STEREOCONTROLLED SYNTHESIS OF NEW TETRAHYDROFURO[2,3-d]THIAZOLE DERIVATIVES VIA ACTIVATED VINYLOGOUS IMINIUM IONS

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Abstract – Heterocyclization of (Z)-5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidines, bearing electron-withdrawing groups conjugated to an exocyclic double bond at C(2)-position, afforded under reductive conditions, cis-tetrahydrofuro[2,3-d]thiazole derivatives. The reactions of these functionalized push-pull β-enamines occur in a stereocontrolled fashion via activated vinylogous N-methyliminium ions, which are trapped by an internal hydroxyethyl group.

INTRODUCTION

In recent years, a variety of acyclic and cyclic iminium ions with a nucleophilic tether, exemplified by general structures (1) and (3) (Scheme 1), have been successfully used for heterocyclization reactions giving rise to nitrogen-containing heterocycles (2) and (4), respectively. An abundance of strategic preparations of different ring systems with five to seven atoms, based on an endo-mode cyclization of iminium ion (1),
bearing properly located oxygen, sulfur or nitrogen as heteroatom, or nonaromatic and aromatic C=C bond as a \( \pi \)-nucleophile, has confirmed a wide scope of this process. Likewise, the literature documents that synthetically and medicinally important condensed heterocycles, can be derived by an exo-type cyclization of the key cyclic intermediate (3). Extensive experimental evidence underlines the correlation between the presence of electron-withdrawing groups (EWG), such as the acyl, tosyl, COOR or CONR\(_2\), at the nitrogen atom of iminium ions (1) and (3), and their increasing cationic character, thus, making them more reactive toward nucleophiles. \(^1\),\(^7\)

![Scheme 1](image)

The synthetic utility of vinylogous iminium ions (5) (Scheme 1) for ring closure reactions has been also examined, however, in an exceedingly limited number of cases.\(^8\) Within this context, Hart\(^8\) has reported one of the rare examples when a vinylogous iminium ion (6) undergoes intramolecular \( \pi \)-cyclization, forming a useful tricyclic intermediate (7), en route to envisioned synthesis of the alkaloid depentylperhydrogephyrotoxin (8).\(^9\)

Now we wish to demonstrate an ability of new vinylogous N-alkyliminium ions of type (5), possessing the hydroxyethyl group as an internal nucleophile (A = O; R\(_1\) = Me), to participate in heterocyclization, that is, as one would anticipate, strongly driven by the presence of various electron-withdrawing groups at the \( \alpha \)-position of the C=C bond. Our studies, described below, represent to the best of our knowledge, (i) the first example of 5-exo-trig intramolecular cyclization of push-pull 3-methyl-(Z)-4-oxothiazolidine alcohols (12a-d), obtained from 2-alkylidene-5-carboethoxymethyl-4-oxothiazolidines (9a-d),\(^10\) to new cis-condensed thiazolidine compounds (13a-d) (Scheme 2), including (ii) the determination of the stereochemistry by a single-crystal X-Ray analysis of a representative of the series, cis-(Z)-2-(3-methyltetrahydrofuro[2,3-\(d\)]thiazol-2(5\(H\))-ylidene)-1-phenylethanolone (13a).
RESULTS AND DISCUSSION

In our preliminary study, thiazolidine β-enamino derivatives (9a-d), containing the carboethoxymethyl substituent at C(5) position, were found to react with NaBH₄ in ethanol to afford in chemoselective fashion the corresponding alcohols (11a-d) (R=H). However, N-methyl-substituted 4-oxothiazolidine derivative (10a) having the (Z)-configuration, as confirmed by a single-crystal X-Ray structure (Figure 1a), was converted under analogous conditions into the bicyclic product (13a), albeit in a small yield (21%). Despite the considerable amounts of other products being formed (vide infra), this result prompted us to further explore whether the thiazolidines (9a-d) can be employed for the synthesis of not easily obtainable bicyclic products (13a-d) via a reduction-alkylation-ring closure sequence, involving the C(5) and C(4) positions of the starting derivatives.13

![Chemical structures](image)

(i) NaBH₄ (4.5-9 equiv.), EtOH, 2 h, reflux (ii) K₂CO₃, MeI, EtOH, 1h, rt. (iii) NaBH₄ (2.3 equiv.), EtOH, 4 h, rt.

Precursors (9a-d), required for the synthesis of 11a-d with built-in alcohol nucleophile, were obtained by base-catalyzed reactions of β-oxo nitriles and diethyl mercaptosuccinate.10 The unambiguous assignment of the (Z)-configuration to the exocyclic C=C bonds of compounds (9a-c) has been established by NOE correlation between the lactam and vinyl hydrogens and crystallographic studies, whereas the heterocycle (9d), having the nitrile substituent as EWG, was obtained as a mixture of both isomers. As indicated above, the regioselective reduction of the side-chain acetate group in 9a-d with excess NaBH₄ gave rise to alcohols (11a-d) in good yields (49-64 %), without affecting the enaminone moiety, or affording the products of reductive ring opening. The resistance of this structural fragment to reduction by metal hydrides or catalytic reduction, is considered to reside in strong deactivation of EWG function and C=C bond due to resonance delocalization.11,14
Standard alkylation of (Z)-11a-c, afforded, without configuration change, the corresponding 3-methyl-4-oxothiazolidine alcohols (12a-c) (Table 1, 78-92%). This is expected in view of the greater stability of (Z)-configured thiazolidines (9a-c) in the solid state and in polar solvents, versus the (E)-analogs, particularly due to the strong nonbonded electrostatic S---O interaction of the 1,5-intra-type in the former isomers.15 Interestingly, 12d (EWG = CN) was also isolated as a single (Z)-isomer. Apparently, the steric bias provided by the N-methyl substituent is sufficient to fix the (Z)-configuration. The ring closure upon treatment of 12a-d with NaBH₄ in ethanol at room temperature, proceeded in a stereocontrolled manner, and the cis-fused products (13a-d) were isolated after preparative TLC purification as single Z-isomers, in reasonable yields (36-56%, Table 1). Besides the elemental analyses, the spectroscopic results are fully consistent with the structures of the new bicyclic products (13a-d). The two five-membered rings are cis-fused. The conclusive structural evidence stems from ¹H-NMR spectral data: the vicinal coupling constants Jₓz being alike (6.2-6.6 Hz) in all bicyclic structures (Table 1, Entries 2,4,6 and 8) closely match those of comparable systems reported previously.¹²b,c In addition, the cis-geometry was also supported by the H,H-ROESY experiment.

**Table 1.** Yields and selected ¹H and ¹³C NMR chemical shifts (ppm) of 4-oxothiazolidine alcohols (12a-d) in DMSO-d₆ and bicyclic thiazolidine derivatives (13a-d) in CDCl₃

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound/EWG</th>
<th>=CH</th>
<th>Hₓ</th>
<th>Hᵧ</th>
<th>Jₓz (Hz)</th>
<th>C(2)</th>
<th>C(2')</th>
<th>ΔδC₂,C₂'</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Z)-12a /COPh</td>
<td>6.92</td>
<td>4.12b</td>
<td></td>
<td>6.5</td>
<td>161.4</td>
<td>95.4</td>
<td>66.0</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>(Z)-13a /COPh</td>
<td>6.04</td>
<td>4.12</td>
<td>5.67</td>
<td>6.5</td>
<td>165.7</td>
<td>87.5</td>
<td>78.0</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>(Z)-12b /CO₂Et</td>
<td>5.57</td>
<td>4.12b</td>
<td></td>
<td>6.2</td>
<td>158.5</td>
<td>89.4</td>
<td>69.1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>(Z)-12b /CO₂Et</td>
<td>5.84</td>
<td>4.10</td>
<td>5.61</td>
<td>6.2</td>
<td>162.9</td>
<td>79.6</td>
<td>83.3</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>(Z)-12c /CONH(CH₂)Ph</td>
<td>5.55</td>
<td>3.97b</td>
<td>6.46</td>
<td>6.2</td>
<td>166.1</td>
<td>93.2</td>
<td>72.9</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>(Z)-13c /CONH(CH₂)Ph</td>
<td>4.67</td>
<td>4.06</td>
<td>5.55</td>
<td>6.2</td>
<td>166.0</td>
<td>82.2</td>
<td>83.8</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>(Z)-12d /CN</td>
<td>5.27</td>
<td>4.41b</td>
<td></td>
<td>6.2</td>
<td>160.4</td>
<td>67.1</td>
<td>93.3</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>(Z)-13d /CN</td>
<td>3.94</td>
<td>4.25</td>
<td>5.65</td>
<td>6.6</td>
<td>160.8</td>
<td>55.8</td>
<td>105.0</td>
<td>40</td>
</tr>
</tbody>
</table>

a Yields refer to pure isolated products.

b Part of an ABX spin-coupling system with protons of the neighboring methylene group.

Thus, the proton attached to C-6a of 13a which resonates at δ 4.12, assuming the β-orientation, exhibits NOE interactions with H-3a and H-6 positioned at the β-face. From the H,H-ROESY spectrum of 13a the correlation between the N-CH₃ and vinyl proton confirmed the (Z)-configuration of the C=C bond. The selected ¹³C NMR shift differences between the olefinic carbon atoms, i.e. ΔδC₂,C₂' values in compounds
(12) and (13) are worth noting (Table 1). Larger $\Delta \delta_{C(2)C(2')}$ values in the bicyclic derivatives (13a-d) from 78-105 ppm, respectively (Table 1, Entries 2,4,6 and 8) versus the corresponding $\Delta \delta_{C(2)C(2')}$ values (66-93 ppm) in alcohols (12a-d) (Table 1, Entries 1,3,5 and 7) correlate with an increase of the push-pull effect$^{16}$ in 13. An explanation is in accord with the presence of the more effective electron-donor (i.e. an amine) in the fused thiazolidines (13) in comparison to an amide functionality in substrates (12).

Unequivocal evidence, for the cis-ring juncture stereochemistry and (Z)-configuration assigned to 13a-d, was provided by an X-Ray crystal structure analysis of the representative of the series 13a (Figure 1b).

Figure 1a. Perspective view of the crystal structure of (Z)-(5-ethoxycarbonylmethyl-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (10a), showing the crystallographic numbering scheme. Selected bond lengths (Å): C2-N3 1.388(2), C2-C21 1.358(2), N3-C4 1.378(2), C4-O41 1.220(2), C4-C5 1.512(2), C21-C22 1.446(2). The S1...O21 non-bonded distance is 2.605(1) Å.

Figure 1b. Perspective view of the crystal structure of (Z)-2-(3-methyltetrahydrofurano[2,3-d]thiazol-2(3H)-ylidene)-1-phenylethanone (13a). Selected bond lengths (Å): C2-N3 1.347(2), C2-C9 1.381(2), N3-C4 1.451(2), C4-O8 1.420(2), C4-C5 1.544(2), C9-C10 1.426(2).

Compound (13a) crystallizes in the space group P2$_1$/c, but with two molecules in the asymmetric unit. Figure 2 shows a perspective view of one molecule with selected bond lengths. The thiazolidine ring is almost planar (mean deviation from the meanplane = 0.013 and 0.18 Å, for the two independent molecules) as a consequence of containing an unsaturated linkage. The conformation of the side chain is similar to that in 10a (Figure 1), although the non-bonded S-O distance$^{10,17}$ has increased slightly to 2.724(1) and 2.729(1) Å, for the two independent molecules.

In accordance with the spectroscopic results, semiempirical calculations with MOPAC (PM3, geometry optimisation) and ab initio calculations with Gaussian (HF, 6-31G*, geometry optimisation) show that the cis-isomers (13a-d) are preferred from an energetic point of view. As exemplified for 13a, the cis-isomer is 19.5 kcal more stable in comparison to the trans-analog. (Figure 2).

Figure 2. The cis- and trans-configurations of 13a
The large energy difference is attributed to severe angle strain imposed upon a trans-fusion of the almost flat thiazolidine ring to the tetrahydrofuran ring. As a result, the thiazolidine ring in the trans-fused compound (13a) is forced to adopt a relatively nonplanar conformation, where there is no optimal conjugation between nitrogen (and sulfur) and EWG through the intervening C=C bond. Release of the angle strain-constraint in the cis-arrangement of the two five-membered rings, in combination with the resonance effect attenuation, is responsible for this exclusive lower energy configuration of the cis-isomer (13a).

Based on numerous regioselective hydride reduction of ring-substituted cyclic imides to hydroxylactams,\(^1,18\) it is clear that the reduction of 4-oxothiazolidine alcohols (12) with NaBH\(_4\) in ethanol leads, in a first step, to \textit{in situ} formation of a diol (14) (Scheme 3).

This step sets the stage for the conversion of the diol (14) into the vinylogous \(N\)-methyliminium ion (15), with hydroxyethyl group at the C(5)-position as a reactive nucleophile. Subsequent 5-exo-trig heterocyclization by nucleophilic attack onto the iminium \(\pi\)-bond affords the \textit{cis}-fused tetrahydrofurothiazolidine (13). In general, it has been found that \(N\)-acyliminium ion cyclization gives rise to a lower yield if the iminium carbon atom is bonded to a carbon-carbon double or triple bond.\(^19\) Our experimental results indicate that ring closure of vinylogous methyliminium ion (15) is assisted by the electron-withdrawing group at the \(\alpha\)-carbon atom of the exocyclic C=C bond. The aforementioned \textit{cis}-disposition of the angular hydrogens in the transition-state structure and in the product (13) involves the minimization of angular strain, thus dictating the stereochemical course of the reaction. The evidence regarding the postulated iminium ion (15) as a key intermediate has been also obtained in direct heterocyclization of the \(N\)-methyl-4-oxothiazolidine (10a) to 13a (21% yield) under reductive conditions (Scheme 2). The formation of by
products, 3-methylthiazole derivative (17a) (18%) and 4-ethoxy-3-methylthiazolidine derivative (18a) (1-2%), is consistent with the presence of 16a as a transient species, thereby also leading to 13a via 15a. Another distinct pathway to the double enamine species (17a), involves dehydration of a hydroxythiazolidine (19a), obtained by initial hydride reduction of 10a, thus, reducing the yield of cyclization product (13a).19

CONCLUSION

In summary, the study on the intramolecular heterocyclization of (Z)-5-(2-hydroxyethyl)-3-methyl-4-oxothiazolidines, giving rise to new stereodefined tetrahydrofuro[2,3-d]thiazole derivatives, has been presented. This transformation, involving the activated vinylogous N-methyliminium ion, possessing the hydroxyethyl group as the internal nucleophile and different electron-withdrawing groups at the α-position of the exocyclic C=C bond, represents the new extension of the iminium ion chemistry with the potential toward synthesis of other bicyclic thiazolidine derivatives of synthetic and biological relevance.

EXPERIMENTAL

Melting points were determined on a Micro-Heitzisch Boetius PHMK apparatus or Bhchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer and are reported as wave numbers (cm⁻¹). Samples for IR spectral measurements were prepared as KBr disks. The NMR spectra were obtained using a Varian Gemini 2000 instrument (¹H at 200 MHz, ¹³C at 50.3 MHz). ¹³C NMR resonance assignments were aided by the use of the DEPT technique to determine numbers of attached hydrogens. The 2D ROESY have been performed on a Bruker Avance 500 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from TMS as an internal standard in the solvents specified. Low-resolution MS spectra were recorded using a Finnigan MAT 8230 BE spectrometer at 70 eV (EI). Isobutane was used as the ionizing gas for the chemical ionization (CI) mass spectra. The UV spectra were measured on a Beckman DU-50 spectrophotometer. Analytical thin-layer chromatography (TLC) was carried out on Kieselgel G nach Stahl, and the spots were visualized by iodine. Column chromatography was carried out on SiO₂ (silica gel 60Å, 12-26, ICN Biomedicals). Elemental analyses were performed at the microanalysis laboratory at the Department of Chemistry, University of Belgrade.

General procedure for the preparation of 3-methyl-4-oxothiazolidine alcohols (12a-d)

To a stirred solution of 4-oxothiazolidine alcohol (11) (0.5 mmol) and K₂CO₃ (69 mg, 0.5 mmol) in dry acetone (3-5 mL), protected by aluminum foil, a 10% molar excess of MeI (78 mg, 0.55 mmol) in acetone (~ 1-1.5 mL) was added in one portion at rt. The progress of the reaction was followed by TLC.
reaction mixture was refluxed for an additional 1-2.5 h until consumption of starting material. After evaporation of solvent under reduced pressure, the crude residue was purified by column chromatography (silica gel; toluene/ethyl acetate gradient 100:0 to 50:50, v/v) to afford 3-methyl-4-oxothiazolidine alcohols (12). Analytically pure sample was obtained by crystallization from toluene in the case of 12a, 12b and 12d or from chloroform/n-hexane mixture for 12c.

(Z)-5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)-1-phenylethanone (12a).

The title compound was obtained as a white solid in 86% yield (90 mg) from 100 mg (0.38 mmol) of 11a and 60 mg (0.027 mL, 0.42 mmol) of methyl iodide. mp 134-135 °C; IR (KBr): \( \nu_{\text{max}} 3412, 3065, 2922, 2865, 1690, 1626, 1575, 1510, 1464, 1423, 1349, 1225, 1128, 1052, 695, 632 \text{ cm}^{-1} \); \(^1H\) NMR (DMSO-d6): \( \delta \) 1.75-1.93 (1H, m, CH\(_2\)H\(_6\)CH\(_3\)S), 2.16-2.31 (1H, m, CHA\(_2\)H\(_6\)CH\(_3\)S; the coupling constants of H\(_A\) and H\(_B\) protons were not determined as signals are of higher order and structure elucidation being already unequivocal), 3.27 (3H, s, NCH\(_3\)), 3.59 (2H, m, CH\(_2\)OH), 4.12 (1H, dd, \( J_{AX} \) and \( J_{BX} \) cannot be determined as the signal is buried below the quartet centered at \( \delta \) 4.09), 4.78 (1H, br t, OH), 6.92 (1H, s, =CH), 7.47-7.63 (3H, m, p-Ph and m-Ph), 7.83 (2H, dd, \( J_{o,m} = 7.8 \text{ Hz}; J_{o,p} = 1.8 \text{ Hz, o-Ph} \)); \(^{13}C\) NMR (DMSO-d6): \( \delta \) 30.4 (NCH\(_3\)), 35.9 (CHA\(_2\)H\(_6\)CH\(_3\)S), 42.8 (CH\(_X\)), 58.5 (CH\(_2\)OH), 95.4 (=CH), 127.7 (m-Ph), 128.8 (o-Ph), 132.4 (p-Ph), 138.5 (C\(_1\)-Ph), 161.4 (C=), 175.3 (CO\(_{\text{lactam}}\)), 187.5 (CO\(_{\text{ketone}}\)); MS (CI): \( m/z \) 278 (M\(^+\) + 1); UV (DMSO): \( \lambda_{\text{max}} (\varepsilon) \) 333.9 nm, (33,600). Anal. Calcd for C\(_{14}\)H\(_{15}\)NO\(_3\)S: C, 60.63; H, 5.45; N, 5.05; S, 11.56; Found: C, 60.58; H, 5.48; N, 5.12; S, 11.80.

Ethyl (Z)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)ethanoate (12b).

The title compound was obtained as a white solid in 92% yield (49 mg) from 50 mg (0.22 mmol) of 11b and 34 mg (0.015 mL, 0.24 mmol) of methyl iodide. mp 87-89 °C; IR (KBr): \( \nu_{\text{max}} 3352, 3065, 2975, 2931, 1711, 1684, 1575, 1472, 1366, 1333, 1279, 1175, 1122, 1044, 862, 791, 768 \text{ cm}^{-1} \); \(^1H\) NMR (DMSO-d6): \( \delta \) 1.20 (3H, t, \( J = 7.2 \text{ Hz, CH}_2\text{C}_3 \)), 1.69-1.87 (1H, m, CHA\(_2\)H\(_6\)CH\(_3\)S), 2.13-2.28 (1H, m, CHA\(_2\)H\(_6\)CH\(_3\)S; the coupling constants of H\(_A\) and H\(_B\) protons were not determined as signals are of higher order and structure elucidation being already unequivocal), 3.07 (3H, s, NCH\(_3\)), 3.55 (2H, m, CH\(_2\)OH), 4.09 (2H, q, \( J = 7.2 \text{ Hz, CH}_2\text{C}_3 \)), 4.12 (1H, dd, H\(_X\); \( J_{AX} \) and \( J_{BX} \) cannot be determined as the signal is buried below the quartet centered at \( \delta \) 4.09), 4.78 (1H, t, \( J = 5.0 \text{ Hz, OH} \)), 5.57 (1H, s, =CH), \(^{13}C\) NMR (DMSO-d6): \( \delta \) 14.5 (CH\(_2\)CH\(_3\)), 30.0 (NCH\(_3\)), 36.1 (CH\(_2\)H\(_6\)), 43.3 (CH\(_X\)), 58.5 (CH\(_2\)OH), 59.4 (CH\(_2\)CH\(_3\)), 89.4 (=CH), 158.5 (C=), 167.1 (CO\(_{\text{ester}}\)), 175.2 (CO\(_{\text{lactam}}\)); MS (CI): \( m/z \) 245 (M\(^+\) + 1); UV (DMSO): \( \lambda_{\text{max}} (\varepsilon) \) 282.4 nm, (22,600). Anal. Calcd for C\(_{10}\)H\(_{15}\)NO\(_4\)S: C, 48.96; H, 6.16; N, 5.71; S, 13.07; Found: C, 48.95; H, 6.15; N, 5.74; S, 13.35.

(Z)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)-N-(2-phenylethyl)ethanamide (12c).

The title compound was obtained as a white solid in 78% yield (40 mg) from 49 mg (0.16 mmol) of 11c and 25 mg (0.011 mL, 0.18 mmol) of methyl iodide. mp 145-146 °C; IR (KBr): \( \nu_{\text{max}} 3348, 3074, 3026, 2923, 2882, 1685, 1640, 1581, 1545, 1475, 1423, 1332, 1298, 1213, 1128, 1128, 1075, 807, 780, 735, 701
1H NMR (DMSO-\(d_6\)): \(\delta\) 1.62-1.79 (1H, m, CH\(_A\)H\(_B\)CH\(_X\)S), 2.01-2.25 (1H, m, CH\(_A\)H\(_B\)CH\(_X\)S; the coupling constants of H\(_A\) and H\(_B\) protons were not determined as signals are of higher order and structure elucidation being already unequivocal the coupling constants of H\(_A\) and H\(_B\) protons cannot be determined as signals are of higher order), 2.72 (2H, \(J=7.2\) Hz, CH\(_2\)Ph), 3.02 (3H, s, NCH\(_3\)), 2.72 (2H, \(J=7.2\) Hz, CH\(_2\)Ph), 3.02 (3H, s, NCH\(_3\)) 3.30 (2H, m, CH\(_2\)NH), 3.40 (1H, dd, \(J_{AX}=9.6\) Hz, \(J_{BX}=3.7\) Hz, CH\(_A\)H\(_B\)CH\(_X\)S), 4.73 (1H, br t, \(J=5.2\) Hz, OH), 5.58 (1H, s, =CH), 7.20-7.33 (5H, m, Ph), 13C NMR (DMSO-\(d_6\)):\(\delta\) 29.6 (NCH\(_3\)), 35.4 (CH\(_A\)HB), 36.4 (CH\(_2\)Ph), 40.0 (CH\(_2\)NH), 58.3 (CH\(_2\)OH), 93.2 (=CH), 126.0 (p-Ph), 128.3 (o-Ph), 128.6 (m-Ph), 139.5 (C\(_1\)-Ph), 151.4 (C=), 166.1 (CO\(_{amide}\)), 174.5 (CO\(_{lactam}\)); MS (Cl): \(m/z\) 245 (M\(^+\) + 1); UV (DMSO): \(\lambda_{max}\) (\(\epsilon\)) 282.4 nm, (22,200). Anal. Calcd for C\(_{16}\)H\(_{20}\)N\(_2\)O\(_3\)S: C, 59.98; H, 6.29; N, 8.74; S, 10.01; Found: C, 59.94; H, 6.20; N, 8.57; S, 10.07.

(Z)-(5-(2-Hydroxyethyl)-3-methyl-4-oxothiazolidin-2-ylidene)ethanenitrile (12d)
The title compound was obtained as a white solid in 80% yield (43 mg) from 50 mg (0.27 mmol) of 11d and 42 mg (0.019 mL, 0.30 mmol) of methyl iodide. mp 106-107\(^\circ\)C; IR (KBr): \(\nu_{max}\) 3466, 3076, 2948, 2888, 2203, 1718, 1585, 1424, 1374, 1317, 1121, 914, 723 cm\(^{-1}\); 1H NMR (DMSO-\(d_6\)): \(\delta\) 1.78-1.96 (1H, m, CH\(_A\)H\(_B\)CH\(_X\)S), 2.17-2.32 (1H, m, CH\(_A\)H\(_B\)CH\(_X\)S; the coupling constants of H\(_A\) and H\(_B\) protons were not determined as signals are of higher order and structure elucidation being already unequivocal), 3.04 (3H, s, NCH\(_3\)), 3.50-3.60 (2H, m, CH\(_2\)OH), 4.41 (1H, dd, \(J_{AX}=9.8\) Hz and \(J_{BX}=3.8\) Hz, CH\(_A\)H\(_B\)CH\(_X\)S), 4.82 (1H, t, \(J=5.0\) Hz, OH), 5.27 (1H, s, =CH), 13C NMR (DMSO-\(d_6\)): \(\delta\) 29.7 (NCH\(_3\)), 35.7 (CH\(_A\)HB), 45.7 (CH\(_X\)), 58.5 (CH\(_2\)OH), 67.1 (=CH), 118.0 (CN), 160.4 (C=), 174.4 (CO\(_{lactam}\)); MS (Cl): \(m/z\) 199 (M\(^+\) + 1); UV (DMSO): \(\lambda_{max}\) (\(\epsilon\)) 273.4 nm, (19,000). Anal. Calcd for C\(_{8}\)H\(_{10}\)N\(_2\)O\(_2\)S: C, 48.47; H, 5.08; N, 14.13; S, 16.17; Found: C, 48.36; H, 5.06; N, 14.07; S, 16.33.

General procedure for the preparation of (Z)-2-(3-methyltetrahydrofuro[2,3-d]thiazol-2-ylidene)derivatives (13a-d)
To a solution containing 0.1 mmol of N-methyl-4-oxothiazolidine alcohol (12) in 5 mL of dry ethanol, 8.7 mg (0.23 mmol) of NaBH\(_4\) in 5 mL of ethanol was added dropwise (~10 min) with vigorous stirring at rt. After the addition was complete, the yellow reaction mixture was stirred for an additional 4 h until complete disappearance of starting material (TLC), whereupon the solution became colorless. The mixture was concentrated under reduced pressure to a small volume (~2 mL). Then, a 5% aqueous solution of ammonium chloride was added, followed by CHCl\(_3\) and the stirring was continued for 30 min. The aqueous layer was extracted with CHCl\(_3\) and combined organic fractions were washed with water, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude residue was purified by thin-layer chromatography (toluene/ethyl acetate as eluant; 40:60, v/v). Analytically pure samples (13a-d) were obtained by crystallization from n-hexane (13b and 13d) or n-hexane/toluene mixture (13a and 13c).
cis-(Z)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3H)-ylidene)-1-phenylethanone (13a)

The title compound was obtained as a white solid in 56% yield (14.7 mg) from 29 mg (0.1 mmol) of 9a. mp 121-122 °C; IR (KBr): $\nu_{\text{max}}$ 3053, 2974, 2939, 1602, 1571, 1525, 1433, 1355, 1264, 1213, 1084, 1061, 1028, 973, 801, 727, 691 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 2.12 (1H, br dd, $J_{AB}=12.6$ Hz, $J_{AQ}=4.8$ Hz, $J_{AX}=0.9$ Hz, $J_{AZ}=1.0$ Hz, $CH_AH_BCH_XS$), 2.33 (1H, ddt, $J_{AB}=12.9$ Hz, $J_{BQ}=11.1$ Hz, $J_{BX}=J_{BZ}=7.4$ Hz, $CH_AH_BCH_XS$), 3.83 (1H, dd, $J_{BQ}=11.1$ Hz, $J_{QZ}=8.8$ Hz, $J_{AQ}=5.0$ Hz, $CH_QHZO$), 4.02 (1H, ddd, $J_{QZ}=8.8$ Hz, $J_{BZ}=7.4$ Hz, $J_{AZ}=1.0$ Hz, $CH_QHZO$), 4.12 (1H ddd, 1H, $J_{BX}=7.4$ Hz, $J_{XY}=6.6$ Hz, $J_{AX}=0.9$ Hz, $OCH_YCH_XS$), 5.67 (1H, d, $J_{XY}=6.6$ Hz, $OCH_YCH_XS$), 6.08 (1H, s, =CH), 7.36-7.47 (3H, m, m- and p-Ph), 7.90-7.95 (2H, m, o-Ph) the simulated coupling constants, determined by PERCH NMR software$^{21}$ are in perfect agreement with these assigned by H,H-COSY; $^{13}$C NMR (CDCl$_3$): $\delta$ 33.7 (NCH$_3$), 35.2 ($CH_AH_B$), 44.6 ($CH_X$), 65.8 ($CH_QH_2$), 87.5 (=CH), 99.1 ($CH_Y$), 127.2 (m-Ph), 128.2 (o-Ph), 131.0 (p-Ph), 139.7 (C$_1$-Ph), 165.7 (C=), 186.9 (CO$_{ketone}$); MS (EI, 70 eV): $m/z$ (rel. intensity): 261 (M$^+$, 57), 259 (100), 245, 243, 241, 105 (97), 86 (39), 82 (58), 51 (26); UV (DMSO): $\lambda_{\text{max}}$ ($\varepsilon$) 338.0 nm (19,700); Anal. Calcd for C$_{14}$H$_{15}$NO$_2$S: C, 64.34; H, 5.78; N, 5.36; S, 12.27; Found: C, 64.24; H, 5.82; N, 5.30; S, 12.59.

cis-(Z)-Ethyl (3-methyltetrahydrofuro[2,3-d]thiazol-2(3H)-ylidene)ethanoate (13b)

The title compound was obtained as a white solid in 36% yield (20 mg) from 60 mg (0.25 mmol) of 9a. mp 48-49 °C; IR (KBr): $\nu_{\text{max}}$ 3070, 2976, 2948, 2884, 1672, 1567, 1437, 1367, 1243, 1156, 1092, 1046, 1000, 963, 896, 779, 713 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 1.26 (3H, t, $J=7.1$ Hz, $CH_2CH_3$) 2.11 (1H, br dd, $J_{AB}=12.9$ Hz, $J_{AQ}=4.9$ Hz, $J_{AX}=0$ Hz, $J_{AZ}=1.0$ Hz, $CH_AH_BCH_XS$), 2.29 (1H, ddt, $J_{AB}=12.9$ Hz, $J_{BQ}=11.0$ Hz, $J_{BX}=J_{BZ}=7.2$ Hz, $CH_AH_BCH_XS$), 2.94 (3H, s, NCH$_3$), 3.83 (1H, dd, $J_{BQ}=11.0$ Hz, $J_{QZ}=8.6$ Hz, $J_{AQ}=4.9$ Hz, $CH_QH_2$), 3.98 (1H, ddd, $J_{QZ}=8.6$ Hz, $J_{BZ}=7.2$ Hz, $J_{AX}=1.0$ Hz, $CH_QH_2$), 4.10 (1H dd, 1H, $J_{BX}=7.2$ Hz, $J_{XY}=6.2$ Hz, OCH$_YCH_XS$), 4.15 (2H, q, $J=7.2$ Hz, $CH_2CH_3$), 4.84 (1H, s, =CH), 5.61 (1H, d, $J_{XY}=6.2$ Hz, OCH$_YCH_XS$); $^{13}$C NMR (CDCl$_3$): $\delta$ 14.5 ($CH_2CH_3$), 33.0 (NCH$_3$), 35.3 ($CH_AH_B$), 44.4 ($CH_X$), 59.1 ($CH_2CH_3$), 65.6 ($CH_QH_2$), 79.6 (=CH), 99.5 ($CH_Y$), 162.9 (C=), 169.1 (CO$_{ester}$); MS (CI): 230 (M$^+$ + 1)); UV (DMSO): $\lambda_{\text{max}}$ ($\varepsilon$) 279.0 nm (23,400); Anal. Calcd for C$_{10}$H$_{13}$NO$_3$S: C, 52.38; H, 6.59; N, 6.11; S, 13.98; Found: C, 52.24; H, 6.61; N, 6.07; S, 14.00.

cis-(Z)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3H)-ylidene)-N-(2-phenylethyl)ethanamide (13c)
The title compound was obtained as a white solid in 40% yield (28 mg) from 75 mg (0.23 mmol) of 12c. mp 151-153 °C; IR (KBr): ν_{max} 3303, 3063, 3026, 2925, 2875, 1627, 1561, 1436, 1383, 1254, 1196, 1082, 1028, 989, 778, 750, 703 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.10 (1H, br dd, J_{AB}=12.6 Hz, J_{AQ}=5.0 Hz, J_{AX}=0 Hz, J_{AZ}=1.2 Hz, CH₃H₆CH₃S), 2.26 (1H, ddt, J_{AB}=12.6 Hz, J_{BQ}=10.7 Hz, J_{BX}=J_{BZ}=7.2 Hz, CH₃H₆CH₃S), 2.83 (2H, t, J=7.0 Hz, CH₂Ph), 2.88 (3H, s, NCH₃), 3.56 (2H, m, J=7.0 and 6.2 Hz, CH₂NH), 3.86 (1H, ddd, J_{BQ}=10.8 Hz, J_{QZ}=8.6 Hz, J_{AQ}=5.0 Hz, CH₂H₂O), 3.95 (1H, ddd, J_{AQ}=5.0 Hz, J_{AX}=1.2 Hz, CH₂H₂O), 4.06 (1H dd, J_{AX}=1.2 Hz, CH₂H₂O), 4.06 (1H, s, =CH), 5.55 (1H, d, J_{AX}=6.2 Hz, OCH₂CH₃S), 7.19-7.30 (5H, m, Ph); ¹³C NMR (CDCl₃): δ 29.6 (NCH₃), 35.3 (CH₃H₆), 36.3 (CH₂Ph), 40.5 (CH₂NH), 46.6 (CH₃), 65.6 (OCH₂), 82.3 (=CH), 99.1 (CH₂), 126.3 (p-Ph), 128.5 (o-Ph), 128.9 (m-Ph), 139.5 (C₆H₅), 166.0 (C=), 162.1 (CO amide); MS (ESI): Calcd for C₁₆H₂₀N₂O₂S: 305.13182 (M + H⁺); Found: 305.1318; UV (DMSO): λ_{max} (ε) 277.0 nm (12,900).

cis-(Z)-(3-Methyltetrahydrofuro[2,3-d]thiazol-2(3H)-ylidene)ethanenitrile (13d)
The title compound was obtained as a white solid in 40% yield (7.5 mg) from 20 mg (0.1 mmol) of 12d. mp 59-61 °C; IR (KBr): ν_{max} 3061, 2927, 2860, 2187, 1578, 1423, 1395, 1310, 1259, 1092, 1034, 964, 896, 859, 691 cm⁻¹; ¹H NMR (DMSO-d₆): δ 2.12 (1H, br dd, J_{AB}=13.3 Hz, J_{AQ}=5.1 Hz, J_{AX}=1.0 Hz, J_{AZ}=1.1 Hz, CH₃H₆CH₃S), 2.32 (1H, ddt, J_{AB}=13.3 Hz, J_{BQ}=11.0 Hz, J_{BX}=J_{BZ}=7.4 Hz, CH₃H₆CH₃S), 2.88 (3H, s, NCH₃) 3.88 (1H, ddd, J_{BQ}=11.0 Hz, J_{QZ}=8.9 Hz, J_{AQ}=5.1 Hz, CH₂H₂O), 3.94 (1H, s, =CH), 4.04 (1H, ddd, J_{QZ}=8.9 Hz, J_{BZ}=7.4 Hz, J_{AZ}=1.2 Hz, CH₂H₂O), 4.25 (1H, ddd, J_{XY}=6.6 Hz, J_{BX}=7.4 Hz, J_{AX}=1 Hz, CH₃H₆CH₃S), 4.82 (1H, t, J=5.0 Hz, OH); ¹³C NMR (DMSO-d₆): δ 29.7 (NCH₃), 35.7 (CH₃H₆), 45.7 (CH₃), 58.5 (CH₂OH), 67.1 (=CH), 118.0 (CN), 160.4 (C=), 174.4 (CO lactam); MS (CI): m/z 199 (M⁺ + 1); UV (DMSO): λ_{max} (ε) 264.0 nm, (26,100). Anal. Calcd for C₈H₁₀N₂O₃S: C, 52.7; H, 5.53; N, 15.37; S, 17.59; Found: C, 52.77; H, 5.59; N, 15.06; S, 17.56.

Crystal structure determination of compounds (10a) and (13a)
Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS²¹ and refined on F², using all data, by full-matrix least-squares procedures using SHELXTL.²² Hydrogen atoms were included in calculated positions, with isotropic displacement parameters 1.2 times the isotropic equivalent of the carrier carbons. Full tables of atom coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. CCDC 265572 and 265573 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].
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