nOes into the CONH_2 carbon, which, as discussed below, was not the case. Thus in reducing the problem to a distinction between isomers (**6**) and (**7**), both N(9)H and N(14)H could be assigned *via* the measured H-H nOe connectivities [N(14)H gave nOe into the Ph *ortho* protons]. N(9)H gave nOes on both ring C=O carbons, which could thus be identified and distinguished from the sidechain C=O. Irradiation of the aliphatic CH proton (H-11 in **6g** and H-12 in **7g**) gave nOe on one of these ring carbonyls and no nOe on the sidechain C=O; this result verifies the structure of **6g**, and is inconsistent with that of **7g**. The observed C-H nOes also confirmed the assignments of the quaternary carbons. Compound (**6f**), obtained in the reaction of **3b** with maleimide, could then be identified by direct analogy with **6g** on the grounds of chemical shift considerations. For both **6f** and **6g** nOe connections were observed between the H_2 -7 and H-11 as well as the C(6)-Ph *ortho* and H-11 protons; this verifies the depicted stereochemistry of the C=C exo double bond.

In the reaction of **3b** with maleimide or *N*-phenylmaleimide, the trans acylation within **5** leading to **6** may be regarded as the driving force of the process by continuously depleting **5** from the **3**⇌**5** equilibrium. A similar trans acylation is not possible in the case of the analogous adducts formed with **3c** and **3e**, and this rationalizes the fact that for the latter compounds no reaction with maleimide or *N*-phenylmaleimide was observed.

EXPERIMENTAL

Mps are uncorrected. IR spectra were taken on a Nicolet 205 FT-IR spectrophotometer (compounds **2a**, **3b,c**, **6f**) or a Perkin Elmer Spectrum 1000 FT-IR instrument (compounds **2b**, **3a**, **3d,e**, **4b,c,e**, **6g**) using KBr pellets. NMR measurements were carried out on a Varian VXR-300 instrument (¹H: 300 MHz, ¹³C: 75 MHz, compounds **2a,b**, **3a-e**, **6f,g**) or a Varian UNITYplus 500 (¹H: 500 MHz, ¹³C: 125 MHz, compounds **4b**, **4c**, **4e**). Chemical shifts are given relative to $\delta_{\text{TMS}}=0.00$ ppm. NOes were measured in non-degassed samples with 4 s and 8 s preirradiation times, respectively, for the ¹H{¹H} and ¹³C{¹H} nOe difference experiments. Assignments were corroborated by HETCOR (VXR-300) and HSQC, NOESY (mixing time = 0.8 s) HMBC and DQFCOSY experiments (UNITYplus-500). All pulse programs were run by using the standard spectrometer software package, except for the ¹³C{¹H} nOe difference experiment for which a home-written program was utilized as based on the sequence of Sanchez-Ferrando.⁶ TG measurements were carried out on a Mettler TA 3000 thermoanalyser with a TG 50 thermobalance. Thermograms were recorded over a temperature range of 25-250 °C with a heating rate of 10 °C/min under nitrogen gas flow. Analytical thin layer chromatography was performed by precoated silica gel 60 F-254 plates (0.2 mm thick) of EM Laboratories and visualized either by UV or by iodine in dichloromethane following drying. MS spectra were recorded on a VG-TRIO-2 mass spectrometer using direct insertion. The ionization energy was 70 eV, the source temperature was 250 °C.

Synthesis

3-Benzylthiazolidin-2-ylidenemethane derivatives (2-3). A/ *N*-benzylcysteamine (**1**) (1.67 g, 0.01 mol) and the appropriate *S,S*-dimethyl dithioketal (0.01 mol) were refluxed in the solvent as specified below (15 ml) for 30 min until the evolution of methanethiol gas has ceased. The product (**2a**, **2b**, **3d**, **3e**) was separated by filtration after cooling the reaction mixture, or by removing the solvent followed by recrystallization.

Methyl (Z)-(3-benzylthiazolidin-2-ylidene)cianoacetate (2a). Solvent: methanol, yield 72 %, mp 136 °C (from toluene). Anal. Calcd for C₁₄H₁₄N₂O₂S: C, 61.29; H, 5.14; N, 10.21; S, 11.69. Found: C, 61.45; H, 5.29; N, 10.47; S, 11.78. IR: 2192, 1693, 1530, 1269, 737, 695 cm⁻¹. MS: 274 (M⁺, 25), 273 (15), 215 (5), 148 (8), 91 (100), 65 (28). ¹H NMR (CDCl₃), δ: 3.02 (2H, t, J=7.5 Hz, H₂-5); 3.76 (3H, s, OMe); 3.77 (2H, t, J=7.5 Hz, H₂-4); 5.17 (2H, s, H₂-7); 7.24-7.41 (5H, m, Ph). Measured H→H nOe connection: H₂-7→Ph *ortho* protons (4.7 %), H₂-3 (4.3 %). ¹³C NMR (CDCl₃), δ: 26.1 (C-5); 51.7 (OMe); 53.1 (C-7); 56.5 (C-4); 67.2 (C-6); 117.6 (CN); 127.2, 128.0, 128.8 (Ph CH carbons); 134.5 (Ph *ipso* carbon); 167.3 (CO); 172.3 (C-2). Measured H→C nOe connections: H₂-7→Ph *ipso* carbon, C-2, C-6, CN.

(Z)-(3-Benzylthiazolidin-2-ylidene)cianoacetamide (2b). Solvent: ethanol, yield 31 %, mp 190 °C (from iPrOH). Anal. Calcd for C₁₃H₁₃N₃OS: C, 60.21; H, 5.05; N, 16.20; S, 12.36. Found: C, 60.30; H, 5.15; N, 16.47; S, 12.64. IR: 2184, 1648, 1524, 1392, 740, 699 cm⁻¹. MS: 259 (M⁺, 24), 258 (16), 242 (13), 215 (8), 157 (5), 155 (5), 148 (5), 91 (100), 65 (40). ¹H NMR (CDCl₃), δ: 2.98 (2H, t, J=7.5 Hz, H₂-5); 3.75 (2H, t, J=7.5 Hz, H₂-4); 5.13 (2H, s, H₂-7); 5.65 (2H, br, NH₂); 7.24-7.43 (5H, m, Ph). ¹³C NMR (CDCl₃), δ: 26.0 (C-5); 52.1 (C-7); 56.4 (C-4); 67.1 (C-6); 119.2 (CN); 126.8, 127.5, 128.8 (Ph CH carbons); 135.9 (Ph *ipso* carbon); 166.8 (CO); 170.4 (C-2). Measured H→C nOe connections: H₂-7→Ph *ipso* carbon, C-2, C-6, CN.

(Z)-2-(3-benzylthiazolidin-2-ylidene)-1-phenylethanone (3d). Solvent: xylene, yield 41%, mp 106-107 °C (from 75 % ethanol). Anal. Calcd for C₁₈H₁₇NOS: C, 73.19; H, 5.80; N, 4.74; S, 10.85. Found: C, 72.93; H, 5.33; N, 4.90; S, 11.80. IR: 1606, 1572, 1512, 743, 694 cm⁻¹. MS: 295 (M⁺, 28), 278 (11), 190 (35),

163 (7), 162 (6), 131 (13), 130 (16), 105 (31), 91 (100), 77 (39), 65 (23). ^1H NMR (CDCl_3), δ : 3.07 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-5}$); 3.64 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-4}$); 4.60 (2H, s, $\text{H}_2\text{-7}$); 6.26 (1H, s, H-6); 7.22-7.45 and 7.85 (8H, m and 2H, m, 2 x Ph). Measured H \rightarrow H nOe connections: $\text{H}_2\text{-7}\rightarrow\text{CH}_2\text{Ph}$ *ortho* protons (3.0 %), $\text{H}_2\text{-4}$ (3.1 %), H-6 (6.8 %); H-6 $\rightarrow\text{H}_2\text{-7}$ (9.1 %), CH_2Ph *ortho* protons (ca. 2 %), CPh *ortho* protons (16.3 %). ^{13}C NMR (CDCl_3) characteristic signals, δ : 27.4 (C-5); 52.1 (C-7); 53.7 (C-4); 88.0 (C-6); 135.1 (CH_2Ph *ipso* carbon); 166.9 (C-2); 186.1 (CO).

(*Z*)-3-Benzyl-2-nitromethylidenethiazolidine (3e). Solvent: ethanol, yield 90 %, mp 138-139 °C (from toluene). Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 55.91; H, 5.12; N, 11.85; S, 15.57. Found: C, 55.79; H, 5.13; N, 11.89; S, 14.07. IR: 1541, 1523, 1351, 1605, 728, 690, 3117 cm^{-1} . MS: 236 (M^+ , 3), 206 (8), 190 (65), 188 (23), 162 (13), 144 (14), 130 (28), 91 (100), 65 (45). ^1H NMR (CDCl_3), δ : 3.16 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-5}$); 3.85 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-4}$); 4.48 (2H, s, $\text{H}_2\text{-7}$); 7.07 (1H, s, H-6); 7.20 and 7.28-7.41 (5H, m, Ph). ^{13}C NMR (CDCl_3), δ : 27.4 (C-5); 52.5 (C-7); 55.6 (C-4); 109.4 (C-6); 127.0, 128.2, 129.0 (Ph CH carbons); 133.5 (Ph *ipso* carbon); 165.9 (C-2). Measured H \rightarrow H nOe connections: $\text{H}_2\text{-7}\rightarrow\text{Ph}$ *ortho* protons (3.2 %), $\text{H}_2\text{-4}$ (3.2 %), H-6 (7.9 %); H-6 $\rightarrow\text{H}_2\text{-7}$ (8.6 %), Ph *ortho* protons (ca. 1 %).

B/ *N*-benzylcysteamine (1) (1.67 g, 0.01 mol) and the appropriate cyanoacetic acid derivative (0.01 mmol) were refluxed in either methanol (10 mL) or ethanol (10 mL) (see below) until all of the starting material transformed (TLC, benzene:methanol:acetic acid = 10:3:0.1). The product (3a,b,c) was separated by filtration after cooling the reaction mixture, then purified by recrystallization.

Methyl (*Z*)-(3-benzylthiazolidin-2-ylidene)acetate (3a). Solvent: methanol, yield 77 %, mp 94-95 °C (from MeOH). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.87; H, 6.19; N, 5.73; S, 13.65. IR: 1669, 1546, 1138, 740, 696 cm^{-1} . MS: 249 (M^+ , 52), 221 (24), 218 (14), 190 (7), 148 (14), 130 (8), 122 (12), 91 (100), 65 (38). ^1H NMR (CDCl_3), δ : 3.05 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-5}$); 3.60 (2H, t, $J=7.5$ Hz, $\text{H}_2\text{-4}$); 3.64 (3H, s, OMe); 4.43 (2H, s, $\text{H}_2\text{-7}$); 5.01 (1H, s, H-6); 7.24-7.38 (5H, m, ArH). Measured H \rightarrow H nOe connections: $\text{H}_2\text{-7}\rightarrow\text{Ph}$ *ortho* protons (3.3 %), $\text{H}_2\text{-4}$ (3.2 %), H-6 (9.2 %); H-6 $\rightarrow\text{H}_2\text{-7}$ (9.5 %), Ph *ortho* protons (2.2 %). ^{13}C NMR (CDCl_3), δ : 27.0 (C-5); 50.3 (OMe); 51.6 (C-7); 54.0 (C-4);

79.4 (C-6); 127.0, 127.5, 128.6 (Ph CH carbons); 135.3 (Ph *ipso* carbon); 164.1 (C-2); 169.3 (CO).

(*Z*)-(3-benzylthiazolidin-2-ylidene)acetamide (**3b**). Solvent: ethanol, yield 62 %, mp 164 °C (from EtOH).

Anal. Calcd for C₁₂H₁₄N₂OS: C, 61.51; H, 6.02; N, 11.95; S, 13.68. Found: C, 61.45; H, 6.20; N, 12.12; S, 14.38. IR: 3482, 3305, 1619, 1552, 748, 698 cm⁻¹. MS: 234 (M⁺, 32), 218 (5), 206 (8), 190 (25), 162 (10), 161 (12), 148 (5), 130 (5), 104 (10), 103 (10), 91 (100), 65 (42). ¹H NMR (DMSO-d₆), δ: 2.93 (2H, t, J=7.5 Hz, H₂-5); 3.52 (2H, t, J=7.5 Hz, H₂-4); 4.43 (2H, s, H₂-7); 5.06 (1H, s, H-6); 6.30 (1H, br, NH₂); 7.25-7.41 (5H, m, Ph). Measured H→H nOe connections: H₂-7→Ph *ortho* protons (6.6 %), H₂-4 (3.2 %), H-6 (8.9 %); H-6→H₂-7 (8.1 %), Ph *ortho* protons (4.6 %), NH₂ (~5 %), NH₂→H-6 (5.5 %). ¹³C NMR (DMSO-d₆), δ: 26.7 (C-5); 50.9 (C-7); 53.3 (C-4); 82.9 (C-6); 127.2, 127.3, 128.5 (Ph CH carbons); 136.5 (Ph *ipso* carbon); 159.0 (C-2); 169.2 (CO).

(*Z*)-(3-benzylthiazolidin-2-ylidene)acetonitrile (**3c**). Solvent: ethanol, yield 48 %, mp 94-95 °C (from EtOH).

Anal. Calcd for C₁₂H₁₂N₂S: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.33; H, 5.68; N, 13.05; S, 14.98. IR: 2181, 1563, 1452, 1244, 728, 691 cm⁻¹. MS: 216 (M⁺, 28), 188 (6), 148 (13), 91 (100), 65 (36). ¹H NMR (CDCl₃), δ: 3.19 (2H, t, J=7.5 Hz, H₂-5); 3.72 (2H, t, J=7.5 Hz, H₂-4); 4.05 (1H, s, H-6); 4.37 (2H, s, H₂-7); 7.25-7.40 (5H, m, Ph). Measured H→H nOe's: H₂-7→Ph *ortho* protons (2.8 %), H₂-4 (2.8 %), H-6 (6.9 %); H-6→H₂-7 (7.5 %), Ph *ortho* protons (1.5 %). ¹³C NMR (CDCl₃), δ: 27.5 (C-5); 51.3 (C-7); 55.8 (C-4); 55.8 (C-6); 121.3 (CN); 127.0, 127.8, 128.8 (Ph CH carbons); 134.7 (Ph *ipso* carbon); 164.8 (C-2).

Compounds (4b,c,e). A solution of **3** (10 mmol) and azodicarboxylic acid diethyl ester (1.74 g, 10 mmol) was refluxed in benzene (15 mL), then 10 mmol of azodicarboxylic acid diethyl ester was added every two h until the starting thiazolidine disappeared (in general three equivalents proved to be sufficient). The reaction was monitored by TLC (toluene:methanol:acetic acid = 10:3:0.1). The product (**4a,b,c**) was separated by filtration after cooling the reaction mixture, then purified by recrystallization.

Diethyl N-[(3-benzylthiazolidin-2-ylidene)carbamoylmethyl]bicarbamate (4b). Yield 72 %, mp 161-163 °C (from EtOH). Anal. Calcd for C₁₈H₂₄N₄O₅S: C, 52.93; H, 5.92; N, 13.72; S, 7.85. Found: C, 52.81;

H, 5.90; N, 13.71; S, 8.44. IR: 1729, 1708, 1638, 1530, 1254, 770, 705 cm^{-1} . Ms: 408 (M^+ , 2), 320 (8), 91 (100), 65 (10). $^1\text{H NMR}^7$ (DMSO- d_6), δ : 0.92 and 1.22 (3H and 3H, t, $J=7.1$ Hz, $2 \times \text{OCH}_2\text{CH}_3$); 2.80 (2H, m, H_2 -5); 3.32-3.50 (2H, m, H_2 -4); 3.52 and 3.82 (1H and 1H, m, OCH_2CH_3); 4.12 (2H, q, $J=7.1$ Hz, OCH_2CH_3); 4.38 (1H, d, $J=16.4$ Hz, H_x -7); 4.63 (1H, d, $J=16.4$ Hz, H_y -7); 7.16-7.38 (5H, m, Ph), 9.69 (1H, br, NH). $^{13}\text{C NMR}^7$ (DMSO- d_6), δ : 14.0 and 14.3 ($2 \times \text{OCH}_2\text{CH}_3$); 26.8 (C-5); 52.1 (C-7); 55.2 (C-4); 61.4 and 62.0 ($2 \times \text{OCH}_2\text{CH}_3$); 102.3 (C-6); 127.0, 127.1, 128.4 (Ph CH carbons); 137.0 (Ph *ipso* carbon); 154.6, 157.5, 157.7, ($3 \times \text{CO}$); 168.5 (C-2).

Diethyl N-[(3-benzylthiazolidin-2-ylidene)cyanomethyl]bicarbamate (4c). Yield 69 %, mp 158-160 $^\circ\text{C}$ (from EtOH). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 55.37; H, 5.68; N, 14.35; S, 8.21. Found: C, 55.08; H, 5.72; N, 14.30; S, 8.65. IR: 2179, 1754, 1704, 1563, 1238, 738, 700 cm^{-1} . MS: 390 (M^+ , 7), 317 (8), 302 (4), 215 (4), 91 (100), 65 (4). $^1\text{H NMR}^7$ (DMSO- d_6), δ : 1.19 (6H, br, $2 \times \text{OCH}_2\text{CH}_3$); 3.11 (2H, t, $J=7.5$ Hz, H_2 -5); 3.80 (2H, t, H_2 -4); 4.05 and 4.12 (2H and 2H, br, $2 \times \text{OCH}_2\text{CH}_3$); 4.88 (2H, s, H_2 -7); 7.19-7.41 (5H, m, Ph), 9.84 (1H, br, NH). $^{13}\text{C NMR}^7$ (DMSO- d_6), δ : 14.3 ($2 \times \text{OCH}_2\text{CH}_3$); 26.1 (C-5); 50.9 (C-7); 57.8 (C-4); 60.7 and 62.4 ($2 \times \text{OCH}_2\text{CH}_3$); 77.7 (C-6); 117.6 (CN); 127.2, 127.5, 128.6 (Ph CH carbons); 136.1 (Ph *ipso* carbon); 154.7 and 155.7 ($2 \times \text{CO}$); 166.2 (C-2).

Diethyl N-[(3-benzylthiazolidin-2-ylidene)nitromethyl]bicarbamate (4e). Yield 73 %, mp 173-174 $^\circ\text{C}$ (from EtOH). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$: C, 49.75; H, 5.40; N, 13.65; S, 7.81. Found: C, 49.70; H, 5.39; N, 13.64; S, 8.19. IR: 3296, 1760, 1737, 1547, 1228, 743, 697 cm^{-1} . MS: 410 (M^+ , 10), 275 (12), 203 (17), 189 (48), 188 (38), 91 (100), 65 (15). $^1\text{H NMR}^7$ (DMSO- d_6), δ : 0.92 and 1.15 (3H and 3H, br, $2 \times \text{OCH}_2\text{CH}_3$); 3.12 (2H, t, $J=7.5$ Hz, H_2 -5); 3.70-4.1 (6H, m, H_2 -4 and $2 \times \text{OCH}_2\text{CH}_3$); 4.78 (1H, d, $J=16.1$ Hz, H_x -7); 5.88 (1H, br, H_y -7); 7.20-7.41 (5H, m, Ph), 9.38 (1H, br, NH). $^{13}\text{C NMR}^7$ (DMSO- d_6), δ : 13.8 and 14.3 ($2 \times \text{OCH}_2\text{CH}_3$); 26.3 (C-5); 52.5 (C-7); 57.7 (C-4); 60.8 and 63.0 ($2 \times \text{OCH}_2\text{CH}_3$); 121.7 (C-6); 127.0, 127.4, 128.6 (Ph CH carbons); 136.3 (Ph *ipso* carbon); 155.6 ($2 \times \text{CO}$); 162.8 (C-2).

(Z)-4-(3-Benzylthiazolidin-2-ylidene)-2,5-dioxopyrrolidine-3-acetamide (6f). A solution of **3b** (2.34 g, 10 mmol) and maleimide (0.98 g, 10 mmol) in ethanol (20 mL) was refluxed for 24 h. Having allowed the

solution to cool and stand for a few days, a light pink precipitate formed, which melted upon drying at 85 °C (this product contained, according to thermogravimetric measurements, 18.2 % of crystal ethanol). The crude product was recrystallized from toluene to give white crystals (1.9 g, 58 %), mp 187 °C (no crystal ethanol was detected by thermogravimetry). Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.67. Found: C, 57.04; H, 5.19; N, 12.54; S, 10.05. IR: 3196, 1735, 1666, 1546, 737, 699 cm^{-1} . MS: 331 (M^+ , 2), 240 (32), 223 (38), 91 (100), 65 (17). 1H NMR⁸ (DMSO- d_6), δ : 2.42 (1H, dd, $J=16.0$ Hz and 8.1 Hz, H_x-11); 2.54 (1H, dd, $J=16.0$ Hz and 2.9 Hz, H_y-11); 2.90-3.04 (2H, m, H_2-5); 3.46-3.68 (2H, m, H_2-4); 3.80 (1H, dd, $J=8.1$ Hz and 2.9 Hz, H-12); 4.57 (1H, d, $J=16.1$ Hz, H_x-7); 4.75 (1H, d, $J=16.1$ Hz, H_y-7); 6.81 (1H, br s, H_x-14) 7.30 (1H, br s, H_y-14); 7.22-7.42 (5H, m, Ph); 10.50 (1H, s, H-9). ^{13}C NMR⁸ (DMSO- d_6), δ : 27.0 (C-5); 36.3 (C-11); 41.3 (C-12); 51.9 (C-7); 54.7 (C-4); 91.7 (C-6); 127.1, 127.5, 128.7 [C(6)-Ph CH carbons]; 137.1 [C(6)-Ph *ipso* carbon]; 156.2 (C-2); 171.0, 171.1 (C-13, C-8); 177.8 (C-10). Measured H→H nOe connections: H-11→ H_2-12 (8.3 %), H_x-7 (2.6 %), H_y-7 (4.2 %), C(6)-Ph *ortho* protons (6 %).

(Z)-4-(3-Benzylthiazolidin-2-ylidene)-2,5-dioxo-N-phenylpyrrolidine-3-acetamide (6g). A solution of **3b** (2.34 g, 10 mmol) and *N*-phenylmaleimide (0.98 g, 10 mmol) was refluxed in ethanol (20 mL) for 2 h. The reaction was monitored by TLC (toluene:methanol:acetic acid = 10:3:0.1). The precipitates were filtered, washed with ethanol and dried to give white crystals (2.9 g, 72 %), mp 241-242 °C. Anal. Calcd for $C_{22}H_{21}N_3O_3S$: C, 64.85; H, 5.19; N, 10.31; S, 7.87. Found: C, 64.13; H, 5.23; N, 10.35; S, 8.60. IR: 3196, 1735, 1666, 1546, 737, 699 cm^{-1} . IR: 3317, 3165, 1727, 1689, 1639, 1527, 1597, 767, 752, 699, 686 cm^{-1} . MS: 407 (M^+ , 14), 316 (19), 223 (50), 197 (12), 169 (7), 91 (100), 77 (10), 65 (28). 1H NMR⁸ (DMSO- d_6), δ : 2.64 (1H, dd, $J=16.0$ Hz and 9.1 Hz, H_x-11); 2.80 (1H, dd, $J=16.0$ Hz and 2.9 Hz, H_y-11); 2.91-3.01 (2H, m, H_2-5); 3.52-3.65 (2H, m, H_2-4); 3.91 (1H, dd, $J=9.1$ Hz and 2.9 Hz, H-12); 4.62 (1H, d, $J=16.3$ Hz, H_x-7); 4.83 (1H, d, $J=16.3$ Hz, H_y-7); 7.00-7.57 (10H, m, Ph); 9.61 (1H, s, H-14); 10.59 (1H, s, H-9). Measured H→H nOe connections: H-14→NPh *ortho* protons (9.7 %), H_x-11 (4.2 %), H_y-11 (0.7 %); H-9→no nOe; H-11→ H_2-12 (8.2 %), H_x-7 (2 %), H_y-7 (3.1 %), C(6)-Ph *ortho* protons (6 %). ^{13}C

NMR⁸ (DMSO-d₆), δ (characteristic signals): 27.0 (C-5); 37.7 (C-11); 41.6 (C-12); 52.0 (C-7); 54.8 (C-4); 91.3 (C-6); 137.0 [C(6)-Ph *ipso* carbon]; 139.0 [N(14)-Ph *ipso* carbon]; 156.4 (C-2); 168.2 (C-13); 170.9 (C-8); 177.6 (C-10). Measured H→C nOe connections: H-14→N(14)-Ph *ipso* carbon, C-13; H-12→C-10, C-6; H-9→C-8, C-10.

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7. The room-temperature NMR spectra of **4b**, **4c** and **4e** exhibited the presence of two or more signal sets arising from slow or moderately slow many-site exchange processes due to hindered rotations possibly involving the C(2)=C(6), the C(6)-N, the N(3)-C(7) and the N-CO bonds. The existence of these exchange processes was verified by 2D exchange spectroscopy (NOESY) and by the fact that the system moves toward coalescence upon heating the sample. In each case the NMR data are given for the most populated species (the population of other interconverting isomers was below 50 %). Otherwise the exchange processes were not investigated in detail.
8. Compounds (**6f,g**) were present as a ca. 6:1 mixture of amide rotamers; nmr data are given for the main component.

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