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Aminomethylation of morpholinium and *N*-methylmorpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates

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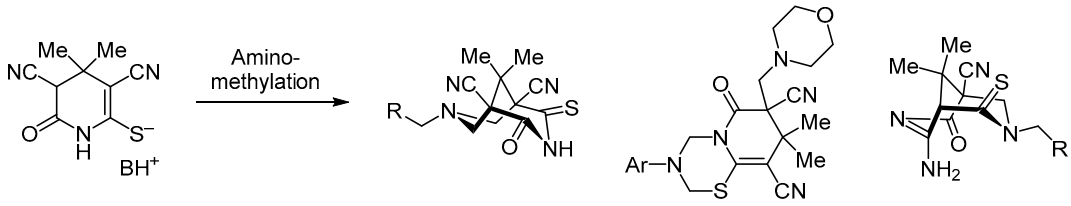


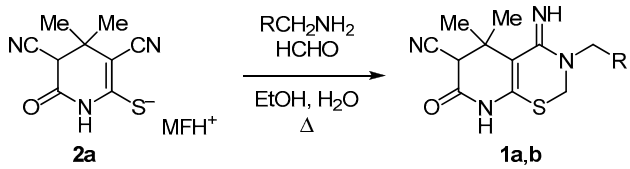
The structure of reaction products obtained from 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates, primary amines, and formaldehyde substantially depends on the nature of counter-ion (morpholinium or *N*-methylmorpholinium), as well as on the primary amine structure and the ratio of reactants. Aminomethylation of these thiolates with highly nucleophilic amines RCH_2NH_2 and excess formalin (2 equiv and more) produced 7-RCH_2-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile salts, which gave the respective bispidines upon acidification. Performing this reaction with aromatic amines in the case of *N*-methylmorpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate led to analogous bispidines, while the morpholinium salt gave 3-aryl-8,8-dimethyl-7-[(morpholin-4-yl)methyl]-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-7,9-dicarbonitriles. The treatment of thiolates with 1 equiv of HCHO and 1 equiv of RCH_2NH_2 led to 7-RCH_2-4-amino-9,9-dimethyl-2-oxo-6-thioxo-3,7-diazabicyclo[3.3.1]non-3-ene-1-carbonitriles. The molecular and crystal structures of key compounds were studied in detail by X-ray structural analysis.

Keywords: bispidines, 3,7-diazabicyclo[3.3.1]nonanes, pyrido[2,1-*b*][1,3,5]thiadiazines, tetrahydropyridine-2-thiolates, aminomethylation, Mannich reaction, recyclization, tandem reactions, X-ray structural analysis.

An unusual synthesis of pyrido[3,2-*e*][1,3]thiazine derivatives **1** by aminomethylation of morpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (**2a**) using 4 equiv of formaldehyde and 1 equiv of benzylamine or furfurylamine was recently described by Nikishin[1,2] (Scheme 1).

These findings were clearly different from both the general trends of Mannich reactions, as well as the results of our studies regarding the aminomethylation reactions of analogous pyridine-2-thiolates and related compounds,[3–23] therefore we decided to study this reaction in detail and to

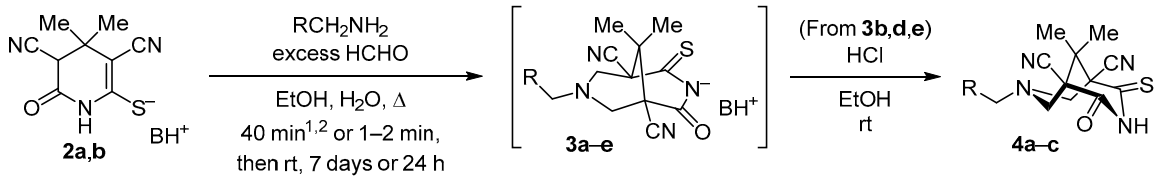
Scheme 1



2a **1a,b**

MFH^+ = morpholinium ion; **1 a** R = Ph, **b** R = 2-furyl

Scheme 2



2 a BH^+ = MFH^+, **b** BH^+ = *N*-methylmorpholinium ion ($NMMH^+$); **3 a** BH^+ = MFH^+, R = Ph; **b** BH^+ = $NMMH^+$, R = Ph; **c** BH^+ = MFH^+, R = 2-furyl; **d** BH^+ = $NMMH^+$, R = H; **e** BH^+ = MFH^+, R = CH_2Ph; **4 a** R = Ph, **b** R = H, **c** R = CH_2Ph

determine the structure of the obtained products. Since the morpholinium salt **2a** and *N*-methylmorpholinium salt **2b** were reported in a dissertation[2] with the same designation, we decided to investigate the reactivity of both salts under the conditions of aminomethylation reaction. We found that the results of the aforementioned publications[1,2] could not be reproduced even when all the indicated conditions were followed exactly. For example, refluxing alcohol solutions of thiolates **2a**,**b** with 1 equiv of $PhCH_2NH_2$ and 4 equiv of HCHO as 37% formalin for 2 h failed to produce a precipitate of the product. It was shown by HPLC-MS and ^{1}H NMR analysis of the yellow resinous residue obtained after evaporation of the reaction solution that in both cases the only reaction products were the respective 7-benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile salts **3a**,**b** (Scheme 2). Previously we had described[19] the formation of similar salts ("bispidinates") during aminomethylation of 3,5-bisnucleophilic pyridine substrates. Careful acidification of the reaction mixture led to the formation of crystalline 7-benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (**4a**) (37% yield from salt **2a**, 39% yield from salt **2b**). The application of a method that we previously tested with analogous substrates,[7,8,19] based on a brief heating of thiolate and amine with a large excess of formalin (≥ 10 equiv), allowed to increase the yield of compound **4a** to 46%. Other aliphatic amines reacted analogously with the thiolates **2a**,**b** in the presence of excess HCHO, producing after acidification the bispidines **4b**,**c** (Scheme 2). It should be emphasized that the obtained results were entirely predictable and closely matched the behavior of analogous tetrahydropyridine derivatives under the Mannich reaction conditions.[4,7,8,19]

It should be noted that our attempts to obtain the bispidine **4d** (R = 2-furyl) failed: treating the thiolate **2a** with furfurylamine (1 equiv) and excess HCHO under various conditions gave only intractable resinous mixtures. According to HPLC-MS data, besides the bispidine **4d** the mixture contained at least two additional compounds with higher molecular mass.

The structure of diazabicyclononanes **4** was confirmed by a set of spectral methods, as well as the X-ray structural analysis results for compound **4a** (Fig. 1).

Compound **4a** existed in crystalline state as two conformers that differed by the orientation of benzyl substituent relative to the carbonyl and thione groups. The substituent in both conformers had an equatorial orientation (the torsion angle C(12)–N(2)–C(6)–C(4) was 178.84(18)°) and assumed an *–sc* conformation relative to the N(2)–C(6) bond (the torsion angle C(6)–N(2)–C(12)–C(13) was –69.0(2)°). Both conformers occupied equivalent positions in the crystal, resulting in disordered oxygen and sulfur atom positions in the carbonyl and thione groups populated in 0.590(6) : 0.410(6) ratio. The N(2) nitrogen atom had a pyramidal configuration, with the sum of valence angles at the atom equal to 332.1°. The molecules were linked in the crystal structure with N(1)–H(1)···N(4^i) hydrogen bonds [i: $1-x, -1/2+y, 1/2-z$] (H···N 2.38 Å, N–H···N 140°) as infinite chains along the *b* axis.

The bispidines **4** were isolated as bright-yellow crystals, readily soluble in acetone, hot alcohols, AcOH, insoluble in ether and cold EtOH. IR spectra of diazabicyclononanes **4** featured a weak absorption band, corresponding to the stretching vibrations of non-conjugated C≡N groups (2246–2258 cm^{-1}). ^{1}H NMR spectra of compounds **4a**–**c**,**e** contained characteristic singlets of diastereotopic methyl groups at 1.29–1.36 and 1.46–1.56 ppm, signals of

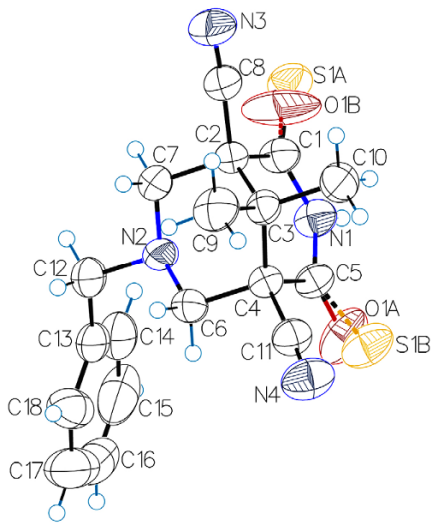
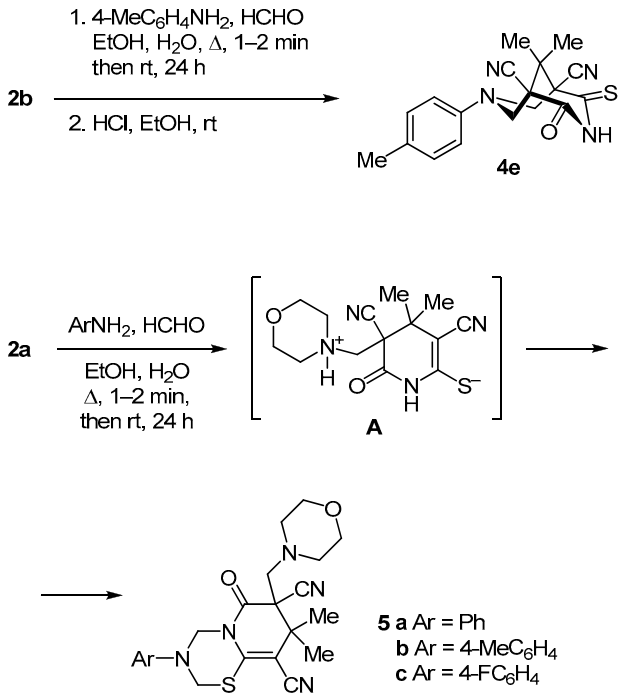


Figure 1. The molecule of compound **4a** with atoms represented by thermal vibration ellipsoids of 50% probability. The bonds involving the minor component are shown as dotted lines.

Scheme 3



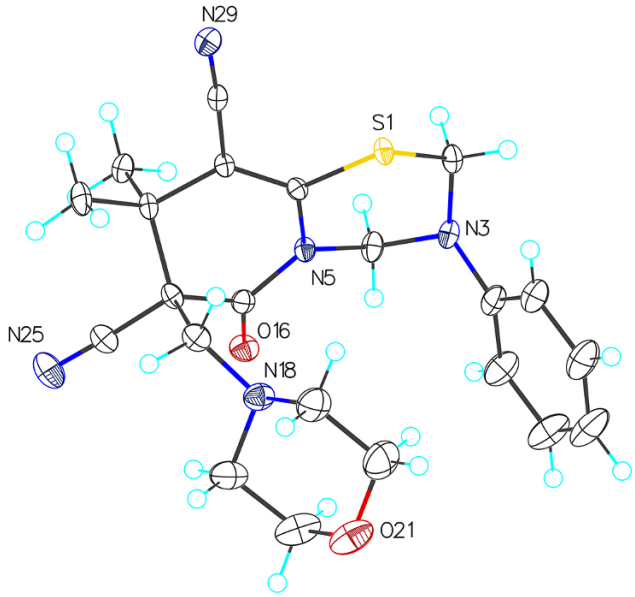


Figure 2. The molecule of compound **5a** with atoms represented by thermal vibration ellipsoids of 50% probability.

CH_2NCH_2 group in the region of 3.00–3.97 ppm, as well as a broadened NH proton singlet in the downfield region at 13.55–13.81 ppm.

The different reactivity of morpholinium and *N*-methylmorpholinium salts **2a**,**b** was observed by using the less reactive anilines $ArNH_2$ in the reaction instead of primary amines RCH_2NH_2. For example, the *N*-methylmorpholinium thiolate **2b** reacted with *p*-toluidine and excess HCHO, giving the expected diazabicyclononane **4e**, while aminomethylation of the morpholinium salt **2a** unexpectedly led to 3-aryl-8,8-dimethyl-7-[(morpholin-4-yl)methyl]-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-7,9-dicarbonitriles **5a**–**c** (Scheme 3). Obviously, the change in reaction direction was caused by blocking of the reaction site at the C-5 atom, which was subjected to competing aminomethylation with the participation of morpholine at the first reaction step, with the preferential formation of betaine intermediate **A**. The latter further reacted with $ArNH_2$ and HCHO as an *S*,*N*-bisnucleophile, with the closure of 1,3,5-thiadiazine ring. As we have shown several times in the past,[3,12–14,16,17,21–23] the formation of pyrido[2,1-*b*]-[1,3,5]thiadiazine system is a general outcome of aminomethylation reactions for all partially hydrogenated pyridine-2-thiolates that do not contain an electron-withdrawing substituent at the C-5 atom.

The structure of compounds **5a**–**c** was confirmed by spectral data sets, including one-dimensional ^{13}C (DEPT-135, APT) and two-dimensional (^1H–^{13}C HSQC, ^1H–^{13}C HMBC) NMR experiments, as well as single crystal X-ray structural analysis of 8,8-dimethyl-7-[(morpholin-4-yl)methyl]-6-oxo-3-phenyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-7,9-dicarbonitrile (**5a**) (Fig. 2). The S(1)–C(2)–N(3)–C(4)–N(5)–C(9A) ring in the central bicyclic system assumed a chair conformation, while the N(5)–C(6)–C(7)–C(8)–C(9)=C(9A) ring had a half-boat conformation. The phenyl substituent at the N(3) atom occupied an axial position, enabling stereoelectronic interactions *lp*-N(3)–C(2)–S(1) and *lp*-N(3)–C(4)–N(5) (the respective pseudodihedral angles were 178° and 175°), analogously to the conformational features observed for aryl-substituted 1,3,5-thiadiazinanes.[24] The presence of anomeric effect was also indicated by the bond lengths:[25] the N(3)–C(4) bond (1.4330(15) Å) was substantially shortened compared to the C(4)–N(5) bond (1.4970(15) Å), while the S(1)–C(2) bond was lengthened to 1.8428(12) Å, compared to the values typical for C(sp^3)–S bonds (1.817 Å).[26]

Crystals of compound **5a** were formed by van der Waals interactions, among which the relatively close intermolecular contact (Fig. 3) of cyano group with the S–CH_2 bond should be noted: N(3)···S(2^i) (3.1704(12) Å) and N(3)···H($2B^i$)–C(2^i) (N···C 3.1855(17) Å), with the C(12)≡N(3)···S(1^i) angle

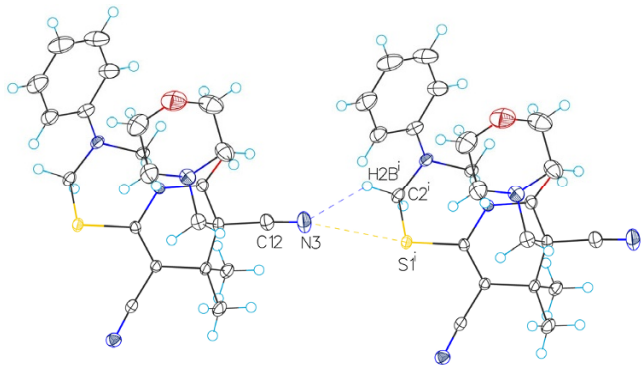


Figure 3. The C≡N···(CH_2–S) contact in the crystal of compound **5a**. Only the atoms participating in the interaction have been identified, the index *i* in superscript corresponds to symmetry operation (1 + *x*, –1 + *y*, +*z*).

equal to 168.32(12) Å, indicating the directional nature of C≡N···S interaction.

The Cambridge Crystallographic Data Center (CCDC)[27] contains only one example of geometrically analogous intermolecular contact in crystals of (4-oxo-3-phenyl-1,3-thiazolidin-2-ylidene)malononitrile.[28] At the same time, the complete interaction map prediction procedure[29] performed with CCDC Mercury 3.5 program indicated that the position of cyano group nitrogen atom in the crystal structure **5a** corresponds to the region of maximum probability for the formation of contact involving the oxygen atom of carbonyl group. The complete interaction mapping procedure relied on statistical data about intermolecular contacts between the most common functional groups and therefore was not applied to nitriles (due to the relatively small number of similar structures available from CCDC), but we can assume that the nitrogen atom of C≡N group has similar electronic properties to the oxygen atom of C=O group, and thus the aforementioned C≡N···CH_2–S contact is energetically favorable and significant for the formation of crystal structure, instead of being forced.

IR spectra of compounds **5a**–**c**, unlike the spectra of diazabicyclononanes **4a–c**,**e**, contained two absorption bands corresponding to the stretching vibrations of conjugated (2201–2204 cm^{-1}) and non-conjugated (2247–2249 cm^{-1}) nitrile groups. An interesting feature of the HPLC-MS data (obtained with ES-API ionization) for the compounds **5a**–**c** was the absence of molecular ion peaks, while the peaks of $[M–CH_2N(CH_2CH_2)_2O+2H]^+$ and $[M–CH_2N(CH_2CH_2)_2O]^-$ ions were observed instead. A complete assignment of ^1H and ^{13}C NMR signals for compounds **5a**–**c** was based on the analysis of two-dimensional ^1H–^{13}C HSQC and ^1H–^{13}C HMBC spectra for compound **5a**. The most significant correlations of ^1H–^{13}C HMBC NMR spectrum for compound **5a** are shown in Figure 4.

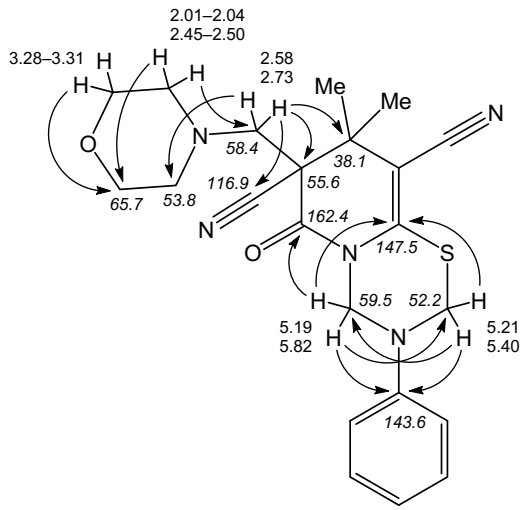


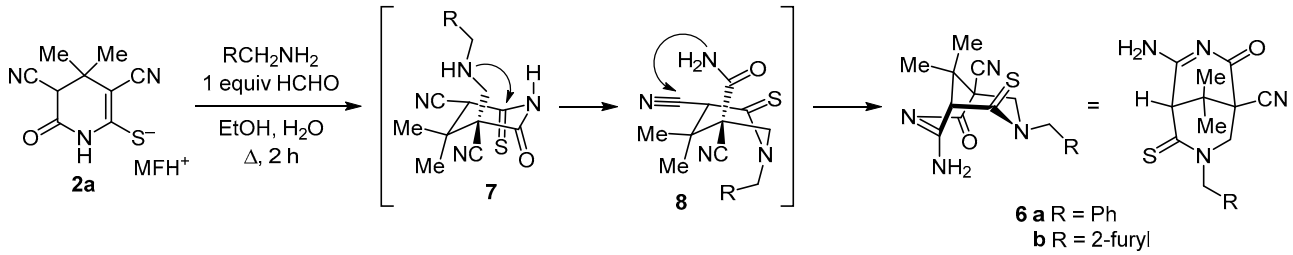
Figure 4. The principal correlations in the ^1H–^{13}C HMBC spectrum of compound **5a**.

Thus, we have clearly established that aminomethylation of thiolates **2a**,**b** either by literature procedures[1,2] or in the presence of excess formalin led to bispidines **4** or pyridothiadiazines **5**, depending on the structure of primary amine and the substrates **2a**,**b**. The direction of this reaction was substantially affected not only by the nature of reactants, but also by their ratio, in particular the amount of formalin used. We noticed that 4 equiv of formaldehyde were used[1,2] for the synthesis of pyridothiazines **1**, while the thiolate **2a** and HCHO actually reacted in equimolar ratio. It should also be noted that the formation of bispidines **4** was observed in all cases when the amount of formaldehyde used in the reaction was equal or higher than required by the reaction stoichiometry (2 equiv). Detailed analysis of spectral data and HPLC-MS results for compounds **1a**,**b**[1,2] allowed to make the following conclusions: a) the described compounds arise from the condensation of thiolates **2** with HCHO and primary amine in 1:1:1 ratio, and b) the presented spectral data of the products do not correspond to the reported pyrido[3,2-*e*]-[1,3]thiazine structures of compounds **1a**,**b**. In order to reproduce these results, we proposed that the amount of formaldehyde actually used in the reaction was 1 equiv instead of the indicated 4 equiv*. Indeed, the interaction of thiolate **2a**, 1 equiv of HCHO, and 1 equiv of benzylamine (or furfurylamine) in aqueous EtOH led to the formation of products identical to those described in the literature[1,2] as pyrido[3,2-*e*][1,3]thiazines **1a**,**b**. In order to establish the actual structure, the obtained samples were characterized by a set of spectral methods (IR, ^1H NMR, ^{13}C NMR, solid state ^{13}C DEPT-135 and APT, ^1H–^{13}C HSQC, ^1H–^{13}C HMBC, and NOESY), as well as HPLC-MS and elemental analysis. It was established that the obtained compounds had the structure of 7-RCH_2-4-amino-9,9-dimethyl-2-oxo-6-thioxo-3,7-diazabicyclo-[3.3.1]non-3-ene-1-carbonitriles **6a**,**b**. Besides that, the structure of 4-amino-7-benzyl-9,9-dimethyl-2-oxo-6-thioxo-3,7-diazabicyclo[3.3.1]-non-3-ene-1-carbonitrile (**6a**) was studied by X-ray structural analysis (Fig. 5).

The low quality of the studied crystals resulted in a relatively low accuracy of intermolecular distances (the average accuracy of C–C bond lengths was ±0.012 Å), which did not allow to discuss in detail the molecular geometry of compound **6a**. Nevertheless, we should note that both rings of the 3,7-diazabicyclo[3.3.1]non-3-ene system assumed a sofa conformation with the C(9) atom deviating from the plane of other atoms. Molecules of compound **6a** formed ribbons in the crystal structure along the crystallographic axis *a*, linked by N(2)–H(2A)···N(11) (N···N 2.933(9) Å, N–H···N 163(8)°) and N(2)–H(2B)···O (22) (N···O 2.821(8) Å, N–H···O 170(8)°) hydrogen bonds, and the positions of hydrogen bond acceptors matched the predictions made from the complete interaction maps for carbonyl groups.[29]

* This assumption was confirmed during the private communication with the authors of works:[1,2] instead of 37% formalin, HCHO solution with lower concentration with a density of $d \sim 1.01$ g/ml, obtained by separation of the paraformaldehyde from formalin stored in the cold, was used.

Scheme 4



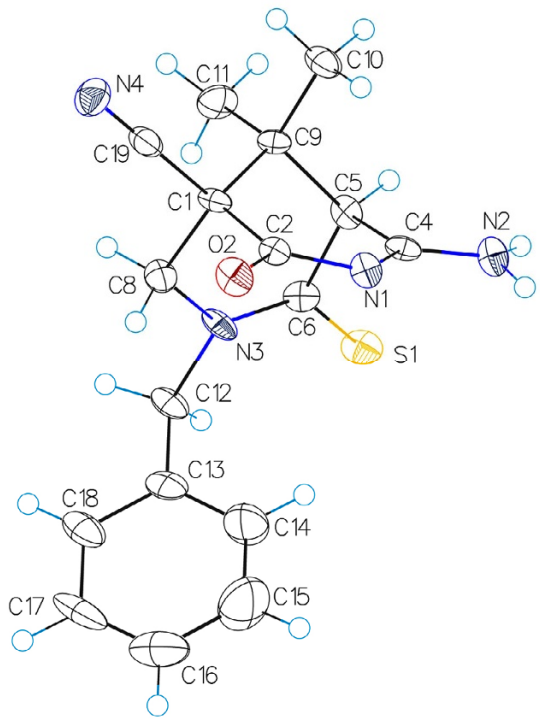


Figure 5. The molecule of compound **6a** with atoms represented by thermal vibration ellipsoids of 50% probability.

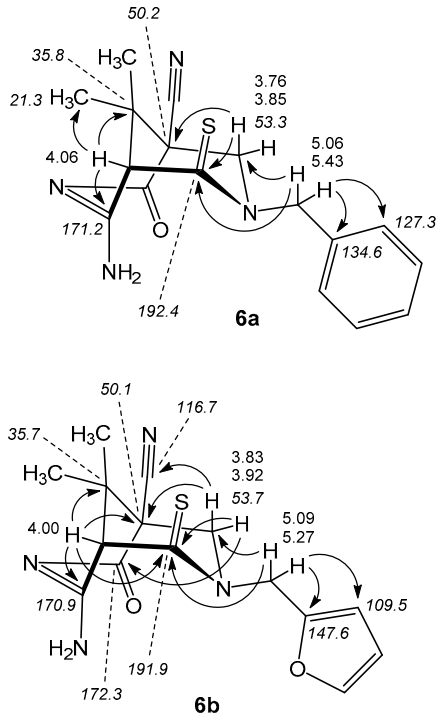


Figure 6. The correlations in $^{1}H–^{13}C$ HMBC spectra of compounds **6a**,**b**.

A possible mechanism for the formation of bicyclic systems **6a**,**b** is presented in Scheme 4. The initial products of C(5)-aminomethylation **7a**,**b** probably undergo recyclization to piperidines **8a**,**b**, followed by cascade cyclization process that leads to the formation of compounds **6a**,**b**.

Compounds **6a**,**b** are pale-yellow or white powders, practically insoluble in alcohols, acetone, MeCN, pyridine, THF, water, and aqueous acids. Compounds **6a**,**b** have limited solubility in DMSO and in hot AcOH. There is a weak absorption band in IR spectra of compounds **6a**,**b**, corresponding to the stretching vibrations of non-conjugated C≡N group at 2245–2247 cm^{-1}, and a wide carbonyl absorption band at 1661–1662 cm^{-1}. The absorption bands corresponding to stretching vibrations of N–H bonds are observed at 3294–3296 cm^{-1}. Cross peaks were observed in 2D NOESY spectra of compounds **6a**,**b** between the proton signals of methyl groups and the 5-CH protons, as well as between the protons of 8-CH_2 group and those of CH_3 and CH_2Ar groups. The most significant correlations in $^{1}H–^{13}C$ HMBC spectra of compounds **6a**,**b** are shown in Figure 6.

The aminomethylation reaction of thiolates **2a**,**b** is generally quite sensitive both towards the ratio of reactants used and their nature. Thus, even a small excess of HCHO relative to the starting thiolates **2** resulted in preferential formation of bispidines **4**. At the same time, when thiolate **2a** and formaldehyde were used in equimolar ratio, the addition of excess amine did not affect the direction of reaction and helped to increase the yield of compounds **6**. The reaction of thiolate **2a** with 1 equiv of formaldehyde and 1 equiv of aromatic amine (*p*-toluidine or *p*-anisidine) according to an analogous scheme did not result in the formation of bicyclic structures **6**: after refluxing for 30 min and cooling of the reaction mixture the starting thiolate **2a** crystallized in 31–33% yield. Quite interesting results were obtained by refluxing an ethanol solution containing equimolar amounts of furfurylamine, formaldehyde, and thiolate **2a** without the addition of water: yellow crystals were isolated from the reaction mixture, the analysis of which by spectral methods revealed that this sample was structurally closely related (but not identical!) to compound

6b. According to ^{1}H NMR data for a crude sample of bicyclic compound **6b**, the new compound was also detected there as impurity (~7–10 mol %) and represented an isomer of compound **6b**.

Based on the spectral data set (IR, ^{1}H and ^{13}C NMR, DEPT-135, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, and NOESY), as well as the results of HPLC-MS analysis, the structure of 4-amino-7-(2-furylmethyl)-9,9-dimethyloxo-2-thioxo-3,7-diazabicyclo-[3.3.1]non-3-ene-1-carbonitrile (**9**) was assigned to the obtained isomer (Scheme 5). ^{1}H NMR spectra of compounds **6b** and **9** were quite similar (Fig. 7), and the mass spectra of compounds **9** and **6b** contained molecular ion peaks at *m*/*z* values of 317.1 $[M+H]^+$ and 315.0 $[M–H]^-$. Key differences were found in 2D ^{1}H–^{13}C HMBC spectra: the C(6)=S carbon signal (191.9 ppm) in the spectrum of compound **6b** gave cross peaks with three groups of protons: 8-CH_2 (3.83/3.92 ppm), 5-CH (4.00 ppm), and NCH_2Fur (5.09/5.27 ppm), while ^{1}H–^{13}C HMBC spectrum of compound **9** only contained correlations of the C=S carbon signal (209.0 ppm) with the 8-CH_2 protons (3.71/3.79 ppm). The 5-CH proton singlet (4.00 ppm) in spectrum of compound **6b** gave cross peaks with the signals of C=S and C-4 carbon atoms (191.9 and 170.9 ppm), but not with C=O carbon atom (172.3 ppm), while the spectrum of bicyclic compound **9** contained cross peaks of 5-CH proton singlet (3.40 ppm) with the signals of C=O (161.7 ppm) and C-4 carbon atoms (164.5 ppm), but not with the C=S carbon signal (209.0 ppm).

Thus, the aminomethylation reaction of thiolate **2a** with formaldehyde and primary amines of benzyl type at the ratio of 1:1:1 proceeded non-selectively at the positions C-3 and C-5, at least in the case of furfurylamine (Scheme 5). This was indirectly supported by the low yields of products **6a**,**b**. Compound **9** probably can be considered to be the product of kinetic control, and also had a better solubility compared to the compound **6b**. Obviously, the reaction proceeded through the formation of intermediates **10** and **11**, which were isomeric to the intermediates **7** and **8**.

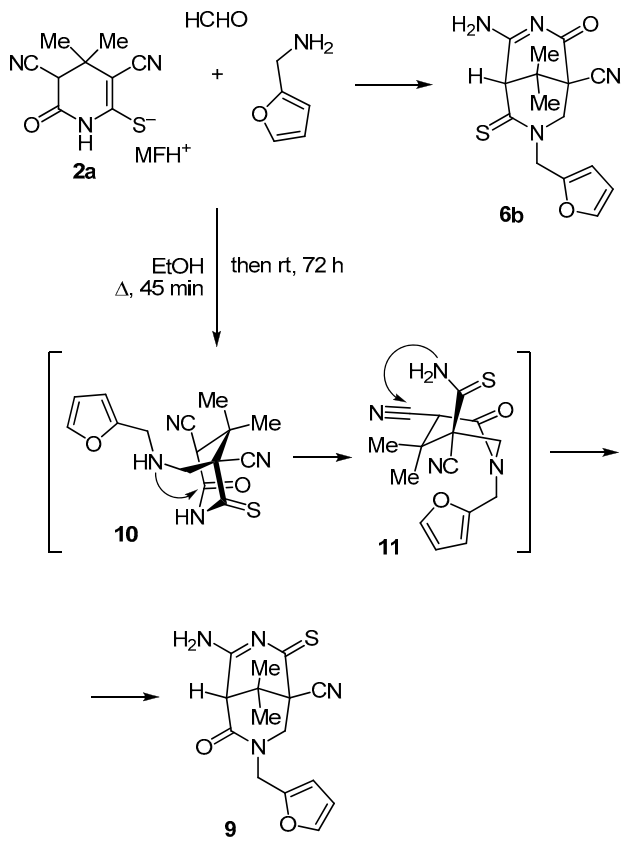
To summarize these observations, the following conclusions can be made:

– the published results[1,2] describing the synthesis of pyrido[3,2-*e*][1,3]thiazine derivatives by aminomethylation of morpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate are in doubt and can be explained by inaccurate experimental data and erroneous interpretation of spectral features;

– the direction of aminomethylation reactions of morpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate and the analogous *N*-methylmorpholinium salt with primary amines and formaldehyde substantially depend on the structure of cationic part in the starting salts **2a**,**b** and the nucleophilicity of primary amines, as well as the amount of formaldehyde used in the reaction;

– two previously unreported reactions were identified, demonstrating new directions of aminomethylation in N,C,S-polynucleophilic substrates of pyridine series: 1) the reaction leading to 7-[(morpholin-4-yl)methyl]pyrido-[2,1-*b*][1,3,5]thiadiazines and 2) unusual cascade process leading to the formation of 3,7-diazabicyclo[3.3.1]non-3-ene derivatives. Detailed study of the new reactions will be the topic of our further studies.

Scheme 5



Experimental

IR spectra were recorded on an Infraspek FSM-1201 FT-IR spectrometer with ATR accessory. ^{1}H NMR spectra were acquired on Bruker DPX-400 (400 MHz, compounds **2b**, **4a**,**b**), Bruker Avance II 400 (400 MHz, compounds **5a**, **6a**,**b**, **9**), and Bruker Avance 500 (500 MHz, the rest of the compounds) spectrometers in 1:2 CCl_4–DMSO-d_6 (compounds **5a**, **6a**,**b**, **9**) or DMSO-d_6 (the rest of the compounds), with TMS as internal standard. ^{13}C NMR spectra were acquired on a Bruker Avance 500 (126 MHz) spectrometer in DMSO-d_6 (compounds **2a**, **4a**,**e**, **5c**) and on a Bruker Avance II 400 (101 MHz) spectrometer in 1:2 CCl_4–DMSO-d_6 (the rest of the compounds), with TMS as internal standard. ^{13}C APT NMR spectra were acquired on a Bruker Avance 500 (126 MHz) spectrometer in DMSO-d_6, with TMS as internal standard. ^{13}C DEPT-135 NMR spectra, as well as two-dimensional NMR spectra (NOESY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC) were acquired on a Bruker Avance II 400 spectrometer in 1:2 CCl_4–DMSO-d_6, with TMS as internal standard. HPLC-MS analysis of compound **2b** was performed on a Shimadzu LC-10AD liquid chromatograph with Shimadzu SP D-10A UV-Vis

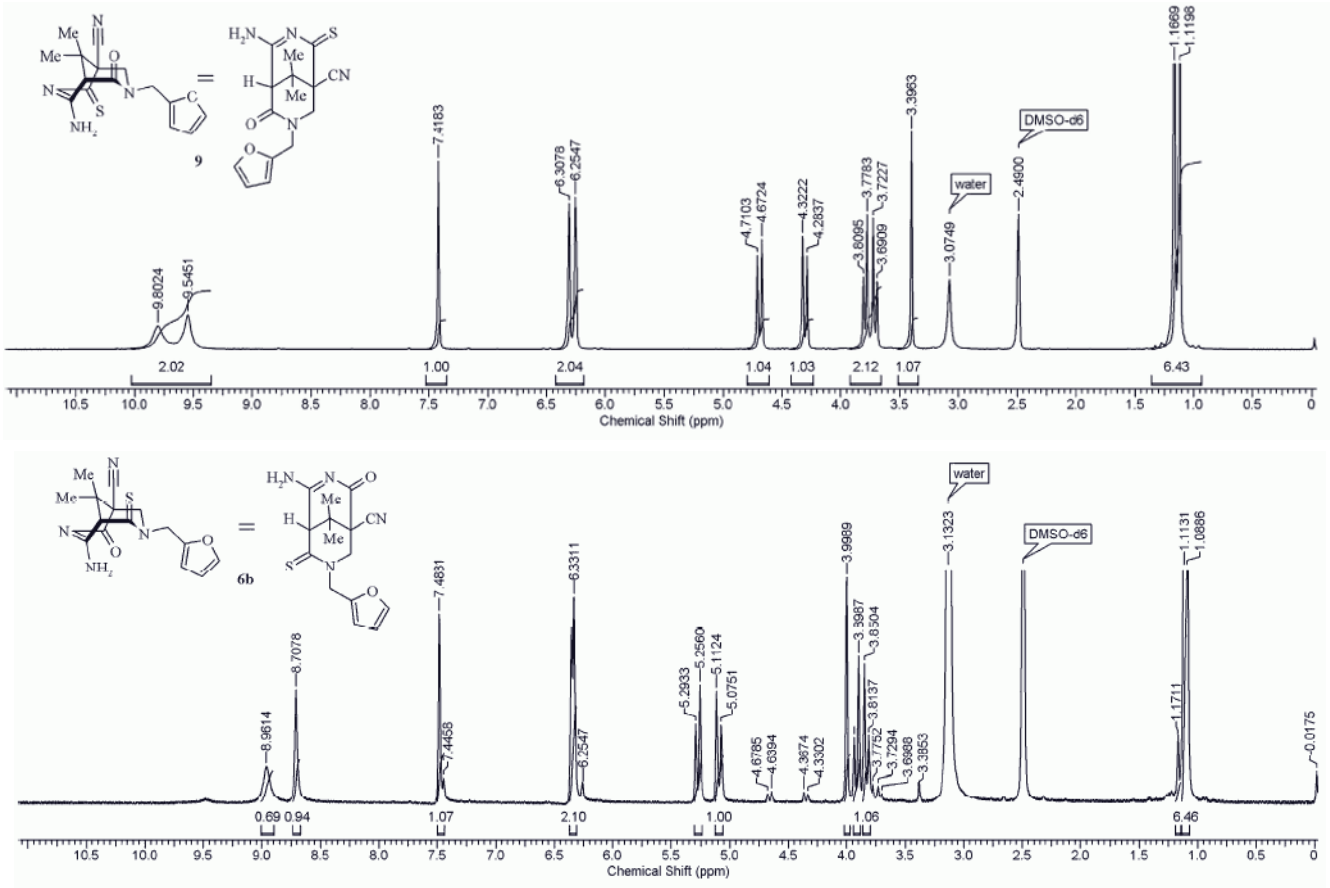


Figure 7. ^{1}H NMR spectra of the isomeric compounds **9** and **6b** (400 MHz, 1:2 CCl_4–DMSO-d_6).

(254 nm) and Sedex 75 ELSD detectors, in combination with PE SCIEX API 150EX mass spectrometer, with electrospray ionization at atmospheric pressure (ES-API). HPLC-MS analysis for the rest of the compounds was performed on an Agilent 1200 instrument, Rapid Resolution HT Cartrige 4.6×30 mm, 1.8 μm, Zorbax SB-C18 column, DAD and MS detectors, ES-API ionization. Mass spectra were recorded on a Minpribor MX1321 spectrometer using a system for direct introduction of sample, ionization methods: fast atom bombardment (FAB, compound **5c**) and electron impact (EI, the ionization chamber temperature was 200°C and ionizing electron energy was 70 eV, compounds **4a**, **5c**). Elemental analysis was performed on a Carlo-Erba 1106 Elemental Analyzer. The individuality of the synthesized compounds was controlled by TLC on Silufol UV 254 plates in 1:1 acetone–hexane system, visualization with iodine vapor or UV light.

The starting **3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates 2a**,**b** were obtained according to a published procedure[30] with some modifications: cyanothioacetamide[32] (1.30 g, 13.0 mmol) and base (morpholine or *N*-methylmorpholine) (19.5 mmol) were added to a solution of isopropylidene cyanoacetic ester[31] (3.0 g, 19.6 mmol) in 96% EtOH (12 ml). The mixture was stirred at room temperature, a precipitate of salt **2a** formed after 1–2 min, salt **2b** – after 20–25 min. The reaction mixture was maintained at 20°C for 48 h, the product was filtered off, washed with Me_2CO and Et_2O, giving thiolates **2a**,**b**, which were used in subsequent reactions without additional purification.

Morpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (2a). Yield 87%, beige powder, mp 217–219°C (decomp.) (mp 213–215°C[1]). IR spectrum, ν, cm^{-1}: 3223, 3198 (N–H), 2253 (5-C≡N), 2185 (3-C≡N), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.02 (3H, s, CH_3); 1.19 (3H, s, CH_3); 3.09–3.11 (4H, m, CH_2NCH_2); 3.73–3.75 (4H, m, CH_2OCH_2); 4.14 (1H, s, 5-CH); 8.67 (2H, very br. s, NH_2^+); 9.39 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 23.5; 26.8; 35.3; 42.9; 47.1; 63.3; 85.7; 116.3; 122.7; 161.1; 167.3. ^{13}C APT NMR spectrum, δ, ppm: 23.4* (CH_3); 26.7* (CH_3); 35.3 (C-4); 42.9 (CH_2NCH_2); 47.1* (C-5); 63.2 (CH_2OCH_2); 85.7 (C-3); 116.2 (5-CN); 122.6 (3-CN); 161.0 (C=O); 167.2 (C-2). ^{13}C DEPT-135 NMR spectrum, δ, ppm: 23.0 (CH_3); 26.4 (CH_3); 42.6* (CH_2NCH_2); 46.8 (C-5); 62.9* (CH_2OCH_2). Mass spectrum, *m/z*: 410.8 $[2M–2C_4H_9NO–H]^-$, 205.8 $[M–C_4H_9NO–H]^-$, 88.2 $[C_4H_9NO+H]^+$.

* Here and further an asterix in ^{13}C APT and DEPT-135 NMR spectra indicates opposite phase signals. The assignment of signals was based on ^{1}H–^{13}C HMBC spectra (see the Supplementary information).

***N*-Methylmorpholinium 3,5-dicyano-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (2b)**. Yield 82%, pale-yellow powder, mp 193–195°C (mp 190–192°C[30]). IR spectrum, ν, cm^{-1}: 3153, 3104 (N–H), 2251 (5-C≡N), 2175 (3-C≡N), 1701 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.02 (3H, s, CH_3); 1.19 (3H, s, CH_3); 2.80 (3H, s, NCH_3); 3.11–3.33 (4H, m, CH_2NCH_2); 3.63–3.91 (4H, m, CH_2OCH_2); 4.15 (1H, s, 5-CH); 9.40 (1H, s, NH); 9.60 (1H, very br. s, NH^+). Mass spectrum, *m*/*z*: 432.5 $[2M–2C_5H_{11}NO+H_2O]^+$.

Synthesis of 7-benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (4a) by the reaction of thiolates 2a,b with 1 equiv of benzylamine and 4 equiv of HCHO. Following a published procedure,[1,2] thiolate **2a** (2.94 g, 10 mmol) was added to a hot solution of benzylamine (1.1 ml, 10 mmol) and 37% formalin (3.0 ml,* 40 mmol) in 96% EtOH (15 ml). The mixture was refluxed for 40 min, during this time no precipitation was observed. The reaction with thiolate **2b** (3.08 g, 10 mmol) was performed analogously. Samples of reaction mixtures were analyzed by ^{1}H NMR and HPLC-MS, and no significant amounts of compound **1a** (*M* 326.4) were found. The main products in the reaction mixture were 7-benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile salts **3a**,**b**. Longer refluxing of the reaction mixture also did not result in the formation of product **1a**; evaporation of the solvent gave yellow resin, which according to HPLC-MS also predominantly consisted of salt **3a** or **3b**. After maintaining the obtained solution for one week at 25°C, it was treated by careful addition of a mixture consisting of concd. HCl and EtOH (1:1) until pH 3–4 was reached. After 96 h, the crystalline precipitate was filtered off, washed with cold EtOH and Et_2O. The yield of 7-benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (**4a**) in analytically pure form was 1.25 g (37%, from thiolate **2a**) or 1.31 g (39%, from thiolate **2b**), bright-yellow crystals, mp 208–210°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 3252, 3188 (N–H), 2258 (2 C≡N), 1726 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, s, CH_3); 1.46 (3H, s, CH_3); 3.00 (1H, d, ^2J = 11.6), 3.10 (1H, d, ^2J = 11.6) and 3.19–3.23 (2H, m, 6,8-CH_2); 3.70 (2H, AB quartet, ^2J = 13.7, N$C\underline{H}_2$Ph); 7.15 (2H, d, ^3J = 7.5, H Ph); 7.24–7.31 (3H, m, H Ph); 13.81 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 20.3 (CH_3); 23.3 (CH_3); 38.3 (C-9); 51.9 (C-1(5)); 52.0 (C-6(8)); 54.4 (C-5(1)); 58.3 (C-8(6)); 60.4 (N$\underline{C}H_2$Ph); 114.9 (C≡N); 115.9 (C≡N); 127.5 (C Ar); 128.2 (C Ar); 128.4 (C Ar); 136.3 (C Ar); 164.5 (C=O); 200.6 (C=S). Mass spectrum (ES-API), *m*/*z*: 339.1 $[M+H]^+$, 337.0 $[M–H]^-$. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 338 $[M]^+$ (8), 133 (13), 120 $[PhCH_2NH{=}CH_2]^+$ (8), 92 (9), 91 $[PhCH_2]^+$ (100), 65 (10), 43 (19). Found, %: C 63.84; H 5.45; N 16.50. $C_{18}H_{18}N_4OS$. Calculated, %: C 63.88; H 5.36; N 16.55.

Synthesis of 7-R-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles 4a–c,e (General method). A mixture of thiolate **2a**,**b** (1.1 mmol), 37% formalin that was free of paraform impurity (0.7 ml, 9.5 mmol), and the respective primary amine (1.1 mmol) in 96% EtOH (10 ml) was heated until dissolution, the obtained light-yellow solution was refluxed with vigorous stirring for 1–2 min. After 24 h, the reaction mixture was acidified with a 1:3 solution of concd. HCl in EtOH to pH 3–4. The yellow crystalline product was filtered off after 3–4 days and then recrystallized from a suitable solvent (*n*-BuOH for compounds **4a**,**e**, EtOH for compound **4b**, double recrystallization from *n*-BuOH – for compound **4c**).

7-Benzyl-9,9-dimethyl-2-oxo-4-thioxo-3,7-diazabicyclo-[3.3.1]nonane-1,5-dicarbonitrile (4a) was obtained from thiolate **2b**. Yield 170 mg (46%), bright-yellow crystals. The spectral characteristics of the sample were identical to those given above.

7,9,9-Trimethyl-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]-nonane-1,5-dicarbonitrile (4b) was obtained from thiolate **2b**. Yield 84 mg (29%), bright-yellow crystals, mp 222–224°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 3065 (N–H), 2251 (2C≡N), 1718 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 (3H, s) and 1.46 (3H, s, 9,9-$(CH_3)_2$); 2.29 (3H, s, NCH_3); 3.00–3.13 (4H, m, 6,8-CH_2); 13.55 (1H, s, NH). Mass spectrum, *m*/*z*: 263.1 $[M+H]^+$, 261.1 $[M–H]^-$. Found, %: C 55.18; H 5.08; N 21.40. $C_{12}H_{14}N_4OS$. Calculated, %: C 54.94; H 5.38; N 21.36.

9,9-Dimethyl-2-oxo-7-(2-phenylethyl)-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (4c) was obtained from thiolate **2a.** Yield 124 mg (32%), bright-yellow fine crystalline powder, mp 174–176°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 3438, 3220, 3174 (N–H), 2246 (2C≡N), 1729 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.29 (3H, s, CH_3); 1.46 (3H, s, CH_3); 2.61–2.64 (2H, m, $CH_2C\underline{H}_2$Ph); 2.70–2.73 (2H, m, $C\underline{H}_2CH_2$Ph); 3.14–3.25 (4H, m, 6,8-CH_2); 7.14–7.24 (5H, m, H Ph); 13.61 (1H, s, NH). ^{13}C APT NMR spectrum, δ, ppm: 20.3* (CH_3); 23.3* (CH_3); 31.9 ($CH_2\underline{C}H_2$Ph); 38.3 (C-9); 52.0 (C-1(5)); 52.2 (C-5(1)); 54.9 (NCH_2); 56.3 (NCH_2); 60.4 (NCH_2); 115.0 (C≡N); 116.1 (C≡N); 125.9* (C Ar); 128.2* (C Ar); 128.6* (C Ar); 139.4 (C Ar); 164.5 (C=O); 200.6 (C=S). Mass spectrum, *m*/*z*: 353.0 $[M+H]^+$, 351.2 $[M–H]^-$. Found, %: C 64.68; H 5.88; N 15.86. $C_{19}H_{20}N_4OS$. Calculated, %: C 64.75; H 5.72; N 15.90.

9,9-Dimethyl-7-(4-methylphenyl)-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (4e) was obtained from thiolate **2b**. Yield 137 mg (39%), dark-yellow crystals, mp 200–202°C, R_f 0.84. IR spectrum, ν, cm^{-1}: 3419, 3227, 3109 (N–H), 2253 (2C≡N), 1713 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, s) and 1.56 (3H, s, 9,9-$(CH_3)_2$); 2.19 (3H, s, ArCH_3); 3.79–3.97 (4H, m, 6,8-CH_2); 6.82 (2H, d, ^3J = 8.2, H Ar); 7.04 (2H, d, ^3J = 8.2, H Ar); 13.75 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.9 (CH_3); 20.1 (CH_3); 23.5 (CH_3); 38.5 (C-9); 49.8 (C-1(5)); 51.8 (C-5(1)); 53.1 (NCH_2); 60.3 (NCH_2); 114.7 (C≡N); 115.8 (C≡N); 116.9 (C Ar); 129.5 (C Ar); 130.2 (C Ar); 145.2 (C Ar); 164.4 (C=O); 200.3 (C=S). ^{13}C APT

* Error in the calculation was made in the paper:[1] 40 mmol of 37% formalin (*d* 1.1 g / ml) correspond to the volume of 3.0 ml instead of 3.6 ml as the authors indicated. However, in general it does not change the picture as a reproduction of the method with specified amount, as well as with a greater excess of HCHO, leads to the same result.

NMR spectrum, δ, ppm: 19.9* (CH_3); 20.0* (CH_3); 23.5* (CH_3); 38.4 (C-9); 49.9 (C-1(5)); 51.8 (C-5(1)); 53.1 (NCH_2); 60.3 (NCH_2); 114.7 (CN); 115.8 (CN); 116.9* (C Ar); 129.5* (C Ar); 130.2 (C Ar); 145.2 (C Ar); 164.3 (C=O); 200.3 (C=S). Mass spectrum, *m*/*z*: 339.1 $[M+H]^+$, 337.0 $[M–H]^-$. Found, %: C 63.80; H 5.44; N 16.57. $C_{18}H_{18}N_4OS$. Calculated, %: C 63.88; H 5.36; N 16.55.

Synthesis of 3-aryl-8,8-dimethyl-7-[(morpholin-4-yl)-methyl]-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*]-[1,3,5]thiadiazine-7,9-dicarbonitriles 5a–c (General method). A mixture of thiolate **2a** (320 mg, 1.09 mmol), the corresponding primary amine (1.05–1.15 equiv), and 37% formalin that was free of paraform impurity (1 ml, 13.6 mmol) was stirred and refluxed in 96% EtOH (10 ml) for 1–2 min and maintained at 25°C for 24 h. The crystalline precipitates of thiadiazines **5a**–**c** were filtered off and washed with EtOH.

8,8-Dimethyl-7-[(morpholin-4-yl)methyl]-6-oxo-3-phenyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]-thiadiazine-7,9-dicarbonitrile (5a). Yield 156 mg (34%), colorless needles, mp 191–193°C, R_f 0.64. IR spectrum, ν, cm^{-1}: 2249, 2204 (2C≡N), 1684 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, s, CH_3); 1.24 (3H, s, CH_3); 2.01–2.04 (2H, m) and 2.45–2.50 (2H, m, $N(C\underline{H}_2CH_2)_2O$, overlap with DMSO signal); 2.58 (1H, d, ^2J = 13.9) and 2.73 (1H, d, ^2J = 13.9, $C\underline{H}_2N(CH_2CH_2)_2O$); 3.28–3.31 (4H, m, $N(CH_2C\underline{H}_2)_2O$); 5.19 (1H, d, ^2J = 13.9) and 5.82 (1H, d, ^2J = 13.9, 4-CH_2); 5.21 (1H, d, ^2J = 12.7) and 5.40 (1H, d, ^2J = 12.7, 2-CH_2); 6.96 (1H, t, ^3J = 7.2, H-4 Ph); 7.16 (2H, d, ^3J = 8.1, H-2,6 Ph); 7.28–7.32 (2H, m, H-3,5 Ph). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3); 24.5 (CH_3); 38.1 (C-8); 52.2 (C-2); 53.8 ($N(\underline{C}H_2CH_2)_2O$); 55.6 (C-7); 58.4 ($\underline{C}H_2N(CH_2CH_2)_2O$); 59.5 (C-4); 65.7 ($N(CH_2\underline{C}H_2)_2O$); 94.3 (C-9); 114.9 (9-CN); 116.7 (C-2,6 Ph); 116.9 (7-CN); 121.5 (C-4 Ph); 129.0 (C-3,5 Ph); 143.6 (C-1 Ph); 147.5 (C-9a); 162.4 (C=O). ^{13}C APT NMR spectrum, δ, ppm: 21.6* (CH_3); 24.6* (CH_3); 38.0 (C-8); 52.3 (C-2); 53.9 ($N(\underline{C}H_2CH_2)_2O$); 55.9 (C-7); 58.4 ($\underline{C}H_2N(CH_2CH_2)_2O$); 59.7 (C-4); 65.7 ($N(CH_2\underline{C}H_2)_2O$); 94.5 (C-9); 115.4 (9-CN); 116.9* (C-2,6 Ph); 117.4 (7-CN); 121.7* (C-4 Ph); 129.3* (C-3,5 Ph); 143.7 (C-1 Ph); 147.8 (C-9a); 162.8 (C=O). ^{13}C DEPT-135 NMR spectrum, δ, ppm: 21.3 (CH_3); 24.3 (CH_3); 51.9* (C-2); 53.6* ($N(\underline{C}H_2CH_2)_2O$); 58.1* ($\underline{C}H_2N(CH_2CH_2)_2O$); 59.2* (C-4); 65.4* ($N(CH_2\underline{C}H_2)_2O$); 116.5 (C-2,6 Ph); 121.2 (C-4 Ph); 128.8 (C-3,5 Ph). Mass spectrum, *m*/*z*: 325.0 $[M–CH_2N(CH_2CH_2)_2O+2H]^+$, 323.1 $[M–CH_2N(CH_2CH_2)_2O]^-$. Found, %: C 62.61; H 6.09; N 16.60. $C_{22}H_{25}N_5O_2S$. Calculated, %: C 62.39; H 5.95; N 16.54.

8,8-Dimethyl-3-(4-methylphenyl)-7-[(morpholin-4-yl)-methyl]-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*]-[1,3,5]thiadiazine-7,9-dicarbonitrile (5b). Yield 47 mg (10%), colorless needles, mp 184–186°C, R_f 0.64. IR spectrum, ν, cm^{-1}: 2247, 2201 (2C≡N), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, s) and 1.20 (3H, s, 8,8-$(CH_3)_2$); 1.95–2.00 (2H, m, $N(C\underline{H}_ACH_2)_2O$); 2.21 (3H, s, $ArC\underline{H}_3$); 2.43–2.50 (3H, m, $C\underline{H}_AN(C\underline{H}_BCH_2)_2O$, overlap with DMSO signal); 2.77 (1H, d, ^2J = 13.0, $C\underline{H}_BN(CH_2CH_2)_2O$); 3.25–3.30 (4H, m, $N(CH_2C\underline{H}_2)_2O$, overlap with H_2O signal); 5.16–5.22 (2H, m, 2,4-CH_A); 5.41 (1H, d, ^2J = 11.9, 2-CH_B); 5.79 (1H, d, ^2J = 13.0, 4-CH_B); 7.07–7.13 (4H, m, H Ar). Mass spectrum, *m*/*z*: 339.2 $[M–CH_2N(CH_2CH_2)_2O+2H]^+$, 337.2 $[M–CH_2N(CH_2CH_2)_2O]^-$. Found, %: C 63.29; H 6.35; N 15.96. $C_{23}H_{27}N_5O_2S$. Calculated, %: C 63.13; H 6.22; N 16.01.

3-(4-Fluorophenyl)-8,8-dimethyl-7-[(morpholin-4-yl)-methyl]-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*]-[1,3,5]thiadiazine-7,9-dicarbonitrile (5c). Yield 239 mg (50%), colorless fine crystals, mp 201–203°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 2247, 2204 (2C≡N), 1684 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, s, CH_3); 1.21 (3H, s, CH_3); 1.97–2.00 (2H, m) and 2.41–2.43 (2H, m, $N(C\underline{H}_2CH_2)_2O$); 2.55 (1H, d, ^2J = 13.9) and 2.78 (1H, d, ^2J = 13.9, $C\underline{H}_2N(CH_2CH_2)_2O$); 3.25–3.28 (4H, m, $N(CH_2C\underline{H}_2)_2O$); 5.17–5.22 (2H, m, 2,4-CH_A); 5.42 (1H, d, ^2J = 12.6, 2-CH_B); 5.81 (1H, d, ^2J = 13.5, 4-CH_B); 7.15–7.19 (2H, m, H Ar); 7.23–7.26 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.7 (CH_3); 24.6 (CH_3); 38.0 (C-8); 52.7 (C-2); 53.9 ($N(\underline{C}H_2CH_2)_2O$); 55.9 (C-7); 58.4 ($\underline{C}H_2N(CH_2CH_2)_2O$); 60.3 (C-4); 65.7 ($N(CH_2\underline{C}H_2)_2O$); 94.6 (C-9); 115.4 (9-CN); 115.8 (d, $^2J_{HF}$ = 22.2, C-3,5 Ar); 117.4 (7-CN); 118.9 (d, $^3J_{HF}$ = 8.0, C-2,6 Ar); 140.4 (d, $^4J_{HF}$ = 2.3, C-1 Ar); 147.8 (C-9a); 157.5 (d, $^1J_{HF}$ = –237.1, C-4 Ar); 162.9 (C=O). Mass spectrum (ES-API), *m*/*z*: 343.0 $[M–CH_2N(CH_2CH_2)_2O+2H]^+$, 341.1 $[M–CH_2N(CH_2CH_2)_2O]^-$, 88.2 $[O(CH_2CH_2)_2NH_2]^+$. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 341 $[M–CH_2N(CH_2CH_2)_2O]^+$ (10), 137 (12), 123 (16), 100 $[CH_2N(CH_2CH_2)_2O]^+$ (100), 95 (9), 56 (15). Mass spectrum (FAB), *m*/*z* (I_{rel}, %): 342.0 $[M–CH_2N(CH_2CH_2)_2O+H]^+$. Found, %: C 60.13; H 5.65; N 15.89. $C_{22}H_{24}FN_5O_2S$. Calculated, %: C 59.85; H 5.48; N 15.86.

Synthesis of 4-amino-7-benzyl-9,9-dimethyl-2-oxo-6-thioxo-3,7-diazabicyclo[3.3.1]non-3-ene-1-carbonitrile (6a). Benzylamine (0.60 ml, 5.49 mmol) was added to a mixture of 96% EtOH (8 ml) and distilled H_2O (5 ml), followed by the addition of 37% formalin (*d* 1.1 g/ml, 0.28 ml, 3.68 mmol). The mixture was stirred for 2–3 min, and then thiolate **2a** (1.082 g, 3.68 mmol) was added. The reaction mixture was stirred and refluxed for 2 h (precipitation of the product started after 15–20 min). The pale-yellow precipitate was filtered off after 24 h and washed with EtOH. Yield 0.458 g. Additional crop of the product can be obtained by maintaining the filtrate for 72 h at 20°C. The total yield of the crude bicyclic product **6a** was 493 mg (41%). Analytically pure sample of this compound can be obtained by recrystallization from a large volume of AcOH (solubility ~30 mg in 10–15 ml AcOH, the precipitate was white, amorphous powder, R_f 0.50, mp >350°C (subl. from 302°C) (mp 290–293°C[1,2])) or from DMSO (slow precipitation of yellow crystalline agglomerates, no melting or decomposition was observed below 350°C). When using an equimolar amount of benzylamine, the yield decreased to 19%. When the reaction was performed under analogous conditions, but without the addition of water, product **6a** was obtained in 17% yield, and contained the starting thiolate **2a** as impurity. IR spectrum, ν, cm^{-1}: 3294 (N–H), 2245 (C≡N), 1662 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, s, CH_3); 1.13 (3H, s, CH_3); 3.76 (1H, d, ^2J = 14.7) and 3.85

(1H, d, ^2J = 14.7, 8-CH_2); 4.06 (1H, s, 5-CH); 5.06 (1H, d, ^2J = 14.7) and 5.43 (1H, d, ^2J = 14.7, NC$\underline{H}_2$Ph); 7.20 (2H, d, ^3J = 7.1, H-2,6 Ph); 7.28–7.33 (3H, m, H-3,4,5 Ph); 8.81 (1H, br. s) and 9.03 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 22.9 (CH_3); 35.8 (C-9); 50.2 (C-1); 53.3 (C-8); 55.2 (N$\underline{C}H_2$Ph); 59.8 (C-5); 116.3 (C≡N); 127.3 (C-2,6 Ph); 127.6 (C-4 Ph); 128.4 (C-3,5 Ph); 134.6 (C-1 Ph); 171.2 (C-4); 172.4 (C=O); 192.4 (C=S). ^{13}C APT NMR spectrum, δ, ppm: 21.3* (CH_3); 23.0* (CH_3); 35.9 (C-9); 50.4 (C-1); 53.5 (C-8); 55.3 (N$\underline{C}H_2$Ph); 60.0* (C-5); 116.6 (C≡N); 127.3* (C-2,6 Ph); 127.8* (C-4 Ph); 128.6* (C-3,5 Ph); 134.7 (C-1 Ph); 171.4 (C-4); 172.7 (C=O); 192.4 (C=S). ^{13}C DEPT-135 NMR spectrum, δ, ppm: 21.1 (CH_3); 22.7 (CH_3); 53.1* (C-8); 55.0* (N$\underline{C}H_2$Ph); 59.6 (C-5); 127.1 (C-2,6 Ph); 127.4 (C-4 Ph); 128.2 (C-3,5 Ph). Mass spectrum, *m*/*z*: 327.0 $[M+H]^+$, 325.0 $[M–H]^–$. Found, %: C 62.50; H 5.64; N 17.20. $C_{17}H_{18}N_4OS$. Calculated, %: C 62.55; H 5.56; N 17.16.

Synthesis of 4-amino-7-[(furan-2-yl)methyl]-9,9-dimethyl-2-oxo-6-thioxo-3,7-diazabicyclo[3.3.1]non-3-ene-1-carbonitrile (6b). Furfurylamine (0.24 ml, 2.69 mmol) was added to a mixture of 96% EtOH (5 ml) and distilled H_2O (2 ml), followed by the addition of 37% formalin (*d* 1.1 g/ml) (0.18 ml, 2.40 mmol). The mixture was heated to reflux, and thiolate **2a** (707 mg, 2.40 mmol) was added. The reaction mixture was stirred and refluxed for 1 h. After maintaining for 24 h, the precipitate was filtered off and washed with EtOH. Yield 77 mg (10%), pale-yellow amorphous powder, R_f 0.45. According to ^{1}H NMR data, the obtained sample contained up to 10 mol % of the isomeric compound **9** as impurity. Analytically pure sample of this compound can be obtained by recrystallization from AcOH. The purified sample decomposed above 330°C (mp 310–312°C[1,2]). IR spectrum, ν, cm^{-1}: 3296 (N–H), 2247 (C≡N), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (3H, s, CH_3); 1.11 (3H, s, CH_3); 3.83 (1H, d, ^2J = 14.5) and 3.92 (1H, d, ^2J = 14.5, 8-CH_2); 4.00 (1H, s, 5-CH); 5.09 (1H, d, ^2J = 14.9) and 5.27 (1H, d, ^2J = 14.9, NC$\underline{H}_2$Fur); 6.32–6.36 (2H, m, H-3,4 Fur); 7.48–7.49 (1H, m, H-5 Fur); 8.71 (1H, br. s) and 8.96 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.1 (CH_3); 22.9 (CH_3); 35.7 (C-9); 48.8 (N$\underline{C}H_2$Fur); 50.1 (C-1); 53.7 (C-8); 59.8 (C-5); 109.5 (C-3 Fur); 110.2 (C-4 Fur); 116.7 (C≡N); 142.6 (C-5 Fur); 147.6 (C-2 Fur); 170.9 (C-4); 172.3 (C=O); 191.9 (C=S). ^{13}C APT NMR spectrum, δ, ppm: 21.1* (CH_3); 22.9* (CH_3); 35.8* (C-9); 48.8 (N$\underline{C}H_2$Fur); 50.1 (C-1); 53.7 (C-8); 59.9* (C-5); 109.5* (C-3 Fur); 110.5* (C-4 Fur); 116.7 (C≡N); 143.2* (C-5 Fur); 147.7 (C-2 Fur); 171.2 (C-4); 172.7 (C=O); 191.9 (C=S). DEPT-135 ^{13}C NMR spectrum, δ, ppm: 20.9 (CH_3); 22.7 (CH_3); 48.6* (N$\underline{C}H_2$Fur); 53.5* (C-8); 59.6 (C-5); 109.2* (C-3 Fur); 110.0* (C-4 Fur); 142.3* (C-5 Fur). Mass spectrum, *m*/*z*: 317.0 $[M+H]^+$, 314.8 $[M–H]^–$.

Synthesis of 4-amino-7-[(furan-2-yl)methyl]-9,9-dimethyl-6-oxo-2-thioxo-3,7-diazabicyclo[3.3.1]non-3-ene-1-carbonitrile (9). A mixture of furfurylamine (0.22 ml, 2.5 mmol) and 37% formalin (*d* 1.1 g/ml) (0.20 ml, 2.7 mmol) in 96% EtOH (5 ml) was heated to reflux, and the thiolate **2a** (736 mg, 2.5 mmol) was added. The mixture was refluxed in a flask with reflux condenser for 45 min, while the initially heterogeneous mixture turned into a red solution containing a small amount of crystalline precipitate. The solution was maintained for 72 h at 20°C, the crystalline precipitate that formed was filtered off and washed with EtOH. The obtained mixture (291 mg) consisted of fine white needles ("white fraction", R_f 0.0) and large bright-yellow crystals ("yellow fraction", R_f 0.50), which was mechanically/manually separated. According to ^{1}H NMR spectral data, the "white fraction" was the starting thiolate **2a**, while the "yellow fraction" (~90 mg, ~12%) was pure bicyclic compound **9**, mp 242–244°C. Compound **9** was insoluble in EtOH, moderately soluble in acetone, readily soluble in DMSO. IR spectrum, ν, cm^{-1}: 3296 (N–H), 2247 (C≡N), 1661 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, s, CH_3); 1.17 (3H, s, CH_3); 3.40 (1H, s, 5-CH); 3.71 (1H, d, ^2J = 12.6) and 3.79 (1H, d, ^2J = 12.6, 8-CH_2); 4.30 (1H, d, ^2J = 15.3) and 4.69 (1H, d, ^2J = 15.3, NC$\underline{H}_2$Fur); 6.25–6.26 (1H, m, H-3 Fur); 6.30–6.32 (1H, m, H-4 Fur); 7.41–7.42 (1H, m, H-5 Fur); 9.55 (1H, br. s) and 9.80 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 22.7 (CH_3); 37.2 (C-9); 41.8 (N$\underline{C}H_2$Fur); 51.9 (C-5); 54.1 (C-8); 57.1 (C-1); 108.6 (C-3 Fur); 110.1 (C-4 Fur); 117.0 (C≡N); 142.3 (C-5 Fur); 148.8 (C-2 Fur); 161.7 (C=O); 164.5 (C-4); 209.0 (C=S). ^{13}C DEPT-135 NMR spectrum, δ, ppm: 22.2 (CH_3); 22.5 (CH_3); 41.5* (N$\underline{C}H_2$Fur); 51.6 (C-5); 53.8* (C-8); 108.3 (C-3 Fur); 109.9 (C-4 Fur); 142.1 (C-5 Fur). Mass spectrum, *m*/*z*: 317.0 $[M+H]^+$, 315.0 $[M–H]^–$. Found, %: C 60.07; H 5.15; N 17.68. $C_{15}H_{16}N_4O_2S$. Calculated, %: C 56.95; H 5.10; N 17.71.

X-ray structural study of compounds 4a, **5a**, **6a**. Crystals of compound **4a** ($C_{18}H_{18}N_4OS$, *M* 338.42) were obtained by crystallization from *n*-BuOH. X-ray structural studies were performed on an Xcalibur 3 automatic four-circle diffractometer (MoKα radiation, graphite monochromator, CCD detector, ω-scanning, $2\theta_{max}$ 65.3°). The structure was solved by direct method using the SHELX-97 software suite.[33]

Crystals of compound **5a** ($C_{22}H_{25}N_5O_2S$, *M* 423.53) were obtained from aqueous EtOH. X-ray structural studies were performed on a Bruker APEX II CCD single crystal diffractometer at 100 K (MoKα radiation). The structure was solved by charge-flipping algorithm (olex2.solve) and refined by method of least squares with Olex2 program[34] using the SHELXL 2014/7 software suite.[35]

Crystals of compound **6a**, obtained from DMSO, were of very low quality. X-ray structural studies were performed on a Bruker APEX DUO CCD single crystal diffractometer at 100 K (CuKα radiation). The sample was a twinned crystal; indexing was performed with CELL_NOW program, but the attempts to integrate the two basic domains were not successful. As a result, the structure was solved and refined by using integrated data from one domain without taking into account the twinning, which led to high values of probability factors, for example, R_1 was 13.8%. However, the difference Fourier map for the structure of compound **6a** did not contain extra peaks, the thermal vibration ellipsoids on all atoms were acceptable, and the analysis of bond lengths and valence

angles with CCDC MOGUL program[36] did not reveal substantial deviations from the average values at CCDC, indirectly confirming the correctness of the determined structure. The structure was solved by charge-flipping method (olex2.solve) and refined by method of least squares with Olex2 program[34] using the SHELXL 2014/7 software suite.[35]

The complete crystallographic information about structures of compounds **4**–**6a** was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1057031, CCDC 1057070, CCDC 1057027, respectively).

The Supplementary information file, containing spectra of the obtained compounds, as well as X-ray structural analysis data for compounds **4a**, **5a**, **6a**, is available online at http://link.springer.com/journal/10593.

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