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Synthesis of *N*-{5-Oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo-[4,5-*d*]imidazol-1(2*H*)-yl}formamides

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X = O, S; R^1 = Me, Et; R^2 = Me, Et, Ph; R^3 = H, Me

9 examples
19–70% yield

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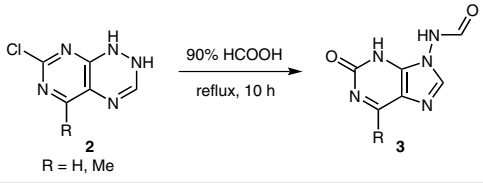
Abstract A synthetic route to novel *N*-{5-oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl}formamides, by a tandem N-formylation and ring-contraction reaction of 5,7-disubstituted 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones(thiones) with formic acid, has been developed.

Key words N-heterocycles, thioanalogues of glycolurils, formylation, ring contraction, tandem reaction

Glycolurils (tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones) possess a wide range of biological activities[1] and have found applications as anion-binding receptors and molecular capsules,[2] molecular templates for intramolecular Claisen-type condensation,[3] and as precursors in combinatorial[4] and supramolecular chemistry.[5]

Mono- and dithio analogues of glycolurils (5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones and tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dithiones) have been studied to a considerably lesser extent. However, they have already been recognized as substrates for the template-directed crossed-Claisen condensation,[6] organocatalysts for *N*-Boc protection of amines[7] or α-monobromination of 1,3-dicarbonyl compounds,[8] and as building blocks for the synthesis of semithiobambusurils.[9] Some monothio analogues of glycolurils demonstrate sedative,[10] anxiolytic,[11] and cytotoxic[12] activities. While glycolurils are easily accessible compounds, their thio analogues represent a yet unfulfilled synthetic challenge.[13]

One of the approaches to the synthesis of mono- and dithio analogues of glycolurils is the triazine ring-contraction reaction of 5,7-dialkyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones(thiones) **1** with (hetero)aromatic aldehydes in acid medium (HCl) or with nitrous acid.[10,12,14] In general, triazine ring contraction to the imidazolidine ring takes place upon treatment of the corresponding 1,2,4-triazine derivatives with reagents such as sodium dithionite or zinc in acetic acid,[15] benzaldehyde derivatives in acidic medium,[12,14a,16] hydroxylamine-*O*-sulfonic acid,[17] mercuric(II) oxide,[18] or organolithium reagents.[19] There are a few examples of 1,2,4-triazine ring contraction in the reaction with hydrochloric, acetic, or formic acids.[16,20] For example, attempts to bring about acid hydrolysis of the 7-chloro-1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazines **2** in aqueous formic acid led to ring-contraction products **3** in around 6% yield (Scheme 1).[20b]

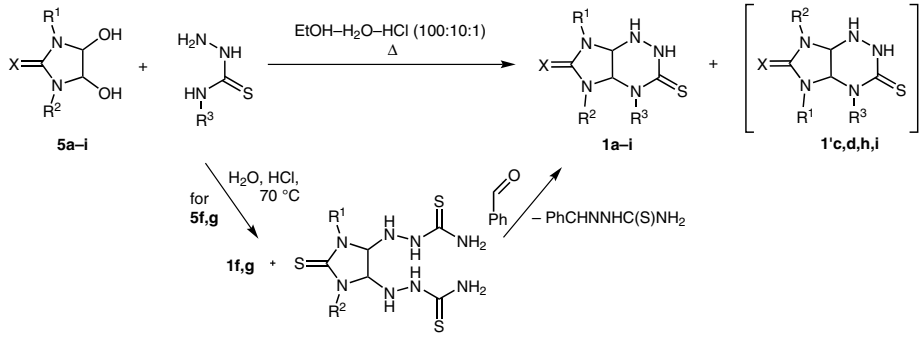


2
R = H, Me

3

Scheme 1 Ring contraction of compounds **2**

Earlier, upon treatment of several compounds **1** with hydrochloric acid, 1,2,4-triazine ring contraction was not observed.[12,14b] To the best of our knowledge, formic acid has not yet used specifically for this purpose. Furthermore, formic acid is not only an acid and acylating agent, but also a



1,5: X = O, R^3 = H, R^1 = R^2 = Me (**a**), Et (**b**), R^2 = Ph, R^1 = Me (**c**), Et (**d**), R^1 - R^3 = Me (**e**); X = S, R^3 = H, R^1 = R^2 = Me (**f**), Et (**g**), R^2 = Ph, R^1 = Me (**h**), Et (**i**)

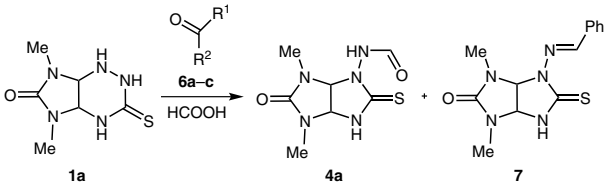
Scheme 2 Synthesis of starting compounds **1**

reducing agent, for example, in the Leuckart–Wallach reaction.[21] Accordingly, an investigation into the reaction of compounds **1** with formic acid became our objective.

Herein, we report the first synthesis of *N*-(5-oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl)formamides **4** by tandem N-formylation and triazine ring-contraction reaction of 5,7-disubstituted 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-ones(thiones) **1** with formic acid.

The starting materials **1** were prepared by cyclization of 4,5-dihydroxyimidazolidine-2-ones **5a–i** with thiosemicarbazide following procedures described earlier (Scheme 2).[14d,22] Known compounds **1a**,**b**,**e–g** were obtained in 36–70% yields. The yields of the major regioisomers (R^1 = Alk, R^2 = Ph) of the novel unsymmetrically substituted imidazotriazines **1c**,**d**,**h**,**i** were 39–63% (minor regioisomers **1'c**,**d**,**h**,**i** were not isolated). The structures and purity of compounds **1c**,**d**,**h**,**i** were ascertained by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and NOESY spectroscopic analyses (see Supporting Information).[23]

With this set of imidazotriazines in hand, we examined their reaction with formic acid and carbonyl compounds **6**. Our investigations were initiated with the reaction of model compound **1a**, benzaldehyde **6a**, and excess of formic acid under heating (Scheme 3), when a mixture of two compounds in a ratio 1:6 was obtained, as evidenced by NMR spectroscopic analysis. The minor product was the known (*E*)-4-(benzylideneamino)-1,3-dimethyl-5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one (**7**).[22b] The major product turned out novel compound **4a** resulting from tandem N-formylation and triazine ring contraction of imidazotriazine **1a**. The yield of the major compound **4a** was 25%. In an attempt to avoid the formation of products resulting from tandem hydrazone formation–ring contraction, we used ketones **6b**,**c**. However, the reaction of one equivalent each of **1a** and **6b** in excess of formic acids led to formamide **4a** in low yield and no other products were isolated. To optimize the reaction conditions, solvent, reaction time, and temperature were varied (Table 1).



6a: R^1 = H, R^2 = Ph, **6b**: R^1 = R^2 = Me, **6c**: R^1 = Me, R^2 = Et

Scheme 3 Reaction of compound **1a** with carbonyl compound and HCOOH

Heating imidazotriazine **1a** to reflux in 90% formic acid led to its decomposition (Table 1, entry 1). When compound **1a** was heated to reflux in a mixture of 90% formic acid and acetone, **6b**, in the ratio 1:1, 1:3, and 1:5, product **4a** was formed in 29–55% yields. It is evident that a reduction in temperature with the increasing proportion of ace-

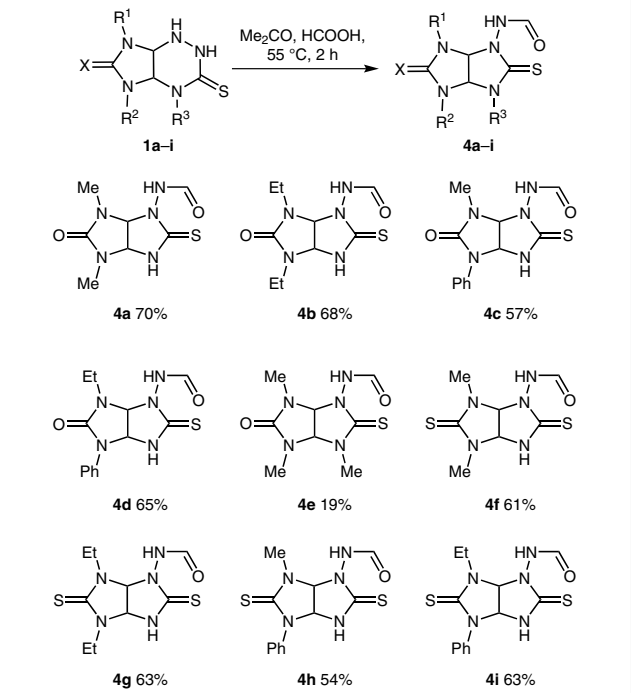
Table 1 Optimization of the Reaction Conditions for the Imidazotriazine **1a**

Entry	Solvent	Temp (°C)	Time (h)	Yield of **4a** (%)[a]
1	HCOOH	reflux	2	0
2	HCOOH–acetone (1:1)	reflux	2	29
3	HCOOH–acetone (1:3)	reflux	2	54
4	HCOOH–acetone (1:5)	reflux	2	55
5	HCOOH–acetone (1:3)	55	2	70
6	HCOOH–acetone (1:5)	55	2	67
7	HCOOH–acetone (1:3)	50	2	46
8	HCOOH–acetone (1:3)	55	3	70
9	HCOOH–acetone (1:3)	r.t.	24	56
10	HCOOH–butan-2-one (1:5)	reflux	2	40
11	HCOOH–butan-2-one (1:5)	55	2	41
12	HCOOH–butan-2-one (1:3)	55	2	45
13	HCOOH–MeOH (1:3)	55	2	0

[a] Isolated yield.

tone in the mixture of solvents resulted in an increase of the product yield (Table 1, entries 2–4). Further investigations showed that formamide **4a** was formed at 55 °C, 50 °C, and room temperature in good yields for 2–24 hours (Table 1, entries 5–9). The optimal yield was obtained at 55 °C for two hours (Table 1, entry 5). Carrying out reaction in a mixture of formic acid with other solvents (butanone and MeOH) did not lead to improvement of the product yield (Table 1, entries 10–12), or compound **4a** was not formed at all (Table 1, entry 13).

The scope of the tandem N-formylation–triazine ring-contraction reaction of imidazotriazines **1** was subsequently investigated under the optimized conditions. All the studied compounds **1a–i** reacted with formic acid to give the corresponding formamides **4a–i** (Scheme 4).[24] Products **4a–d**,**f–i** obtained from starting materials **1a–d**,**f–i** without substituents in the triazine ring were obtained in 54–70% yields; however, introducing a methyl group at N(4) atom of imidazotriazine **1e** led to a dramatic decrease in the yield of compound **4e** (19%).



Scheme 4 Synthesis of *N*-{5-oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl}formamides **4a–i**

All compounds **4a–i** were characterized by IR, NMR, and HRMS analysis. In the ^{1}H NMR and ^{13}C NMR spectra of formamides **4a–i** in DMSO-d_6, signals for two rotamers were observed. The signals were assigned using {^{1}H-^{13}C} and {^{1}H-^{15}N} HSQC methods. The single-crystal structure of compound **4b** was also obtained (Figure 1).

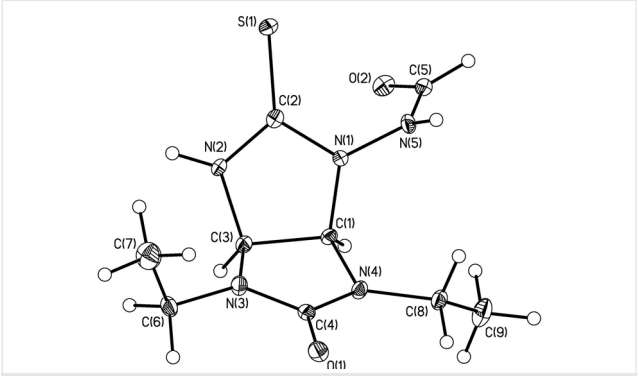
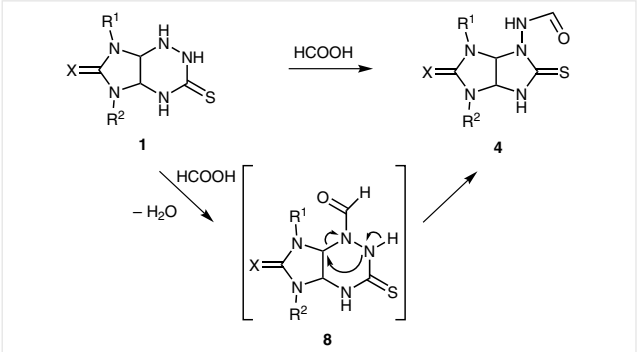


Figure 1 ORTEP view of **4b** with nonhydrogen atoms as thermal ellipsoids (p = 50%)

Results of the analysis of the experimental powder diffraction patterns of the compounds **4a**,**b**,**f–i** show that the investigated samples were single-phase (see Supporting Information).

A plausible mechanism for the formation of compounds **4** is depicted in Scheme 5 and includes a tandem sequence of N-formylation of imidazotriazine **1** at N(1) and subsequent triazinane ring contraction to the imidazolidine. The proposed pathway of the reaction is based on the fact that intermediates **8** were identified by ^{1}H NMR analysis or isolated in some experiments. For example, stirring imidazotriazine **1a** in 90% formic acid at room temperature for two hours gave derivative **8a** (X = O, R^1 = R^2 = Me) in 26% yield (see Supporting Information).



Scheme 5 Proposed mechanism for the formation of compounds **4**

In conclusion, we have developed a simple protocol for the synthesis of novel mono- and dithio analogues of glycolurils possessing the formamide function. Novel *N*-{5-oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl}formamides were synthesized by the reaction of 5,7-disubstituted 3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazine-6-ones(thiones) with formic acid in moderate to good yields. The compounds synthesized may be used as precursors of hitherto unknown thio analogues of *N*-aminoglycolurils.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588388.

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(23) **Representative Analytical Data**

7-Methyl-5-phenyl-3-thioxoperhydroimidazo[4,5-*e*]-1,2,4-triazin-6-one (1c)

White solid; yield 0.537 g (51%); mp 258–260 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.73 (s, 3 H, Me), 5.02 (d, *J* = 8.5 Hz, 1 H, CH), 5.45–5.48 (dd, *J* = 8.5, 1.9 Hz, 1 H, CH), 5.86 (br s, 1 H, N(1)H), 7.13 (t, *J* = 7.2 Hz, 1 H, *p*-PhH), 7.35 (t, *J* = 7.8 Hz, 2 H, *m*-PhH), 7.48 (d, *J* = 8.1 Hz, 2 H, *o*-PhH), 8.62 (s, 1 H, N(4)H), 9.52 (s, 1 H, N(2)H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.0, 62.1, 69.0, 122.0, 123.9, 128.6, 137.5, 155.8, 184.9. IR: 3208, 2971, 1698, 1595, 1529, 1500, 1477, 1439, 1396, 1303, 1261, 1147, 1120, 746. ESI-HRMS: *m/z* [M + H] calcd for $C_{11}H_{13}N_5OS$: 264.0914; found: 264.0907.

7-Methyl-5-phenylperhydroimidazo[4,5-*e*]-1,2,4-triazin-3,6-dithione (1h)

Yellowish solid; yield 0.514 (46%); mp 216–218 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.05 (s, 3 H, Me), 5.32–5.38 (m, 2 H, CH), 5.97 (s, 1 H, N(1)H), 7.30 (d, *J* = 7.6 Hz, 2 H, *o*-PhH), 7.33 (t, *J* = 7.4 Hz, 1 H, *p*-PhH), 7.42 (t, *J* = 7.6 Hz, 2 H, *m*-PhH), 8.70 (s, 1 H, N(4)H), 9.65 (s, 1 H, N(2)H). ^{13}C NMR (75 MHz,

DMSO-d_6): δ = 31.1, 66.7, 73.8, 127.2, 128.6, 129.1, 138.2, 181.1, 186.3. IR: 3177, 2959, 1595, 1554, 1500, 1407, 1388, 1335, 1293, 1265, 1213, 1136, 1108, 698. Anal. Calcd for $C_{11}H_{13}N_5S_2$: C, 47.29; H, 4.69; N, 25.07; S, 22.95. Found: C, 47.32; H, 4.70; N, 25.05; S, 22.91.

(24) **Synthesis of *N*-{4,6-Disubstituted 5-Oxo-2-thioxo(2,5-dithioxo)hexahydroimidazo[4,5-*d*]imidazol-1(2*H*)-yl}formamides 4a–i; General Procedure**

To a solution (or suspension) of imidazotriazine **1** (2 mmol) in acetone (22.5 mL) was added 90% formic acid (7.5 mL). The resulting mixture was heated to 55 °C and stirred for 2 h. Then the reaction mixture was cooled to r.t. and allowed to stand for 72 h to attain complete precipitation. The precipitate of compound **4** was filtered, washed with MeOH, and dried.

Representative Analytical Data

***N*-{4,6-Dimethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]-imidazol-1(2*H*)-yl}formamide (4a)**

White solid; yield 0.321 g (70%); mp 231–233 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): 70:30 (*cis*/*trans*): δ = 2.71 (s, 3 H, NMe), 2.78 (s, 2.1 H, NMe, *cis*), 2.81 (s, 0.9 H, NMe, *trans*), 5.34–5.45 (m, 2 H, CHCH), 8.08 (d, *J* = 10.5 Hz, 0.3 H, HCO, *trans*), 8.12 (s, 0.7 H, HCO, *cis*), 9.93 (s, 0.7 H, NH, *cis*), 9.97 (d, *J* = 10.5 Hz, 0.3 H, NNH, *trans*), 10.04 (s, 0.3 H, NH, *trans*), 10.52 (s, 0.7 H, NNH, *cis*). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.08 (NMe, *trans*), 28.12 (NMe, *cis*), 28.9 (NMe, *cis*), 29.6 (NMe, *trans*), 68.1 (CH, *trans*), 68.3 (CH, *cis*), 75.2 (CH, *cis*), 76.3 (CH, *trans*), 157.3 (CO, *cis*), 157.4 (CO, *trans*), 159.9 (HNCO, *cis*), 167.5 (HNCO, *trans*), 183.4 (CS, *cis*), 184.4 (CS, *trans*). IR: 3258, 2944, 2891, 1703, 1680, 1520, 1486, 1419, 1253, 1220, 1047, 754. ESI-HRMS: *m/z* [M + H] calcd for $C_7H_{11}N_5O_2S$: 230.0706; found: 230.0700.

***N*-{4,6-Diethyl-5-oxo-2-thioxohexahydroimidazo[4,5-*d*]-imidazol-1(2*H*)-yl}formamide (4b)**

White solid; yield: 0.35 g (68%); mp 228–229 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): 70:30 (*cis*/*trans*): δ = 1.02–1.07 (m, 6 H, Me), 3.06–3.41 (m, 4 H, NCH_2), 5.45–5.58 (m, 2 H, CHCH), 8.06 (d, *J* = 10.3 Hz, 0.3 H, HCO, *trans*), 8.13 (s, 0.7 H, HCO, *cis*), 9.94 (d, *J* = 10.3 Hz, 0.3 H, NNH, *trans*), 9.95 (s, 0.7 H, NH, *cis*), 10.05 (s, 0.3 H, NH, *trans*), 10.56 (s, 0.7 H, NNH, *cis*). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.76 (Me, *trans*), 12.86 (Me, *cis*), 12.92 (Me), 36.0 (NCH_2), 36.6 (NCH_2, *cis*), 37.0 (NCH_2, *trans*), 66.5 (CH, *trans*), 66.6 (CH, *cis*), 73.2 (CH, *cis*), 74.2 (CH, *trans*), 156.8 (CO, *cis*), 157.0 (CO, *trans*), 160.2 (HNCO, *cis*), 167.8 (HNCO, *trans*), 183.7 (CS, *cis*), 184.6 (CS, *trans*). IR: 3200, 2988, 2973, 1709, 1677, 1539, 1501, 1470, 1436, 1252, 1229, 1068, 756. ESI-HRMS: *m/z* [M + H] calcd for $C_9H_{15}N_5O_2S$: 258.1019; found: 258.1021.