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New access to thioglycolurils by condensation of 4,5-dihydroxyimidazolidin-2-ones(thiones) with HSCN

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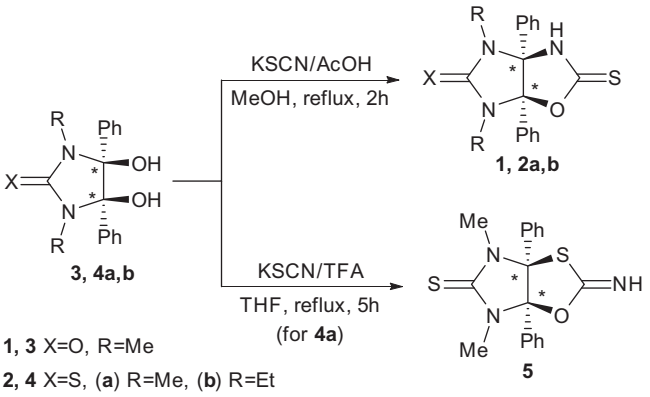
ABSTRACT

A general and highly effective protocol for the direct synthesis of mono- and dithioglycolurils containing various substituents at the 1,3-nitrogen atoms has been developed based on the condensation of easily accessible dihydroxyimidazolidin-2-ones with HSCN under mild reactions conditions.

Nitrogen- and sulfur-containing fused heterocycles have a broad range of biological activities and are attractive compounds for medicinal chemistry.[1] Bicyclic structures containing a C–C-bridgehead imidazolidin-2-one(thione) moiety fused with imidazolidin-2-one,[2] tetrahydrothiophene,[3] pyrrolidine[4] and tetrahydrofuran[5] motifs are important classes of compounds in pharmaceutical chemistry. Some of these compounds constitute the core structures of commercial drugs such as biotin (which show antimicrobial, antidiabetic and antibacterial activities).[3]

Our research group has significant experience in the synthesis of similar heterocyclic systems, including tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diones(glycolurils), of which the best known is the tranquilizer mebicar (1,3,4,6-tetramethylglycoluril).[2a] Analogues of mebicar are also important: albicar (1,4-diethyl-3,6-dimethylglycoluril) and bicaret (1,3,4,6-tetraethylglycoluril), have passed several preclinical and laboratory tests.[2d–g] Therefore, the development of new strategies for the synthesis of heterocyclic compounds incorporating the imidazolidin-2-one(thione) moiety fused with any nitrogen- or sulfur-containing heterocycles represent a challenging task for organic and medical chemistry.

Recently, we reported difficult to synthesize bicyclic heterocyclic structures **1** and **2**, in which the imidazolidin-2-one(thione) ring was fused with an oxazolidine ring.[6] These compounds were prepared by the reaction of either 4,5-dihydroxy-4,5-diphenylimidazolidin-2-one (4,5-Ph_2DHI) **3** or the analogous thiones (4,5-Ph_2-DHIT) **4a**,**b** with KSCN/AcOH in MeOH. The reaction of 4,5-Ph_2DHIT **4b** with KSCN/TFA in THF has been previously reported,[7] furnishing heterocyclic system **5**, in which the imidazolidine ring was fused with an oxathiazoline ring (Scheme 1).



Scheme 1. Reactions of 4,5-Ph_2DHI **3** and 4,5-Ph_2DHIT **4** with KSCN/H^+.

Unfortunately, both of these reactions afforded only a limited number of structures **1**, **2a**,**b** and **5** and therefore, it was of interest

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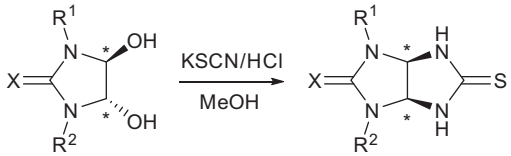
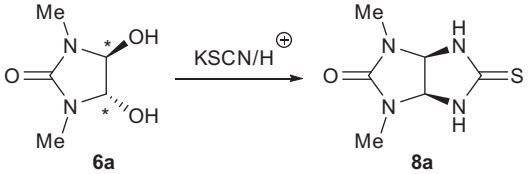


6a-g, 7a-k **8a-g, 9a-k**

6, 8 X = O
7, 9 X = S
R^1, R^2 = H, Alk, Ph

Scheme 2. Synthesis of monothioglycolurils **8** and dithioglycolurils **9**.

Table 1
Screening of conditions for the synthesis of thioglycoluril **8a**



6a **8a**

Entry	Solvent	Acid	*T* (°C)	Time (min)	KSCN equiv[a]	Yield (%)
1	H_2O	HCl	80	30	1.25	15
2	H_2O	HCl	80	30	2.25	27
3	H_2O	HCl	80	30	3.25	28
4	Me_2CO	HCl	Reflux	30	2.25	35
5	MeOH	HCl	Reflux	10	2.25	37
6	**MeOH**	**HCl**	**Reflux**	**30**	**2.25**	**78**
7	MeOH	HCl	Reflux	60	2.25	69
8	MeOH	AcOH	Reflux	30	2.25	34
9	MeOH	TFA	Reflux	30	2.25	40

[a] KSCN/acid molar ratio (1:1).

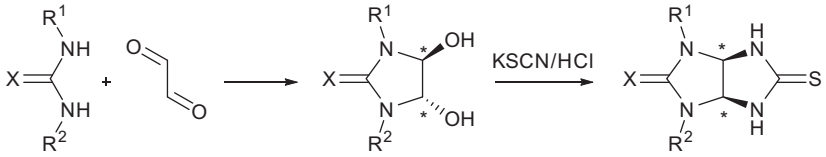
to extend the range of initial DHI and DHIT substrates used in the reaction with KSCN.

During the last decades, mono- and dithioglycolurils **8** and **9** have attracted the attention of many chemists. Dithioglycolurils **9** have found use as organocatalysts for the Boc protection of amines[8] or for the α-monobromination of 1,3-dicarbonyl compounds[9] while monothioglycolurils have been applied as building blocks for the synthesis of semithiobambusurils.[10] Both thioglycoluril types have been used in the template-directed crossed-Claisen condensation,[11] and as molecular clips.[12] However, known methods for their synthesis are limited,[11b,12–15] and recently developed methods generally consist of a large number of steps.[16,17] Herein, we present a new, effective synthetic route to access monothioglycolurils (5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-ones) **8** and dithioglycolurils (tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dithiones) **9** based on the reaction of DHI **6** and DHIT **7** with KSCN in MeOH (water, acetone) in the presence of hydrochloric acid (Scheme 2).

We began our investigation by optimizing the reaction conditions for the preparation of model thioglycoluril **8a** from the reaction of DHI **6a** with KSCN. A variety of acids, solvents, reactant molar ratios and temperatures were screened (Table 1).

In water, the yield of thioglycoluril **8a** increased (27–28%) as the KSCN/DHI **6a** molar ratio was increased (Table 1, entries 2, 3). The use of acetone as the solvent further increased the yield of **8a** to 35% (Table 1, entry 4). The replacement of water by MeOH was found to have the greatest influence on the yield of **8a**; therefore the reaction duration and nature of the acid used were next examined (Table 1, entries 5–9). The optimal conditions for the formation of thioglycoluril **8a** (78%) were determined as heating a solution of DHI **6a** (1.0 equiv) with KSCN (2.25 equiv) and HCl (2.25 equiv) in MeOH for 30 min (Table 1, entry 6).

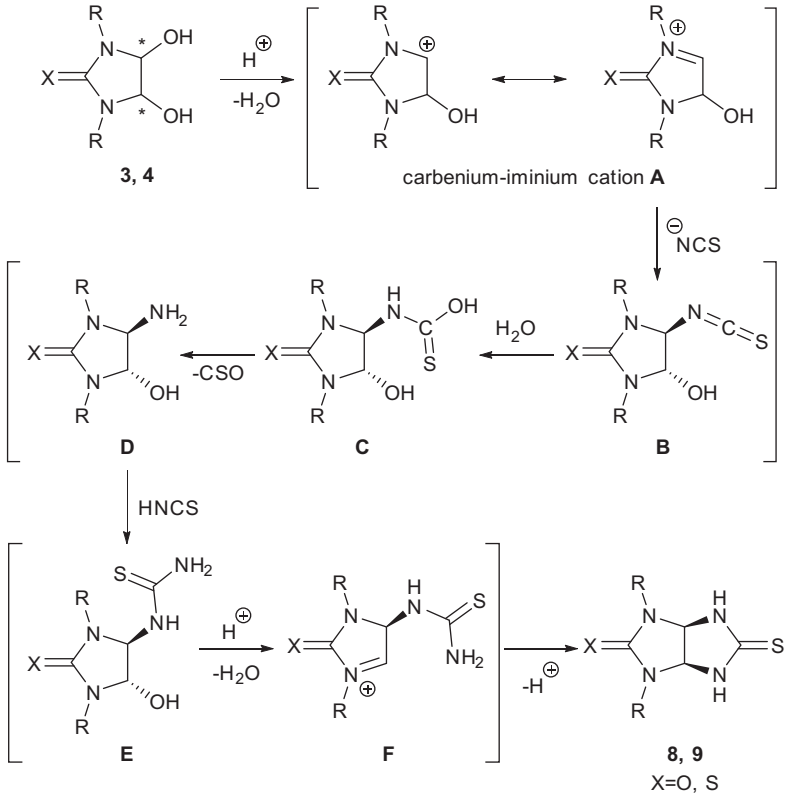
Table 2
Substrates scope for the synthesis of thioglycolurils **8** and **9**



10a-g, 11a-k **6a-g, 7a-k** **8a-g, 9a-k**

Entry	DHI or DHIT	R^1	R^2	X	Conditions	**8, 9**	Yield (%) (lit)
1	**6a**	Me	Me	O	i	**8a**	78 (71[15a])
2	**6b**	H	H	O	i	**8b**	68 (5–24[15a])
3	**6c**	Et	Et	O	i	**8c**	67
4	**6d**	Me	Ph	O	i	**8d**	42
5	**6e**	Et	Ph	O	i	**8e**	57
6	**6f**	Me	*t*-Bu	O	ii	**8f**	21[a]
7	**6g**	H	*c*-C_6H_{11}	O	ii	**8g**	74
8	**7a**	Me	Me	S	i	**9a**	89
9	**7b**	Et	Et	S	i	**9b**	78
10	**7c**	Me	Et	S	i	**9c**	81
11	**7d**	H	H	S	iii	**9d**	70
12	**7e**	Ph	Ph	S	iii	**9e**	82
13	**7f**	Me	Ph	S	iii	**9f**	69
14	**7g**	Et	Ph	S	iii	**9g**	64
15	**7h**	$(CH_2)_2OH$	Ph	S	iii	**9h**	53
16	**7i**	$(CH_2)_3OH$	Ph	S	iii	**9i**	67
17	**7j**	H	Me	S	iii	**9j**	92
18	**7k**	H	Ph	S	iii	**9k**	60

(i) KSCN (2.25 equiv), HCl (2.25 equiv), H_2O, 80 °C, 30 min.
(ii) KSCN (2.25 equiv), HCl (2.25 equiv), MeOH, reflux, 30 min.
(iii) KSCN (2.25 equiv), HCl (2.25 equiv), acetone, reflux, 30 min.
[a] The second product in this reaction was 1-(*tert*-butyl)-3-methyl-4-thioxoimidazolidin-2-one **12**.



Scheme 3. Plausible mechanism for the formation of thioglycolurils **8** and **9**.

In order to extend the reaction to the synthesis of a series of thioglycolurils **8** and **9**, the range of examined DHI **6a–g** and DHIT **7a–k** compounds was expanded. These compounds were easily accessible by the condensation of ureas and thioureas, respectively, with glyoxal in water with gentle heating.[10,18]

Having a wide range of DHI **6a–g** and DHIT **7a–k** compounds in hand, we investigated their reaction with KSCN/HCl under the optimized conditions (Table 2). It was established that these conditions were only suitable for DHI **6a–e** and DHIT **7a–c** (Table 2, entries 1–5, 8–10). Because DHI **6f** and **6g** were poorly soluble in MeOH, water was used as a replacement solvent (Table 2, entries 6, 7). Acetone was used instead of MeOH for the successful synthesis of dithioglycolurils **9d–k** from DHIT **7d–k** (Table 2, entries 11–18).

The structures of all novel compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. Single crystal X-Ray diffraction was performed for compounds **8a**,**c**, **9b**,**c**, **7a**,**c** and **12** [CCDC 1050192–1050198 contains supplementary crystallographic data for these compounds].

A plausible mechanism for the formation of thioglycolurils **8** or **9** is outlined in Scheme 3. Initially, formation of the carbenium–iminium cation **A**, followed by nucleophilic attack by the NCS anion furnishes adduct **B** with the OH and NCS groups located on different sides of the imidazolidinone ring. This *trans*-orientation of the OH and NCS groups prevents the intramolecular cyclization of intermediate **B** to give the imidazothiazole ring. Addition of water to the NCS group gives unstable hydroxycarbamothioic *O*-acid **C** which after elimination of the CSO fragment gives aminol **D**. Addition of HNCS to the NH_2 group of intermediate **D** generates the thiourea containing intermediate **E**. Finally, protonation of the OH group of intermediate **E** and subsequent elimination of H_2O forms cation **F** which undergoes intramolecular cyclization to furnish the desired thioglycolurils **8** or **9**.

Conclusion

In conclusion, we have developed a new, facile and efficient synthetic route to thioglycolurils using easily accessible reagents, DHI, DHIT, KSCN and HCl, proceeding under mild conditions.[19] This method proved to be suitable for the synthesis of both mono- and dithioglycolurils **8** and **9**, but it was especially effective for the synthesis of dithioglycolurils **9**, which were previously less accessible than thioglycolurils **8**. The advantages of this method are operational simplicity, step economy and the use of environmentally friendly reagents. The developed method provides a powerful tool for the synthesis of an extensive series of thioglycoluril derivatives that have previously been difficult to synthesize.

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Supplementary data

Supplementary data (experimental procedures, analytical and spectral data of all synthesized compounds, X-ray data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.071.

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19. *General procedure for the preparation of the thioglycolurils* ***8a–e*** *and* ***9a–k***. Hydrochloric acid (35.5%) (2 mL, 0.0225 mol) was added to a solution of 4,5-dihydroxyimidazolidin-2-one(thione) **6** or **7** (0.01 mol) and KSCN (2.19 g, 0.0225 mol) in MeOH (for **8a–e**, **9a–c**) (30 mL) or Me_2CO (for **9d–k**) (35 mL) at room temperature. The precipitate was filtered and washed with MeOH or Me_2CO, respectively. The filtrate was heated at reflux for 30 min with stirring. Then the reaction mixture was cooled and kept for 12–48 h at rt to furnish a precipitate. The precipitate was filtered and washed with MeOH or Me_2CO to give product **8a–e** or **9a–k**.
Synthesis of monothioglycoluril ***8f***. Hydrochloric acid (35.5%) (2 ml, 0.0225 mol) was added to a solution of 1-(*tert*-butyl)-4,5-dihydroxy-3-methylimidazolidin-2-one **6f** (1.88 g, 0.01 mol) and KSCN (2.19 g, 0.0225 mol) in H_2O (20 mL) at rt. The reaction mixture was stirred at 80 °C for 30 min and cooled. The white precipitate of 1-(*tert*-butyl)-3-methyl-4-thioxoimidazolidin-2-one **12** was filtered, and monothioglycoluril **8f** was precipitated from the filtrate after standing for 24 h at rt. Both precipitates were recrystallized from MeOH.
Synthesis of monothioglycoluril ***8g***. Hydrochloric acid (35.5%) (2 mL, 0.0225 mol) was added to a solution of 1-cyclohexyl-4,5-dihydroxyimidazolidin-2-one **6g** (2.00 g, 0.01 mol) and KSCN (2.19 g, 0.0225 mol) in H_2O (20 mL) at rt. The reaction mixture was stirred at 80 °C for 30 min, cooled, and kept for 12–48 h at rt to give a white precipitate of **8g**. The precipitate was filtered and washed with MeOH.