The Mannich reaction in the synthesis of N,S-containing heterocycles
6.* New approaches to the synthesis of pyrimido[4,3-*b*][1,3,5]thiadiazine derivatives

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Aminomethylation of 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles in the Mannich reaction with *p*-toluidine and formaldehyde unexpectedly gave pyrimido[4,3-*b*][1,3,5]thiadiazine derivatives. The same compounds were obtained in an independent way involving a multicomponent cascade condensation of aromatic aldehydes, cyanothioacetamide, *p*-toluidine, and formaldehyde.

Key words: pyrimido[4,3-*b*][1,3,5]thiadiazines, aminomethylation, the Mannich reaction, multicomponent cascade synthesis, 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles.

Proceeding further in our investigations of the Mannich synthesis of fused S-containing azines,[1—4] we studied aminomethylation of 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles **1**. Thiopyrans **1** are easily accessible[5—7] and have two amino groups and the nucleophilic C(3) and C(5) centers, which makes them promising objects for the Mannich aminomethylation. For instance, double aminomethylation of 3,5-binucleophilic thiopyrans is known to be a convenient route to 3-thia-7-azabicyclo[3.3.1]nonane derivatives,[8,9] which have revealed themselves as potent antiarrhythmic drugs.[9—11]

We found that treatment of thiopyran **1a** (Ar = Ph) with an equimolar amount of *p*-toluidine and an excess of formaldehyde does not lead to a bicyclic system (as could be expected by analogy with related pyridine derivatives).[4] Instead, pyrimido[4,3-*b*][1,3,5]thiadiazine derivative **2a** was obtained in 7% yield as the sole product (Scheme 1). When two, three, and four equivalents of the primary amine were used, the yields of compound **2a** were 11, 25, and 33%, respectively. An analogous reaction with 4 equivalents of *p*-toluidine gave compound **2b** in 40% yield. It should be noted that cross-recyclization of thiopyrans **1** under the action of nucleophilic agents in basic media has been studied in detail and is a convenient route to functionalized thiazoles and pyridines and the corresponding fused systems.[12—17] Nevertheless, the transformation of thiopyrans **1** into compounds **2** we describe here has no direct literature analogs and represents a new type of the tandem reaction: cross-recyclization—Mannich cascade cyclocondensation.

According to a plausible mechanism, this transformation involves the retro-Michael reaction[12—17] with elimination of malononitrile and formation of unsaturated thioamides **3**. Their sequential aminomethylation leads, *via* product **4** of the intramolecular Michael aza reaction, to compounds **2**. This scheme of transformations is supported by the previously reported[18] formation of pyrimido[4,3-*b*][1.3.5]thiadiazines **2** from (*E*)-2-(het)aryl-2-cyanoprop-2-enethioamides **3** under the conditions of the Mannich reaction. Since the reaction with thioamides **3** actually consumes two equivalents of the amine, one can assume that the low yield of compound **2a** in the thiopyran : amine ratio = 1 : 2 is due to aminomethylation of malononitrile as a side process leading to nonisolable products. The structures of compounds **2a,b** were confirmed by spectroscopic data an independent synthesis: multicomponent "one pot" cyclocondensation of an appropriate aromatic aldehyde, cyanothioacetamide (**5**), *p*-toluidine, and formaldehyde (method *B*). In this case, the yields of the target products were somewhat higher (37—52%). The IR spectra of compounds **2a,b** show an absorption band at ν = 2165—2168 cm^{-1} due to the stretching vibrations of the conjugated C≡N group. Among the most characteristic signals in the ^1H NMR spectra of

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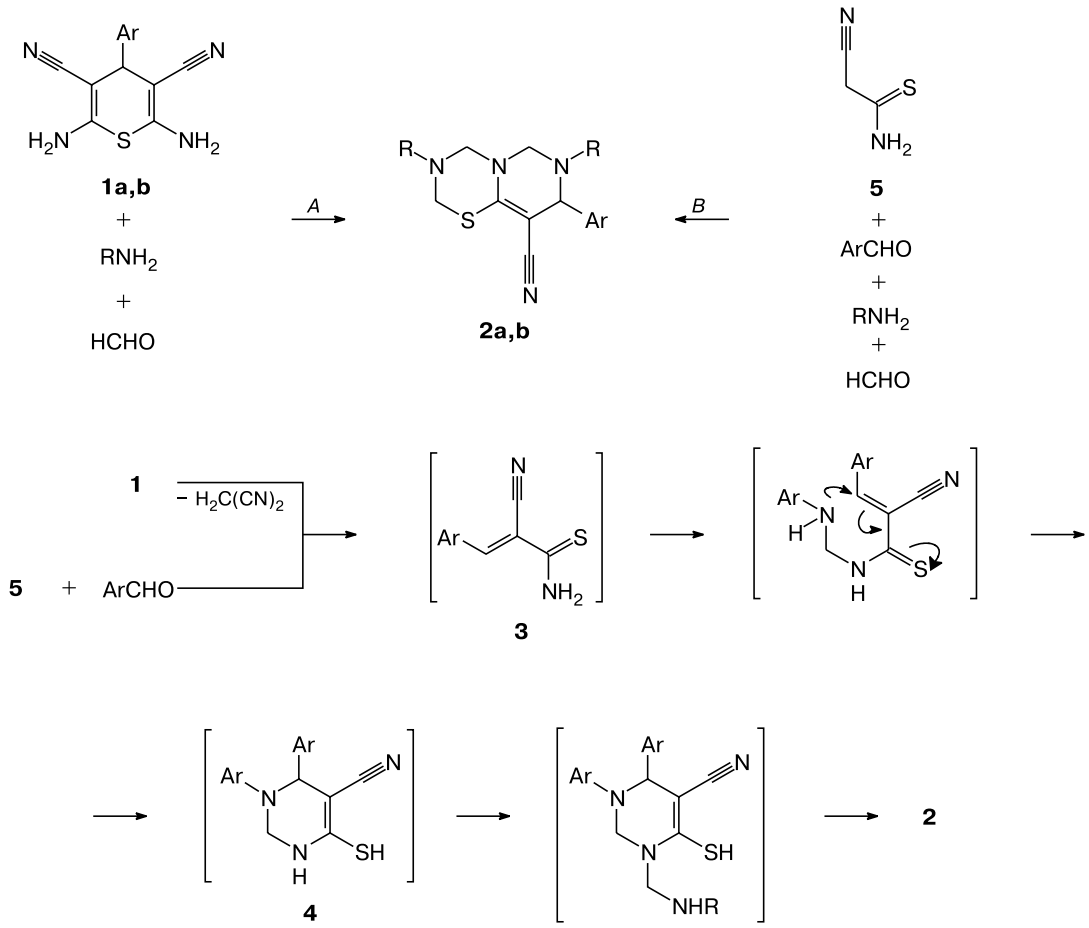
Scheme 1



R = 4-MeC_6H_4; Ar = Ph (**a**), 2-ClC_6H_4 (**b**)

pyrimido[6,1-*b*][1.3.5]thiadiazines **2**, a broadened singlet at δ 5.13—5.25 for the C(8)H proton is worth noting. Signals for the $C(2)H_2$, $C(4)H_2$, and $C(6)H_2$ protons appear as three doublets of doublets at δ 4.33—5.20.

To summarize, we proposed convenient routes to pyrimido[4,3-*b*][1.3.5]thiadiazines, a new heterocyclic system, *via* a multicomponent "one pot" synthesis from acyclic precursors and a new tandem (cross-recyclization—cyclocondensation) reaction of 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles.

Experimental

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 instrument (199.97 MHz) in DMSO-d_6 with Me_4Si as the internal standard. IR spectra were recorded on an IKS-29 spectrophotometer (in Nujol). Elemental analysis was carried out on a Perkin—Elmer C,H,N-Analyzer instrument. The purity of the compounds obtained was checked by TLC on Silufol UV 254 plates in acetone—heptane (1 : 1). Spots were visualized with the iodine vapor or under UV light. Melting points were determined on a Kofler hot stage.

Pyrimido[4,3-*b*][1,3,5]thiadiazines (2a,b). Method *A*. A mixture of appropriate thiopyran **1a,b** (2 mmol), *p*-toluidine (8 mmol), and an excess of 37% HCHO (2.5 mL) in EtOH (15 mL) was refluxed for 3 min. The solution was filtered through a paper filter and left at ~20 °C for 72 h. Crystals of compounds **2a,b** were separated and recrystallized from an appropriate solvent.

Method *B*. Three drops of *N*-methylmorpholine were added to a mixture of cyanothioacetamide (**5**) (0.5 g, 5 mmol) and an appropriate aromatic aldehyde (5 mmol) in EtOH (15 mL). The mixture was stirred for 0.5 h and then *p*-toluidine (1.07 g, 10 mmol) and an excess of 37% HCHO (5 mL) were added. The reaction mixture was refluxed with stirring for 3 min and left at ~20 °C for 24 h. A colorless crystalline precipitate of pyrimidothiadiazine **2a,b** was filtered off, washed with EtOH, and recrystallized from an appropriate solvent.

3,7-Bis(4-methylphenyl)-8-phenyl-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (2a). The yield was 33 (method *A*) and 37% (method *B*). Colorless crystals, m.p. 180—182 °C (from Me_2CO—EtOH, 1 : 1).

Found (%): C, 74.06; H, 6.00; N, 12.74. $C_{27}H_{26}N_4S$. Calculated (%): C, 73.94; H, 5.98; N, 12.77. IR (Nujol), ν/cm^{-1}: 2168 (C≡N). ^{1}H NMR (DMSO-d_6), δ: 2.25, 2.23 (both s, 3 H each, 2 $\underline{H}_3CC_6H_4$); 4.33 (dd, 2 H, NCH_2S, ^2J = 13.0 Hz); 4.87 (dd, 2 H, NCH_2N, ^2J = 13.6 Hz); 5.13 (s, 1 H, C(8)H); 5.20 (dd, 2 H, NCH_2N, ^2J = 12.7 Hz); 7.00 (m, 8 H, 2 $H_3CC_6\underline{H}_4$); 7.32 (m, 5 H, Ph).

8-(2-Chlorophenyl)-3,7-bis(4-methylphenyl)-3,4,7,8-tetrahydro-2*H*,6*H*-pyrimido[4,3-*b*][1,3,5]thiadiazine-9-carbonitrile (2b). The yield was 40 (method *A*) and 52% (method *B*), colorless crystals. The physical parameters, spectroscopic characteristics, and elemental analysis data for compound **2b** agree with those for a sample obtained earlier.[18]

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