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-dihydroxyimidazolidine-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 Schiff 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 (Figure 1),2,6–26 including compounds I, II, V, 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 (DHT; 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.
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 $^1$H 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 to produce the earlier reported 2-thioxoimidazolidin-4-one (the most characteristic signal of CH$_2$ protons: s, δ = 4.06); we also detected ethylurea (2c) (for the reaction of urea into semithioglycoluril 1d), with a 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)$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents (ratio)</th>
<th>Aq. HCl (%)</th>
<th>Time</th>
<th>Conversion (%)$^b$</th>
</tr>
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<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>
<td>2c, 4 (1:1)</td>
<td>0.08</td>
<td>1 h</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<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>71</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 2c (2.5 mmol, 1 equiv), 3 or 4, H$_2$O (10 mL), aq. HCl (35%), 76–80 °C.

$^b$ Conversion of 2c into 1d according to $^1$H NMR spectroscopy.

$^c$ Reaction conditions: 2c (0.22 g, 2.5 mmol), 4 (0.40 g, 3.0 mmol), H$_2$O (10 mL), aq. HCl (35%, 0.08 mL), 76–80 °C, 30 min.
As 1-cyclohexyl-DHI 5a had been prepared before,32 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.34

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 2d). As no side products were detected (Figure 2d), 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, o do not produce...
Semithioglycolurils 1i, p (entries 9, 16). Imidazooxazine 6 was isolated in 9% yield instead of product 1i (entry 9), although signals of the protons of compound 1i were found in a 1H NMR spectrum of the reaction mixture.

As ureas 2k–o do not dissolve in H2O, it was necessary to develop another synthetic approach to DHI 5k–n. As a model reaction, we chose the reaction between 1-benzylurea 2l 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 1H NMR spectroscopy. The best results were achieved in refluxing i-PrOH at pH 7. Under these conditions, a 100% conversion of urea 2l to DHI 5l (Table 3, entry 9; see also Supporting Information, SI, Figure S1) was observed, so there was no need to isolate DHI 5l for the following reaction with NaSCN and hydrochloric acid. Target thioglycoluril 1l was synthesized in 63% yield (Table 2, approach 2, entry 12). The same methodology was applied for the synthesis of DHI 5k, m, n and semithioglycolurils 1k, m, n (yields 61–65%) (entries 11, 13, 14). Urea 2o did not produce DHI 5o, and it was separated from the reaction mixture without any change.

Semithioglycolurils 1i, o, p can be synthesized only by approach 1, while compound 2n can only be obtained by approach 2 (Table 2). The yields of semithioglycolurils 1e, g, h, k–m from approach 2 are 8–35% higher. For compounds 1a, c, f, the approach 1 resulted in higher yields (by 11–56%). The yields of compounds 1b, 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 1a, b, d, j (SI, Figures S2 and S3), which revealed two conglomerates (1a and 1j crystallized in the P212121 space group) and two racemates (1b and 1d crystallized in the C2/c space group) among these semithioglycolurils. Of the four, only 1j has a substituent at one of its nitrogen atoms, the C(Me)2CH2OH group, which is able to form a hydrogen bond; however, its resulting crystal structure is isostructural with the one for 1a 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

### Table 3 Screening of Conditions for the Synthesis of DHI 5l (Approach 2)a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>pH</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>7</td>
<td>1</td>
<td>15</td>
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<tr>
<td>2</td>
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<td>24</td>
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<td>4</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>i-PrOH</td>
<td>7</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>i-PrOH</td>
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<td>2</td>
<td>71</td>
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<tr>
<td>10</td>
<td>i-PrOH</td>
<td>10</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>

a Reaction conditions: 2l (2 mmol), glyoxal hydrate trimer (0.8 mmol), reflux.

b Conversion of 2l into 5l according to 1H NMR spectroscopy.

c Reaction conditions: 2l (0.30 g, 2 mmol), glyoxal hydrate trimer (0.16 g, 0.8 mmol), i-PrOH (5 mL), reflux, 5 h.
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)°, NHO 167(1)° and N–S 3.464(4) Å, NHS 172(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 semithioglycolurilis 1b and 1d (SI, Figure S5) form centrosymmetric dimers through N–H–S hydrogen bonds (N–S 3.535(6) Å, NHS 160(1)° in 1b and N–S 3.569(3) Å, NHS 149(1)° in 1d). They assemble chiral chains produced by an N–H–O hydrogen bond (N–O 2.874(8) Å, NHO 177(1)° in 1b and N–O 2.885(4) Å, NHS 144(1)° in 1d) of the NH group that is on the same side of the molecule as the above substituents, into centrosymmetric sheets. Additionally stabilized by N–H–S hydrogen bonds formed the third NH group in 1b (N–S 3.464(6) Å, NHS 161(1)°), those are held together by weak van der Waals interactions. In 1d, the same NH group is involved in an N–H–S hydrogen bond with the neighboring chiral chain (N–S 3.563(3) Å, NHS 137(1)°), thus completing a centrosymmetric hydrogen-bonded 3D framework. As a result, the semithioglycolurilis 1b and 1d were crystallized as race-mates (SI, Table S1), and 1a and 1j, as conglomerates. A possible explanation for this behavior is that the isopropyl and ethyl substituents are diverted towards the NH group in the former two compounds, somehow favoring the centro-symmetric arrangement of their molecules.

In summary, reactions of 1-substituted ureas with 4,5-dihydroxy- or 4,5-dimethoxyimidazolidine-2-thione (approach 1) or with glyoxal, using the resulting 1-substituted 4,5-dihydroxyimidazolidine-2-ones, with NaSCN and hydrochloric acid in a two-step one-pot procedure (approach 2) were studied in detail by 1H NMR spectroscopy. As a result of this comprehensive study, two new methods for the synthesis of 1-substituted semithioglycolurilis were developed to provide 16 different products, 13 of which were reported for the first time. Two of these compounds produced the first conglomerates reported for semithioglycolurilis, as unambiguously identified by X-ray diffraction. This research has made 1-substituted semithioglycolurilis available, so that they can now be used in the synthesis of new heterocyclic compounds.

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-thioxohexahydroimidazol[4,5-d]imidazol-2(1H)-one (1a, b) were synthesized earlier from 1-methyl- and 1-isopropylurea and 3 (DMIT). 2,5-Dicyclohexyl-5-thioxohexahydroimidazol[4,5-d]imidazol-2(1H)-one (1c) was prepared earlier from 1-cyclohexyl-4,5-dihydroxyimidazolidine-2-one, KSCN, and HCl. 1-Alkylureas 2b, 2c, 2e, 2f, 2i, 2h, 2l, 2j, 2k were synthesized by previously reported procedures from the corresponding amines, hydrochloric acid, and KOH. 1-Phenethylurea (2n) was synthesized from 2-phenylethanamine, hydrochloric acid, and urea. 4,5-Dimethoxyimidazolidine-2-thione (3) was prepared from 4,5-di-hydroxyimidazolidine-2-thione (4), MeOH, and hydrochloric acid. 4,5-Dihydroxyimidazolidine-2-thione was synthesized by the condensation of thiourea with 40% aq glyoxal. 4,5-Dihydroxyimidazolidine-2-thione (4; 0.40 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–m, o, p; Approach 1

4,5-Dihydroxyimidazolidine-2-thione (4; 0.40 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 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 (4.0 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-alkylureas 2a–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 (4.0 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 1k:** The next day, the resulting precipitate of thioglycoluril 1k was collected by filtration, washed with MeOH, and dried in air.

**For 1l, m, n:** 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.
1-Isopropyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1b)\(^3\)

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\(_2\)O)).

IR (KBr): 2975, 2894, 1677, 1533, 1492, 1337, 1225, 1210, 1105, 880, 1099, 1060, 1020, 886, 724 cm\(^{-1}\).

1\(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 0.61\) (t, \(J = 7.3\) Hz, 3 H, Me), 1.37–1.57 (m, 2 H, CH\(_2\)), 2.91–3.00 (m, 1 H, CH\(_2\)), 3.08–3.33 (m, 1 H, CH\(_3\)), 5.38 (d, \(J = 8.5\) Hz, 1 H, CH), 5.44 (d, \(J = 8.5\) Hz, 1 H, CH), 7.45 (s, 1 H, NH), 8.98 (s, 1 H, NH), 9.11 (s, 1 H, NH).

13\(^{1}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta = 11.07\) (Me), 20.31, 41.91 (CH\(_3\)), 66.27, 71.45 (CH–CH), 158.66 (C=O), 182.71 (C=S).

HRMS (ESI): m/z [M + Na\(^+\)] \(^{+}\) calcld for C\(_{13}\)H\(_{17}\)N\(_4\)O\(_2\)S + Na: 225.0417; found: 225.0417.

1-Cyclohexyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1c)\(^4\)

1-Propyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1d)\(^5\)

1-Buttlyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1e)\(^6\)

1-Pentyloxethyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1f)\(^7\)

1-tert-Butyl-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1g)\(^8\)

1-(2-Hydroxyethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1h)\(^9\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1i)\(^10\)

1-(2-Hydroxyethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1j)\(^11\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1k)\(^12\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1l)\(^13\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1m)\(^14\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1n)\(^15\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1o)\(^16\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1p)\(^17\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1q)\(^18\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1r)\(^19\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1s)\(^20\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1t)\(^21\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1u)\(^22\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1v)\(^23\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1w)\(^24\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1x)\(^25\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1y)\(^26\)

1-(Cyclopropylmethyl)-5-thioxohexahydroimidazo[4,5-d]imidazol-2(1H)-one (1z)\(^27\)
1-(1-Hydroxy-2-methylprop-2-yl)-5-thioxohexahydroimidazo-[4,5-d][imidazol-2(1H)-one (1j)
Beige powder: yield: 0.27 g (45%) (approach 1), 3.00 g (63%) (approach 2); mp 259–260 °C (MeOH).
IR (KBr): 3345, 3177, 1689, 1529, 1503, 1422, 1328, 1266, 1142, 1102, 885, 748, 691 cm⁻¹.
1H NMR (300 MHz, DMSO-d₆): δ = 3.49 (dd, J = 15.9 Hz, J = 6.8 Hz, 1 H, CH₂), 3.92 (dd, J = 15.5 Hz, J = 3.7 Hz, 1 H, CH₂), 5.08–5.25 (m, 2 H, CH₂), 6.37 (q, J = 8.3 Hz, 2 H, CH–CH), 5.63–5.78 (m, 1 H, CH), 7.6 (s, 1 H, NH), 9.05 (s, 1 H, NH), 9.17 (s, 1 H, NH).
13C NMR (75 MHz, DMSO-d₆): δ = 42.46 (CH₂), 66.32, 71.02 (CH–CH), 117.49 (CH₃), 133.06 (CH), 158.31 (C=O), 182.78 (C=S).
1-Allyl-5-thioxohexahydroimidazo[4,5-d][imidazol-2(1H)-one (1k)
Violet powder: yield: 0.20 g (40%) (approach 1); mp >300 °C (MeOH).
IR (KBr): 3435, 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, J = 10.9 Hz, 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, 126.83 (CH(Ph)), 138.01 (C(Ph)), 158.31 (C=O), 182.78 (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, 1103, 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, J = 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 (COOH), 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 °C2).

**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 KCN (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).

**Synthesis**

**X-ray Diffraction**

**Acknowledgment**
X-ray diffraction data were collected using the equipment of the Center for Molecular Composition Studies of the A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences (INEOS RAS).

**Supporting Information**
Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707391.

**References**