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Mendeleev Commun., 2019, **29**, 94–95

Mendeleev Communications

A first synthesis of 8- and 8,10-substituted barbiturils and their thio analogues

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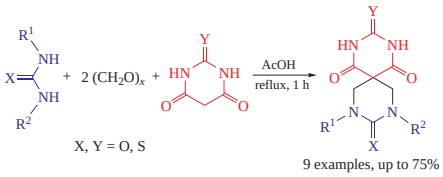
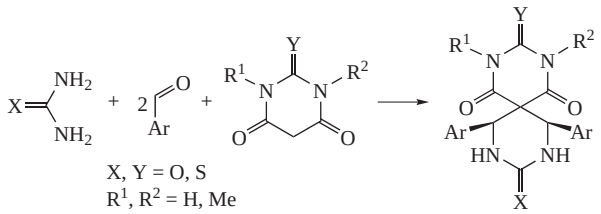
DOI: 10.1016/j.mencom.2019.01.032

Multicomponent condensations of alkyl(thio)ureas, formaldehyde and (thio)barbituric acids afford new spiro heterocyclic compounds, *viz.*, 8- and 8,10-substituted 2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraones (barbiturils) and their thio analogues.

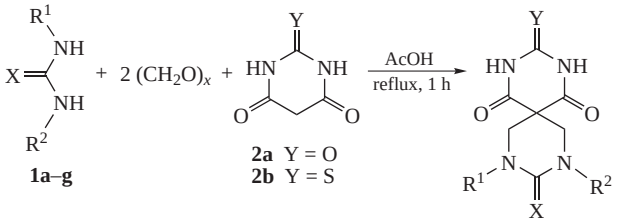


Methods for synthesizing annulated bicyclic bisureas and their thio analogues are continuously developed.[1] Two main groups of compounds can be distinguished in the series of cyclic bisureas: glycolurils and propanediureas. Glycolurils and their analogues manifest antibacterial, nootropic, neurotropic activites as well as gelling properties, are used as explosive compounds and starting materials for obtaining various polyheterocyclic compounds.[1(*a*)–(*f*)] Propanediureas are the building blocks for the preparation of molecular clips and cucurbituril analogues.[1(*g*)–(*j*)] However, spiro-linked bicyclic bisureas and especially their thio analogues have been less studied. Substituted 2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraones (barbiturils) and their thio analogues are of special interest since the urea fragment in these compounds is included into pharmacophoric barbituric acid moiety. A series of 2,4-disubstituted 7,11-diarylbarbiturils and their thio analogues have been studied to date. They were synthesized by three-component condensation of (thio)urea, aromatic aldehydes, and barbituric acids (Scheme 1).[2–12] The reactions were performed under reflux in various solvents,[2–4] under solvent-free conditions,[3,5–12] either without[3,8,10] or with catalysts[2,3,5–7,9–12] as well as under microwave[7,9,10,12] or ultrasonic irradiation.[3]



Scheme 1

Here, we report on a synthesis of new 8-substituted and 8,10-disubstituted barbiturils and their thio analogues using the previously unexplored condensations of 1-mono- and 1,3-disubstituted (thio)ureas, paraformaldehyde, and (thio)barbituric acids (Scheme 2). The reactions of alkylated ureas **1a**–**c** or (thio)ureas **1d**–**g**, paraformaldehyde and barbituric compounds **2a**,**b** in 1:2:1 molar ratio were carried out using a number of techniques. Three-component solvent-free procedure performed at 100–130 °C for 10–50 min gave complex mixtures (^{1}H NMR data). A similar result was obtained when microwave irradiation in a household oven at an average power output for 4 min was applied. In the further studies of this condensation, reflux conditions in glacial acetic acid for 1 h were used. In this way, barbiturils or their thio analogues **3** were obtained (see Scheme 2, Method 1).†



	X	R^1	R^2
a	O	Me	Me
b	O	Me	H
c	O	Et	Et
d	S	Me	Me
e	S	Et	Et
f	S	Me	Et
g	S	Me	H

Reactants	Product	Yield (%)
1a + **2a**	**3a**	27
1b + **2a**	**3b**	61
1d + **2a**	**3c**	75
1e + **2a**	**3d**	24
1f + **2a**	**3e**	15
1a + **2b**	**3f**	33
1c + **2b**	**3g**	22
1d + **2b**	**3h**	18
1g + **2b**	**3i**	69

Scheme 2

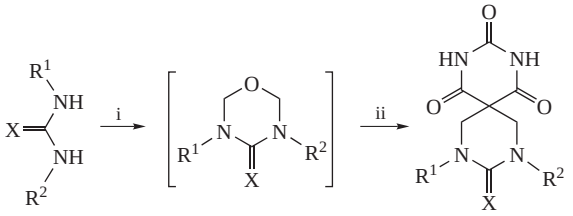
† ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.5 MHz) in DMSO-d_6. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II instrument using the electrospray ionization method (ESI).[14] Melting points were determined on a GALLENKAMP instrument (Sanyo). Ureas **1a**,**b**, thioureas **1d**,**e**,**g**, paraformaldehyde, barbituric (**2a**) and thiobarbituric (**2b**) acids were purchased from Acros. 1,3-Diethylurea **1c** and 1-ethyl-3-methylthiourea **1f** were obtained as reported.[15,16]

Compounds **3a**–**i**, *Method 1*, (*general procedure*). A suspension of urea **1a**–**c** (4.2 mmol) or thiourea **1d**–**g** (4.2 mmol), parafomaldehyde (0.25 g, 8.4 mmol) and barbituric **2a** or thiobataituric acid **2b** (4.2 mmol) in acetic acid (15 ml) was refluxed with stirring for 1 h, and then cooled to ~20 °C. The precipitate of compounds **3c**–**e**,**i** was filtered off and washed with acetic acid and water. For the separation of compounds **3a**,**b**,**f**–**h**, the mixture was evaporated to dryness and suspended in hot EtOH (10 ml) with stirring for 5 min, and the solid was filtered off. Compounds **3a**,**b**,**f**–**h** were crystallized from the filtrate and recrystallized from EtOH.

The reactions of ureas **1a–c** or thioureas **1d–g** with paraformaldehyde and barbituric acid **2a** or thiobarbituric acid **2b** gave the target barbiturils **3a**,**b** or thiobarbiturils **3c–i** in yields from 15 to 75% (see Scheme 2). Prolongation of these reactions did not improve the yields. HCl-assisted three-component version in water led to complex mixtures containing no target products **3**.

Furthermore, we studied whether this reaction could be performed in one-pot two-stage version with intermediate formation of urons (Scheme 3, Method 2). We found that the following reactants were suitable fot this procedure: urea **1a**, thioureas **1d–f**, and barbituric acid **2a**; the products **3a**,**c–e** were thus obtained. At the first stage, condensation of (thio)ureas **1a**,**d–f** with $(CH_2O)_x$ was performed (H_2O, concentrated hydrochloric acid, reflux, 2 h).[13] At the second stage, barbituric acid **2a** was reacted at 65 °C. The yields of products **3a** (55%) and **3e** (27%) were somewhat higher than those achieved in Method 1 (see Scheme 2). Thiobarbituric acid **2b** turned to be unsuitable in Method 2 even when the reaction mixture was boiled. Also, (thio)barbiturils **3** were not formed if AcOH was used instead of HCl/H_2O system.

Apparently, Method 1 (see Scheme 2) is more general than Method 2 (see Scheme 3) and allows one to obtain a series of new barbiturils and their thio analogues. However, Method 2 is preferrable for the preparation of compounds **3a** and **3e**.



1a,**d–f** Urons **3a**,**c–e**

1a, **3a** X = O, $R^1 = R^2$ = Me (55%)
1d, **3c** X = S, $R^1 = R^2$ = Me (75%)
1e, **3d** X = S, $R^1 = R^2$ = Et (22%)
1f, **3e** X = S, R^1 = Me, R^2 = Et (27%)

Scheme 3 *Reagents and conditions*: i, $(CH_2O)_x$, H_2O, HCl, Δ, 2 h; ii, **2a**, 65 °C, 12 h.

8,10-Dimethyl-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone **3a**. White powder, yield 27% (Method 1), 55% (Method 2), mp 228–230 °C. ^{1}H NMR, δ: 2.75 (s, 6 H, 2 Me), 3.56 (s, 4 H, 2 CH_2), 11.28 (s, 2 H, 2 NH). ^{13}C NMR, δ: 35.21 (Me), 49.52 (C), 51.97 (CH_2), 150.22 (C^3=O), 156.11 (C^9=O), 169.81 (C^1=O + C^5=O). HRMS, *m*/*z*: 241.0934 $[M+H]^+$ (calc. for $C_9H_{13}N_4O_4$, *m*/*z*: 241.0931).

8-Methyl-2,4,8,10-tetraazaspiro[5.5]undecane-1,3,5,9-tetraone **3b**. Light yellow powder, yield 61% (Method 1), mp 272–274 °C. ^{1}H NMR, δ: 2.75 (s, 3 H, Me), 3.41 (d, 2 H, $C^{11}H_2$, ^3J 3.4 Hz), 3.54 (s, 2 H, C^7H_2), 6.50 (br. s, 1H, N^{10}H), 11.26 (s, 2 H, $N^2H + N^4H$). ^{13}C NMR, δ: 34.52 (Me), 46.26 (C^7H_2), 48.91 (C), 50.73 ($C^{11}H_2$), 150.29 (C^3=O), 155.55 (C^9=O), 169.86 (C^1=O + C^5=O). HRMS, *m*/*z*: 227.0785 $[M+H]^+$ (calc. for $C_8H_{11}N_4O_4$, *m*/*z*: 227.0775).

For more details, see Online Supplementary Materials.

In conclusion, a general method for synthesizing hitherto unknown (thio)barbiturils with a new substitution type has been developed. For this purpose three-component one-stage (Method 1) and two-stage one-pot (Method 2) procedures were elaborated, with their preference being dictated by the nature of certain reactants.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.032.

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Received: 3rd July 2018; Com. 18/5627