

# Multicomponent reactions of amines with aldehydes and H<sub>2</sub>S as efficient route to heterocycles and thioaza macrocycles

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**Abstract** Here we provide new experimental results on multicomponent reactions of amines with aldehydes and H<sub>2</sub>S in the directed synthesis of functionally-substituted 1,3-thiazetidines, 1,3,5-dithiazinanes, 1,3,5-thiadiazinanes, 1,5-dithia-3,7-diazacyclooctanes, and thioaza macrocycles. X-ray analysis gave insight into the structure of the synthesized compounds. New kinds of multicomponent reactions (MCR) have been discovered and characterized.

**Keywords** MCR · Multicomponent reactions · Amines · Aldehydes · Hydrogen sulfide · X-ray analysis · Macroheterocycles

## Introduction

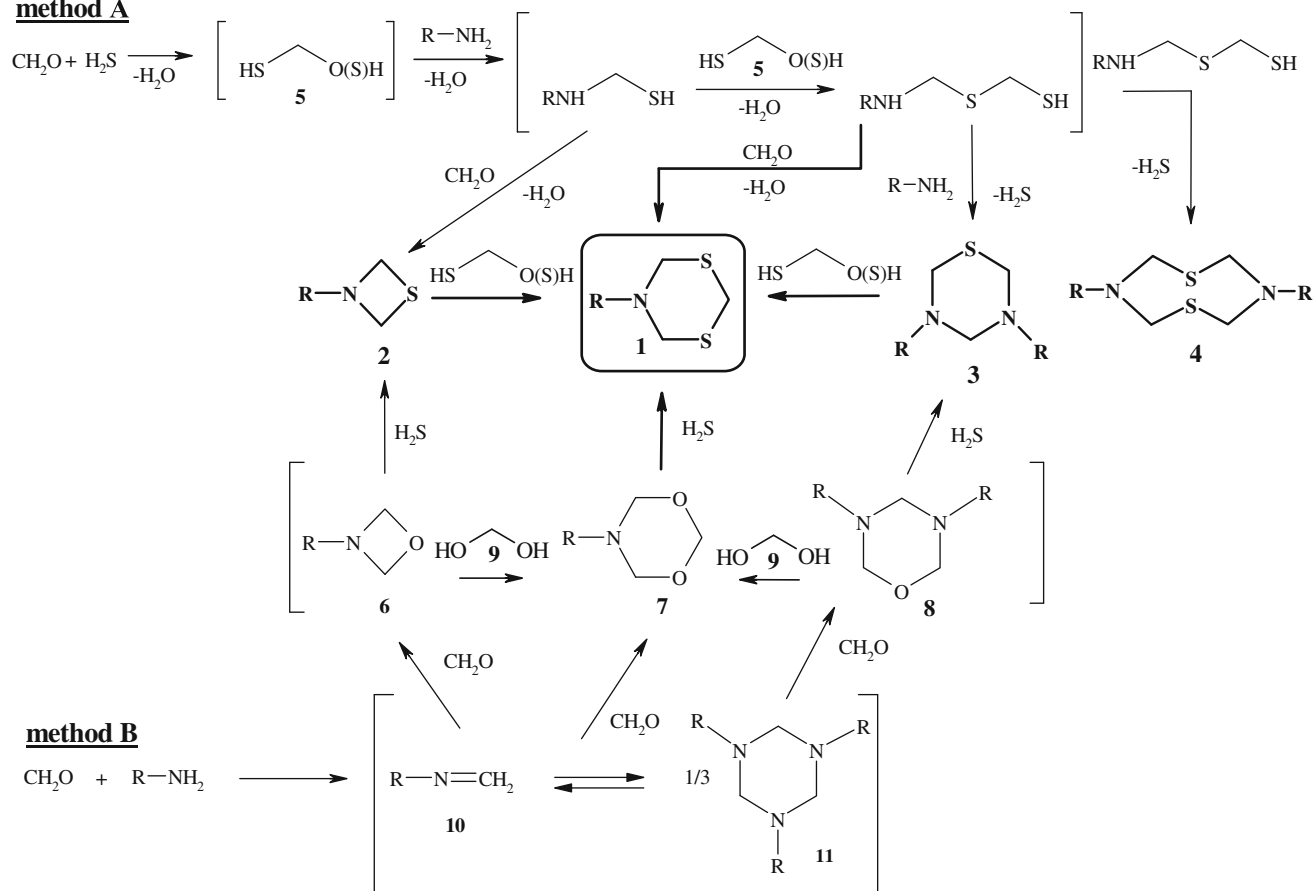
Nowadays, there is an increased in one-pot synthesis of heterocycles by methodology of cascade heterocyclization enlarges [1,2]. Multicomponent condensation of primary amines with formaldehyde and hydrogen sulfide is attributed to cascade “domino” reaction and leads to formation of 1,3,5-dithiazinanes [3–11]. Sulfur- and nitrogen-containing heterocycles, including the 1,3,5-dithiazinane **1** (Scheme 1) and its derivatives, represent special interest as potential antibacterial [12], antiviral preparations and also selective sorbents [12,13], flotation agents for metals and complexes in supramolecular chemistry [14].

There is precedent that multicomponent reaction (MCR) of amines with aldehydes and hydrogen sulfide leads to other types of heterocyclic systems, such as 1,3-thiazetidines **2**, 1,3,5-thiadiazinanes **3**, and 1,5-dithia-3,7-diazacyclooctanes **4** (Scheme 1) [15–19]. These alternate outcomes are the result of reaction variations, namely, the order of mixing of reagents, their concentration, and the temperature mode. As a result this MCR, in our opinion, can be presented by two types of chemical transformations. According to the first procedure, it is the result of consecutive condensation of amines with thio- and semi-thioacetal of formaldehyde **5** prepared by bubbling gaseous H<sub>2</sub>S through formaldehyde water solution (**method A**, Scheme 1). Formation of various classes of heterocycles **1–4** depends on the concentration of initial reactants. According to the second procedure, it is the result of interaction of H<sub>2</sub>S with cyclic adducts **6–8** prepared by condensation of amines with formaldehyde water solution (**method B**). Intermediates **6–8** are formed from imine **10** or triazine **11** due to amount of formaldehyde.

Thus, multistage consecutive attack of binucleophilic thioacetal of formaldehyde **5** to amine RNH<sub>2</sub> (**method A**) or hydrates of formaldehyde **9** to imine **10** (**method B**) by “domino” principle leads to the formation of various heterocyclic systems depending on the molar ratio of reactants. As a rule, 1,3,5-dithiazinane **1** is the stable and major product of this MCR.

However, the route of MCR and, accordingly, composition of formed heterocycles may also depend on the structure of initial amines, especially on the structure of binucleophilic amines containing OH-, SH-, NH<sub>2</sub>-groups. The nature of starting amines can influence the speed of reaction (kinetic control) and stability of the products (thermodynamic control). For the last 6 years, we have researched the synthesis of novel types of sulfur- and nitrogen-containing mono- and poly-heterocycles and studied the influence of the starting

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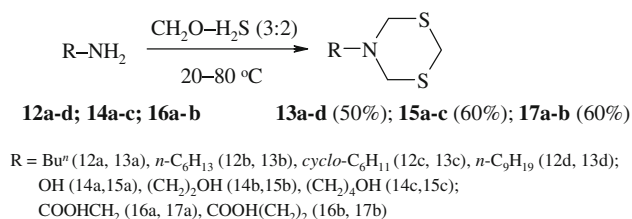
**method A****Scheme 1** Two routes of MCR of amines, aldehydes and H<sub>2</sub>S

amines on the mechanism of the above-mentioned MCR. Therefore, various mono- [20,25,26], bi- [21,22,30,35,36] and heterofunctional amines and hydrazine [32,33] were involved in the multicomponent “domino” condensation with formaldehyde and H<sub>2</sub>S.

**MCR of primary amines with CH<sub>2</sub>O and H<sub>2</sub>S**

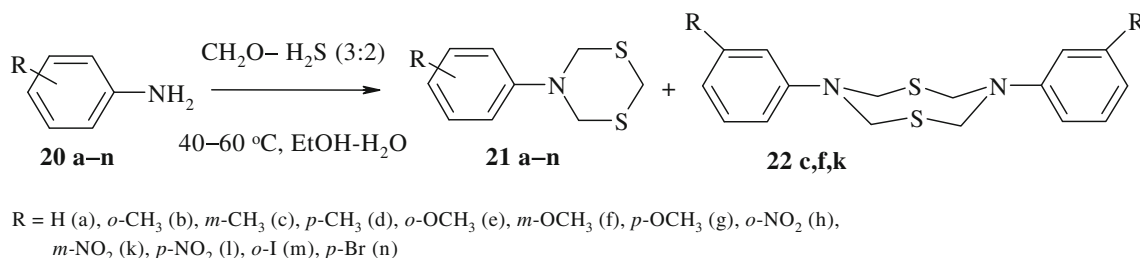
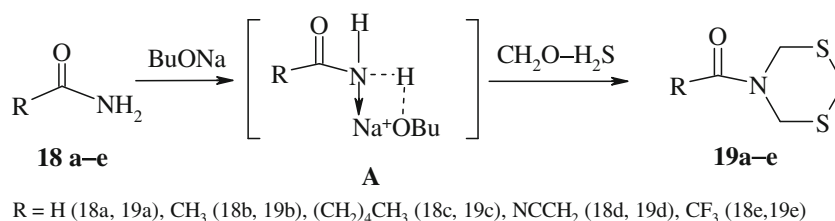
Aliphatic amines **12a–d** [20], aminoalcohols **14a–c** [21] and aminoacids **16a–b** [22] in liquid-phase reaction with the thiomethylating reagent “CH<sub>2</sub>O–H<sub>2</sub>S” [23] (3:2 ratio, H<sub>2</sub>O) underwent regioselective heterocyclization to afford *N*-substituted 1,3,5-dithiazinanes **13a–d**, **15a–c**, and **17a–b** (Scheme 2). We have established that electron-seeking groups in initial amines help to increase the yield of 1,3,5-dithiazinanes.

According to Kurchan et al. [24] 1,3,5-dithiazinanes **17a**, **b** can also be synthesized by cyclothiomeylation of aminoacids with formaldehyde and sodium hydrosulfide in an alkaline medium. However, the method based on H<sub>2</sub>S is more convenient as the reaction conditions do not require the use of alkali and expensive sodium hydrosulfide.

**Scheme 2** Synthesis of the *N*-substituted 1,3,5-dithiazinanes by MCR of aliphatic amines with CH<sub>2</sub>O and H<sub>2</sub>S

It should be noted that heterocyclization of aminobutanol **14c** and aminoacids **16a**, **b** by the CH<sub>2</sub>O–H<sub>2</sub>S system is carried out only with the NH<sub>2</sub>-group. An increase in molar ratio of “CH<sub>2</sub>O–H<sub>2</sub>S” (4:3) facilitates the participation of both functional groups in the condensation process and oxy-methylation of OH-group is observed in the case of NH<sub>2</sub>OH **14a** and aminoethanol **14b** [21].

In a similar way, multicomponent heterocyclization of carboxylic amides **18a–e** with CH<sub>2</sub>O and H<sub>2</sub>S (3:2 ratio; Scheme 3) can be carried out in the presence of BuONa, which facilitates a hydrogen exchange through the generation of complex A [25]. Next cascade domino condensation of complex A with the mixture CH<sub>2</sub>O–H<sub>2</sub>S

**Scheme 3** MCR of carboxylic amides, CH<sub>2</sub>O and H<sub>2</sub>S in the presence of BuONa**Scheme 4** Synthesis of *N*-aryl-1,3,5-dithiazinanes

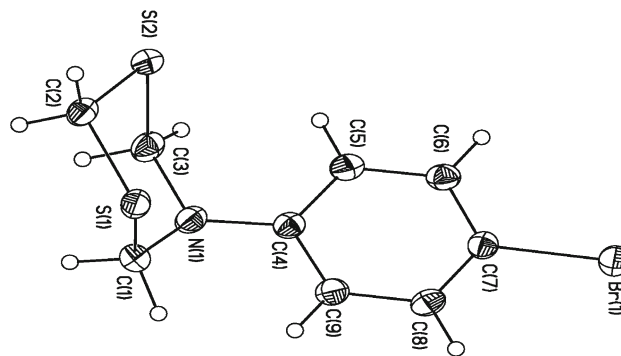
regioselectively leads to *N*-acyl-1,3,5-dithiazinanes **19a-e**. The yield of **19a-e** depends on the electron-seeking properties of substituent of the carboxyl amide and increases in the row  $(\text{CH}_2)_4\text{CH}_3$  (30%) <  $\text{CH}_3$  (35%) <  $\text{H}$  (40%) <  $\text{CNCH}_2$  (67%) <  $\text{CF}_3$  (95%). Note that amides **18a-c** are not involved in the MCR without BuONa.

Unlike aliphatic amines the MCR of aromatic amines with “CH<sub>2</sub>O–H<sub>2</sub>S” leads to a mixture of various kinds of heterocyclic compounds, such as 1,3,5-dithiazinanes, 1,3,5-thiadiazinanes, and 1,5-dithia-3,7-diazacyclooctanes [26–29].

For the first time, we have succeeded in the more selective synthesis of various types of heterocycles from anilines **20a-n**. For example, directed synthesis of *N*-aryl substituted 1,3,5-dithiazinanes **21a-n** (~80%) was carried out by method **A** at the ratio of aniline: CH<sub>2</sub>O:H<sub>2</sub>S equal to 1:3:2 at 40–60 °C in EtOH–H<sub>2</sub>O media for 10–12 h (Scheme 4). Under these conditions, 1,5-dithia-3,7-diazacyclooctanes **22c,f,k** (~10%) from *m*-anilines have been also detected as a minor product. According to experimental data, the yield of 1,3,5-dithiazinanes based on *o*-aniline **21b,e,h,m** increases in the row  $\text{OCH}_3$  (34%) <  $\text{CH}_3$  (40%) <  $\text{I}$  (50%) <  $\text{NO}_2$  (64%) and based on *p*-aniline **21d,g,i,n** in the row  $\text{OCH}_3$  (60%) <  $\text{CH}_3$  (68%) <  $\text{Br}$  (70%) <  $\text{NO}_2$  (76%).

The structures of *N*-aryl substituted 1,3,5-dithiazinanes **21a-n** were proved by <sup>1</sup>H- and <sup>13</sup>C-NMR, the structure of **21n** also was confirmed by single-crystal X-ray diffraction (Fig. 1).

Previously, we reported on the interaction between *p*-aminobenzoic acid ethyl ester **23** and CH<sub>2</sub>O–H<sub>2</sub>S reagent (2:3:1 ratio) at 0 °C in 3–4 h resulting in the formation of *N,N*-diaryl-1,3,5-thiadiazinane **24** in 93% yield (Scheme 5) [30]. The referred methodology allows performing the directed

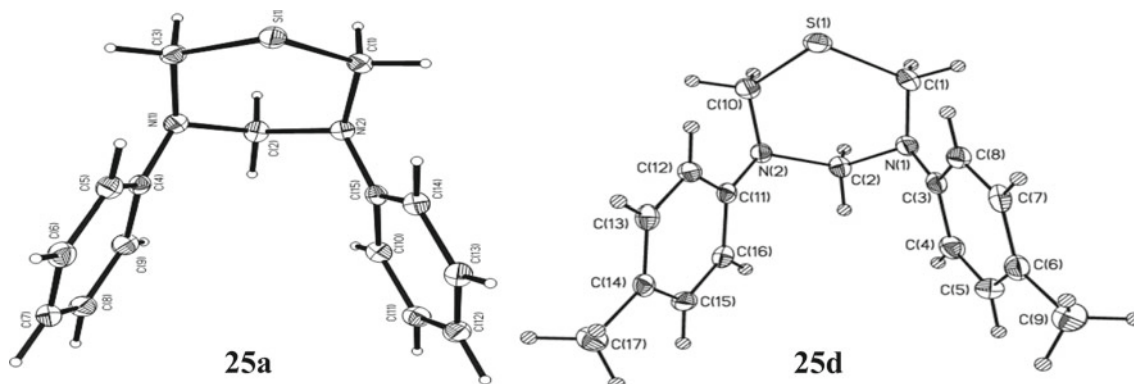
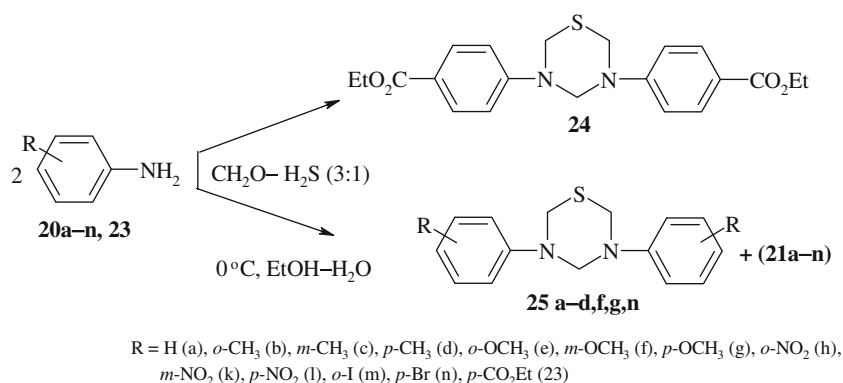
**Fig. 1** Crystal structure of compound **21n**

synthesis of 1,3,5-thiadiazinanes based on anilines **20a-n** giving rise to the target **25a-d,f,m** as major product. The corresponding **21a-n** are also observed as minor product (5–10%). Note that the *p*-anilines favor the formation of 1,3,5-thiadiazinanes and its yields increase in the row  $p\text{-OCH}_3$  (23%) <  $p\text{-CH}_3$  (52%) <  $p\text{-Br}$  (83%) <  $p\text{-COOEt}$  (93%). The conversion of *p*-isomers is 30–100% according to the nature of substituent.

X-ray analysis was first performed for *N,N*-diaryl-1,3,5-thiadiazinanes **25a,d** which are compared to *N,N*-dialkyl derivatives. The cycles **25a,d** have a *chair* conformation with axial phenyl substituents (anomeric effect) in *cis*-configuration (Fig. 2).

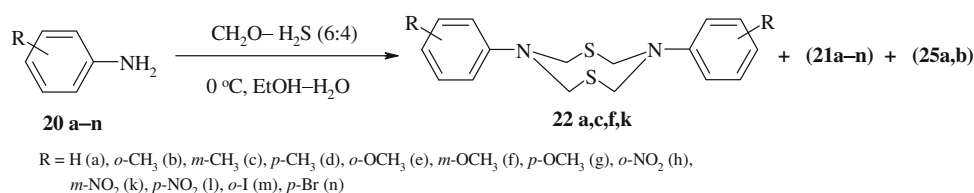
The formation of 1,5-dithia-3,7-diazacyclooctanes is realized at a molar ratio of amine–CH<sub>2</sub>O–H<sub>2</sub>S equal to 1:6:4 at 0 °C in EtOH–H<sub>2</sub>O media (Scheme 6). According to our new experimental data, only aniline and *m*-isomers favor the formation of 1,5-dithia-3,7-diazacyclooctanes **22a,c,f,k**.

**Scheme 5** Synthesis of *N*-aryl-1,3,5-thiadiazinanes



**Fig. 2** General view of compounds **25a, d** (crystal structures)

**Scheme 6** synthesis of *N, N*<sup>1</sup>-diaryl-1,5-dithia-3,7-diazacyclooctanes

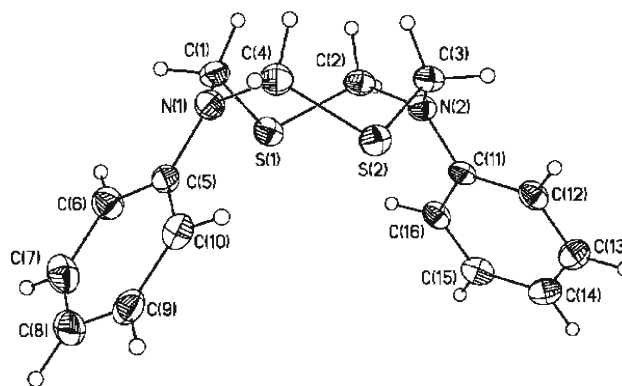


Its yields increase in the row  $m\text{-NO}_2$  (44%) <  $m\text{-OCH}_3$  (48%) <  $m\text{-CH}_3$  (50%) < H(70%). However, *ortho* and *para* isomers in these conditions (1:6:4, 0 °C, EtOH-H<sub>2</sub>O) mainly form 1,3,5-dithiazinanes **21a–n**.

The structures of **22a,c,f,k** were proved by <sup>1</sup>H and <sup>13</sup>C NMR, the structure of **22a** was confirmed by single-crystal X-ray diffraction (Fig. 3).

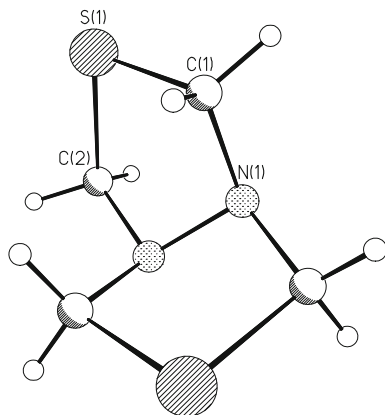
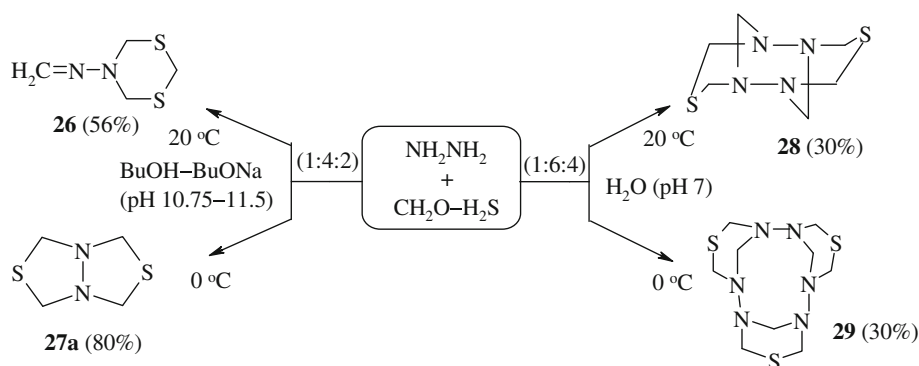
### MCR of binucleophilic amines with aldehydes and H<sub>2</sub>S

About half a century ago [31], a product with a molecular formula C<sub>4</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub> was obtained in 11% yield by the MCR of hydrazine with formaldehyde and H<sub>2</sub>S. We studied the effect of pH and temperature on the route of heterocyclization of hydrazine and the thiomethylating reagent CH<sub>2</sub>O-H<sub>2</sub>S. As a result, the conditions of the reaction to obtain mono- **26**, bi- **27a**, tri- **28** and tetra- **29** cyclic compounds have been optimized (Scheme 7) [32,33].



**Fig. 3** General view of compound **22a** (crystal structure)

We have determined the structure of bicycane **27a** by dynamic NMR in solution [32] and by X-ray analysis (Fig. 4) [34].

**Scheme 7** MCR of hydrazine, CH<sub>2</sub>O and H<sub>2</sub>S in different conditions (pH, temperature)**Fig. 4** General view of compound **27a** (crystal structure)

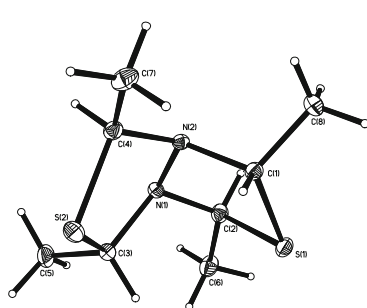
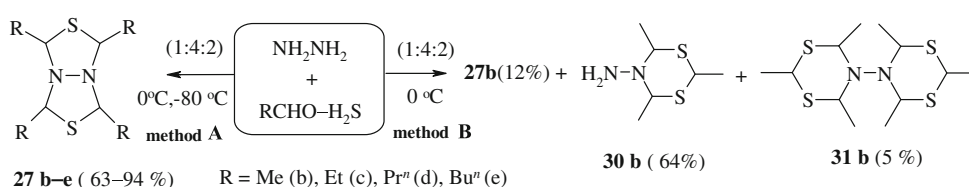
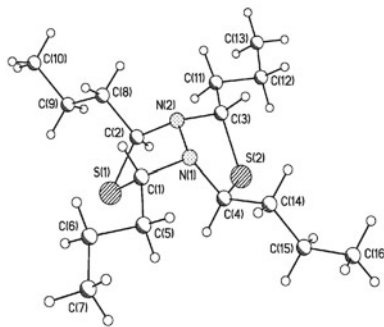
In the crystal structure **27a** occupies a special position on a C<sub>2</sub> axis passing through the middle of the N–N bond [34]. Its five-membered cycles adopt a twist conformation with both carbon atoms deviating from S–N–N planes by 0.63 Å and *cis*-fused. Moreover, the C(2)–N bond is shorter than,

by 0.0458(8) Å, the equivalent C(1)–N bond and the C(2)–S(1) bond is longer than C(1)–S(1) by 0.0462(8) Å. These differences could not be explained by intermolecular interactions.

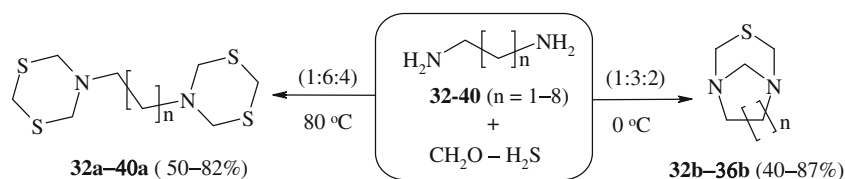
Particular heterocyclization has been detected in the MCR of hydrazine with acetic aldehyde and H<sub>2</sub>S (Scheme 8). Thus, the hydrazine is condensed regioselectively with CH<sub>3</sub>CHO and H<sub>2</sub>S from 0 °C to –80 °C to form 2,4,6,8-tetramethyl-3,7-dithia-1,5-diazabicyclo[3.3.0]octane **27b** by method **A**. The reverse order of mixing (method **B**) of initial reactants at 0 °C leads predominantly to 2,4,6-trimethyl-(1,3,5-dithiazinan-5-yl) amine **30b**.

The synthesis of 2,4,6,8-tetraalkyl-dithiadiazabicyclooctanes **27 b–e** by method **A** is carried out by the MCR of hydrazine with other aliphatic aldehydes and H<sub>2</sub>S. Synthesis of *N*-amino-2,4,6-trialkyl-1,3,5-dithiazinanes by method **B** cannot be performed with other aldehydes.

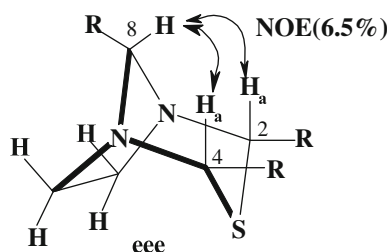
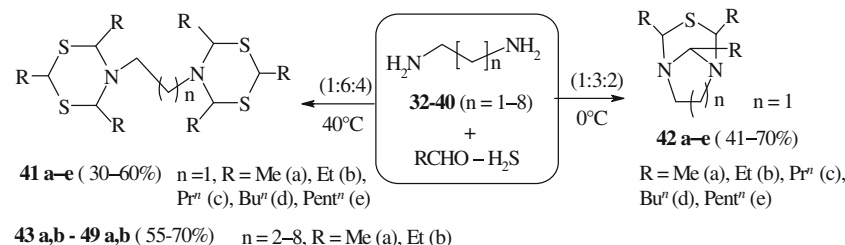
The structures of bicyclanes **27b,d** and **30b** were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR, mass spectrometry and single-crystal X-ray diffraction (Fig. 5). It was ascertained that in a crystal form the alkyl substituents of heterocycles **27b,d**

**Scheme 8** Two routes of MCR of hydrazine, acetic aldehyde and H<sub>2</sub>S in dependence from order of mixing of the reagents**27b**

**Scheme 9** MCR of aliphatic  $\alpha$ ,  $\omega$ -diamines,  $\text{CH}_2\text{O}$  and  $\text{H}_2\text{S}$  in different conditions (molar ratio, temperature)



**Scheme 10** MCR of aliphatic  $\alpha$ ,  $\omega$ -diamines, aliphatic aldehydes and  $\text{H}_2\text{S}$  in different conditions (molar ratio, temperature)



**Fig. 6** NOE-Diff data for **42a-e**

are in the equatorial position with *trans-transoid-trans* configuration. As it can be seen in the crystal, the alkyl substituents of dithiazinane **30b** occupy the equatorial position, while the  $\text{NH}_2$  group occupies the axial position. Molecule **30b** adopts a conformation where a hydrogen bond between ( $\text{N}2$ )  $\text{H}1 \dots \text{S}(2)$  is favored.

It follows that the difference in reactivity of hydrazine depending on the nature of carbonyl compound and the reaction conditions allows to changing the route of the heterocyclization of hydrazine with aldehydes and  $\text{H}_2\text{S}$ . In result, the MCR of hydrazine, aldehydes, and  $\text{H}_2\text{S}$  by method A represents “one-pot” regioselective synthesis of novel series of 2,4,6,8-tetraalkyl-3,7-dithia-1,5-diazabicyclooctanes **27b-e**.

Recently, we showed that multicomponent heterocyclization of aliphatic  $\alpha$ ,  $\omega$ -diamines **32-40** with  $\text{H}_2\text{S}$  and  $\text{CH}_2\text{O}$  at  $80^\circ\text{C}$  selectively leads to  $\alpha$ ,  $\omega$ -bis-(1,3,5-dithiazinane-5-yl) alkanes **32a-40a** [35]. The decrease in temperature to  $0^\circ\text{C}$  changes the route of the reaction and gives rise to the formation of annulated bicyclanes namely 3-thia-1,5-diazabicyclo[3.2.1]octanes **32b-36b** as the principle products (Scheme 9).

Next, we investigate the use of these methods for the synthesis of alkyl-substituted binuclear heterocycles on the base of diamines **32-40** with higher aldehydes ( $\text{RCHO}$ ,  $\text{R} = \text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $n - \text{C}_3\text{H}_7$ ,  $n - \text{C}_4\text{H}_9$ ,  $n - \text{C}_5\text{H}_{11}$ ), and  $\text{H}_2\text{S}$ .

As a result, symmetrical *bis*-(2,4,6-trialkyl-1,3,5-dithiazinane-5-yl)ethanes **41a-e** have been obtained by cyclocondensation of ethane-1,2-diamine **32** with  $\text{RCHO}$  and  $\text{H}_2\text{S}$  at a reagent molar ratio 1:6:4 at  $40^\circ\text{C}$  (Scheme 10). The yields of **41a-e** decrease with chain growth in the alkyl radical of starting aldehydes. Decrease in the quantity of thiomethylating mixture  $\text{RCHO-H}_2\text{S}$  (3:2 ratio) at  $0^\circ\text{C}$  caused the formation series of novel 2,4,8-trialkyl-3-thia-1,5-diazabicyclo[3.2.1]octanes **42a-e** (Scheme 10). The yields of **42a-e** increase with chain growth in aliphatic alkyl radical of aldehydes.

According to 1D, 2D NMR, and NOE-Diff experiments, we found that alkyl-thiadiazabicyclanes **42a-e** form only one stereoisomer with equatorial position of alkyl substituents (Fig. 6).

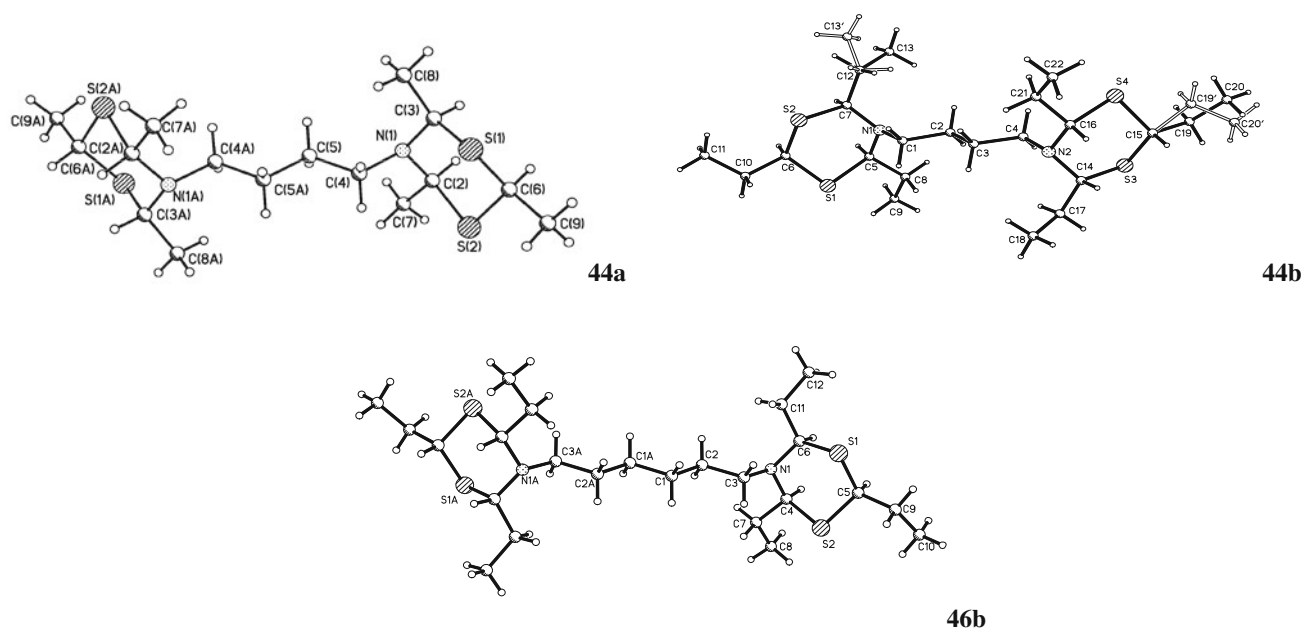
Thus, a new “one-pot” method of stereoselective synthesis of 2,8-*anti*-4,8-*anti*-2,4-*cis*-2,4,8-trialkyl thiadiazacyclooctanes **42a-e** was found by MCR of ethane-1,2-diamine **32** with aliphatic aldehydes and  $\text{H}_2\text{S}$  at  $0^\circ\text{C}$ .

The MCR of aliphatic  $\alpha$ ,  $\omega$ -diamines such as 1,3-propane, 1,4-butane, 1,5-pentane, 1,6-hexane, 1,7-heptane, 1,8-octane, or 1,9-nonane diamine with  $\text{RCHO}$  ( $\text{R} = \text{Me}$ ,  $\text{Pr}^n$ ) and  $\text{H}_2\text{S}$  (1:6:4 ratio) at  $0^\circ\text{C}$  and at  $40^\circ\text{C}$  produces only the  $\alpha$ ,  $\omega$ -bis(2,4,6-trialkyl-1,3,5-dithiazinane-5-yl)alkanes **43a**, **b-49a,b**. The structures of  $\alpha$ ,  $\omega$ -bis(2,4,6-trialkyl-1,3,5-dithiazinane-5-yl)alkanes **44a**, **44b**, and **46b** were confirmed by single-crystal X-ray diffraction analysis (Fig. 7).

In the course of our research, we have established a new kind of the thiomethylation reaction, i.e., multicomponent intermolecular condensation, for producing *N,S*-containing macroheterocycles from binucleophilic anilines,  $\text{CH}_2\text{O}$  and  $\text{H}_2\text{S}$ .

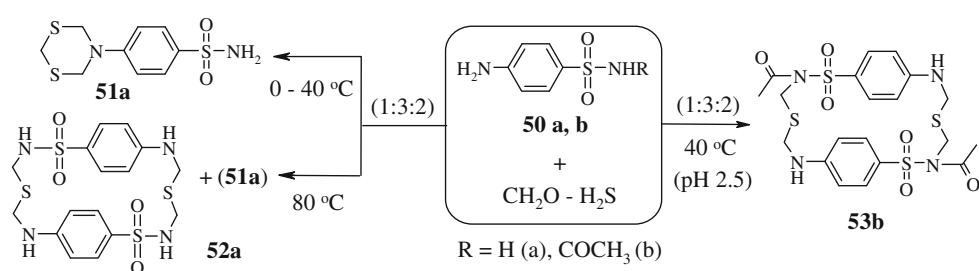
It was previously shown that cyclothiomethylation of *p*-aniline sulfamide **50a** at  $80^\circ\text{C}$  together with the formation of dithiazinane **51a** (56%) undergoes intermolecular condensation to give cyclodimer **52a** (14%) [30]. Analogous inter-



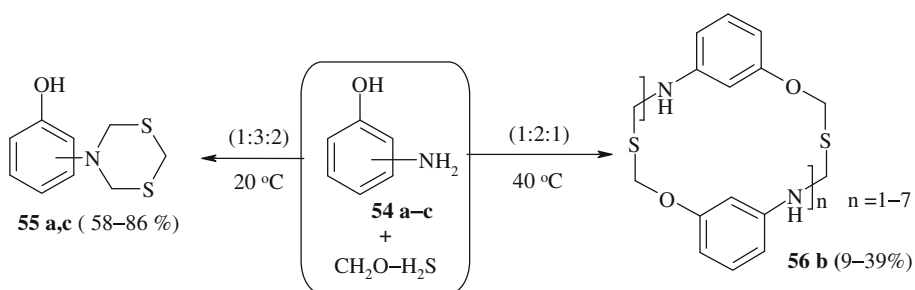


**Fig. 7** General view of compounds **44a**, **44b** and **46b** (crystal structures)

**Scheme 11** MCR of *p*-aniline sulfamides, CH<sub>2</sub>O and H<sub>2</sub>S in different conditions (pH, temperature)



**Scheme 12** MCR of *o*-, *m*-, *p*-aminophenols in the synthesis of 1,3,5-dithiazinanes and thioaza macrocycles



molecular cyclocondensation of *p*-aniline sulfacetamide **50b** in acidic media (pH 2.5) leads to cyclodimer **53b** (50%), which is built from two fragments of *p*-aniline sulfacetamide linked by dimethyl sulfide chain (Scheme 11).

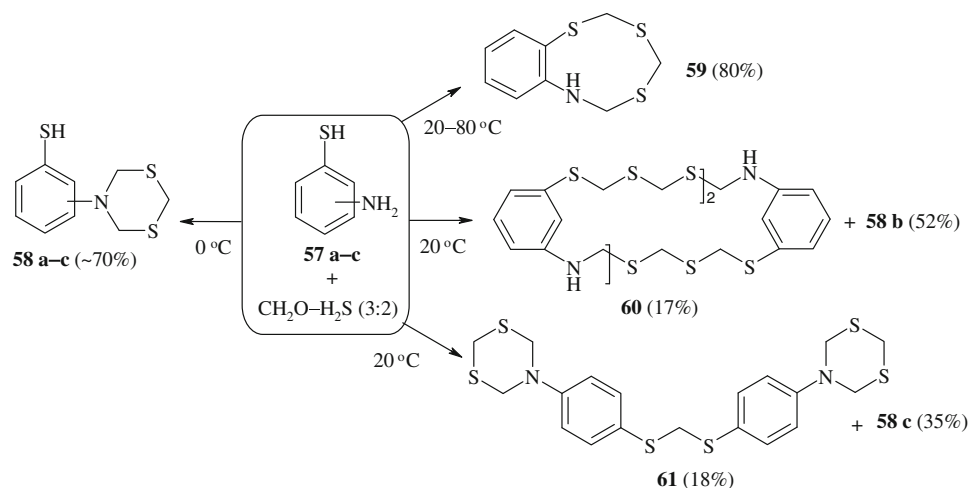
The route of cyclocondensation of OH-substituted anilines, namely *o*-, *m*- and *p*-aminophenols **54a–c** with CH<sub>2</sub>O and H<sub>2</sub>S depends on the relative position of amino and hydroxyl groups (Scheme 12) [36].

Aminophenols, *o*- and *p*-isomers, were established to interact with CH<sub>2</sub>O and H<sub>2</sub>S as a reactant mixture (3:2 ratio) to form 1,3,5-dithiazinanes **55a, c**. *m*-Aminophenol with CH<sub>2</sub>O and H<sub>2</sub>S at a ratio 1:2:1 in EtOH–H<sub>2</sub>O media

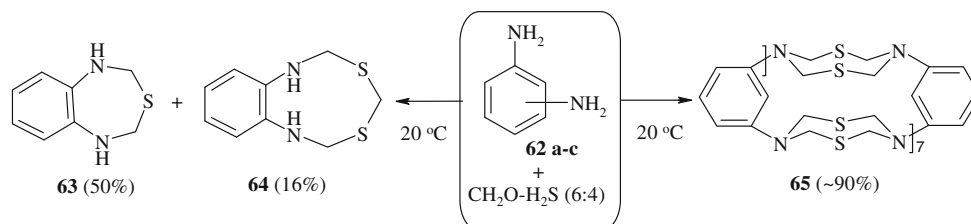
at 40 °C undergoes intermolecular condensation simultaneously involving OH and NH<sub>2</sub> groups to form macroheterocycle **56b**. Different reactivity of isomeric aminophenols under interaction with CH<sub>2</sub>O and H<sub>2</sub>S is caused by the change in NH<sub>2</sub> group basicity and OH-group acidity according to their arrangement in the aromatic ring.

Heterocyclization of *o*-, *m*-, *p*-aminothiophenols **57a–c** with CH<sub>2</sub>O and H<sub>2</sub>S (1:3:2 ratio, EtOH–H<sub>2</sub>O media) at 0 °C proceeds at the NH<sub>2</sub> group of the original monomer to afford the 1,3,5-dithiazinanes **58a–c** in ~70% yield. An increase in temperature facilitates the participation of both functional groups in the condensation process. For example, the inter-

**Scheme 13** MCR of *o*-, *m*-, *p*-aminothiophenols, CH<sub>2</sub>O and H<sub>2</sub>S at different temperature



**Scheme 14** MCR of *o*-, *m*-phenylenediamines, CH<sub>2</sub>O and H<sub>2</sub>S



action between *o*-aminothiophenol **57a** and the thiomethylating reagent CH<sub>2</sub>O-H<sub>2</sub>S at a ratio 1:3:2 at 20–80 °C was shown to produce 6,7-dihydro-1,3,5,7-benzotrithiazonine **59** in 80% yield. Under similar conditions, *meta* **57b** and *para* **57c** isomers enter the condensation reaction with CH<sub>2</sub>O and H<sub>2</sub>S at 20 °C to form 1,3,5-dithiazinanes **58b, c** and products of intermolecular condensation **60, 61** (Scheme 13). Macroheterocycle **60** was isolated by fractional crystallization and its identity confirmed by <sup>1</sup>H- and <sup>13</sup>C-NMR, and mass spectrometry.

Reactivity of *o*-, *m*-, *p*-phenylenediamine **62a–c** in MCR with CH<sub>2</sub>O and H<sub>2</sub>S depends on their basicity. Therefore, *para* isomer **62c** with higher basicity ( $K_b = 110 \times 10^{-10}$ ) [37] does not interact with CH<sub>2</sub>O-H<sub>2</sub>S. Under similar conditions, *ortho* **62a** ( $K_b = 3.3 \times 10^{-10}$ ) and *meta* **62b** ( $K_b = 7.6 \times 10^{-10}$ ) isomers undergo cyclocondensation with formation of thioaza heterocycles **63–65** (Scheme 14).

In summary, it was shown that the route of these MCR depends on the structure of substituted anilines. Therefore, *o*-aminothiophenol **57a** and *o*-phenylenediamine **62a** undergo intramolecular condensation, while *m*-isomers **57b** and **62b** undergo intermolecular condensation by CH<sub>2</sub>O and H<sub>2</sub>S at 20 °C with formation of macroheterocycles.

## Conclusion

Thus, the developed regioselective one-pot methods through the MCR of primary amines with aldehydes and H<sub>2</sub>S

appeared to be effective pathways to synthesize functionally substituted 1,3,5-dithiazinanes, 1,3,5-thiadiazinanes, and 1,5-dithia-3,7-diazacyclooctanes. The stereochemical structures of the synthesized heterocycles have been confirmed by X-ray analysis, and it has been demonstrated that the anomeric effect occurs for cycles with N–C–S system.

Our research into heterocyclization of bifunctional amines with CH<sub>2</sub>O and H<sub>2</sub>S have resulted in discovery of the new kinds of MCR, such as intramolecular cyclization of aliphatic diamines and hydrazine in the synthesis of the novel classes of *N,S*-containing annulated bicyclooctanes as well as intermolecular condensation of bifunctional anilines with CH<sub>2</sub>O and H<sub>2</sub>S in the synthesis of thioaza macrocycles.

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