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Highly selective synthesis of tricyclic compounds from semithioglycoluril, formaldehyde and amines

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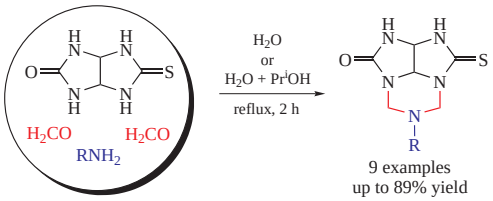
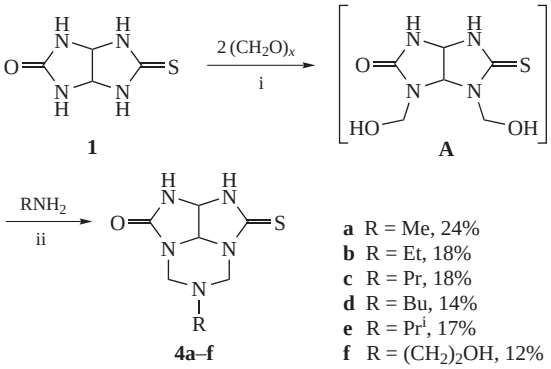
A highly selective one-pot synthesis of new 6-substituted 4-thioxohexahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]-inden-1(2*H*)-ones by cycloaminomethylation of semithioglycoluril with formaldehyde and amines is proposed. A mechanism for the process is suggested.



The chemical properties of glycolurils unsubstituted at nitrogen atoms have already been studied for over 100 years. These compounds were subjected to alkylation,[1,2] halogenation,[3,4] acylation,[5,6] nitration,[7,8] and cycloaminomethylation.[9,10] In particular, they were widely studied in reactions with formaldehyde.[8,9,11–13] Products of these reactions are used as halogenating agents,[4] bleaching activators,[6] high-energy compounds,[7,8] host agents,[12] molecular reactors[14] or polymer stabilizers,[15] and pharmacologically active compounds.[16] However, studies on the chemical properties of semithioglycolurils are in their infancy.[17–22] Semithioglycoluril, 5-thioxohexahydroimidazo[4,5-*d*]imidazol-2(1*H*)-one **1**, was obtained using the techniques reported previously.[23] We have recently developed a synthesis of tetracycles of type **2** from semithioglycoluril **1**, paraformaldehyde and amines and have shown that one of the obtained compounds could serve as an inhibitor of *Cryptococcus neoformans*.[24] Apart from that, one synthesis of hexacyclic compound **3** from semithioglycoluril, formaldehyde and ethylenediamine was reported.[25]

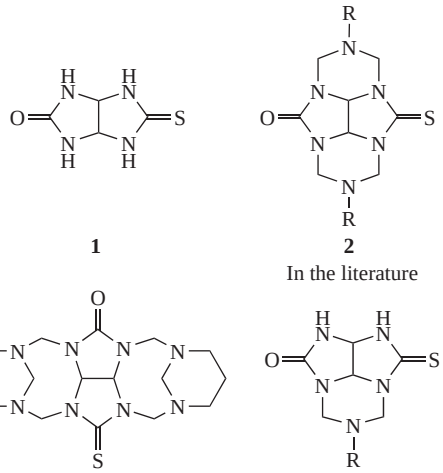
In this study, we were the first to obtain tricyclic compounds of type **4** by cycloaminomethylation of semithioglycoluril **1**. Scarce examples on obtaining tricyclic compounds by cycloaminomethylation of N-unsubstituted glycolurils or dithioglycoluril are available in literature,[12] however, they were not the main products, and data on reaction times or yields were often missing. In our experiments, we started from two-stage condensation of semithioglycoluril **1** with two equivalents of paraformaldehyde and one equivalent of various primary amines without isolation of possible intermediate **A** under optimum conditions reported for tetracycles of type **2** (ref. 24, Scheme 1). The yields of the target tricycles **4a–f** amounted to 12–24%. Apparently, cycloaminomethylation under these conditions occurred non-selectively. The ^{1}H NMR spectra of the reaction mixtures contained, besides the proton signals for tricycles **4a–f**, numerous signals from various N-hydroxymethylated semithioglycolurils and products of their reactions with amines, as well as signals of unreacted starting semithioglycoluril **1**.



1 **A** **4a–f**

a R = Me, 24%
b R = Et, 18%
c R = Pr, 18%
d R = Bu, 14%
e R = Pr^i, 17%
f R = $(CH_2)_2$OH, 12%

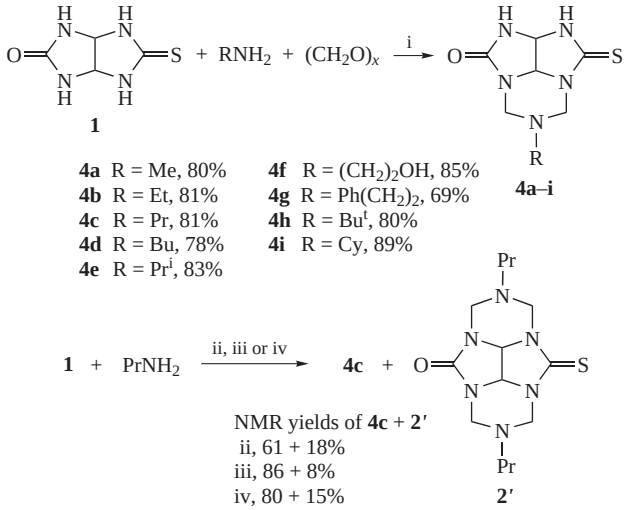
Scheme 1 *Reagents and conditions*: i, H_2O, Et_3N, reflux, 2 h; ii, 40 °C, 30 min (in the case of compound **4d**, Pr^{i}OH was added).



1 **2** In the literature

3 In the literature **4** This work

Therefore, we attempted the one-stage cycloaminomethylation of semithioglycoluril **1** with paraformaldehyde and primary amines, with *n*-propylamine having been chosen for the model reaction (Scheme 2). This reaction was studied under the conditions[25] for the preparation of polycycles of type **3**, namely, refluxing in MeOH for 12 h. In fact, by the end of the fifth hour of refluxing the ^{1}H NMR spectrum of the reaction mixture contained signals of three compounds, namely, the target tricycle **4c**, unreacted

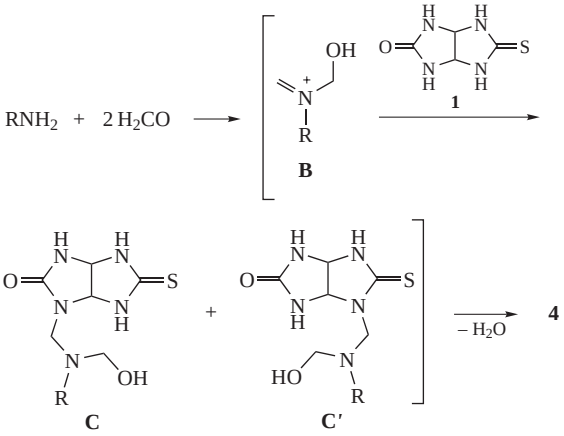


Scheme 2 *Reagents and conditions*: i, $(H_2CO)_x$ (2 equiv.), RNH_2 (1 equiv.), H_2O or H_2O + Pr^iOH, reflux, 2 h; ii, $(H_2CO)_x$ (2 equiv.), $PrNH_2$ (1 equiv.), MeOH, reflux, 5 h; iii, $(H_2CO)_x$ (2 equiv.), $PrNH_2$ (1 equiv.), H_2O, reflux, 2 h; iv, $(H_2CO)_x$ (2 equiv.), $PrNH_2$ (1.1 equiv.), H_2O, reflux, 2 h.

semithioglycoluril **1** and tetracycle **2′**. The ratio of these products was determined from the proton signals of CH–CH groups (Figure 1). The conversion of semithioglycoluril **1** to tricycle **4c** and tetracycle **2′** was 61 and 18%, respectively, whereas 21% of semithioglycoluril **1** remained unchanged and this ratio stalled during further driving the reaction. This result may be explained by the poor solubility of semithioglycoluril **1** in MeOH. When MeOH was replaced with H_2O, in 2 h the conversion of semithioglycoluril **1** to tricycle **4c** was 86% and that to tetracycle **2′** was 8%, which indicated the improved selectivity towards tricyclic product (the isolated yield of tricycle **4c** was 81%). To increase the conversion of semithioglycoluril **1** to tricycle **4c**, we attempted to slightly raise the amounts of paraformaldehyde and amine to 2.2 and 1.1 equiv., respectively. In this case, the reaction mixture contained 5% of compound **1**, 80% of tricycle **4c** and 15% of tetracycle **2′**. Thus, the best results were achieved using the reactant ratio $\mathbf{1}:(CH_2O)_x:PrNH_2 = 1:2:1$.

The procedure that we developed was used to synthesize a series of tricycles **4** (see Scheme 2).† For compounds **4a**,**b**,**e**,**f**, the reactions were performed in H_2O. In the case of the synthesis of tricycles **4d**,**g**–**i**, Pr^iOH was added to dissolve the corresponding starting amines. The target tricycles **4a**–**i** were obtained in high yields (69–89%). Their structures were confirmed by ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry.

The high selectivity of the reactions studied can be explained by the tentative mechanism of tricycle formation (Scheme 3). Taking into account that the reactivity of amines[26] is higher than that of semithioglycoluril **1**,[24] we assume that amine would first react with two equivalents of formaldehyde to give iminium intermediate **B**, whose aminomethylation with semithioglycoluril **1** affords intermediates **C** and **C′**. Their final cyclization leads to the ultimate tricycles **4**.



Scheme 3

In summary, one-pot multicomponent condensation of N-unsubstituted semithioglycoluril with formaldehyde and amines gives selectively new tricyclic compounds, 6-substituted 4-thioxohexahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]inden-1(2*H*)-ones. The compounds obtained seem promising for biological studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.028.

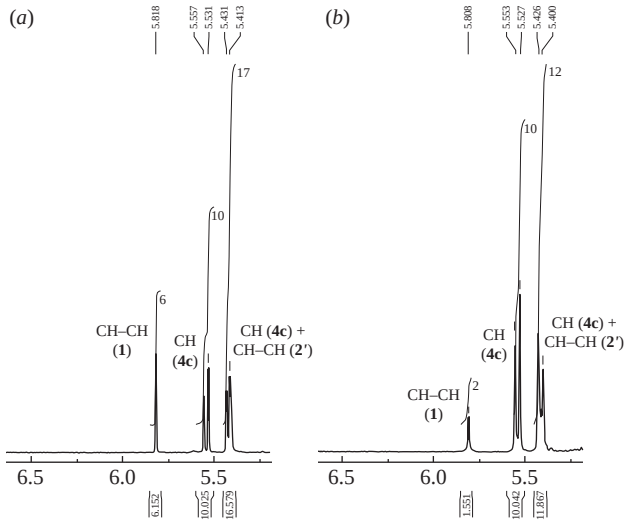

Figure 1 A fragment of ^1H NMR spectra of the reaction mixture upon condensation of compounds **1** with 2 equiv. paraformaldehyde and 1 equiv. propylamine (*a*) after 9 h refluxing in MeOH and (*b*) after 2 h refluxing in H_2O.

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† *6-Methyl-4-thioxohexahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]-inden-1(2*H*)-one* **4a**. Beige powder, yield 80%, mp 234–236 °C (H_2O). ^1H NMR, δ: 2.13 (s, 3H, Me), 4.22 (d, 2H, C^7H_{ax}, ^2J 13.4 Hz), 4.35–4.44 (m, 2H, C^5H_{ax} + C^7H_{eq}), 4.95 (d, 1H, C^5H_{eq}, ^2J 13.1 Hz), 5.45 (d, 1H, $C^{2a}H$, ^3J 7.8 Hz), 5.55 (d, 1H, $C^{7b}H$, ^3J 7.8 Hz), 8.05 (s, 1H, N^2H), 9.54 (s, 1H, N^3H). ^{13}C NMR, δ: 38.10 (Me), 60.92 (C^7H_2), 63.38 (C^5H_2), 63.58 ($C^{2a}H$), 70.48 ($C^{7b}H$), 159.19 (C=O), 182.02 (C=S). HRMS, *m*/*z*: 214.0761 $[M+H]^+$ (calc. for $C_7H_{11}N_5OS+H$, *m*/*z*: 214.0757).

*6-Ethyl-4-thioxohexahydro-5*H*-2,3,4a,6,7a-pentaazacyclopenta[*cd*]-inden-1(2*H*)-one* **4b**. White powder, yield 81%, mp 209–211 °C (H_2O). ^1H NMR, δ: 1.01 (t, 3H, Me), 2.28–2.45 (m, 2H, CH_2), 4.21 (d, 1H, C^7H_{ax}, ^2J 13.8 Hz), 4.41 (d, 1H, C^5H_{ax}, ^2J 13.4 Hz), 4.52 (d, 1H, C^7H_{eq}, ^2J 13.8 Hz), 5.09 (d, 1H, C^5H_{eq}, ^2J 13.4 Hz), 5.42 (d, 1H, $C^{2a}H$, ^3J 7.7 Hz), 5.55 (d, 1H, $C^{7b}H$, ^3J 7.7 Hz), 8.02 (s, 1H, N^2H), 9.50 (s, 1H, N^3H). ^{13}C NMR, δ: 12.92 (Me), 42.95 (CH_2Me), 58.87 (C^7H_2), 60.80 (C^5H_2), 63.67 ($C^{2a}H$), 70.76 ($C^{7b}H$), 159.01 (C=O), 181.69 (C=S). HRMS, *m*/*z*: 228.0916 $[M+H]^+$ (calc. for $C_8H_{13}N_5OS+H$, *m*/*z*: 228.0914).

For characteristics of compounds **4c**–**i**, see Online Supplementary Materials.

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