Synthesis and Structure of 1-Substituted Semithioglycolurils

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Abstract Two methods for the synthesis of previously unavailable 1-substituted semithioglycolurils were developed. These methods consist of the cyclocondensation of 1-substituted ureas with 4,5-dihydroxy- or 4,5-dimethoxymidazolidine-2-thione or glyoxal, followed by the reaction of the resulting 1-substituted 4,5-dihydroxymidazolidine-2-ones with HSCN in a two-step one-pot procedure. Two of the desired semithioglycolurils were obtained as conglomerates.

Key words semithioglycolurils, cyclocondensation, heterocycles, urea derivatives, thiourea derivatives, glyoxal

Since the first synthesis of a glycoluril, published by Hugo Schif in 1877,1 the chemistry of these compounds has been actively developing. Hundreds of glycolurils with different combinations of substituents at nitrogen and carbon atoms have been synthesized.2–5 Thio-, amino-, and sulfo-based analogues of glycolurils are less available.2,6 More and more research has focused on semithioglycolurils I–IX (Figure 1),2,6–26 including compounds I, II, VII, and VIII that were synthesized in our laboratory.6,12–26

Although a wide range of trisubstituted semithioglycolurils I and II have been reported, they are still actively investigated, as some of them have antifungal and cytotoxic activities.12,13 Other compounds III–IX are represented by several examples and used as scaffolds in the synthesis of semithiobambusurils (III and VII),11,27 in Claisen condensation matrices (IV),18 and in the synthesis of tri-, tetra-, and polycyclic systems (V)28–31 and iminoglycolurils (V, VII, VIII).9 Methods for the preparation of a small number of compounds III–IX reported in the literature are underdeveloped. The focus of this article is on a methodology for the synthesis of 1-substituted semithioglycolurils.

Semithioglycolurils have so far been represented by only three examples (Scheme 1).6,14,25 Compounds 1a,b were obtained by the reaction of 1-alkylureas 2a,b with 4,5-dimethoxymidazolidine-2-thione (DMIT; 3) or 4,5-dihydroxyimidazolidine-2-thione (DHIT; 4) (approach 1).6,25 Semithioglycoluril 1c was prepared by the condensation of 1-cyclohexyl-4,5-dihydroxyimidazolidin-2-one (5a) with KSCN and hydrochloric acid (approach 2).14 Here, these approaches were studied in detail, and two methods for the synthesis of 1-substituted semithioglycolurils were developed.

Figure 1 Previously reported semithioglycolurils
To develop approach 1, we started with the reactions of DMIT (3) and DHIT (4) with ethylurea (2c) in water by varying the amount of hydrochloric acid (pH 1) and time used for heating the reaction mixture (10 min, 30 min, 1 h, and 2 h) at 76–80 °C (Table 1). By 1H NMR monitoring of dried reaction mixture aliquots, the dependence of the conversion of ethylurea (2c) into thioglycoluril 1d on the reaction conditions was analyzed. The conversion rate was estimated by analyzing the proton signals of the Me groups of urea according to 1H NMR spectroscopy. For a more complete transformation of ethylurea (2c) into thioglycoluril 1d, we used a larger amount of DHIT (1.5 equiv) after 30 minutes of heating, but DHIT was still present in the resulting product (entry 11). The use of DHIT (4; 1.2 equiv) in this reaction led to an increase in the conversion of ethylurea (2c) to thioglycoluril 1d up to 71% after 30 minutes (entry 12). The yield of thioglycoluril 1d was 52% after its purification (Table 2, approach 1, entry 3). Thus, the best yield of thioglycoluril 1d was achieved in the reaction of DHIT (4; 2.5 mmol, 1 equiv) with ethylurea (2c) in a 4:2c ratio of 1:2:1 in water with 35% hydrochloric acid (0.08 mL) at 76–80 °C for 30 min (Table 1, entry 12).

The target glycolurils 1a–m, o–p were synthesized in 15–65% yield by using the optimized conditions of condensation of DHIT (4) with 1-substituted ureas 2a–m, o–p (Table 2, approach 1, entries 1–13, 15, 16). In total, 15 compounds were synthesized by approach 1.

Table 1 Screening of Conditions for the Synthesis of Thioglycoluril 1d (Approach 1)∗

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (ratio)</th>
<th>Aq HCl (35%) (mL)</th>
<th>Time</th>
<th>Conversion (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2c, 3 (1:1)</td>
<td>0.027</td>
<td>30 min</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>2c, 3 (1:1)</td>
<td>0.027</td>
<td>1 h</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>2c, 3 (1:1)</td>
<td>0.08</td>
<td>10 min</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>2c, 3 (1:1)</td>
<td>0.08</td>
<td>30 min</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>2c, 3 (1:1)</td>
<td>0.08</td>
<td>1 h</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>2c, 3 (1:1)</td>
<td>0.08</td>
<td>2 h</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>2c, 4 (1:1)</td>
<td>0.08</td>
<td>10 min</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>2c, 4 (1:1)</td>
<td>0.08</td>
<td>30 min</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
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<td>0.08</td>
<td>1 h</td>
<td>65</td>
</tr>
<tr>
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<td>2c, 4 (1:1)</td>
<td>0.08</td>
<td>2 h</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>2c, 4 (1:1.5)</td>
<td>0.08</td>
<td>30 min</td>
<td>65</td>
</tr>
<tr>
<td>12</td>
<td>2c, 4 (1:1.2)</td>
<td>0.08</td>
<td>30 min</td>
<td>71c</td>
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a Reaction conditions: 2c (2.5 mmol, 1 equiv), 3 or 4, H2O (10 mL), aq HCl (35%), 76–80 °C.
b Conversion of 2c into 1d according to 1H NMR spectroscopy.
c Reaction conditions: 2c (0.22 g, 2.5 mmol), 4 (0.40 g, 3.0 mmol), H2O (10 mL), aq HCl (35%, 0.08 mL), 76–80 °C, 30 min.

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When the volume of hydrochloric acid (0.08 mL) was increased, the conversion of 2c into 1d increased to 41 and 64%, for 10 minutes and 1 hour of reaction time, respectively (Table 1, entries 3 and 5), and remained constant even after 2 hours of reaction (entry 6). Similar results were observed when we used DHIT (4); however, the reaction rate of forming semithioglycoluril 1d increased. After 10 minutes, the conversion of 2c into 1d was 52% (entry 7), and increased to 64% after 30 minutes (entry 8). Therefore, it is more efficient to use DHIT (4) rather than DMIT (3), with a reaction time of 30 minutes. Apart from that, we noticed that DHIT (4) is partially consumed in a competing reaction to produce the earlier reported 2-thioxoimidazolidine-4-one (thiodydantoin)32 (the most characteristic signal of CH2 protons: s, δ = 4.06); we also detected ethylurea (2c) in the reaction mixture. For a more complete transformation of ethylurea (2c) into semithioglycoluril 1d, we used a larger amount of DHIT (4) (1.2 and 1.5 equiv; Table 1, entries 12 and 11, respectively). 1H NMR monitoring of this reaction showed that the conversion of 2c into 1d was 65% with DHIT (1.5 equiv) after 30 minutes of heating, but DHIT was still present in the resulting product (entry 11). The use of DHIT (4; 1.2 equiv) in this reaction led to an increase in the conversion of ethylurea (2c) to thioglycoluril 1d up to 71% after 30 minutes (entry 12). The yield of thioglycoluril 1d was 52% after its purification (Table 2, approach 1, entry 3). Thus, the best yield of thioglycoluril 1d was achieved in the reaction of DHIT (4; 2.5 mmol, 1 equiv) with ethylurea (2c) in a 4:2c ratio of 1:2:1 in water with 35% hydrochloric acid (0.08 mL) at 76–80 °C for 30 min (Table 1, entry 12).

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<td>6</td>
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<td>0.08</td>
<td>2 h</td>
<td>65</td>
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<tr>
<td>11</td>
<td>2c, 4 (1:1.5)</td>
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<td>30 min</td>
<td>65</td>
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<td>12</td>
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<td>0.08</td>
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As 1-cyclohexyl-DHI 5a had been prepared before, approach 2 made use of the condensation of DHI 5 with NaSCN and hydrochloric acid, so that 1-substituted DHI 5b–o had to be prepared (Table 2). To do so, a model reaction of ethylurea 2c and glyoxal was examined under the same conditions that were used for the synthesis of 1,3-dimethyl-DHI, with H2O as the solvent, at pH 10 and 50–55 °C. The next goal was to determine the reaction time needed for ethylurea 2c to completely transform into DHI 5d. We used 1H NMR monitoring of dried reaction mixture aliquots (after 5 min, 1 h, 2 h and 3 h; Figure 2). It was established that the conversion of urea 2c into DHI 5d was complete after 3 hours. After this time, the signals of the protons of urea 2c disappeared, while new signals of the DHI protons appeared in the 1H NMR spectrum (Figure 2). As no side products were detected (Figure 2), we used a reaction mixture in the reaction with NaSCN and hydrochloric acid, without isolation of DHI 5d (as well as of DHI 5b, c, e–h, j).

Table 2: Comparison of Two Approaches to the Synthesis of Semithioglycolurils 1a–p

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Urea</th>
<th>DHI</th>
<th>Product</th>
<th>Yield (%) of 1 by approach 1a</th>
<th>Yield (%) of 1 by approach 2b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>2a</td>
<td>5b</td>
<td>1a</td>
<td>31%</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>2b</td>
<td>5c</td>
<td>1b</td>
<td>50%</td>
<td>52%</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>2c</td>
<td>5d</td>
<td>1d</td>
<td>52%</td>
<td>58%</td>
</tr>
<tr>
<td>4</td>
<td>Pr</td>
<td>2d</td>
<td>5e</td>
<td>1e</td>
<td>20%</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>t-Bu</td>
<td>2e</td>
<td>5f</td>
<td>1f</td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>Cy</td>
<td>2f</td>
<td>5a</td>
<td>1c</td>
<td>65%</td>
<td>9%</td>
</tr>
<tr>
<td>7</td>
<td>CH3C-C3H7</td>
<td>2g</td>
<td>5g</td>
<td>1g</td>
<td>45%</td>
<td>53%</td>
</tr>
<tr>
<td>8</td>
<td>(CH2)3OH</td>
<td>2h</td>
<td>5h</td>
<td>1h</td>
<td>26%</td>
<td>54%</td>
</tr>
<tr>
<td>9</td>
<td>(CH2)2OH</td>
<td>2i</td>
<td>5i</td>
<td>1i</td>
<td>15%</td>
<td>0 (1)15, 9 (6)16</td>
</tr>
<tr>
<td>10</td>
<td>Me2CCH2OH</td>
<td>2j</td>
<td>5j</td>
<td>1j</td>
<td>41%</td>
<td>45%</td>
</tr>
<tr>
<td>11</td>
<td>All</td>
<td>2k</td>
<td>5k</td>
<td>1k</td>
<td>40%</td>
<td>62%</td>
</tr>
<tr>
<td>12</td>
<td>Bn</td>
<td>2l</td>
<td>5l</td>
<td>1l</td>
<td>45%</td>
<td>63%</td>
</tr>
<tr>
<td>13</td>
<td>PMB</td>
<td>2m</td>
<td>5m</td>
<td>1m</td>
<td>46%</td>
<td>65%</td>
</tr>
<tr>
<td>14</td>
<td>(CH2)2Ph</td>
<td>2n</td>
<td>5n</td>
<td>1n</td>
<td>–</td>
<td>61%</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>2o</td>
<td>–</td>
<td>1o</td>
<td>34%</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>(CH2)2CO2H</td>
<td>2p</td>
<td>5p</td>
<td>1p</td>
<td>36%</td>
<td>–</td>
</tr>
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</table>

* Reaction conditions: 1. 2 (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), H2O (10 mL), NaOH (to pH 10), 50–55 °C, 3 h. 2. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), aq HCl (35%, 4.4 mL); NaCl precipitate removed by filtration; filtrate refluxed, 30 min.

As 1-cyclohexyl-DHI 5a had been prepared before, approach 2 made use of the condensation of DHI 5 with NaSCN and hydrochloric acid, so that 1-substituted DHI 5b–o had to be prepared (Table 2). To do so, a model reaction of ethylurea 2c and glyoxal was examined under the same conditions that were used for the synthesis of 1,3-dimethyl-DHI, with H2O as the solvent, at pH 10 and 50–55 °C. The next goal was to determine the reaction time needed for ethylurea 2c to completely transform into DHI 5d. We used 1H NMR monitoring of dried reaction mixture aliquots (after 5 min, 1 h, 2 h and 3 h; Figure 2). It was established that the conversion of urea 2c into DHI 5d was complete after 3 hours. After this time, the signals of the protons of urea 2c disappeared, while new signals of the DHI protons appeared in the 1H NMR spectrum (Figure 2). As no side products were detected (Figure 2), we used a reaction mixture in the reaction with NaSCN and hydrochloric acid, without isolation of DHI 5d (as well as of DHI 5b,c,e–h,j). Target compound 1d was obtained in 58% yield (Table 2, approach 2, entry 3). Condensation of ureas 2a–e,g,h,j with glyoxal was carried out in water for 3 hours at 50–55 °C. As a result, we synthesized a series of thioglycolurils 1a,b,d,e,f,g,h,j in 31–58% yield (Table 2, approach 2, entries 1–5, 7, 8, 10). It turned out that DHI 5i,p do not produce...
Semithioglycolurils \(1_{i,p} \) (entries 9, 16). Imidazooxazine \(6 \) was isolated in 9% yield instead of product \(1_{i} \) (entry 9), although signals of the protons of compound \(1_{i} \) were found in a \(^1\)H NMR spectrum of the reaction mixture.

As ureas \(2_{k-o} \) do not dissolve in \(H_2O\), it was necessary to develop another synthetic approach to DHI \(5_{k-n} \). As a model reaction, we chose the reaction between 1-benzylurea \(2_{l} \) and glyoxal. The reaction was carried out in MeOH or \(i\)-PrOH at pH 7 or 10 (Table 3). Reaction progress was again monitored by \(^1\)H NMR spectroscopy. The best results were achieved in refluxing \(i\)-PrOH at pH 7. Under these conditions, a 100% conversion of urea \(2_{l} \) to DHI \(5_{l} \) (Table 3, entry 9; see also Supporting Information, SI, Figure S1) was observed, so there was no need to isolate DHI \(5_{l} \) for the following reaction with NaSCN and hydrochloric acid. Target thioglycoluril \(1_{l} \) was synthesized in 63% yield (Table 2, approach 2, entry 12). The same methodology was applied for the synthesis of DHI \(5_{k,m,n} \) and semithioglycolurils \(1_{k,m,n} \) (yields 61–65%) (entries 11, 13, 14). Urea \(2_{o} \) did not produce DHI \(5_{o} \), and it was separated from the reaction mixture without any change.

Semithioglycolurils \(1_{i,o,p} \) can be synthesized only by approach 1, while compound \(2_{n} \) can only be obtained by approach 2 (Table 2). The yields of semithioglycolurils \(1_{e,g,h,k-m} \) from approach 2 are 8–35% higher. For compounds \(1_{a,c,f} \), the approach 1 resulted in higher yields (by 11–56%). The yields of compounds \(1_{b,d,j} \) were almost the same (50–52%, 52–58%, 41–45%, respectively), so that they can be synthesized by either of the proposed two methods.

The formation of the target semithioglycolurils \(1 \) was unambiguously confirmed by X-ray diffraction data collected for \(1_{a,b,d,j} \) (SI, Figures S2 and S3), which revealed two conglomerates \((1_{a} \) and \(1_{j} \) crystallized in the \(P2_1,2_1,2_1 \) space group) and two racemates \((1_{b} \) and \(1_{d} \) crystallized in the \(C2/c \) space group) among these semithioglycolurils. Of the four, only \(1_{j} \) has a substituent at one of its nitrogen atoms, the \(\text{C(Me)}_2\text{CH}_2\text{OH} \) group, which is able to form a hydrogen bond; however, its resulting crystal structure is isostuctural with the one for \(1_{a} \) with the methyl group in the same position of the urea. In both cases, the formation of a conglomerate can be attributed to homochiral chains of semithioglycoluril molecules (SI, Figure S4), held together

![Figure 2](image-url)
by hydrogen bonds of the NH groups that are on the opposite side of the molecule from the above substituent (N···O 2.820(3) Å, NHO 178(1)°, N···O 3.306(2) Å, NHS 137(1)° in 1a and N=O 2.765(5) Å, NHO 176(1)° and N–S 3.464(4) Å, NHS 172(1)° in 1j). The third NH group links these homochiral chains (N–O 2.834(3) Å, NHO 163(1)° in 1a and N–O 3.018(5) Å, NHO 167(1)° in 1j), which are rotated to each other by ca. 90° to result in a non-centrosymmetric hydrogen-bonded 3D framework. The OH group in 1j is involved in an intramolecular hydrogen bond with an adjacent oxygen atom O(1) (O···O 2.614(5) Å, OHO 156(1)°) and in a hydrogen bond with the third NH group from the molecule in a perpendicular chain, as the oxygen atom O(1) in 1a does (see above). In contrast, the semithioglycoluril 1b and 1d (SI, Figure S5) form centrosymmetric dimers through N–H···S hydrogen bonds (N···S 3.564(3) Å, NHS 137(1)°), those are held together by weak van der Waals interactions.

In summary, reactions of 1-substituted ureas with 4,5-dihydroxyimidazolidine-2-thione (approach 1) or with glyoxal, using the resulting 1-substituted dihydroxy- or 4,5-dimethoxyimidazolidine-2-one, KSCN, and HCl.14 1-Alkylurea 1b,35,42 1c,36 2c,46 2e,47 2f,30 2h,38 2i,38 and 2p48 were synthesized by previously reported procedures from the corresponding amines, hydrochloric acid, and KOCN. 1-Phenethylurea (2n)40 was synthesized from 2-phenylethanimine, hydrochloric acid, and urea. 4,5-Dimethoxyimidazolidine-2-thione (3) was prepared from 4,5-dihydroxyimidazolidine-2-thione (4), MeOH, and hydrochloric acid.12 4,5-Dihydroxyimidazolidine-2-thione was synthesized by the condensation of thiourea with 40% aq glyoxal.41

Thioglycolurils 1a–m, o, p; Approach 1

4,5-Dihydroxyimidazolidine-2-thione (4; 0.4 g, 3.0 mmol) and the appropriate urea 2a–m, o, p (25 mmol) were suspended in H2O (10 mL). Aq HCl (35%, 0.08 mL) was added, and the solution was heated to 76–80 °C and stirred for 30 min. The next day, the resulting precipitate was collected by filtration and air-dried (for 1a–k, p). The resulting precipitates of 11, m, o were purified by recrystallization (EtoH).

Thioglycolurils 1a, b, d, h, j, k; Approach 2

A mixture of the appropriate 1-alkylurea 2a–e, g–j (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and H2O (10 mL) was heated to 50–55 °C. Aq NaOH was added dropwise until pH 10 was reached by the reaction mixture, which was then stirred for 3 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t.

For 1h: The next day, the resulting precipitate of thioglycoluril 1h was collected by filtration, washed with MeOH, and dried in air.

For 1a, b, d, g: The reaction mixture was evaporated to dryness, after which CHCl3 (10 mL) was added under stirring. The precipitate was collected by filtration and washed with H2O (5 mL).

For 1j: The reaction mixture of 1j was evaporated to dryness, and then the resulting mixture was dissolved in H2O (10 mL) and CHCl3 (15 mL). The organic layer was collected and then evaporated to dryness. After the addition of MeOH (5 mL), the precipitate was collected by filtration and air-dried.

Thioglycolurils 1k–n; Approach 2

A mixture of the appropriate 1-alkylurea 2k–n (20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and 1-propanol (10 mL) was heated to reflux and stirred for 5 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t. The resulting precipitate was collected by filtration and air-dried.

1-Methyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1a)

Beige powder; yield: 0.22 g (51%) (approach 1); brown crystals; yield: 1.07 g (31%) (approach 2); mp 283–285 °C (MeOH) (283–285 °C (H2O))

All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. 1H and 13C NMR spectra were recorded at 25–29 °C with a Bruker AM300 and Bruker DRX500 spectrometer and TMS as internal standard. HRMS (ESI) data were collected using a Bruker microOTOF II mass spectrometer. 1-Methyl- and 1-isopropyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1a, b) were synthesized earlier from 1-methyl- and 1-isopropyurea and 3 (DMIT).25 1-Cyclohexyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1c) was prepared earlier from 1-cyclohexyl-4,5-dihydroxyimidazolidine-2-one, KSCN, and HCl.14 1-Alkylurea 2b,35 2c,36 2e,47 2f,30 2h,38 2i,38 and 2p48 were synthesized by previously reported procedures from the corresponding amines, hydrochloric acid, and KOCl. 1-Phenethylurea (2n)40 was synthesized from 2-phenylethanimine, hydrochloric acid, and urea.
1-Isopropyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1b)<sup>35</sup>
Beige powder; yield: 0.25 g (50%) (approach 1); brown crystals; yield: 2.08 g (52%) (approach 2); mp 260–261 °C (MeOH) (260–261 °C (H<sub>2</sub>O)).
IR (KBr): 2975, 2894, 1677, 1533, 1492, 1337, 1225, 1210, 1105, 880, 755, 634, 586 cm<sup>-1</sup>.
1H NMR (300 MHz, DMSO-<d>): δ = 0.61 (d, <i>J</i> = 6.6 Hz, 6 H, Me), 3.78–3.92 (m, 1 H, CH), 5.37 (d, <i>J</i> = 8.4 Hz, 1 H, CH), 5.52 (d, <i>J</i> = 8.5 Hz, 1 H, CH), 7.42 (s, 1 H, NH), 8.99 (s, 1 H, NH), 9.04 (s, 1 H, NH).
13C NMR (75 MHz, DMSO-<d>): δ = 18.98, 21.42 (Me), 43.20 (CH), 66.61, 69.87 (CH–CH), 158.34 (C=O), 182.80 (C=S).

1-Cyclohexyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1c)<sup>14</sup>
Beige powder; yield: 0.39 g (65%) (approach 1); mp 294–296 °C (H<sub>2</sub>O) (294–296 °C (H<sub>2</sub>O)).
1H NMR (300 MHz, DMSO-<d>): δ = 1.02 (t, <i>J</i> = 7.1 Hz, 3 H, Me), 3.01 (dq, <i>J</i> = 14.2 Hz, 7.1 Hz, 1 H, CH<sub>2</sub>), 3.26 (dq, <i>J</i> = 14.4 Hz, 7.2 Hz, 1 H, CH<sub>2</sub>), 5.37 (d, <i>J</i> = 8.4 Hz, 1 H, CH), 5.46 (d, <i>J</i> = 8.4 Hz, 1 H, CH), 7.49 (s, 1 H, NH), 9.02 (s, 1 H, NH), 9.15 (s, 1 H, NH).
13C NMR (75 MHz, DMSO-<d>): δ = 12.83 (Me), 35.09 (CH<sub>2</sub>), 66.31, 71.1 (CH–CH), 158.46 (C=O), 182.74 (C=S).
HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S + Na: 209.0468; found: 209.0464.

1-Ethyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1d)
Beige powder; yield: 0.24 g (52%) (approach 1); brown crystals; yield: 2.15 g (58%) (approach 2); mp 256–258 °C (MeOH).
IR (KBr): 3348, 3185, 2980, 2877, 1680, 1527, 1489, 1341, 1309, 1251, 1099, 887, 583 cm<sup>-1</sup>.
1H NMR (300 MHz, DMSO-<d>): δ = 0.83–0.96 (m, 1 H, CH<sub>2</sub>), 0.82–0.96 (m, 1 H, CH<sub>2</sub>), 3.28 (m, 1 H, CH<sub>2</sub>), 3.44 (m, 1 H, CH<sub>2</sub>), 4.45–5.11 (br. s, 1 H, NH).
13C NMR (75 MHz, DMSO-<d>): δ = 74.94, 29.91 (CH<sub>2</sub>), 66.31, 71.1 (CH–CH), 158.46 (C=O), 182.74 (C=S).
HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S + Na: 209.0468; found: 209.0464.

1-Propyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1e)
Beige powder; yield: 0.10 g (20%) (approach 1), 2.20 g (55%) (approach 2); mp 243–245 °C (MeOH).
IR (KBr): 2967, 2932, 2879, 1682, 1531, 1492, 1250, 1206, 1100, 886 cm<sup>-1</sup>.
1H NMR (300 MHz, DMSO-<d>): δ = 0.58 (t, <i>J</i> = 7.3 Hz, 3 H, Me), 1.37–1.57 (m, 2 H, CH<sub>2</sub>), 2.91–3.00 (m, 1 H, CH<sub>2</sub>), 3.08–3.33 (m, 1 H, CH<sub>2</sub>), 5.38 (d, <i>J</i> = 8.5 Hz, 1 H, CH), 5.44 (d, <i>J</i> = 8.5 Hz, 1 H, CH), 7.45 (s, 1 H, NH), 8.98 (s, 1 H, NH), 9.11 (s, 1 H, NH).
13C NMR (75 MHz, DMSO-<d>): δ = 11.07 (Me), 20.31, 41.91 (CH<sub>2</sub>), 66.27, 71.45 (CH–CH), 158.66 (C=O), 182.71 (C=S).
HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S + Na: 223.0624; found: 223.0627.

1-tert-Butyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1f)
Violet powder; yield: 0.33 g (61%) (approach 1); beige powder; yield: 2.61 g (50%) (approach 2); mp 278–280 °C (H<sub>2</sub>O).
IR (KBr): 3182, 2974, 2900, 1687, 1535, 1487, 1254, 1214, 1158, 775, 744 cm<sup>-1</sup>.
1H NMR (300 MHz, DMSO-<d>): δ = 1.32 (s, 9 H, Me), 5.25 (d, <i>J</i> = 8.3 Hz, 1 H, CH), 5.65 (d, <i>J</i> = 8.3 Hz, 1 H, CH), 7.33 (s, 1 H, NH), 8.99 (s, 2 H, NH).
13C NMR (75 MHz, DMSO-<d>): δ = 29.10 (Me), 35.09 (CH<sub>2</sub>), 66.31, 71.1 (CH–CH), 158.57 (C=O), 182.70 (C=S).
HRMS (ESI): m/z [M + Na]<sup>+</sup> calcd for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S + Na: 238.0573; found: 238.0567.
1-(1-Hydroxy-2-methylprop-2-yl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1j)
Beige powder; yield: 0.24 g (41%) (approach 1), 2.07 g (45%) (approach 2); mp 264–266 °C (MeOH).
IR (KBr): 3200, 2065, 1693, 1533, 1489, 1339, 1249, 1203, 1061, 888 cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆); δ = 1.26 (s, 6 H, Me), 3.37 (d, J = 10.9 Hz, 1 H, CH₂), 3.64 (d, J = 10.7 Hz, 1 H, CH₂), 4.77–5.14 (br, s, 1 H, OH), 5.28 (d, J = 8.4 Hz, 1 H, CH), 5.67 (d, J = 8.4 Hz, 1 H, CH), 7.38 (s, 1 H, NH), 8.83 (s, 1 H, NH), 9.00 (s, 1 H, NH).

¹³C NMR (75 MHz, DMSO-d₆); δ = 24.21, 24.29 (Me), 57.55 (CH₃), 66.92, 73.16 (CH=CH), 67.82 (CMe₂), 160.16 (C=O), 183.93 (C=S).


1-Phenyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1n)
Beige powder; yield: 3.20 g (61%) (approach 2); mp 259–260 °C (MeOH).
IR (KBr): 3331, 3164, 1677, 1527, 1487, 1340, 1252, 1024, 1123, 1096, 885, 751, 702, 580 cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆); δ = 2.69–2.90 (m, 2 H, CH₃), 3.19–3.48 (m, 2 H, CH₃), 5.38 (d, J = 8.4 Hz, 1 H, CH), 5.47 (d, J = 8.3 Hz, 1 H, CH), 7.18–7.33 (m, 5 H, Ph), 7.44 (s, 1 H, NH), 8.92 (s, 1 H, NH), 9.20 (s, 1 H, NH).

¹³C NMR (75 MHz, DMSO-d₆); δ = 23.38, 41.96 (CH₃), 66.36, 71.55 (CH=CH), 126.19, 128.36, 128.71 (CH(Ph)), 139.03 (C(Ph)), 158.52 (C=O), 182.70 (C=S).


1-Phenyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1o)
Violet powder; yield: 0.20 g (34%) (approach 1); mp >300 °C (MeOH).
IR (KBr): 3345, 3177, 1689, 1529, 1503, 1422, 1328, 1266, 1142, 1102, 887, 748, 691 cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆); δ = 5.54 (d, J = 8.4 Hz, 1 H, CH), 6.09 (d, J = 8.5 Hz, 1 H, CH), 7.08 (t, J = 7.3 Hz, 1 H, Ph), 7.33 (t, J = 7.8 Hz, 2 H, Ph), 7.56 (d, J = 8.1 Hz, 2 H, Ph), 8.18 (s, 1 H, NH), 9.29 (d, 1 H, NH), 9.42 (s, 1 H, NH).

¹³C NMR (75 MHz, DMSO-d₆); δ = 65.77, 71.79 (CH=CH), 119.10, 123.06, 128.63 (CH(Ph)), 138.01 (C(Ph)), 156.35 (C=O), 183.47 (C=S).


4-(2-Oxo-5-thioxohexahydroimidazo[4,5-d]imidazol-1(2H)-yl)-butanoic Acid (1p)
Beige powder; yield: 0.22 g (36%) (approach 1); mp 215–216 °C (H₂O).
IR (KBr): 3405, 3331, 3181, 1715, 1651, 1500, 1337, 1243, 1205, 1129, 1083, 933, 887, 812 cm⁻¹.

¹H NMR (300 MHz, DMSO-d₆); δ = 1.60–1.80 (m, 2 H, CH₂), 2.16 (t, J = 7.5 Hz, 2 H, CH₂), 3.00 (dt, J = 13.9 Hz, 6.8 Hz, 1 H, CH₂), 3.19 (dt, J = 14.0 Hz, J = 7.6 Hz, 1 H, CH₂), 5.37 (d, J = 8.4 Hz, 1 H, CH), 5.44 (d, J = 8.4 Hz, 1 H, CH), 7.53 (s, 1 H, NH), 9.04 (s, 1 H, NH), 9.14 (s, 1 H, NH), 11.81–12.32 (br, s, 1 H, COOH).

¹³C NMR (75 MHz, DMSO-d₆); δ = 22.64, 31.01, 39.78 (CH₃), 66.34, 71.44 (CH=CH), 158.72 (C=O), 174.05 (C(Ph)), 182.74 (C=S).


1-(4-Methoxybenzyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1m)
Urea (200 mmol, 12.00 g) was dissolved in H₂O (50 mL); then, (4-methoxyphenyl)methanamine (5.2 mL, 40 mmol) and 35% aq HCl (2.5 mL) were added. The reaction mixture was refluxed for 4 h and then cooled to r.t. The resulting precipitate was collected by filtration, washed with H₂O (50 mL), and dried in air.
White crystalline plates; yield: 3.82 g (53%); mp 159–160 °C (H2O) (158–159 °C43).

Ureas 2d,g
The corresponding amine (38 mmol) was dissolved in H2O (40 mL), and then 35% aq HCl (2.1 mL) was added dropwise. The reaction mixture was heated to reflux, and then KOCl (40 mmol, 3.24 g) was added portionwise. The reaction mixture was refluxed for 30 min and then cooled to r.t. The resulting precipitate was collected by filtration and recrystallized from EtOH.

1-Propylurea (2d)
White powder; yield: 3.45 g (89%); mp 109–110 °C (173–174 °C43).

1-(Cyclopropylmethyl)urea (2g)
Beige powder; yield: 3.81 g (88%); mp 122–124 °C (MeOH).

IR (KBr): 3207, 3114, 2920, 1707, 1478, 1434, 1353, 1253, 1080, 953, 780, 679 cm−1.

HRMS (ESI): 

[(8S,8aS)-8-Methoxytetrahydro-2H-imidazo[5,1-b][1,3]oxazine-6(7H)-one (6)]
A mixture of 2i (0.24 g, 20 mmol), glyoxal hydrate trimer (1.61 g, 7.7 mmol), and H2O (10 mL) was heated to 50–55 °C. Then NaOH (H2O) was added dropwise until pH 10 was achieved by the reaction mixture, which was then stirred for 3 h. MeOH (20 mL), NaSCN (3.65 g, 45 mmol), and 35% aq HCl (4.4 mL) were added to the reaction mixture. The precipitate was removed by filtration and washed with MeOH (5 mL). The filtrate was refluxed for 30 min. Then the reaction mixture was cooled to r.t. The reaction mixture was evaporated to dryness, then acetone (5 mL) was added, and the resulting precipitate of compound 6 was collected by filtration and air-dried.

White powder; yield: 0.31 g (9%); mp 164–166 °C (acetone).

IR (KBr): 3416, 3217, 1657, 1605, 1547, 1359, 1310, 1145, 559 cm−1.

HRMS (ESI): 

1H NMR (300 MHz, DMSO-d6): δ = 2.97 (CH2), 11.47 (CH), 43.50 (CH3), 158.71 (C=O).

13C NMR (75 MHz, DMSO-d6): δ = 1.31–1.41 (m, 1 H, CH3), 1.44–1.62 (m, 1 H, CH2), 2.96–3.10 (m, 1 H, CH3), 3.20 (s, 3 H, Me), 3.64–3.77 (m, 2 H, CH2), 3.89–3.98 (m, 1 H, CH3), 4.34 (s, 1 H, CH), 4.79 (s, 1 H, CH), 8.02 (s, 1 H, NH).

X-ray Diffraction
X-ray diffraction data for 1a,b,d,j were collected at 120 K on a Bruker APEX2 DQU CCD diffractometer, using graphite monochromated MoorKa radiation (λ = 0.71073 Å). Using Olex2,44 the structures were solved with the ShelXT43 structure solution program using intrinsic phasing and refined against F2 in the anisotropic-isotopic approximation with the olex2.reite46 refinement package using least-squares minimization. The hydrogen atoms of NH and OH groups were found in the difference Fourier synthesis, the positions of other hydrogen atoms were calculated, and they all were refined in the isotropic approximation within the riding model. Crystal data and structure refinement parameters are given in Table S1 (SI). CCDC 1992118, 1992119, 1992120, and 1992121 (1a, 1b, 1d, and 1j, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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