Multicomponent reactions of urea and its derivatives with CH_2O and H_2S in the synthesis of 1,3,5-thiadiazinane-4-(thi)ones and macroheterocycles

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Dedicated to Professor Usein M. Dzhemilev on the occasion of his 65th birthday

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Abstract

A convenient, efficient, and practical method for the synthesis of 1,3,5-thiadiazinan-4-(thi)ones via a multicomponent condensation of urea (or thiourea), formaldehyde and hydrogen sulfide in the presence of a four-fold molar excess of *n*-BuONa is described. It provides the novel acid- (H_2SO_4) and base- (*n*-BuONa)-promoted approach for the one-pot synthesis of the amidine containing macroheterocycles from guanidine and diphenylguanidine. X-ray powder diffraction analysis gave insight into the structure of the 4-methyl-sulfonyl-*2H*-1,3,5-thiadiazine hydriodide.

Keywords: Urea, guanidine, multicomponent reactions, 1,3,5-thiadiazinane, macroheterocycles, formaldehyde, hydrogen sulfide, X-ray diffraction powder analysis

Introduction

There are known methods of heterocyclization of (thio)urea and their derivatives to the amine or amide containing dithiazinanes,[1,2] thiadiazines,[3] pyrimidines,[4,5] thiazoles,[6] triazoles,[7] and pseudomacrocycles, having copper ion in the chain.[8]

Cyclic acid amides and cyclic peptides are used as antibiotics,[9] bactericides,[10] herbicides and insecticides,[11] as well as extractants, sorbents and analytical reagents.[12]

Recently we have demonstrated syntheses of macroheterocyclic compounds based on condensation of bi- and heterofunctional amines and amides with formaldehyde and H_2S.[13–18]

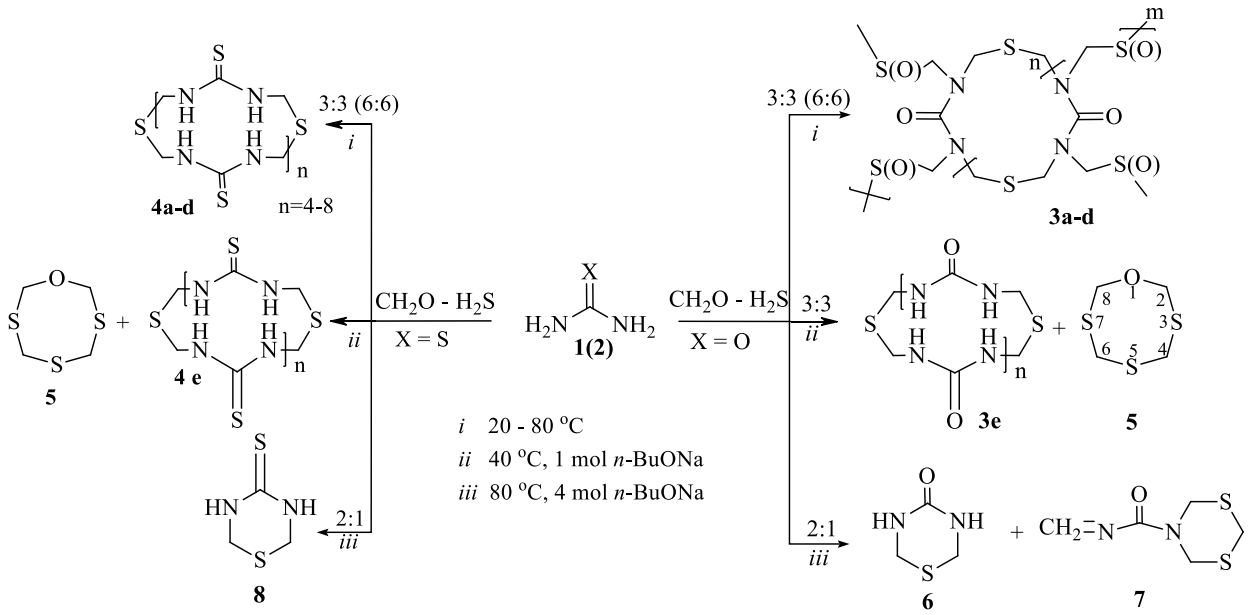
Meanwhile, there is no information about one-pot syntheses of macroheterocycles via multicomponent condensation of (thio)urea with different monomers.

In the present study, we have investigated multicomponent condensation of urea **1**, thiourea **2**, guanidine **8** and *N*,*N*-diphenylguanidine **12** with CH_2O and H_2S in purpose to synthesize 1,3,5-thiadiazinane-4-(thi)ones as well as sulfur- and nitrogen-containing macrocycles with carbamoyl fragments under various conditions (promoters, temperature, molar ratio and order of mixing of starting reagents).

Results and Discussion

It is known that polycondensation of urea **1** and CH_2O is widely used in the synthesis of urea-formaldehyde resins.[19] Condensation of urea **1** with CH_2O and H_2S in aqueous medium also occurs quite intensively with the formation of oxygen-, sulfur- and nitrogen-containing crystalline net polymers **3a–d**.

Thiourea **2** under similar conditions gives a rise to a mixture of cyclic oligomers **4a–d** (n = 4–8), in which the "n" value depends upon the temperature, order of mixing of starting reagents and degree of reaction medium dilution. Thus, at 20 ºC this reaction affords cyclic oligomers **4a** [$n_{average}$ ~ 4 (45%)], at 40 ºC **4b** [$n_{average}$ ~ 6 (21%)], whereas the increase in temperature up to 80 ºC provides the formation of oligomeres with $n_{average}$ ~ 8: **4c** (1:3:3 ratio) and **4d** (1:6:6 ratio). Their yields reach 38 and 35% respectively, depending upon the reagent mixing order. Dilution of the reaction medium reduces the size of the end oligomers.



Scheme 1

It is important to emphasize that the condensation of urea **1** with CH_2O and H_2S in the presence of *n*-BuONa promoter occurs with the formation of cyclic oligomers. For example, the multicomponent condensation with one or two moles of *n*-BuONa proceeds with the formation of cyclooligomers **3e** [$n_{average}$ ~ 15, M_{cr} 1890 ± 10 ($M_{theor.}$ 1878), mp 73–78 ºC] and 1,3,5,7-oxatrithiocane **5** (3:1 ratio) in 30% total yield. As for thiourea **2**, under these conditions, macroheterocycles **4e** [$n_{average}$ ~ 5, M_{cr} 749 ± 10 ($M_{teor.}$ 805), mp 100–105 ºC] and **5** have been formed in 54% total yield.

In the presence of a four-fold molar excess of *n*-BuONa promoter the condensation of urea **1** with a CH_2O and H_2S was found to proceed with the formation of 1,3,5-thiadiazinanyl-4-one **6** (n = 0, mp 215–218 ºC) and 5-(*N*-methylidenecarbomoyl)-1,3,5-dithiazinane **7** (6:1 ratio). In the case of thiourea **2** under similar conditions 1,3,5-thiadiazine-4-thione **8** (n = 0, mp 178–180 ºC) is the end product.

Note that the syntheses of 1,3,5- thiadiazines via the condensation of the acid amides and urea with isocyanates or α,α'-dichloroalkylamines are described in the literature.[3,20] However, in these reactions, only one NH_2 group of urea moiety is involved, as far as the imino form of acid amides or urea is involved in the cyclization reaction.

The NMR data confirmed the formation of macroheterocycles **3e** and **4a–d**. Thus, there are two types of signals, which correspond to the methylene and carbonyl (or thiocarbonyl) carbons. In the ^1H and ^{13}C NMR spectra the resonances at δ_H 4.33 and 4.35, δ_C 43.81–44.30 and δ_C 176.26 (158.12) ppm were assigned to -SCH_2N- and C=O(C=S) moiety, respectively. The broadened signals of NH group were observed at δ_H 6.81 and 8.63 ppm in the ^1H NMR spectra and at ν 3300 cm^{-1} in the IR spectrum.

The ^{13}C NMR spectrum of compounds **5** contains two signals at δ_C 63.65 and 31.82 ppm attributable to the C(2,8) and C(4,6) atoms respectively, which in turn, according to the HSQC experiment, correlate to the signals at δ_H 4.67 and 3.90 ppm (1:1 integrated intensity ratio) in the ^1H NMR spectrum. It is interesting to note that the methylene protons of the -OCH_2S- moiety magnetically nonequivalent, apparently, as a result of conformational features of the eight-membered heterocycle. The HMBC spectrum reveals the expected correlations between H(4) (δ_H 3.90) and C(2) (δ_C 63.65) as well as between H(2) (δ_H 4.67) and C(4) (δ_C 31.82), which testifies in favor of the proposed structure. Mass spectrum of **5** shows the molecular ion peak at *m/z* 169 $[M+H]^+$. As a result, product **5** was identified as 1,3,5,7-oxatrithiocane.

The structures of **6–8** were established by 1D and 2D NMR (Figure 1) techniques, high resolution MALDI TOF mass spectrometry, IR spectroscopy and elemental analysis data as well.

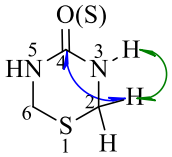
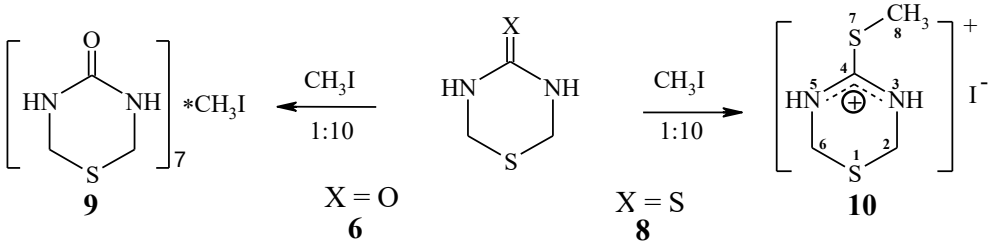


Figure 1. Selected correlations in COSY(↔) and HMBC(↔) spectra of **6** and **8**.

We have studied some transformations of **6** and **8** on the example of their reaction with methyl iodide. It proceeds ambiguously. Thus, the reaction of 1,3,5-thiadiazinane-4-one **6** with CH_3I (excess) provides the formation of the coordinated adduct **9** (mp 226–228 ºC). In comparison with **6** (mp 215–218 ºC) its NMR spectra (^1H, ^{13}C) has the same set of signals at a higher field. Elemental analysis of **9** (powder) has been shown the sulfur content of 24.28% (theor. 23.14%), the nitrogen content of 19.87% (theor. 20.24%), and the iodine content of 12.63% (theor.13.12%), that is consistent with the empirical formula $(C_3H_6N_2SO)_7 \cdot CH_3I$.

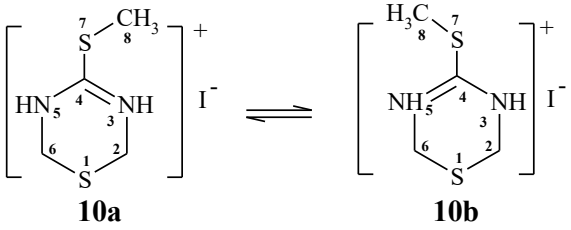
We found that the interaction between 1,3,5-thiadiazinane-4-thione **8** and CH_3I is accompanied by *S*-alkylation of *iso*thiourea moiety to form cyclic S-methyl*iso*uronium salt **10** (Scheme 2). There are known similar S-alkylations of cyclic thioamides and thiohydrazides with methyl iodide.[21]



Scheme 2

The structure of **10** is proved by ^1H, ^{13}C, and 2D NMR spectroscopy, X-ray powder diffraction, high resolution MALDI TOF mass spectrometry as well as IR spectroscopy and elemental analysis data.

The HMBC experiments have shown that the sp^2-hybridized C(4) atom interacts both with the methyl protons at C(8) and the methylene protons in positions 2 and 6. In the ^{13}C NMR spectra of compound **10** the methylene protons and the C(2) and C(6) atoms are magnetically equivalent (δ_H 4.62, δ_C 43.66 ppm), that is why we have assumed two resonance structures **10a** and **10b** in solution (Scheme 3).



Scheme 3

Similar dynamic isomerism in solutions for the cyclic derivatives of *iso*thiourea have been described in the literature.[22]

The structure of **10** in solid was confirmed by Rietveld refinement of corresponding PXRD data. The heterocyclic thiadiazinane ring adopts the chair conformation (Figures 2 and 3).

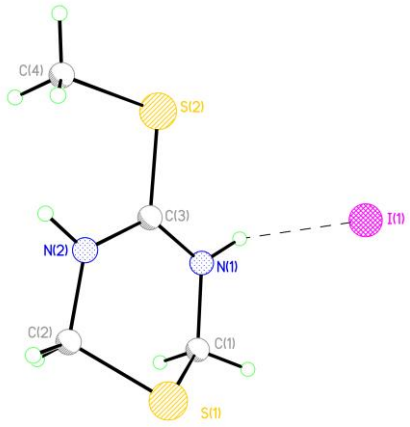


Figure 2. The general view of **10** in crystal.

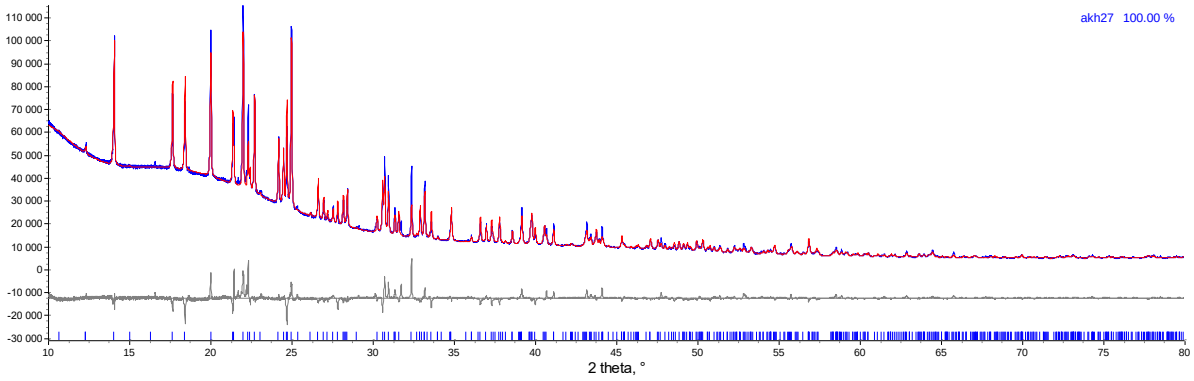


Figure 3. The experimental (blue), calculated (red) and difference PXRD curves for **10**.

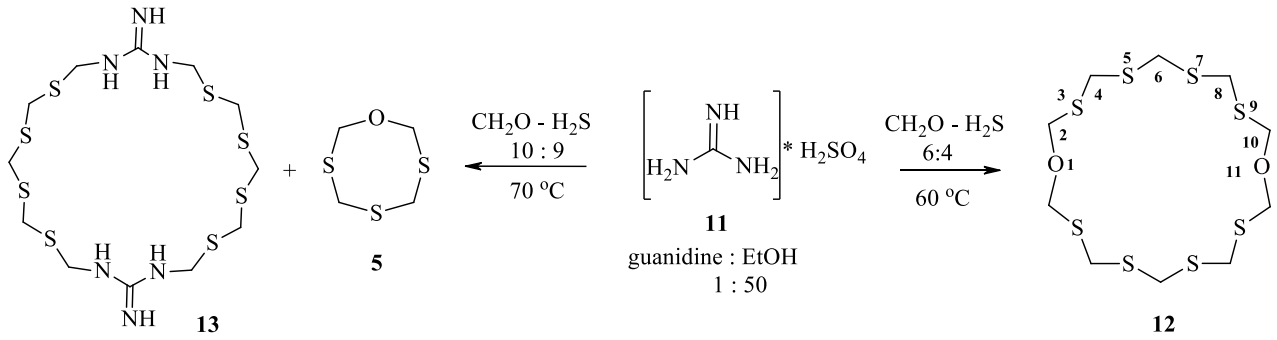
The powder diffraction pattern (see Experimental) of **10** was indexed by TOPAS 4.2 software[23,24] in a monoclinic syngony, with P21/c space group judged from systematic absences. The lattice parameters (after Rietveld refinement) are a= 9.4843(2) Å, b= 14.4289(3) Å, c= 7.40559(15) Å, β= 118.9613(11)°, V= 886.71(3) Å[25].

The crystal structure of **10** contained two N-H···I hydrogen bonds (N···I 3.478 and 3.586 Å, N-H···I 159° and 140°, respectively). The crystal of **10** is found to be formed by infinite hydrogen-bonded chains, bonded to each other with weak C-H···S, S···S and C-H···I van der Waals interactions.

In contrast to the weakly basic urea, the strongly basic guanidine underwent thiomethylation promoted by *n*-BuONa to yield three-dimensional oligomer (92%), cross-linked by the methylenesulfide -CH_2SCH_2- and -$CH_2SCH_2SCH_2$- links.

We have studied the multicomponent condensation of guanidine sulfate salt **11** with CH_2O and H_2S. Thus, under reaction conditions (60 °C, **11**:CH_2O:H_2S = 1:6:4, dilution of **11**:EtOH from 1:15 to 1:50) the reaction proceeds without participation of **11** and resulted in 1,11-dioxa-3,5,7,9,13,15,17,19-octathiacycloeicosane – **12** (70% yield) (Scheme 4). In the ^{13}C NMR spectrum of **12** the signal attributable to the sp^2-hybridized carbon atom (C=NH fragment) is not observed. This spectrum contains only three signals at δ_C 63.30, 31.90 and 31.50 ppm, which correspond to -OCH_2S- and -SCH_2SCH_2S- fragments. In accordance with two-dimensional NMR spectroscopy data (HMBC) there are the interactions between C(2) - H(4), C(4) - H(2) and C(4) - H(6) (Scheme 4). Taking into account that the ^{13}C NMR spectrum does not contain any more signals we have identified compound **12** as a symmetrical cycle, which contains -$OCH_2SCH_2SCH_2$- links. Mass spectrum of **12** demonstrates the molecular ion peak at *m/z* 429 $[M+H]^+$.

The increase in temperature up to 70 °C and in the concentration of the thiomethylating mixture (**11**:CH_2O:H_2S = 1:10:9) favor the formation of the target macroheterocycle **13** in 10% yield along with 1,3,5,7-oxatrithiocane **5** (56%).



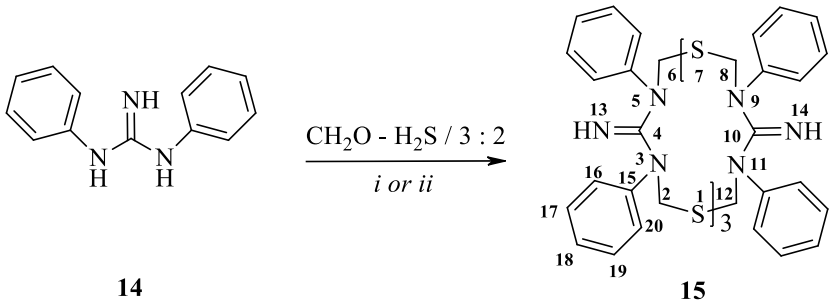
Scheme 4

So, in the temperature range from 20 to 60 ºC the guanidine sulfate salt **11** is not practically involved in the reaction with CH_2O and H_2S. Apparently, the guanidine sulfate salt **11** appears as a promoter in cyclocondensation of CH_2O and H_2S to produce O,S-containing heterocycles **5** and **12**.

It should be noted that cyclic di-, tetra- and polysulfides were isolated from algae and fungi and have antibacterial and fungicidal activity.[26]

The structure of 1,3,5,7,13,15,17,19-octathio-9,11,21,23-tetraazacyclotetracosa-10,22-diimine **13** was established by means of 1D and 2D NMR, IR spectral methods and mass spectrometry. Mass spectrum of compound **13** shows the molecular ion peak at *m/z* 511 $[M+H]^+$.

Multicomponent condensation of *N*,*N*′-diphenylguanidine **14** (**14**:CH_2O:H_2S = 1:3:2) selectively leads to macrocycle **15** in 61% yield. In the presence of *n*-BuONa promoter the yield of **15** reaches 85% (Scheme 5).



Reaction conditions: (*i*) 80 °C, EtOH/H_2O; (*ii*) 40 °C, *n*-BuONa

Scheme 5

The presence of C=NH group in molecule **15** was detected by means of IR (1575, 1660, 3350 cm^{-1}) and NMR ^{13}C (C(4) = 152.75 ppm) methods. In the HMBC spectrum there are the correlations between C(4) - H(2 or 6), which proves the existence of -$SCH_2N(Ph)C(NH)$- linkage.

The molecular mass for macroheterocycle **15**, determined by the Rust cryoscopy method,[27] was 1087 ± 10 (M_{theor}. 1077), and the data of elemental analysis correspond to the empirical formula $C_{60}H_{60}N_{12}S_4$. On the basis of our findings the compound **15** was identified as 3,5,9,11,15,17,21,23-octaphenyl-1,7,13,19-tetrathia-3,5,9,11,15,17,21,23-octaazacyclotetracosa-4,10,16,22-tetraimine.

Conclusions

Thus, for the first time, we have synthesized 1,3,5-thiadiazinane-4-(thi)ones by multicomponent condensation of (thio)urea with CH_2O and H_2S in the presence of four moles of *n*-BuONa promoter. Equimolar amount of *n*-BuONa promotes the formation of macrocycles containing urea fragments and the methylenesulfide -CH_2SCH_2- chains (n = 4–15). A new possibility to design the amidine macroheterocycles containing the methylenesulfide links through the multicomponent condensation of guanidine or *N*,*N'*-diphenylguanidine with CH_2O and H_2S in one preparative stage has been shown.

Experimental Section

General. The original reagents (materials) are commercially available (ZAO "Khimreactivsnab") and, in all experiments, have been used with a purity of not less than 95%. The solvents were purified, dried, and exploited freshly distilled according to.[28]

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 (δ_C = 39.50) on a spectrometer Bruker Avance 400 [400.13 MHz (^{1}H) and 100.62 MHz (^{13}C)] in accordance with a standard Bruker protocol. The chemical shifts (δ) are given in ppm relative to TMS (tetramethylsilane). Homo- and heteronuclear HSQC, HMBC and COSY methods were carry out by standard Bruker program. Infrared spectra (IR) were recorded using FT-IR spectrometer Bruker Vertex 70 ν (vaseline oil). Chromatography-mass-spectrometric analysis of compounds **5, 12, 13** was performed on SHIMADZU LCMS-2010 EV instrument by atmospheric pressure chemical ionization (APCI) mass spectrometry; the maximum temperature of the APCI probe was 500 °C; the temperature of the heating source was 200 °C, the temperature of the vaporizer was 250 °C; nitrogen that was produced by an NM18L ultra-high purity nitrogen generator was used as the nebulizing gas; the liquid flow rate was 0.05 mL min^{-1}, the nebulizing gas flow rate was 2.5 mL min^{-1}; the ion source voltage was as follows: (+), 4.5 kV; (–), 3 kV.

Mass spectra of high-resolution of compounds **6**, **8**, and **10** (regime of negative ions) was recorded in DMSO on a spectrometer "MALDI-TOF Autoflex III" (Bruker, Germany), α-cyano-4-hydroxycinnamic acid as a matrix. Sample of **6** or **8** or **10** was prepared by the "dried droplet method" (1:10). The powder pattern of **10** was measured on Bruker D8 Advance Vario diffractometer with LynxEye detector and Ge (111) monochromator, λ(CuKα1) = 1.54060 Å, θ/2θ scan from 10° to 80°, step size 0.009188°. The measurement was performed in transmission mode, with **10** deposited on sticky tape. Elemental analysis of the samples was carried out using Carlo-Erba Elemental Analyzer model 1106. The melting points were measured using an RNMK 80/2617 melting point apparatus. The pH values of the solutions were measured adjusted using a pH-340 pH-meter.

Multicomponent condensation of urea and its derivatives with CH_2O and H_2S. General procedure

Method A. A solution of formaldehyde (3 or 6 mol) was saturated with H_2S by bubbling for 30 min until the required CH_2O : H_2S ratio (3 : 3 or 6 : 6) was achieved. Then a solution of urea or thiourea (1 mol) in water was added dropwise to the thiomethylating mixture, and the solution was stirred for 5 h at a desired temperature (20, 40, or 80 ºC). The separated powder of compounds **3a–c** and **4a–c** were filtered off, washed with water, and dried.

Method B. A glass reactor equipped with a magnetic stirrer, a reflux condenser, an adapter for gas input, and a dropping funnel was charged at 20 ºC with 37% formaldehyde water solution (6 mol), (thio)urea (1 mol), and the solution was stirred for 1 h at 80 ºC. The reaction mixture was bubbled with hydrogen sulfide for 5 h. The obtained crystals of compounds **3d** and **4d** were filtered off, washed with water, and dried.

The molecular weights of **3a–d** and **4a–d** were determined by the Rust method.[27]

Polymer (3a). Yield 12% (method **A,** 20 °C, 1:3:3 ratio) and 47% (method **A,** 20 °C, 1:6:6 ratio). Mp 133–138 °C. IR ν 710, 1020, 1240, 1370, 1450, 1540, 1630, 2910, 3320 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.28–4.34 (m, NCH_2S); 4.66–4.81 (m, NCH_2O); 5.65–5.89 (m, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 41.29–42.90 (brs, $NHCH_2S$); 47.60–49.66 (brs, $NHCH_2S$); 62.58–64.54

(brs, OCH_2N); 156.77–157.56 (s, C=O) ppm. M_{cr} 1888±10. Anal. Calcd for $C_{48}H_{96}O_{16}N_{32}S_{16}$: C, 30.51; H, 5.08; O, 13.56; N 23.73; S, 27.12%. Found: C, 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

Polymer (3b). Yield 17% (method **A,** 40 °C, 1:3:3 ratio) and 20% (method **A,** 40 °C, 1:6:6 ratio). Mp 268–269 °C. IR ν 710, 1020, 1240, 1370, 1450, 1540, 1630, 2910, 3320 cm^{-1}. M_{cr} 3304±10. Anal. Calcd for $C_{84}H_{168}N_{56}S_{28}$: C, 30.51; H, 5.08; O, 13.56; N, 23.73; S, 27.12%. Found: C, 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

Polymer (3c). Yield 58% (method **A,** 80 °C, 1:3:3 ratio) and 69% (method **A,** 80 °C, 1:6:6 ratio). Mp 172–173 °C. IR ν 710, 1020, 1240, 1370, 1450, 1540, 1630, 2910, 3320 cm^{-1}. M_{cr} 2832±10. Anal. Calcd for $C_{72}H_{144}N_{48}S_{24}$: C, 30.51; H, 5.08; O, 13.56; N, 23.73; S, 27.12%. Found: C. 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

Polymer (3d). Yield 34% (method **B**). Mp 287–288 °C. IR ν 710, 1020, 1240, 1370, 1450, 1540, 1630, 2910, 3320 cm^{-1}. M_{cr} 2950±10. Anal. Calcd for $C_{75}H_{150}N_{50}S_{25}$: C, 30.51; H, 5.08; O, 13.56; N, 23.73; S, 27.12%. Found: C, 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

1,7-Dithia-3,5,9,11-tetraazacyclododecane-4,10-dithione (4a). Yield 28% (method **A,** 20 °C, 1:3:3 ratio) and 45% (method **A,** 20 °C, 1:6:6 ratio). Mp 73–74 ºC. IR ν 700, 1010, 1230, 1360, 1520, 2900, 3300 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.86 (m, 4H, CH_2); 8.26 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.12–44.50 (t, $NHCH_2S$); 181.96–182.10 (s, C=S) ppm. M_{cr} 536±10. Anal. Calcd for $C_{12}H_{24}N_8S_8$: C, 26.87; H, 4.48; N, 20.89; S, 47.76%. Found: C, 25.93; H, 4.56; N, 21.67; S, 47.84%.

1,7,13,19,25,31-Hexathia-3,5,9,11,15,17,21,23,27,29,33,35-dodecaazacyclohexa- triacontane-4,10,16,22,28,34-hexathione (4b). Yield 21% (method **A,** 40 °C, 1:3:3 ratio) and 10% (method **A,** 40 °C, 1:6:6 ratio). Mp 69–73 ºC. IR ν 700, 1000, 1190, 1350, 1520, 2900, 3300 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.86 (m, 4H, H_2C); 8.21 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.20–44.76 (t, $NHCH_2S$); 180.81–183.19 (s, C=8) ppm. M_{cr} 1072±10. Anal. Calcd for $C_{24}H_4N_{16}S_{16}$: C, 26.87; H, 4.48; N, 20.89; S, 47.76%. Found: C, 25.93; H, 4.56; N, 21.67; S, 47.84%.

1,7,13,19,25,31-Hexathia-3,5,9,11,15,17,21,23,27,29,33,35-dodecaazacyclohexa- triacontane-4,10,16,22,28,34-hexathione (4c). Yield 31% (method **A,** 80 °C, 1:3:3 ratio) and 38% (method **A,** 80 °C, 1:6:6 ratio). Mp 69–73 ºC. IR ν 700, 1000, 1190, 1350, 1520, 2900, 3300 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.86 (m, 4H, H_2C); 8.21 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.20–44.76 (t, $NHCH_2S$); 180.81–183.19 (s, C=8) ppm. M_{cr} 1059±10. Anal. Calcd for $C_{24}H_4N_{16}S_{16}$: C, 26.87; H, 4.48; N, 20.89; S, 47.76%. Found: C, 25.93; H, 4.56; N, 21.67; S, 47.84%.

1,7,13,19,25,31,37-Heptathia-3,5,9,11,15,17,21,23,27,29,33,35,39,41-tetradecaazacyclodo-tetracontane-4,10,16,22,28,34,40-heptathione (4d). Yield 35% (method **B**). Mp 73–76 ºC. IR ν 700, 1000, 1170, 1370, 1450, 2900, 3300 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.88 (m, 4H, H_2C); 8.32 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.00-44.30 (t, $NHCH_2S$); 181.02-182.03 (s, C=S) ppm. M_{cr} 938±10. Anal. Calcd for $C_{21}H_{42}N_{14}S_{14}$: C, 26.87; H, 4.48; N, 20.89; S, 47.76%. Found: C, 25.93; H, 4.56; N, 21.67; S, 47.84%.

Method C. A glass reactor equipped with a magnetic stirrer, a reflux condenser, an adapter for gas input, and a dropping funnel was charged at 40 ºC with 37% formaldehyde water solution (6

mol), and the solution was saturated with hydrogen sulfide by bubbling for 1h. In another reactor, the initial urea (thiourea) was mixed at r.t. with *n*-BuONa dissolved in *n*-BuOH in a 1:1 or 1:4 molar ratio, and the mixture was added dropwise to the water solution of CH_2O–H_2S prepared. The resultant reaction mixture was stirred for 4 h at 40 ºC, then it was quenched with dilute HCl. The precipitate (**3e, 4e** and **8**) were separated, washed with water, and dried. Product **5** has been isolated by extraction with chloroform (10 mL x 3). Products **6** and **7**, which were obtained as a mixture, were separated by fractional crystallization in *n*-BuOH/H_2O system.

Cyclooligomers (3e). Yield 42%. Mp 134–139 °C. IR ν 710, 1020, 1240, 1370, 1450, 1540, 1630, 2910, 3320 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.28–4.34 (m, NCH_2S); 5.65–5.89 (m, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 41.29–42.90 (brs, $NHCH_2S$); 47.60–49.66 (brs, $NHCH_2S$); 156.77–157.56 (s, C=O) ppm. M_{cr} 2841±10. Anal. Calcd for $C_{72}H_{144}N_{48}S_{24}$: C, 30.51; H, 5.08; O, 13.56; N, 23.73; S, 27.12%. Found: C. 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

1,7,13,19,25,31,37-Heptathia-3,5,9,11,15,17,21,23,27,29,33,35,39,41-tetradecaazacyclo dotetracontane-4,10,16,22,28,34,40-heptathione (4e). Yield 54% (method **B**). Mp 73–76 ºC. IR ν 700, 1000, 1170, 1370, 1450, 2900, 3300 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.88 (m, 4H, H_2C); 8.32 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.00-44.30 ($NHCH_2S$); 181.02-182.03 (C=S) ppm. M_{cr} 940±10. Anal. Calcd for $C_{21}H_{42}N_{14}S_{14}$: C, 26.87; H, 4.48; N, 20.89; S, 47.76%. Found: C, 25.93; H, 4.56; N, 21.67; S, 47.84%.

1,3,5,7-Oxatrithiocane (5). Yield 56% (method **C**). IR ν 650–710, 820, 1360–1450, 3250 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.90 (s, 4H, SCH_2S); 4,67 (s, 4H, OCH_2S) ppm. ^{13}C NMR (DMSO-d_6) δ 31.82 (SCH_2S); 63.65 (OCH_2S) ppm. MS *m/z*: 189 (10) $[M+H_2O+H]^+$; 169 (100) $[M+H]^+$. Anal. Calcd for $C_4H_8OS_3$: C, 28.71; H, 4.45; S, 59.91%. Found: C, 28.55; H, 4.79; S, 57.16%.

1,3,5-Thiadiazinane-4-one (6). Yield 58% (method **C**). Mp 215–218 ºC. IR ν 782, 1012, 1236, 1377, 1466–1540, 1670, 2910, 3308 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.27 (m, 4H, CH_2); 6.78 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 44.05 (NCH_2S); 155.01 (C=O) ppm. MS *m/z*: 119.095 $[M+H]^+$. Anal. Calcd for $C_3H_6N_2SO$: C, 30.51; H, 5.08; O, 13.56; N, 23.73; S, 27.12%. Found: C, 30.93; H, 5.56; O, 13.05; N, 22.67; S, 27.79%.

***N*-Methylidene-1,3,5-dithiazinane-5-carboxamide (7).** Yield 9% (method **C**). Mp 128–130 ºC. IR ν 700, 1025, 1230, 1360, 1450–1540, 1630, 2920, 3325 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.91 (s, 2H, SCH_2S); 4.35 (s, 4H, NCH_2S); 6.75 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 31.29 (SCH_2S); 53.27 (NCH_2S); 139.19 (HC=N); 158.19 (C=O). Anal. Calcd for $C_5H_8N_2S_2O$: C, 34.07; H, 4.57; N, 15.89; S, 36.38%. Found: C, 35.02; H, 4.24; N, 15.37; S, 37.67%.

1,3,5-Thiadiazinan-4-thione (8). Yield 60% (method **C**). Mp 178–180 ºC. IR ν 670, 977, 1206, 1378–1468, 1575, 1669, 2910, 3466 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.26–4.27 (brs, 4H, NCH_2S); 8.64 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 43.63 (NCH_2S); 175.97 (C=S) ppm. MS *m/z*: 135.105 $[M+H]^+$. Anal. Calcd for $C_{24}H_{48}N_{16}S_{16}$: C, 26.84; H, 4.51; N, 20.87; S, 47.78%. Found: C, 26.43; H, 4.44; N, 21.00; S, 48.02%.

The synthesis of adduct of 1,3,5-thiadiazinane-4-one with CH_3I 9 and 4-methylsulfonyl-2*H*-1,3,5-thiadiazine hydriodide (10)

In a glass ampoule 1,3,5-thiadiazinane-4-(thi)ones **6** or **8** (1 mol) and CH_3I (10 mol) were placed and the ampoule was soldered. The reaction mixture was maintained for 7 days, than the precipitated was filtered off and dried.

Adduct of 1,3,5-thiadiazinane-4-one with CH_3I (9). Yield 99%. Mp 226–228 ºC. IR ν 782, 1012, 1176, 1378, 1466–1537, 1668, 2923, 3308 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.25 (m, 4H, SCH_2N); 6.95 (m, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 43.61 (SCH_2N); 154.51 (C=O) ppm. Anal. Calcd for $(C_3H_6N_2SO)_7 \cdot CH_3I$. Found: C, 27.23; H, 4.56; N, 21.07; S, 23.79; I, 12.63%.

4-Methylsulfonyl-2*H*-1,3,5-thiadiazine hydriodide (10). Yield 99%. Mp 142–145 ºC. IR ν 609, 709, 967, 1023, 1203, 1378–1468, 1542, 1601, 2923, 3443 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.61 (s, 4H, CH_3); 4.62 (brs, 4H, SCH_2N), 10.42 (brs, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 13.83 (CH_3); 43.66 (SCH_2N); 164.17 (C=N) ppm. MS *m/z*: 276.410 $[M]^-$. Anal. Calcd for $C_4H_9IN_2S_2$: C, 17.40; H, 3.28; I, 45.95; N, 10.14; S, 23.22%. Found: C, 17.32; H, 3.24; I, 46.10; N, 10.37; S, 23.17%.

Multicomponent condensation of guanidines (11, 14) with CH_2O and H_2S. General procedure

The reaction of **11** with CH_2O and H_2S (**11**:CH_2O = 1:3 (1:6, 1:10, or 1:100)) was conducted as described in **Method A**. The ethanol solution of **11** (1 mol) was added dropwise to the thiomethylating mixture, and the solution was stirred for 20 h at a desired (20–70 ºC). temperature. The reaction mixture was quenched with dilute NaOH, washed with hot water and alcohol. The precipitate was filtered off, washed with water, and dried.

1,11-Dioxa-3,5,7,9,13,15,17,19-octathiacycloeicosane (12). Yield 70% (1:6, 60 ºC). Mp 109-110 ºC. IR ν 700, 820, 1000, 1085, 1160, 1360–1450, 1595, 1660, 2900, 3350 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.88 (s, 18H, SH_2CS); 4,67–4.69 (brs, 8H, SCH_2O) ppm. ^{13}C NMR (DMSO-d_6) δ 31.50 (SH_2CS); 31.90 (SH_2CS); 63.30 (SH_2CO) ppm. MS *m/z* : 429 (3) $[M+H]^+$; 371 (40); 351 (10) $[CH_2SCH_2SCH_2OCH_2SCH_2SCH_2SCH_2SCH_2OCH_2]^+$; 201 (100) $[M-CH_2SCH_2SCH_2SCH_2SCH_2OCH_2]^+$. Anal. Calcd for $C_{10}H_{20}O_2S_8$: C, 27.71; H, 4.25; S, 60.31%. Found: C, 28.01; H, 4.70; S, 59.83%.

1,3,5,7,13,15,17,19-Octathio-9,11,21,23-tetraazacyclotetracosa-10,22-diimine (13). Yield 10% (1:10, 70 ºC). ^1H NMR (DMSO-d_6) δ 3.95 (s, 12H, SH_2CS); 4.39 (s, 8H, NCH_2S); 7.29 (brs, 6H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 30.52 (SH_2CS); 33.20 (SCH_2S); 45.40 (NCH_2S); 157.70 (C=NH) ppm. MS *m/z*: 511 (5) $[M+H]^+$; 409 (10) $[M-NHC(NH)NHCH_2S]^+$, 371 (12) $[M-CH_2SCH_2SCH_2S]^+$; 255 (4) $[M-CH_2SCH_2SCH_2SCH_2SCH_2NHCNHNH]^+$; 195 (70) $[NHC(NH)NHCH_2SCH_2SCH_2S]^+$, 76 (68) $[SCH_2S]^+$; 73 (12) $[NHC(NH)NHCH_2]^+$; 57 (100) $[NHC(NH)NH]^+$.

The reaction **14** with CH_2O and H_2S (**14**:CH_2O = 1:3) was conducted as described in **Method A, C**.

3,5,9,11,15,17,21,23-Octaphenyl-1,7,13,19-tetrathia-3,5,9,11,15,17,21,23-octaazacyclo-tetracosa-4,10,16,22-tetraimine (15). Yield 61% (method **A,** 40 °C) and 85% (method **C,** 40 °C). Mp 82–85 ºC. IR ν 510, 700–750, 1000, 1170, 1370–1445, 1580, 1635 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 4.08 (brs, NCH_2S); 7.20–7.60 (m, Ph); 8.25 (s, NH) ppm. ^{13}C NMR (DMSO-d_6) δ 45.91 (NCH_2S); 124.03 (CH); 129.83 (CH); 135.07 (CH); 141.85 (CH); 152.75 (C=NH) ppm. M_{cr} 1060±10. Anal. Calcd for $C_{60}H_{60}N_{12}S_4$: C, 66.88; H, 5.61; N, 15.60; S, 11.90%. Found: C, 66.71; H, 5.45; N, 15.38; S, 12.11%.

X-Ray crystal data for (10)

The crystal structure of **10** was solved with direct-space methods using the simulated annealing global optimization algorithm. The starting model starting geometry of the cation for the structure solution was taken from M05-2X/6-311G* isolated state calculation performed in Gaussian software package.[25] During the solution and subsequent refinement, the organic cation was treated as a rigid body (translations and Eulerian angles refined) with geometry taken from quantum-chemical calculation (except for hydrogen atoms moved to idealized x-ray positions) and one torsion angle (C4 S2 C3 N2) refined. The iodine atom was refined isotropically without any constraints and/or restraints (Figure 3).

After structure solution, the thermal parameters for lighter atoms were refined isotropically, with one common thermal parameter Ueq(S) chosen for sulphur atoms, and one more (Ueq(N,C)) for nitrogen and carbon atoms combined. The refinement converged to $Rp/R_P'/ R_{WP}/ R_{WP}'/R_{Bragg}$ values of 2.399/2.231/4.266/3.833/ 4.787 %.

The reasonable geometry of intermolecular contacts and values of isotropic thermal parameters after Rietveld refinement confirmed the correctness of chosen molecular model. The difference curve showed the presence of small amount of unidentifiable impurity in **10**, however, its presence did not affect the Rietveld refinement significantly. All calculations were performed in TOPAS 4.2 software suite.[23,24] Additional details of the Rietveld refinement, refined lattice parameters and atomic coordinates of **10** are included in the crystallographic information file (CCDC 783903) deposited in the Cambridge Structural Database.

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