The Mannich reaction in the synthesis of N,S-containing heterocycles

8.* Aminomethylation of 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates as a method for the synthesis of new functionally substituted 3,7-diazabicyclo[3.3.1]nonane derivatives

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Aminomethylation of 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates upon treatment with primary amines and excess formaldehyde leads to 3,7-diazabicyclo[3.3.1]nonane derivatives. *N*-Methylmorpholinium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate was obtained by the reaction of (*E*)-3-(2-chlorophenyl)-2-cyanoprop-2-enethioamide with 1-cyanoacetyl-3,5-dimethylpyrazole and *N*-methylmorpholine in acetone in quantitative yield.

Key words: the Mannich reaction, 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates, 7,11-dicyano-3-methyl-10-oxo-9-aza-3-azoniaspiro[5.5]undec-7-ene-8-thiolate, 2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitriles, 1-cyanoacetyl-3,5-dimethylpyrazole.

Partially hydrogenated 3-cyano-2-thioxopyridines and related thiolates are known as the heterofunctional reagents with a wide range of synthetic potentialities, many of their derivatives have biological activity.[1] Nevertheless, only isolated examples of aminomethylation of pyridin-2(1*H*)-thione derivatives are described in the literature. Thus, 2-mercaptopyridine upon treatment with HCHO and secondary amines gives *S*-aminomethyl derivatives.[2] As we showed earlier, partially hydrogenated 3-cyanopyridin-2(1*H*)-thiones behave differently under the Mannich reaction conditions: pyrido[2,1-*b*][1,3,5]thiadiazine,[3] 3,7-diazabicyclo[3.3.1]nonane (bispydine),[4] or 3,5,7,11-tetraazatricyclo[7.3.1.$0^{2,7}$]tridec-2-ene[5] derivatives can be obtained depending on the substrate structure. To continue our research in this field, we studied the reaction of 7,11-dicyano-3-methyl-10-oxo-9-aza-3-azoniaspiro[5.5]undec-7-ene-8-thiolate (**1**) with primary amines and formaldehyde. The spiro-coupled betaine **1** is easily synthesized by the poly-component cyclocondensation of cyanothioacetamide, *N*-methylpiperidin-4-one, and ethyl cyanoacetate.[6] It is of interest for aminomethylation due to the presence of four nucleophilic centers (N(9), C(7), C(11), and S atoms). Based on these data, it can be *a priori* suggested that compound **1** in the presence of 1 equivalent of primary amine and excess HCHO will give at the very least one heterocyclization product, either spirobispydine **2** or fused 1,3,5-thiadiazine **3**. It should be noted that the formation of 1,3,5-thiadiazine derivatives under the aminomethylation conditions is a general reaction of 2-mercaptoazoles and -azines, as well as of their 2(1*H*)-thioxo tautomers or the corresponding thiolates. In particular, numerous *symm*-triazolo[3,4-*b*][1,3,5]thiadiazines,[7] thiazolo[3r,4r:1,5][1,2,4]triazolo[3,4-*b*]-[1,3,5]thiadiazines,[8] imidazo[2,1-*b*][1,3,5]thiadiazines,[9,10] 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines,[9] 1,3,5-thiadiazino[3,2-*a*]benzimidazoles,[11] and pyrido[2,1-*b*]-[1,3,5]thiadiazines[3] were synthesized by this method. At the same time, the double Mannich reaction with C(3),C(5)-binucleophilic piperidine derivatives is a convenient general method for the synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives,[12] compounds with a wide range of biological activity and prospective bidentate ligands.

We found that treatment of betaine **1** with primary amines and formaldehyde in boiling ethanol exclusively leads to derivatives of spirobispydine **2** rather than of thiadiazine **3** (Scheme 1).

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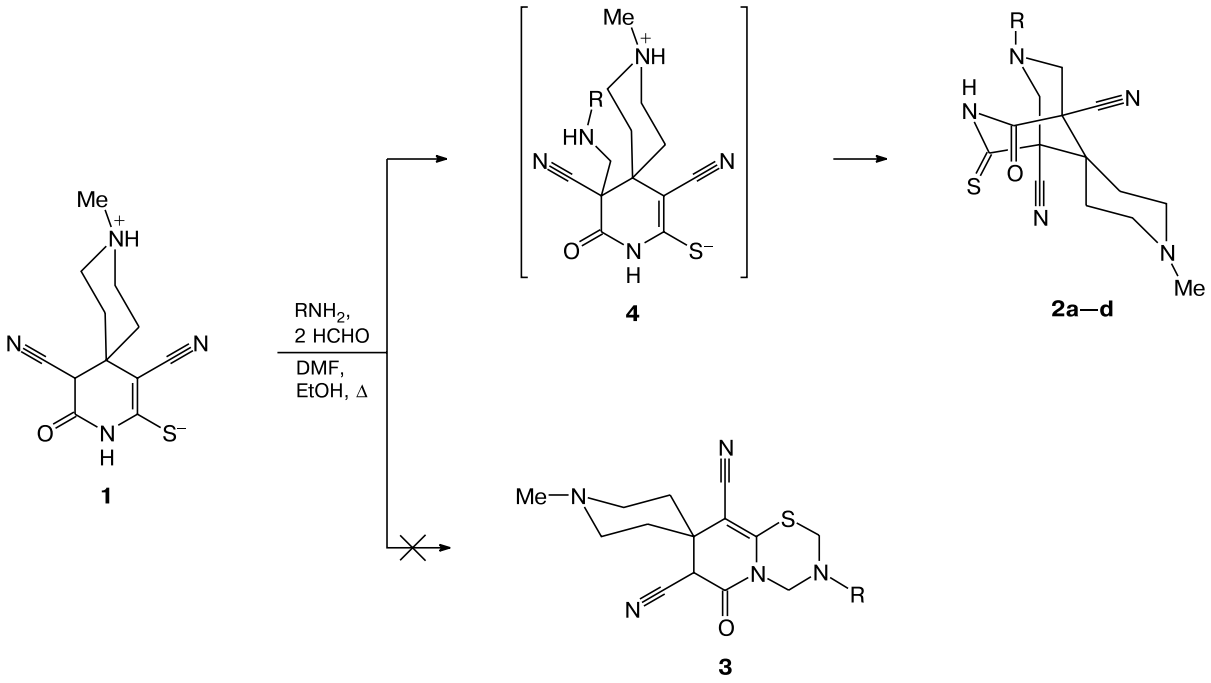
Scheme 1

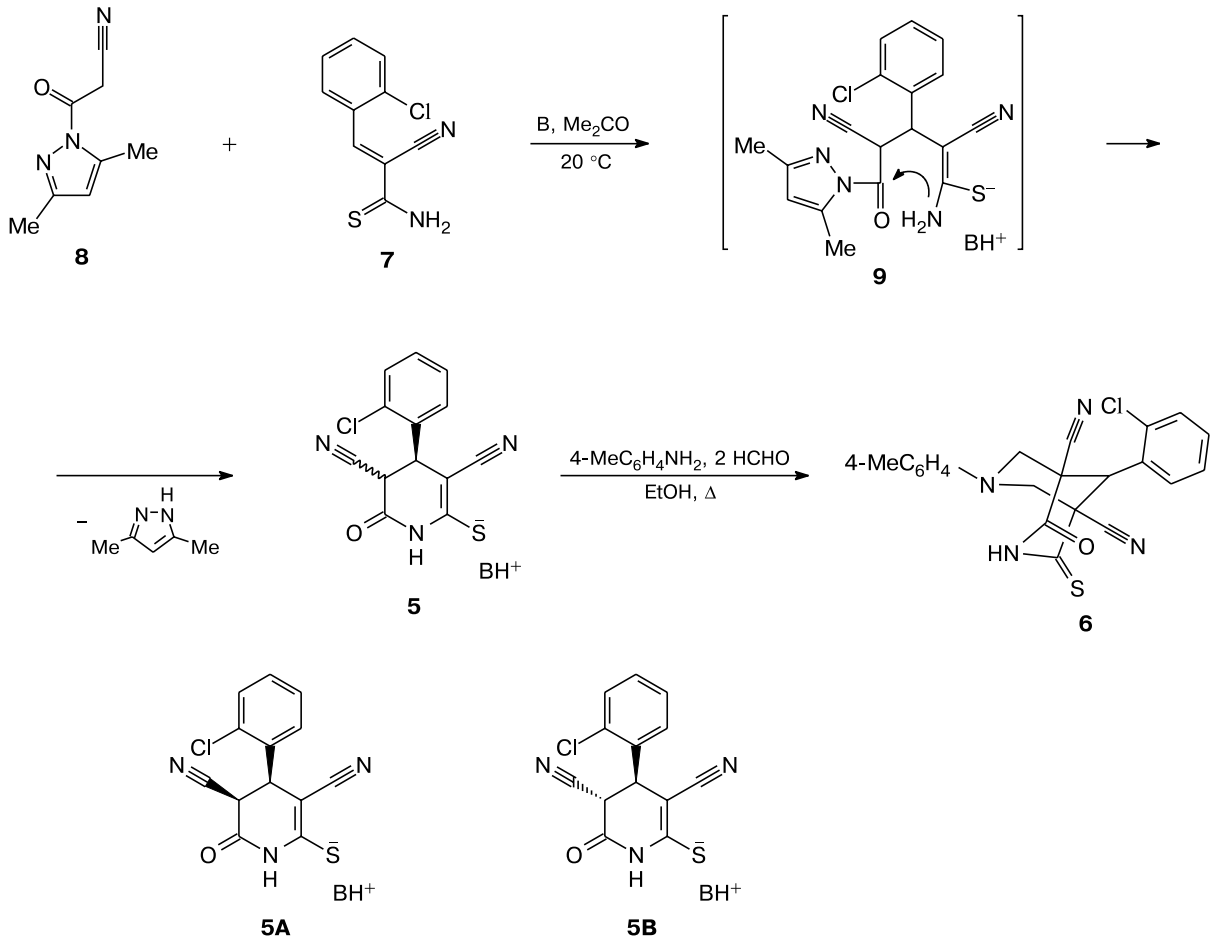


2: R = CH_2Ph (**a**), CH_2CH_2Ph (**b**), Ph (**c**), 4-MeC_6H_4 (**d**)

Both aliphatic and aromatic amines enter the reaction under study. Presumably, the aminomethylation initially proceeds at C(5) atom of the pyridine ring to form intermediate **4**. This suggestion can be indirectly confirmed by the fact that the structural analogs of compound **1**, having no electron-withdrawing substituents at C(5) atom, enter the Mannich reaction exclusively as the S,N-binucleophiles and give no products of aminomethylation at C(3) position.[3] Thus, compound **1**, in contrast to derivatives of 2-mercaptoazoles and -azines, plays the role of the C(3),C(5)- rather than the S,N-binucleophile. The structural analog of betaine **1**, *N*-methylmorpholinium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (**5**), behave similarly. Thus, the reaction of thiolate **5** with *p*-toluidine and formaldehyde gives 3,7-diazabicyclo[3.3.1]nonane **6**. Thiolate **5** can be obtained by the three-component condensation of *o*-chlorobenzaldehyde, ethyl cyanoacetate, and cyanothioacetamide in 73% yield.[13] Since the procedure described can not always be smoothly reproduced, we developed a new method for the synthesis of thiolate **5**, which is based on the reaction of (*E*)-3-(2-chlorophenyl)-3-cyanoprop-2-enethioamide (**7**) with 1-cyanoacetyl-3,5-dimethylpyrazole (**8**) and *N*-methylmorpholine in acetone. Cyanoacetylpyrazole **8** is rather known as the efficient cyanoacetylation agent (see, for example, Refs 14—20) and earlier was never used as the methylene active component in the heterocyclization reactions, which included the Michael addition step. The substitution of ethyl cyanoacetate for cyanoacetylpyrazole **8** allows one to obtain thiolate **5** during few minutes in almost quantitative yield (96%) (Scheme 2). Obviously, the reaction proceeds through the formation of the corresponding Michael adduct **9**. According to the results in work,[13] confirmed by ^{1}H NMR spectroscopy and X-ray analysis data, thiolate **5** exists as a mixture of *cis*- and *trans*-isomers (**5A** and **5B**, respectively) in the ratio close to 1 : 1. The spectral characteristics of thiolate **5** indicate the identity of the latter and the sample synthesized earlier.

The structures of compounds **2a—d**, **5**, and **6** were confirmed by elemental analysis and spectroscopy data. Thus, in the IR spectra of spirobispydines **2a—d**, there are absorption bands, corresponding to the stretching vibrations of the lactam C=O bond (ν = 1657—1640 cm^{-1}). The presence of weak bands of two nonconjugated cyano groups in the region ν = 2240—2230 cm^{-1} unambiguously points out the formation of the product of C(3),C(5)-diaminomethylation. In the ^{1}H NMR spectra of compounds **2a—d**, in addition to signals of the *N*-R-substituents and methylene groups of the piperidine ring, there are either multiplets or pseudotriplets (partially overlapped doublets of doublets) of four protons of the methylene $C(6)H_2$ and $C(8)H_2$ groups, which resonate in the interval δ = 2.93—3.88. These data are in good agreement with the chemical shift values of the methylene protons of the structurally close 3,7-diazabicyclo[3.3.1]nonane deriva-

Scheme 2



B — *N*-methylmorpholine

tives (δ = 2.94—3.37).[4] It should be also noted that the protons of the 1,3,5-thiadiazine ring, forming in the course of the *S*,*N*-diaminomethylation, resonate in the downfield part of the spectrum and are observed in the interval δ = 4.50—6.25.[3,7,9–11].

In conclusion, method for the synthesis of new functionally substituted 3,7-diazabicyclo[3.3.1]nonane derivatives, based on the regioselective aminomethylation of 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates, was proposed and the procedure for the synthesis of the latter was improved.

Experimental

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 spectrometer (199.97 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on a IKS-29 spectrophotometer in Nujol. Elemental analysis was performed on a Perkin—Elmer C,H,N-Analyzer. The individuality of the compounds synthesized was monitored by TLC on Silufol UV 254 plates in acetone—heptane (1 : 1) as the eluent, visualization was made in iodine vapors or by a UV-detector. Melting points were determined on the Kofler heating stage and were not corrected. Betaine **1** was obtained by the known method,[6] (*E*)-3-(2-chlorophenyl)-3-cyanoprop-2-enethioamide (**7**) was obtained according to the general procedure,[21] 1-cyanoacetyl-3,5-dimethylpyrazole (**8**) was obtained by the reaction of cyanoacetohydrazide with acetylacetone in the presence of HCl.[22]

Spiro-3,7-diazabicyclo[3.3.1]nonanes 2 (general procedure). Excess 37% aqueous HCHO (without admixture of paraformaldehyde) (2.5 mL, 34 mmol) and the corresponding primary amine (2.5 mmol) were added to a suspension of betaine **1** (0.6 g, 2.3 mmol) in DMF (4 mL). The mixture obtained was heated with stirring until the complete dissolution, then, EtOH (6 mL) was added. The reaction mixture was refluxed for 2—3 min and kept for 48 h at ~20 °C, the crystalline product was filtered off, washed with hot (50 °C) EtOH to obtain compounds **2a—d**.

7-Benzyl-1r-methyl-2-oxo-4-thioxo-1*H*,5*H*-spiro[3,7-diazabicyclo[3.3.1]nonane-9,4′-piperidine]-1,5-dicarbonitrile (2a). The yield was 63%, m.p. 252—254 °C (decomp., DMF—

EtOH (1 : 1)), colorless crystals. Found (%): C, 64.30; H, 5.91; N, 17.73. $C_{21}H_{23}N_5OS$. Calculated (%): C, 64.10; H, 5.89; N, 17.80. IR, ν/cm^{-1}: 3460 (NH), 2232 (2 C≡N), 1655 (C=O). ^{1}H NMR, δ: 1.92, 2.76 (both m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.29 (s, 3 H, NCH_3); 2.93—3.25 (m, 4 H, C(6)H_2, C(8)H_2, overlapped signals); 3.66 (br.s, 2 H, NC$\underline{H}_2$Ph); 7.12—7.30 (m, 5 H, Ph). Signal of the NH proton is not observed in the ^{1}H NMR spectra of compounds **2a—d**, **5**, and **6**, apparently, due to a deuterium exchange.

1′-Methyl-2-oxo-7-(2-phenylethyl)-4-thioxo-1*H*,5*H*-spiro[3,7-diazabicyclo[3.3.1]nonane-9,4′-piperidine]-1,5-dicarbonitrile (2b). The yield was 79%, m.p. 223—225 °C (decomp., DMF—EtOH (1 : 1)), fine crystalline powder of light yellow color. Found (%): C, 64.71; H, 6.16; N, 17.29. $C_{22}H_{25}N_5OS$. Calculated (%): C, 64.84; H, 6.18; N, 17.18. IR, ν/cm^{-1}: 3450 (NH), 2235 (2 C≡N), 1645 (C=O). ^{1}H NMR, δ: 1.89, 2.63 (both m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.26 (s, 3 H, NCH_3); 2.70—2.80, 3.06—3.27 (m, 8 H, C(6)H_2, C(8)H_2, (C$\underline{H}_2$)$_2$Ph, overlapped signals); 7.18 (m, 5 H, Ph).

1′-Methyl-2-oxo-7-phenyl-4-thioxo-1*H*,5*H*-spiro[3,7-diazabicyclo[3.3.1]nonane-9,4′-piperidine]-1,5-dicarbonitrile (2c). The yield was 40%, m.p. 221—223 °C (decomp., DMF), crystals yellow in color. Found (%): C, 63.50; H, 5.60; N, 18.39. $C_{20}H_{21}N_5OS$. Calculated (%): C, 63.30; H, 5.58; N, 18.45. IR, ν/cm^{-1}: 3460 (NH), 2240 (2 C≡N), 1657 (C=O). ^{1}H NMR, δ: 2.00, 2.88 (both m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.35 (s, 3 H, NCH_3); 3.88 (m, 4 H, C(6)H_2, C(8)H_2, overlapped signals); 6.89 (m, 3 H, C(3)H_{Ar}—C(5)H_{Ar}); 7.26 (m, 2 H, C(2)H_{Ar}, C(6)H_{Ar}).

1′-Methyl-7-(4-methylphenyl)-2-oxo-4-thioxo-1*H*,5*H*-spiro[3,7-diazabicyclo[3.3.1]nonane-9,4′-piperidine]-1,5-dicarbonitrile (2d). The yield was 55%, m.p. 215—217 °C (decomp., DMF—EtOH (2 : 1)), crystals light yellow in color. Found (%): C, 64.31; H, 5.92; N, 17.71. $C_{21}H_{23}N_5OS$. Calculated (%): C, 64.10; H, 5.89; N, 17.80. IR, ν/cm^{-1}: 3450 (NH), 2230 (2 C≡N), 1640 (C=O). ^{1}H NMR, δ: 1.97, 2.90 (both m, 8 H, $(CH_2)_2N(CH_2)_2$); 2.17 (s, 3 H, $\underline{H}_3$C—Ar); 2.36 (s, 3 H, NCH_3); 3.79 (m, 4 H, C(6)H_2, C(8)H_2, overlapped signals); 6.90 (dd, 4 H, Ar, ^3J = 8.6 Hz).

***N*-Methylmorpholinium 4-(2-chlorophenyl)-3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolate (5) ((4*R*,5*R*)(*cis*, 5A) : (4*R*,5*S*)(*trans*, 5B) = 9 : 10).** *N*-Methylmorpholine (0.4 mL, 3.6 mmol) was added in one portion to a stirred solution of unsaturated thioamide **7** (0.5 g, 2.25 mmol) and cyanoacetylpyrazole **8** (0.37 g, 2.26 mmol) in acetone (5 mL), the reddish orange solution instantly became clear and a precipitate of white color was forming during 3 min. The reaction mixture was stirred for another 30 min at ~20 °C, the precipitate was filtered off, washed twice with acetone, dried with ether to obtain thiolate **5** (0.84 g, 96%), m.p. 197—200 °C (decomp.) (*cf.* Ref. 13: m.p. 210—212 °C (for the mixture with the ratio *cis* : *trans* = 1 : 1)). Found (%): C, 55.40; H, 4.92; N, 14.31. $C_{18}H_{19}ClN_4O_2S$. Calculated (%): C, 55.31; H, 4.90; N, 14.33. IR, ν/cm^{-1}: 3180 (NH), 2247, 2177 (2 C≡N), 1680 (C=O). ^{1}H NMR, δ: 2.78 (s, 3 H, NCH_3); 3.18, 3.76 (both m, 4 H each, $O(CH_2CH_2)_2N$); 4.41 (d, 1 H, C(4)H_{cis}, ^3J = 7.3 Hz); 4.45 (dd, 2 H, C(4)H_{trans}, C(5)H_{trans}, ^3J = 11.2 Hz); 4.91 (d, 1 H, C(5)H_{cis}, ^3J = 7.3 Hz); 7.14—7.49 (m, 4 H, Ar); 9.69, 9.71 (both br.s, 1 H each, NH_{cis}, NH_{trans}).

9-(2-Chlorophenyl)-7-(4-methylphenyl)-2-oxo-4-thioxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarbonitrile (6). Excess 37% aq. formaline (1 mL, 13.6 mmol) and *p*-toluidine (0.2 g, 1.87 mmol) were sequentially added to a suspension of thiolate **5** (0.5 g, 1.28 mmol) in EtOH (10 mL). The mixture obtained was refluxed for 2 min, filtered through a paper filter, and kept 48 h at ~20 °C. The precipitate was filtered off, washed twice with cold EtOH to obtain diazabicyclononane **6**. The yield was 0.22 g (41%), decomp.p. > 250 °C (EtOH), yellow crystals. Found (%): C, 62.59; H, 4.10; N, 13.41. $C_{22}H_{17}ClN_4OS$. Calculated (%): C, 62.78; H, 4.07; N, 13.31. IR, ν/cm^{-1}: 3450 (NH), 2235 (2 C≡N), 1650 (C=O). ^{1}H NMR, δ: 2.24 (s, 3 H, $\underline{H}_3$C—Ar); 3.94—4.19 (m, 4 H, C(6)H_2, C(8)H_2, overlapped signals); 4.85 (s, 1 H, C(9)H); 6.93 (q, 4 H, 4-Me$C_6\underline{H}_4$, ^3J = 7.1 Hz); 7.23, 7.45, 7.61 (all m, 4 H, 2-ClC_6H_4).

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