A Facile Preparation of Thioglycolurils from Glycolurils, and Regioselectivity in Thioglycoluril Template-Directed Crossed-Claisen Condensations

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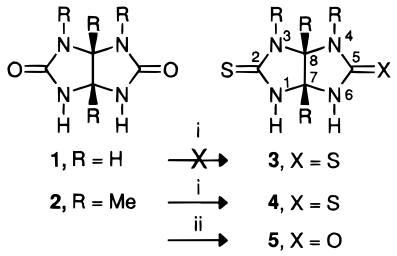
Mono- (**5**) and dithio (**4**) analogues of 3,4,7,8-tetramethylglycoluril (**2**) are readily prepared using Lawesson's reagent (1 equiv or excess, respectively). This novel application of Lawesson's reagent to glycolurils can be extended to *N*-acylglycolurils. Thus the *N*-acetyl and *N*-butanoyl derivatives of **2** are converted into the monoacyl-monothio analogues **8** and **9** in which thionation occurs at the least hindered urea carbonyl. Compared to the parent glycoluril **2**, the thio analogues are more readily acylated; initial acylation of **5** occurs exclusively on the NH site adjacent to sulfur to give **13**, while **4** is converted to either the monoacetyl (**11**) or diacetyl (**12**) derivative by acetic anhydride, depending on temperature. Unlike **2**, acylation of **4** can be accomplished with *tert*-butoxide as base and then acyl halide. Further acetylation of **11** gives **12**, while **8** gives the unsymmetrical diacetyl-monothioglycoluril **15** or acetyl butanoyl thioglycoluril **17**, and **9** gives the isomeric acetyl butanoyl thioglycoluril **16**. Derivative **12** undergoes a crossed Claisen-like condensation between the two acetyl groups to give acetoacetyldithioglycoluril (**18**), in a manner similar to the diacetyl derivative of the parent glycoluril, while **15** undergoes selective crossed-Claisen condensation, predominantly by deprotonation of the acetyl group adjacent to oxygen (2.2:1 ratio of **19**:**20**). In crossed-Claisen condensations, both isomers of acetylbutanoylmonothioglycoluril rearranged to 3-ketohexanoyl and 2-ethyl-3-ketobutanoyl thioglycolurils (**16** to **24** and **25**; **17** to **26** and **27**, respectively). When the selectivities for deprotonation of the acetyl moiety over the butanoyl moiety, and for deprotonation of the acyl group adjacent to oxygen over that adjacent to sulfur, reinforced each other, highly selective crossed-Claisen condensation was achieved (**26**:**27** 6:1). In contrast, when these two selectivities worked in opposition, reversal of the regiochemical outcome occurred (**24**:**25** 0.75:1). The results show that thionation provides a more sophisticated and selective template for development of intramolecular crossed-Claisen methodology using the glycoluril template-directed approach.

Introduction

There is extensive interest in the glycolurils,[1,2a] (e.g. **1**, **2**, Scheme 1), for example, industrially as bleaching activators,[2] as rigid frameworks for supramolecular structures,[3] and, in our laboratory, as templates for effecting efficient intramolecular crossed-Claisen condensations.[4] In the latter regard, we reasoned that replacement of oxygen by sulfur might facilitate the acylation of glycolurils, as well as having an effect on regioselectivity in the crossed-Claisen methodology, either or both of which would facilitate the use of this method in synthesis. However, in seeking a route to prepare sulfur analogues of glycolurils (e.g. **3**, **4**) it was apparent that these compounds have been relatively little explored.

Scheme 1[a]



[a] Toluene, heat, Lawesson's Reagent: (i) 3 equiv, or (ii) 1 equiv.

Condensation reactions of ureas and α-dicarbonyl compounds such as benzil or biacetyl have been extensively studied and generally proceed readily: initial cyclization produces the monocyclic dihydroxyimidazolidine which may be isolated under neutral conditions.[2a,5] Under acidic conditions this intermediate then condenses with another mole of urea to furnish the corresponding

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(1) The IUPAC name for glycoluril **2** is 1,2,5,8-tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione; we have chosen to use the trivial name and the standard numbering system for glycolurils in which the bridgehead carbons are numbered 7 and 8 (see Scheme 1) rather than the 3a,6a numbering system that has also been used; the latter derives from the alternative imidazo[4,5-*d*]imidazoline nomenclature for glycolurils. We have chosen to use a system where N-3 and N-4 are the two methylated nitrogen atoms throughout, rather than N-1 and N-6. For the monothio derivatives, the numbering system has been chosen such that the relative priorities of the two exocyclic nitrogen substituent(s) always determine which nitrogen atom has highest priority, even though this sometimes opposes the numbering system based on preference for the thiocarbonyl over the carbonyl group (e.g. Scheme 2). Only when both substituents are identical does the thiocarbonyl group take precedence over the carbonyl for this numbering scheme (e.g. Scheme 1).

(2) (a) Petersen, H. *Synthesis,* **1973**, 243. (b) Hofmann, J.; Just, G.; Moya, D.; Ostermann, S.; Pritzkow, W.; Visothea, M. P. *J. Prakt. Chem.* **1990**, *332*, 176. (c) Hofmann, J.; Just, G.; Pritzkow W.; Schmidt, H. *J. Prakt. Chem.* **1992**, *334*, 293.

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(4) (a) Sun, S.; Harrison, P. *Tetrahedron Lett.* **1992**, *33*, 7715. (b) Sun, S.; Harrison, P. *J. Chem. Soc., Chem. Commun.* **1994**, 2235. (c) Cow, C.; Harrison, P. *Can. J. Chem.* **1997**, *75*, 884.

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glycoluril.[2a,5,6] While this reaction may be compromised by competing processes, the yields of glycolurils are in general respectable, and a wide range of these interesting bicyclic structures has been prepared by this procedure.[2a] These side reactions include the formation of imidazole and oxazole derivatives,[7] and the interception of the dihydroxyimidazolidine intermediate through 1,2-migrations to furnish hydantoins,[5b,8] a process which also occurs readily in basic solution.[9] Other interesting adducts have also been isolated in this process.[6,7,10] Asymmetrically substituted glycolurils can be readily prepared by isolation of the dihydroxyimidazolidine, followed by treatment with a different urea.[2a,5a,c]

In contrast, condensations of thiourea and α-dicarbonyls often fail to generate the corresponding thioglycolurils. A variety of alternative products have been described in these reactions. Early reports[11] of the preparation of the parent thioglycoluril from thiourea and glyoxal have been corrected: the isomeric iminothiazolino[4,5-*d*]iminothiazoline was obtained.[12] Under alkaline conditions, Butler and co-workers showed that condensation of benzil with thiourea gave both the thioglycoluril and hydantoin.[13] However, the reaction was not general since both *N*-methylthiourea and *N,N′*-dimethylthiourea failed to yield glycolurils, preferring to give the hydantoin and the monocyclic dihydroxyimidazolethione, respectively. Von Dietz and Mayer studied the reaction of thiourea with a range of substituted benzils: thiohydantoins always dominated, while only two thioglycolurils were isolated in 12 and 21% yield.[14] Broan and Butler found that under acidic conditions the corresponding imidazolinethione or the disulfide derived therefrom is the major isolated product; they isolated a monothioglycoluril and proposed a mechanism for the unexpected loss of one thiourea-derived sulfur atom.[15] Further reaction of the imidazolinethione with ureas generates monothioglycolurils in respectable yields;[15,16] however, thioureas give variable results under the same conditions: some fail to react.[16] Nonetheless, the dithioglycoluril is presumably formed under these conditions as an intermediate in Nolte's synthesis of the thio analogue of a molecular clip.[17] The conversion of glycolurils to thioglycolurils using P_2S_5 was not successful in this case. The thio analogue of cucurbituril, a cyclic hexamer containing six glycoluril moieties, has also been prepared from dithioglycoluril.[18] Alternatively, thioglycolurils have been made from 2-aminocyclohexanone oxime and thiocyanate,[19] and by addition of isothiocyanatotrimethylsilane to 1,4-diaza-1,3-dienes;[20] however, these methods are unsuitable for preparation of **4** since it is unlikely that the desired substitution pattern would be obtained.

Herein, we describe a simple method for conversion of glycoluril **2** and several acyl derivatives to the corresponding mono- or dithio derivatives using Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide),[21] and compare the chemistry of these derivatives in the crossed-Claisen-like condensation with the corresponding oxygen analogue.[4]

Table 1. Yields and Selectivities for the Formation of Thioglycolurils

entry	starting material	temp (°C)	equiv of reagent	major product	minor product	% yield
1	**2**	reflux	1.0	**5**	**4**	83[a]
2	**2**	reflux	3.0	**4**	**5**	60[a]
3	**6**	60	1.3	**8**		47[b]
4	**6**	reflux	1.3	**10**	**8**	22[b]
5	**7**	60	1.2	**9**		74[b]

[a] Combined yield of major and minor products. [b] Yields are for the major products after purification by column chromatography.

Results

From the literature described above it was not practical to predict whether the condensation of *N*-methylthiourea with diacetyl would give the desired dithioglycoluril **4** since it is apparent that the reaction products are strongly dependent on substituent(s) on both the urea and α-dicarbonyl components, as well as on reaction conditions; indeed, most studies have focused on benzil and other aromatic α-dicarbonyls. In practice, a variety of acidic and basic conditions failed to yield any thioglycoluril. However, when 3,4,7,8-tetramethylglycoluril (**2**)[4,22] is heated with excess Lawesson's reagent[21] in toluene, the corresponding dithioglycoluril **4** is readily formed (Scheme 1, Table 1). Preliminary studies aimed at converting glycoluril (**1**) to the corresponding dithio derivative **3** under corresponding conditions have to date proved unsuccessful. Compound **2** with 1 equiv of Lawesson's reagent gives a mixture which contains predominantly monothio derivative **5**, along with **4** and unreacted **2**. These products are not readily separated at this stage; however, the mixture can be prepared in large quantities since the starting materials are readily available. Separation can be accomplished at a later stage (see below). All the spectral data, and comparison with literature values, as well as the X-ray structure of **12** (see below), and the transformations described below, support the structure shown, as opposed to the alternative iminothiazolidine ring systems which could result from **3** or **5** by ring opening and reclosing at sulfur.

Further, highly selective monothionation of the glycoluril system occurs when monoacylglycolurils **6** or **7**[4] are treated with Lawesson's reagent (Scheme 2, Table

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(18) Mock, W. L.; Manimaran, T.; Freeman, W. A.; Kuksuk, R. M.; Maggio, J. E.; Williams, D. H. *J. Org. Chem.* **1985**, *50*, 60.
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(20) Takahashi, M.; Miyadai, S. *Heterocycles* **1990**, *31*, 883.
(21) (a) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. For a review of applications of this reagent, see: (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
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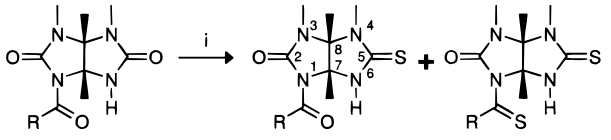
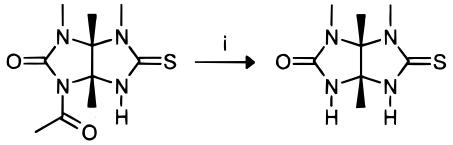
Scheme 2[a]



6 R = Me **8** **10**
7 R = $(CH_2)_2Me$ **9**

[a] (i) Lawesson's Reagent, toluene, heat.

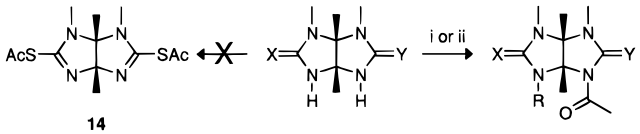
Scheme 3[a]



8 **5**

[a] (i) NaOEt, THF.

Scheme 4[a]



14

X = Y = O	**2**	i	R = H	**6**
X = Y = S	**4**	i or ii	R = H	**11**
X = Y = S	**4**	i	R = Ac	**12**
X = O, Y = S	**5**	i	R = H	**13**

[a] (i) Ac_2O, neat; (ii) KO-*tert*-Bu, THF, then Ac_2O.

Table 2. Yields and Selectivities for the Formation of Acylthioglycolurils

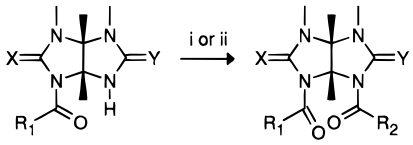
entry	starting material	temp (°C)	method	major product	% yield	note
1	**4**	rt	*a*	**11**	23	*f*
2	**4**	80	*a*	**11**	63	*f,g*
3	**4**	reflux	*a*	**12**	24	*f,h*
4	**11**	0	*b*	**12**	84	
5	**4**	rt	*c*	**11**	85	
6	**5**	reflux	*a*	**13**	36	
7	**8**	0	*b*	**15**	58	
8	**13**	0	*b*	**15**	23	
9	**9**	reflux	*a*	**16**	68	
10	**8**	reflux	*d*	**17**	69	
11	**8**	0	*e*	**17**	64	

[a] Ac_2O, neat. [b] *n*-BuLi, THF, 0 °C, then AcCl. [c] KO-*tert*-Bu, THF, then Ac_2O. [d] Butanoic anhydride, neat. [e] *n*-BuLi, THF, 0 °C, then butanoic anhydride. [f] Yields from glycoluril **2**. [g] **12** (11%) also isolated. [h] **11** (13%) also isolated.

1). Substitution of oxygen by sulfur occurs at the carbonyl group of the glycoluril which is remote from the acyl group to give **8** or **9**, respectively, as the exclusive products at 60 °C. At reflux, excess thionation proceeds at the carbonyl group of the acyl substituent rather than within the glycoluril itself, and product **10** can be readily separated from the reaction mixture.[23] Alcoholysis of **8** using sodium ethoxide in THF cleaves the acetyl group, furnishing pure samples of the monothio derivative **5** (Scheme 3).

Acylation of thioglycolurils by acetic anhydride proceeds readily (Scheme 4, Table 2). Whereas glycoluril **2** requires conditions of reflux to form the monoacetyl derivative **6**,[4,22] treatment of **4** with Ac_2O at room temperature gives the corresponding compound **11**, albeit in poor yield. As the temperature is raised, the yield increases along with the proportion of diacetyl derivative **12**, which predominates in the product mixture at 120 °C. This enhanced reactivity for *N*-acylation of the thiourea moiety compared to the urea is also reflected in the acetylation of **5**, which reacts selectively on the thiourea side of the molecule giving **13**, the complementary derivative to **8**, as well as by the observation that acylation of **4** can be accomplished by deprotonation using potassium *tert*-butoxide prior to addition of acetic anhydride. Acylation of **2** does not occur under corresponding conditions, but rather requires stronger bases such as *n*-BuLi or LDA.[4]

Scheme 5[a]



X = Y = S, **11**	i	**12,**	$R_1 = R_2 = Me$
X = O, Y = S, **8**	i	**15,**	$R_1 = R_2 = Me$
X = S, Y = O, **13**	i	**15,**	$R_1 = R_2 = Me$
X = O, Y = S, **9**	ii	**16,**	$R_1 = (CH_2)_2Me$, $R_2 = Me$
X = O, Y = S, **8**	ii	**17,**	$R_1 = Me$, $R_2 = (CH_2)_2Me$

[a] (i) *n*-BuLi, THF, 0 °C then AcCl; (ii) $(R_2CO)_2O$, heat.

In all cases, the location of the acyl groups was determined largely from the CH_3CO and/or N*H* NMR chemical shift(s) and comparison to those for the known oxygen analogues,[4] as well as to that for compound **12**, for which we have recently obtained a crystal structure by X-ray diffraction.[24] The N*H* signals were shown throughout the series of compounds described herein to occur at ca. 7.1−7.3 ppm when adjacent to the thiocarbonyl group, while at ca. 6.0−6.3 ppm when in the glycoluril urea functionality (Table 3). The CH_3CO groups also consistently exhibited a higher chemical shift when attached to the thiourea moiety (2.7−2.8 ppm) compared to the urea unit (2.4−2.5 ppm). In no case was there any evidence for formation of *S*-acylation products, e.g. **14** (Scheme 4), in contrast to alkylation which has been shown to occur readily on sulfur.[17] These results are similar to observations on thioamides, which also alkylate on sulfur but acylate on nitrogen.[25]

Introduction of a second acyl group onto the thioglycoluril framework was accomplished by two different methods (Scheme 5, Table 2). First, using only minor variations of the conditions used for the glycoluril **2**, treatment of **11** with *n*-BuLi and then acetyl chloride gives **12**, while both **8** and **13** give **15**. Alternatively, acylation may be accomplished using the appropriate anhydride at reflux: **9** and acetic anhydride gives **16**, while **8** and butanoic anhydride provides **17**. Again, the latter results reflect the enhanced reactivity of the thiourea NH sites compared to their urea congeners.

The crossed-Claisen-type condensation of *N*,*N*′-diacyl-mono- and dithioglycolurils under basic conditions using lithium *tert*-amylate (LiO-*tert*-Am) results in an efficient

(23) The reactivity of **10** in the template-directed condensation reaction is being investigated separately.

(24) A detailed description of this structure will be published elsewhere.

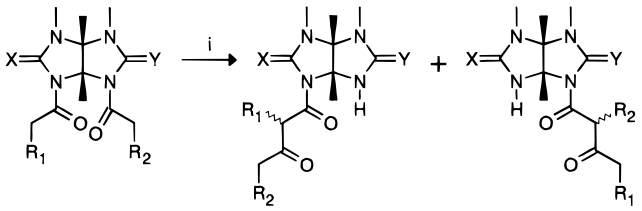
(25) Walter, W.; Voss, J. The Chemistry of Thioamides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Patai, S., Ser. Ed.; Wiley: New York, 1970, pp 383−475.

Table 3. Chemical Shifts of Selected Proton Resonances (ppm) Used To Locate Acyl Groups in Diacylthioglycolurils and Their Condensation Products[a]

entry	compound	δ(NH)[b]	side[c]	δ(CH_3CON)-1	side[c]	δ(CH_3CON)-2	side[c]
1	**6**	6.00	O	2.45	O	–	–
2	**11**	7.32	S	2.75	S	–	–
3	**12**	–	–	2.72	S	2.72	S
4	**8**	7.14	S	2.45	O	–	–
5	**13**	6.09	O	2.83	S	–	–
6	**15**	–	–	2.72	S	2.47	O
7	**16**	–	–	2.8; 2.8 (CH_2)[d]	O	2.67	S
8	**17**	–	–	2.8; 3.4 (CH_2)[d]	S	2.43	O
entry	compound	δ(NH)[b]	side[c]	δ(CH_2CON)-a[d]	side[c]	δ(CH_2CON)-b[d]	side[c]
9	**18**	7.26	S	5.05	S	3.90	S
10	**19**	7.08	S	4.34	O	3.52	O
11	**20**	6.12	O	4.98	S	4.00	S
12	**26**	7.10	S	4.36	O	3.47	O
13	**27**	6.09	O	5.54 (CH)[e]	S	–	–
14	**24**	7.11	S	4.38 (CH)[e]	O	–	–

[a] All chemical shifts were determined in $CDCl_3$. [b] The chemical shift of the NH protons was relatively independent of concentration. [c] "Side" refers to the side of the thioglycoluril on which the group is located, *i.e.* S indicates that the NH or acyl moiety lies on the thiourea side of the molecule, O shows this moiety resides on the urea side. [d] The two values refer to the chemical shifts of the two diastereotopic α-methylene protons. [e] Single proton α to carbonyl.

Scheme 6[a]



12	X = Y = S	**18**	$R_1 = R_2 = H$	**18**
15	X = O, Y = S	**19**	$R_1 = R_2 = H$	**20**
16	X = O, Y = S	**24**	R_1 = Et, R_2 = H	**25**
17	X = O, Y = S	**26**	R_1 = H, R_2 = Et	**27**
21	X = Y = O	**22**	R_1 = H, R_2 = Et	**23**

[a] (i) $LiOCMe_2Et$, THF, 0 °C, 20 min.

Table 4. Yields and Regioselectivities for the Claisen-like Condensation of Diacylthioglycolurils

entry	starting material	major product	minor product	ratio[a]	% yield(s)[b]
1	**12**	**18**	–	–	62
2	**15**	**19**	**20**	67:33	26; 20[c]
3	**16**	**24**	**25**	57:43	33; 15[c,d]
4	**17**	**26**	**27**	86:14	79; 19
5	**21**	**22**	**23**	81:19	88; ND[e]

[a] Determined by proton NMR of crude product. [b] Isolated yield. [c] Quoted as sum of two diastereomers. [d] The diastereomers were subsequently separable (see Experimental Section). [e] ND = not determined.

condensation to provide *N*-acylacyl derivatives in good to excellent yield (Scheme 6, Table 4). Compound **12** furnishes **18** within several minutes in THF at 0 °C; the reaction proceeded with no apparent qualitative differences to the process previously described for the oxygen analogue, i.e. the diacetyl derivative of **2**, although we have not yet been able to determine whether there are differences in rate between these two reactions. The diacetylmonothioglycoluril **15** was then subjected to identical conditions, yielding a mixture of **19** and **20**. Analysis of the crude mixture by proton NMR revealed that the ratio was ca. 2.2:1, favoring deprotonation of the acetyl group on the urea side, while the thiourea acetyl group prefers to act as the electrophilic member of the duet. Structural assignments for these isomeric products, as well as for the condensation products described below, were again based largely on the proton NMR chemical shifts for the NH proton, and for the diastereotopic methylene, or methine, protons of the acetoacetyl side chain, which exhibited an identical trend to the acetyl cases described above (Table 3).

Derivatives **16** and **17** were prepared to further investigate this regioselectivity. The acetylbutanoylglycoluril **21** was used as a control, and all three compounds were simultaneously subjected to lithium *tert*-amylate under identical conditions. Control **21** gave a mixture of **22** and **23** in a ratio of 81:19 by NMR, essentially identical to the ratio we have previously reported.[4a] Compound **16** gave a mixture of **24** and **25** while **17** furnished **26** and **27**. Each crude product was analyzed by proton NMR. Subsequently, isolated yields were determined following separation of the products. The results are given in Table 4.

Discussion

Although Lawesson's reagent has been used for thionation of a wide range of carbonyl groups,[21] the application of this method to glycolurils has not been reported to our knowledge. In one case, P_2S_5 failed to thionate a glycoluril.[17] Indeed, Lawesson showed that this reaction with mono- or disubstituted ureas gave a complex mixture of products, including isothiocyanates derived from cleavage of one of the C−N bonds.[26] A good yield of thioureas is obtained only when the urea is tetrasubstituted. However, the inaccessibility of thioglycolurils **4** and **5** by condensation of *N*-methylthiourea with diacetyl in our hands prompted us to investigate the thionation of the much more readily prepared glycolurils using this valuable methodology. In contrast to trisubstituted ureas,[26] Lawesson's reagent cleanly gives thioglycolurils from glycolurils in warm toluene. Although we have not investigated the mechanism of this reaction, it is possible that the reaction proceeds cleanly because any cleavage of either C−N bond within the glycoluril molecule, by analogy with the urea case, generates an aminoisothiocyanate which can be intercepted in an intramolecular manner to reclose the ring. Dithionation of the glycoluril proceeds readily with excess reagent,

(26) El-Barbary, A. A.; Lawesson, S. O. *Ind. J. Chem.* **1984**, *23B*, 655.

while 1 equiv generates a mixture which appears by NMR to contain more than the statistical amount of monothioglycoluril, suggesting that the second thionation is slower than the first. This effect may be due to the alteration of the reactivity of the remaining carbonyl group as a result of redistribution of electron density from one side of the molecule to the other within the network of interacting nitrogen atoms: decreased electron density at the thiocarbonyl carbon (C-2) compared to the urea carbonyl carbon (C-5)[25] makes N-1 and N-3 more electron deficient in **5** than in **2**. Thus N-4 and N-6 push more electron density from the urea side of the molecule toward C-7 and C-8 in **5**, and hence less into the C=O group (C-5), therefore resulting in lower electron density on the carbonyl oxygen atom than in **2**. Hence lower reactivity of this oxygen toward the electrophilic phosphorus of Lawesson's reagent is expected. Nonetheless, neither ring can completely open during the reaction, since no imidothiazoline products resulting from reclosure of the ring at sulfur were detected. In the case of thionation of monoacylglycolurils, reaction proceeds most readily at the unsubstituted urea-type carbonyl group, then at the acyl carbonyl. Clearly in this case, the second, acyl-substituted urea carbonyl is completely unreactive, perhaps as a result of steric effects. Further investigation of this reaction is currently being undertaken to determine its suitability for thionation of more complex glycolurils and may offer a route to thio analogues of these interesting molecular architectures.

The preparation of the thioglycoluril analogue of the glycoluril **2** was undertaken in part to determine whether milder conditions could be used for the attachment of acyl groups to these systems. In the case of **2**, acylation requires either acyl anhydrides at reflux or a strong base such as *n*-BuLi followed by an acyl halide; in each case only monoacyl derivatives are formed and attachment of a second acyl moiety requires a further round of strong base and acyl halide. Both these steps proceed in yields which are acceptable but not quantitative (ca. 80%/step). In contrast, thioglycolurils may be acylated with anhydrides at or slightly above room temperature. At higher temperature, diacyl derivatives predominate for the dithioglycoluril; unsymmetrical diacylthioglycolurils such as **16** and **17** can be prepared in reasonable yield by performing the sequential acylations with two different anhydrides at increasing temperatures. Acylation of monothioglycoluril **5** proceeds exclusively at the thiourea NH site, demonstrating the higher reactivity of this moiety. The acylation with acyl anhydrides also proceeds using a much milder base (KO-*tert*-Bu). Together, these results reflect the lowering of the NH proton pK_a by several units,[25] resulting in a system that may be acylated under much milder conditions than the oxygen analogue. We are currently investigating the attachment of more complex acyl groups which have proved recalcitrant during attachment to the oxygen analogue.

The glycoluril **2** was originally conceived to develop new methodology for performing crossed-Claisen-like condensations between two attached acyl units. The base-induced condensation of unsymmetrical acetylacylglycolurils has been shown to proceed with modest regioselectivity (83:17 for the acetylbutanoyl derivative),[4a] favoring the linear product derived by deprotonation of the acetyl group over the branched product derived from deprotonation of the longer acyl moiety. This result is consistent with the observation of a primary isotope effect in acetyl[$^2H_3$]acetylglycoluril, showing significant C−H bond breaking in the transition state, and implying bimolecular deprotonation of the diacylglycoluril in the rate-limiting step. Thus, replacement of oxygen by sulfur in the glycoluril core might at first be expected to have little, if any, effect on the regioselectivity of the crossed-Claisen condensation. However, an alteration of the rate-limiting step in the condensation to involve acyl−nitrogen cleavage could affect selectivity since it is expected that the thiourea anion would be a better leaving group than the corresponding urea anion. Furthermore, chelation of the metal counterion of the base[27] plays a vital role in reactions of enolates derived from the analogous acyloxazolidinones of Evans,[28] and thio substitution in the glycoluril could dramatically alter this effect. Another factor to consider was the possibility of intramolecular proton transfer within the putative enolate intermediate. Since we thus could not predict with certainty the outcome of condensations on the thioglycoluril templates, we determined these selectivities experimentally.

Initially, the rearrangement of **12** to **18** was studied. The results show that this Claisen-like condensation on the sulfur analogue yields the desired acetoacetyl derivative, demonstrating the feasibility of this methodology. To test whether any inherent selectivity was conferred upon the reaction by the presence of sulfur, compound **15** was treated with LiO-*tert*-Am. The formation of **19** in preference to **20** shows that the condensation reaction proceeds with significant selectivity in favor of deprotonation at the acetyl group attached to the urea moiety followed by transfer of the acetyl group on the thiourea side. This result can be rationalized by any of the effects mentioned above. Further experiments are being undertaken to test these hypotheses. Nonetheless, from a practical standpoint, the results show that the monothioglycoluril template can, in principle, be used to enhance control of regioselectivity in a crossed-Claisen condensation.

The third condensation experiment pitted this inherent selectivity for deprotonation adjacent to oxygen against the selectivity for deprotonation of acetyl groups over longer-chain acyl moieties which we have previously observed.[4] When an acetyl group is attached to the urea side and a butanoyl group to the thiourea functionality, the two inherent selectivities work in concert. Thus **17** gives **26** with a slightly improved selectivity over **27** compared to the corresponding conversion of **21**, and in better yield. In contrast, the two innate selectivities conflict in **16**, and deprotonation of the butanoyl moiety dominates giving **24**, while the lower yield suggests that the reaction proceeds less readily. This reaction represents the first case in which the branched product predominates in this type of glycoluril-directed crossed-Claisen condensation. Further studies of this intriguing system including optimization of yields, functional group transformations on the β-ketoacylglycolurils prior to repetitive rounds of condensation, and applications to natural product synthesis[4c] are being investigated.

Conclusion

Thio derivatives of glycolurils, which are readily prepared using Lawesson's reagent, extend the crossed-

(27) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1. (c) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299.

(28) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

Claisen methodology initially developed on the glycoluril template. These derivatives are more readily acylated than the oxygen analogue, and should allow access to this method for acyl groups containing more complex functionality. The regioselectivity of the crossed-Claisen condensation can be manipulated using monothioglycolurils bearing two distinct acyl groups in either of the two possible orientations.

Experimental

General. General procedures and sources of material have been published elsewhere.[4c]

Preparation of 3,4,7,8-Tetramethyl-2,5-dithioglycoluril (4). A flask was charged with 3,4,7,8-tetramethylglycoluril (**2**) (2.03 g, 10.2 mmol) and toluene (20 mL). Three equivalents (12.4 g, 30.7 mmol) of Lawesson's reagent was added, and the mixture was heated at reflux for 16 h. The mixture was cooled, quenched with 5% HCl (10 mL), and then partitioned between methanol (50 mL) and hexanes (50 mL). The methanol fraction was evaporated, and the resulting residue was recrystallized from 95% ethanol. The product (1.39 g, 60%) was isolated as a white powder. Mp: >260 °C; ^{1}H NMR (CD_3OD, 200 MHz): δ 3.14 (s, 6H), 1.58 (s, 3H), 1.45 (s, 3H); IR ($CHCl_3$, cm^{-1}) 3439, 3154, 2931, 1490, 1442, 1289, 1085, 547; EI-MS *m/z* 230 [M^+], 142 (base).

3,4,7,8-Tetramethyl-2-thioglycoluril (5). Method 1: This compound was prepared from **2** (2.03 g, 10.3 mmol) as for **4**, except that 1.0 equiv of Lawesson's reagent was used. The product (1.83 g, 83%), a white powder, was obtained as a 2:1 mixture of **5** to **4** and was used in the next step without further purification.

Method 2: To **8** (100 mg, 0.41 mmol) in THF (5 mL) at rt was added sodium ethoxide (1.2 equiv, 0.5 mL of 1 M solution), and the mixture was stirred for 150 min. After quenching with water (30 mL), the mixture was extracted into $CHCl_3$ (3 × 10 mL), and the combined organic layers were washed with water (10 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered, and the solvent was removed to give 86 mg (98%) of **5** as a white powder. Mp: 222−225 °C dec; ^{1}H NMR (CD_3OD + tr $CDCl_3$, 500 MHz) δ 3.16 (s, 3H), 2.88 (s, 3H), 1.58 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (CD_3OD + tr $CDCl_3$, 125 MHz) δ 182.0, 160.0, 86.1, 77.1, 30.7, 26.8, 21.4, 15.9; IR ($CHCl_3$, cm^{-1}) 3439, 3020, 2400, 1686, 1503, 1215, 1082; EI-MS *m/z* 214 [M^+], 143, 126 (base); HRMS calcd for $C_8H_{14}N_4OS$: 214.0884, found: 214.0888; Anal. Calcd for $C_8H_{14}N_4OS$: C 44.80, H 6.58, N 26.14, found: C 44.85, H 6.50, N 24.67.

1-Acetyl-3,4,7,8-tetramethyl-5-thioglycoluril (8). Compound **6** (5.4 g, 23 mmol) was dissolved in toluene (100 mL), 1.3 equiv of Lawesson's reagent (11.9 g, 30 mmol) was added, and the mixture was heated at 60 °C for 16 h. The reaction was quenched with 5% HCl (10 mL), and the mixture was filtered. The yellow solid residue was dissolved in $CHCl_3$, and the product was purified by elution through a plug of silica gel with 70% EtOAc/hexanes. Concentration of the eluate gave **8** as a white solid (2.7 g, 47% yield): mp: 181−182 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.14 (s, 1H), 3.15 (s, 3H), 3.01 (s, 3H), 2.45 (s, 3H), 1.69 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.2, 170.9, 153.1, 82.7, 78.6, 30.3, 27.2, 24.7, 19.2, 15.8; IR ($CHCl_3$, cm^{-1}) 3440, 2994, 2946, 1738, 1665, 1490, 1329, 1284, 1098, 753; EI-MS *m/z* 256 [M^+], 168, 127, 58, 43 (base); HRMS calcd for $C_{10}H_{16}N_4O_2S$: 256.0944, found: 256.1000. Anal. Calcd for $C_{10}H_{16}N_4O_2S$: C 46.82, H 6.29, N 21.86, S 12.51. Found: C 46.95, H 6.31, N 21.51, S 12.10. When this reaction was repeated at reflux, 1-thioacetyl-3,4,7,8-tetramethyl-5-thioglycoluril (**10**) was obtained by recrystallization from $CHCl_3$/EtOAc and then flash column chromatography on silica gel (70% EtOAc/hexanes). The product (1.22 g, 22% yield) was isolated as a yellow solid. Mp: 173−174 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09 (s, 1H), 3.11 (s, 3H), 3.05 (s, 3H), 2.97 (s, 3H), 1.86 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 206.8, 180.9, 151.7, 82.8, 82.3, 31.1, 29.9, 27.5, 17.5, 15.4; IR ($CHCl_3$, cm^{-1}) 3384, 3020, 2988, 1746, 1417, 1331, 1216, 1079; EI-MS *m/z* 314 [M^+], 272, 184, 126, 43 (base). Anal. Calcd for $C_{10}H_{16}N_4OS_2$: C 44.06, H 5.92, N 20.57. Found: C 43.83, H 5.92, N 20.40.

1-Butanoyl-3,4,7,8-tetramethyl-5-thioglycoluril (9). Reaction of **7** (500 mg, 1.8 mmol), toluene (10 mL), and 1.2 equiv of Lawesson's reagent (0.9 g) gave **9** under the same conditions as for **8** except that the organic layers were washed with 0.5 N NaOH (2 × 20 mL) and then with water (20 mL) and brine (20 mL), and chromatography was not necessary. Compound **9** was obtained as a yellow foam (388 mg, 74%): mp: 124 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.17 (s, 1H), 3.12 (s, 3H), 2.98 (s, 3H), 2.79 (m, 2H), 1.66 (s, 3H), 1.57 (m, 2H), 1.54 (s, 3H), 0.89 (t, J = 7.34 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.0, 173.8, 152.4, 82.6, 78.5, 38.1, 30.2, 27.0, 19.2, 17.6, 15.7, 13.5; IR ($CHCl_3$, cm^{-1}) 3435, 3020, 2972, 1738, 1685, 1463, 1215, 1083; EI-MS *m/z* 284 [M^+], 196, 127 (base); HRMS calcd for $C_{12}H_{20}N_4O_2S$: 284.1307, found: 284.1296. Anal. Calcd for $C_{12}H_{20}N_4O_2S$: C 51.37, H 7.19, N 19.98. Found: C 51.50, H 7.31, N 19.72.

1-Acetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (11). Method 1: A mixture of **4** (200 mg, 0.87 mmol) and acetic anhydride (50 mL) was heated to 80 °C for 16 h. Excess acetic anhydride was removed on the rotary evaporator, and the resulting solid residue was purified by flash column chromatography on silica gel using $CHCl_3$ as the eluent. The product (R_f = 0.15) was collected, and the solvent was removed to obtain a white powder (135 mg, 63% from **2**).

Method 2: A mixture of **4** (100 mg, 0.43 mmol) and KO-*tert*-Bu (58 mg, 1.2 equiv) in THF (10 mL) was stirred for 30 min at rt, and then excess acetic anhydride was added. The mixture was stirred for an additional 2 h, and then the solvent was removed. Chromatography as for method 1 gave **11** (94 mg, 85%). Mp: 214−217 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32 (s, 1H), 3.27 (s, 3H), 3.10 (s, 3H), 2.75 (s, 3H), 1.68 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 180.8, 177.1, 172.2, 85.6, 82.9, 31.8, 29.9, 27.9, 18.8, 15.8; IR ($CHCl_3$, cm^{-1}) 3431, 3020, 1681, 1477, 1306, 1216, 1081, 928; EI-MS *m/z* 272 [M^+], 184, 142 (base). Anal. Calcd for $C_{10}H_{16}N_4OS_2$: C 44.06, H 5.92, N 20.57. Found: C 44.65, H 5.78, N 20.30.

1,6-Diacetyl-3,4,7,8-tetramethyl-2,5-dithioglycoluril (12). Method 1: To a solution of **11** (52 mg, 0.19 mmol) in THF (10 mL) at 0 °C was added *n*-BuLi (1.1 equiv, 137 μL of 1.4 M solution), and the mixture was stirred for 10 min. Acetyl chloride (1.2 equiv, 16 μL) was added and stirring continued for 2 h. The reaction was then quenched with $NaHSO_4$ (2 mL of 1 M), and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The organic extracts were washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product (50.4 mg, 84%) was isolated as a white powder after flash column chromatography on silica gel in 70% EtOAc/hexanes.

Method 2: Using method 1 for preparation of **11**, **4** (504.9 mg, 2.36 mmol) gave **12** (158 mg, 24%) as a white powder after chromatography as above. Mp: 172−178 °C dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.22 (s, 6H), 2.72 (s, 6H), 1.86 (s, 3H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 172.8, 87.0, 85.2, 31.2, 29.0, 18.7, 15.1; EI-MS *m/z* 314 [M^+], 273, 184, 142 (base); HRMS calcd for $C_{12}H_{18}N_4O_2S_2$: 314.0871, found: 314.0870. Anal. Calcd for $C_{12}H_{18}N_4O_2S_2$: C 45.80, H 5.77, N 17.82. Found: C 46.13, H 5.87, N 17.87.

1-Acetyl-3,4,7,8-tetramethyl-2-thioglycoluril (13). Using method 1 for the preparation of compound **11**, **5** (505 mg, 2.4 mmol) and acetic anhydride gave **13** as a white powder (199 mg, 36% from **2**) after flash column chromatography using 50% EtOAc/hexanes. Mp: 145−147 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.09 (s, 1H), 3.29 (s, 3H), 2.83 (s, 3H), 2.78 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H); IR ($CHCl_3$, cm^{-1}) 3439, 3019, 1718, 1682, 1485, 1379, 1296, 1215, 1107; EI-MS *m/z* 256 [M^+], 126 (base). Anal. Calcd for $C_{10}H_{16}N_4O_2S$: C 46.82, H 6.29, N 21.55. Found: C 47.27, H 6.32, N 21.55.

1,6-Diacetyl-3,4,7,8-tetramethyl-2-thioglycoluril (15). Method 1: Using method 1 for preparation of **12**, **13** (60 mg, 0.23 mmol) and acetyl chloride (1.2 equiv, 20 μL) gave **15** as a white powder after flash column chromatography on silica gel in $CHCl_3$ (15.8 mg, 23%).

Method 2: A similar procedure was used to convert **8** (75 mg, 0.29 mmol) and acetyl chloride (1.2 equiv, 25 μL) to **15**

(51 mg, 58%). Mp: 177−180 °C dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.20 (s, 3H), 2.98 (s, 3H), 2.72 (s, 3H), 2.47 (s, 3H), 1.89 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 173.3, 170.6, 152.7, 83.3, 81.9, 31.1, 29.4, 26.9, 25.6, 19.0, 14.9; EI-MS *m/z* 298 [M^+], 257, 168, 126 (base); HRMS calcd for $C_{12}H_{18}N_4O_3S$: 298.1090, found: 298.1099.

1-Acetyl-6-butanoyl-3,4,7,8-tetramethyl-2-thioglycoluril (16). Compound **9** (300 mg, 1.1 mmol) and acetic anhydride gave **16** (233 mg, 68%) along with unreacted **9** (18%) after workup as for **11** (method 1) and flash column chromatography on silica gel with 70% EtOAc/hexanes as eluent. Mp: 133−135 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.18 (s, 3H), 2.97 (s, 3H), 2.82 (app quintet, J = 7.2 Hz, 2H), 2.67 (s, 3H), 1.86 (s, 3H), 1.63 (app. q, J = 7.3 Hz, 2H), 1.50 (s, 3H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.2, 173.6, 173.3, 152.5, 83.2, 82.0, 39.0, 31.0, 29.4, 26.9, 19.0, 17.7, 14.9, 13.4; IR ($CHCl_3$, cm^{-1}) 3020, 2972, 1738, 1698, 1475, 1324, 1215, 1094, 1024, 928; EI-MS *m/z* 326 [M^+], 285, 196, 127 (base); HRMS calcd for $C_{14}H_{22}N_4O_3S$: 326.1413, found 326.1423. Anal. Calcd for $C_{14}H_{22}N_4O_3S$: C 51.47, H 6.79, N 17.16. Found: C 51.37, H 7.00, N 16.90.

1-Butanoyl-6-acetyl-3,4,7,8-tetramethyl-2-thioglycoluril (17). Method 1: Treatment of **8** (100 mg, 0.39 mmol) in THF (20 mL) at 0 °C with *n*-BuLi (1.1 equiv, 268 μL of 1.5 M) for 30 min, followed by butyric anhydride (1.2 equiv, 76 μL) with stirring for 2 h, and then workup as for **12** (method 1) gave **17** (81.3 mg, 64%) as a white powder after flash column chromatography (50% EtOAc/hexanes), along with unreacted **8** (18%) and the bis-butanoyl adduct (18%).

Method 2: Reaction of **8** (125 mg, 0.48 mmol) and butyric anhydride (5 mL) gave **17** (110 mg, 69%) using the procedure for **11** (method 1). Mp: 114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.43 (dq, J = 17.0, 6.8 Hz, 1H), 3.17 (s, 3H), 2.94 (s, 3H), 2.78 (dq, J = 16.9, 6.8 Hz, 1H), 2.43 (s, 3H), 1.86 (s, 3H), 1.69 (app. septet, J = 7.4 Hz, 2H), 1.49 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 178.3, 176.5, 170.6, 152.5, 83.4, 81.7, 42.6, 31.1, 26.8, 25.7, 19.0, 18.2, 15.0, 13.5; IR ($CHCl_3$, cm^{-1}) 3020, 2971, 1740, 1695, 1476, 1403, 1330, 1215; EI-MS *m/z* 326 [M^+], 257, 181, 168, 127, 84, 43 (base); HRMS calcd for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1400. Anal. Calcd for $C_{14}H_{22}N_4O_3S$: C 51.47, H 6.79, N 17.16; found: C 51.49, H 6.98, N 17.00.

1-(3′-Oxobutanoyl)-3,4,7,8-tetramethyl-2,5-dithioglycoluril (18). To a solution of **12** (20 mg, 64 μmol) in THF (5 mL) at 0 °C was added 2.5 mL (1.2 equiv) of a solution of LiO-*tert*-Am (30 μL of distilled *tert*-amyl alcohol was added to 5 mL of THF, *n*-BuLi (100 μL of 1.6 M solution) was added slowly at 0 °C, and the mixture was stirred for 30 min). The mixture was stirred for 2 h and then quenched with $NaHSO_4$ (1 mL of 1 M solution). The mixture was extracted into $CHCl_3$ (3 × 10 mL), and the combined organic layers were washed with water (10 mL) and then dried over anhydrous Na_2SO_4. The mixture was filtered, and the solvent was removed. Product **18** (12.4 mg, 62%) was separated from unreacted starting material (5 mg, 20%) by flash column chromatography on silica gel with 50% EtOAc/hexanes. Mp: >260 °C dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (s, 1H), 5.05 (d, J = 16.8 Hz, 1H), 3.90 (d, J = 16.8 Hz, 1H), 3.27 (s, 3H), 3.14 (s, 3H), 2.24 (s, 3H), 1.76 (s, 3H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.7, 181.0, 177.6, 168.6, 85.8, 83.4, 53.9, 49.7, 31.9, 30.1, 18.7, 16.0; EI-MS *m/z* 230, 168, 142 (base); CI-MS (NH_3) *m/z* 315 [M + H]$^+$, 231 (base), 142, 81, 56.

1-(3′-Oxobutanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril (19) and 1-(3′-Oxobutanoyl)-3,4,7,8-tetramethyl-2-thioglycoluril (20). The procedure for preparation of **18** was used to convert **15** (15.5 mg, 52 μmol) to a mixture of **19** and **20**, which was separated by flash column chromatography on silica gel with EtOAc as eluent.

For **19**: yield 4.0 mg, 26%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.08 (s, 1 H), 4.34 (d, J = 16.4 Hz, 1H), 3.52 (d, J = 16.5 Hz, 1H), 3.16 (s, 3H), 2.98 (s, 3H), 2.23 (s, 3H), 1.76 (s, 3H), 1.58 (s, 3H). For **20**: yield 2.95 mg, 20%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.12 (s, 1H), 4.98 (d, J = 16.9 Hz, 1H), 4.00 (d, J = 16.7 Hz, 1H), 3.26 (s, 3H), 2.84 (s, 3H), 2.24 (s, 3H), 1.73 (s, 3H), 1.58 (s, 3H).

1-(3′-Oxo-2′-ethylbutanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril (24) and 1-(3′-Oxohexanoyl)-3,4,7,8-tetramethyl-2-thioglycoluril (25). The procedure for preparation of **18** was used to convert **16** (51.5 mg, 0.16 mmol) to a mixture of **24** and **25**, which was separated by flash column chromatography on silica gel with 70% EtOAc/hexanes as eluent.

For **24**: yield 17.3 mg, 33%; less polar diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (s, 1H), 4.38 (dd, J = 3.8, 9.0 Hz, 1H), 3.15 (s, 3H), 2.96 (s, 3H), 2.27 (s, 3H), 1.97 (m, 2H), 1.74 (s, 3H), 1.55 (s, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.2, 181.3, 169.6, 152.7, 82.8, 79.1, 60.7, 30.3, 29.0, 27.1, 20.5, 18.6, 15.7, 12.6. More polar diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (s, 1H), 4.52 (dd, J = 2.8, 8.1 Hz, 1H), 3.17 (s, 3H), 3.00 (s, 3H), 2.17 (s, 3H), 1.88 (m, 2H), 1.71 (s, 3H), 1.58 (s, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.0, 181.4, 170.5, 152.5, 82.6, 78.9, 60.7, 30.4, 28.9, 27.2, 21.4, 19.4, 15.9, 12.3; EI-MS *m/z* 326 [M^+], 238, 126 (base); HRMS: calcd for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1419.

For **25**: yield 12.4 mg, 15%; mp: 126−127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.10 (s, 1H), 5.01 (d, J = 16.6 Hz, 1H), 3.94 (d, J = 16.6 Hz, 1H), 3.25 (s, 3H), 2.83 (s, 3H), 2.55 (dt, J = 17.2, 7.4 Hz, 1H), 2.45 (dt, J = 17.3, 7.2 Hz, 1H), 1.73 (s, 3H), 1.60 (app. q, J = 7.3 Hz, 2H), 1.57 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.1, 177.8, 169.1, 156.6, 81.9, 81.2, 53.2, 44.8, 31.8, 26.2, 19.2, 16.8, 16.0, 13.7; EI-MS *m/z* 326 [M^+], 214, 126 (base); HRMS: calcd for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1412. Anal. Calcd for $C_{14}H_{22}N_4O_3S$: C 51.47, H 6.79, N 17.16. Found: C 51.44, H 7.17, N 16.77.

1-(3′-Oxohexanoyl)-3,4,7,8-tetramethyl-5-thioglycoluril (26) and 1-(3′-Oxo-2′-ethylbutyryl)-3,4,7,8-tetramethyl-2-thioglycoluril (27). The procedure for preparation of **18** was used to convert **17** (55.4 mg, 0.17 mmol) to a mixture of **26** and **27**, which was separated by flash column chromatography on silica gel with 70% EtOAc/hexanes as eluent. For **26**: yield 42.3 mg, 79%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.10 (s, 1H), 4.36 (d, J = 16.4 Hz, 1H), 3.47 (d, J = 16.4 Hz, 1H), 3.15 (s, 3H), 2.98 (s, 3H), 2.47 (m, 2H), 1.76 (s, 3H), 1.57 (s, 3H), 1.54 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). For **27**: yield 11.4 mg, 19% of a 1.5:1 mixture of two diastereomers (a and b); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.09 (s, 1H, a), 6.08 (s, 1H, b), 5.78 (dd, J = 7.3, 5.7 Hz, 1H, b), 5.54 (dd, J = 9.2, 3.9 Hz, 1H, a), 3.28 (s, 3H, b), 3.25 (s, 3H, a), 2.86 (s, 3H, b), 2.84 (s, 3H, a), 2.28 (s, 3H, a), 2.18 (s, 3H, b), 1.94 (br m, 2H, a and b), 1.73 (s, 3H, a), 1.69 (s, 3H, b), 1.58 (s, 3H, b), 1.57 (s, 3H, a), 0.96 (m, 3H, a and b); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.3, 181.3, 169.6, 153.5, 81.8, 77.2, 62.2, 61.3, 31.8, 29.2, 26.3, 26.2, 21.9, 21.7, 19.7, 19.5, 19.1, 16.0, 15.9, 13.6, 12.5, 12.2; EI-MS *m/z* 326 [M^+], 284, 253, 226, 159, 126 (base); HRMS: calcd for $C_{14}H_{22}N_4O_3S$: 326.1413, found: 326.1439.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **5**, **8**, **9**, **11**, **12**, **15**−**18**, **24**, **26**, and **27**, and ^{1}H NMR spectra for **4**, **13**, **19**, and **20** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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