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The Mannich–Type Synthesis of Macroheterocycles with Pyrido[2,1–*b*][1,3,5]thiadiazine Unit

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New macrocyclic products containing four pyrido[2,1-b][1,3,5]thiadiazine units linked by methylene bridges and phenylene spacers were synthesized by reaction of morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate with aromatic diamines (p-phenylenediamine, benzidine) and excess of HCHO. A rapid solvent-free procedure for synthesis of the starting thiolate was proposed. The structure of the products was confirmed by IR-, solid state NMR ^{13}C data and elemental analysis.

Keywords: Cyanothioacetamide, pyridine-2-thiolates, Guareschi-Thorpe reaction, pyrido[2,1-*b*][1,3,5]thiadiazines, Mannich reaction, diamines, CP/MAS NMR ^{13}C spectra.

Синтез макрогетероциклов с пиридо[2,1–*b*][1,3,5]тиадиазиновым фрагментом по реакции Манниха

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Новые макроциклические продукты, содержащие четыре пиридо[2,1-b][1,3,5]тиадиазиновые субъединицы, связанные метиленовыми мостиками и фениленовыми спейсерами, были синтезированы взаимодействием 4-метил-6-оксо-3-циано-1,6-дигидропиридин-2-тиолата морфолиния с избытком HCHO и ароматическими диаминами (п-фенилендиамином, бензидином). Предложена быстрая solvent-free процедура получения исходного тиолата. Строение продуктов подтверждено данными ИК-спектроскопии, элементного анализа и твердотельными ЯМР ^{13}C-спектрами.

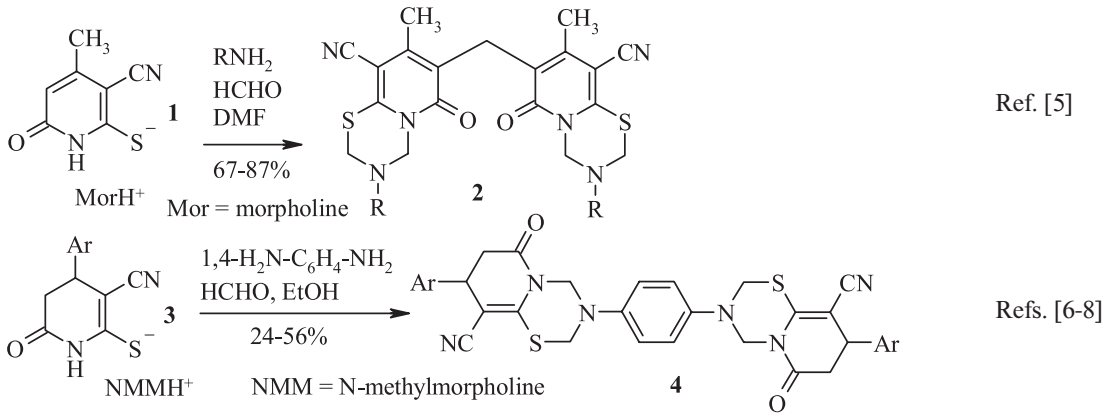
Ключевые слова: Цианотиоацетамид, пиридин-2-тиолаты, реакция Гуарески-Торпа, пиридо[2,1-*b*][1,3,5] тиадиазины, реакция Манниха, диамины, CP/MAS ЯМР ^{13}C спектры.

1,3,5-Thiadiazines have attracted great attention due to a wide spectrum of biological activity (for reviews on the 1,3,5-thiadiazine chemistry, see[1-4]). Recently we have found that thiolate **1** readily reacts with excess of formaldehyde HCHO and primary amines in boiling DMF to give 7,7'-bis(pyrido[2,1-*b*][1,3,5]thiadiazinyl)methanes **2**[5] (Scheme 1). The linking of two pyridine units by a methylene bridge upon treatment with formaldehyde is known as a general reaction for either pyridin-2(1*H*)-ones, or tautomeric 2-hydroxypyridines with an active C-3 position.[6-8] On the other hand, pyridine-2-thiolates **3** react with HCHO and 1,4-phenylenediamine to form Mannich-type products **4** containing two pyridothiadiazine units linked by phenylene spacer[9] (Scheme 1). The ability of thiolate **1** to form bonds oriented in different directions has prompted us to build macrocyclic ensembles with pyrido[2,1-*b*][1,3,5]thiadiazine units under Mannich reaction conditions.

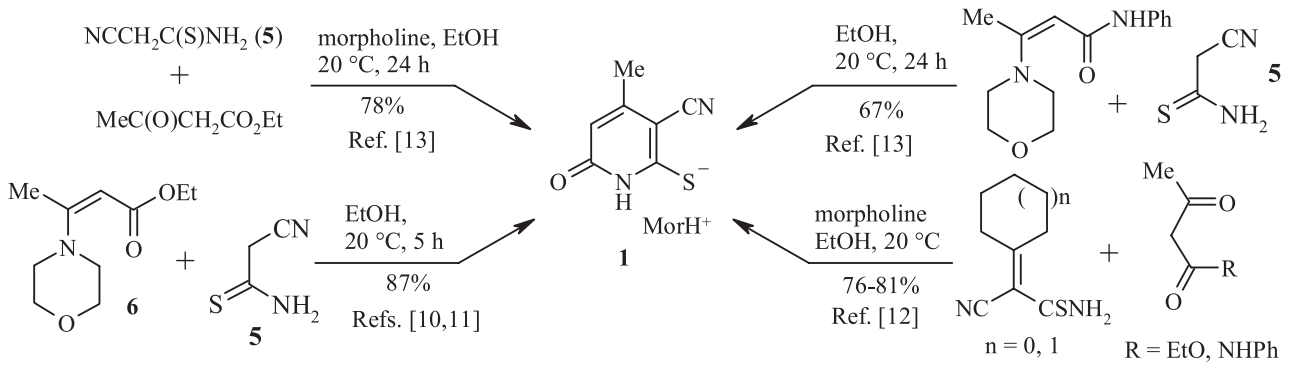
First, we had to develop fast and scalable synthesis of thiolate **1**. The compound **1** could be obtained by reaction of cyanothioacetamide **5** with either ethyl-3-morpholinocrotonate **6**, or 3-morpholinocrotonanilide,[10,11] cycloalkylidene cyanothioacetamide with ethyl acetoacetate in the presence of morpholine,[12] or by ternary Gureschi-Thorpe condensation of cyanothioacetamide **5** with morpholine and acetoacetic ester (EtOH, 20 °C, 24 h)[13] (Scheme 2). The highest yield of salt **1** (87 %) was achieved when β-aminocrotonate **6** was reacted with thioamide **5**; however, this synthesis includes an additional step in which aminocrotonate **6** has to be prepared.

From the practical point of view, the Guareschi-Thorpe ternary condensation seems to be the most effective and convenient approach. However, when we had attempted to prepare thiolate **1** by the reported procedure[13] under carefully controlled conditions, the yield was only 43 % instead of reported 78 %. These results have prompted us to find an alternative procedure, which would combines one-pot approach, reproducibility, gram-scalability and rapidity. The problem was successfully solved by refusing to use any solvent. Thus, when cyanothioacetamide **5**, ethyl acetoacetate and morpholine were slowly melted until an exothermic reaction had completed and the melt was treated with acetone, thiolate **1** was obtained in 66 % yield. When thioamide **5**, ethyl acetoacetate and morpholine were vigorously stirred at the ambient temperature, the mixture had solidified within 10–15 min to obtain thiolate **1** in 55 % yield. The highest yield (76 %) was achieved when thioamide **5** was fused with beforehand prepared mixture of $AcCH_2CO_2Et$ and morpholine (Scheme 3)[§]. Obviously the reaction proceeds *via* the formation of β-aminocrotonate **6** *in situ*, followed by the Guareschi-Thorpe cyclization. The proposed solvent-free procedure could be easily scaled up to produce tens of grams of pure thiolate **1** in reasonable yields.

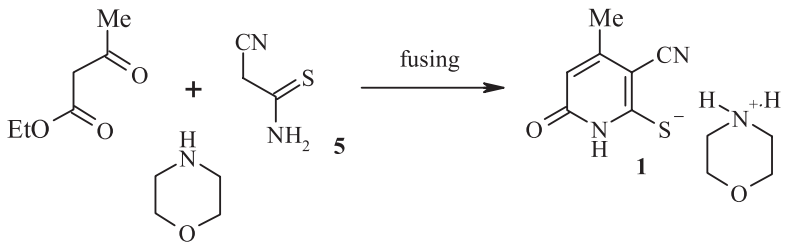
After developing fast and scalable synthesis of thiolate **1**, we have attempted to prepare macrocyclic compounds by the Mannich reaction of thiolate **1** with HCHO excess and aromatic diamines. Thus, when thiolate **1** was treated with 0.5 eq. of 1,4-phenylenediamine (or benzidine) and HCHO



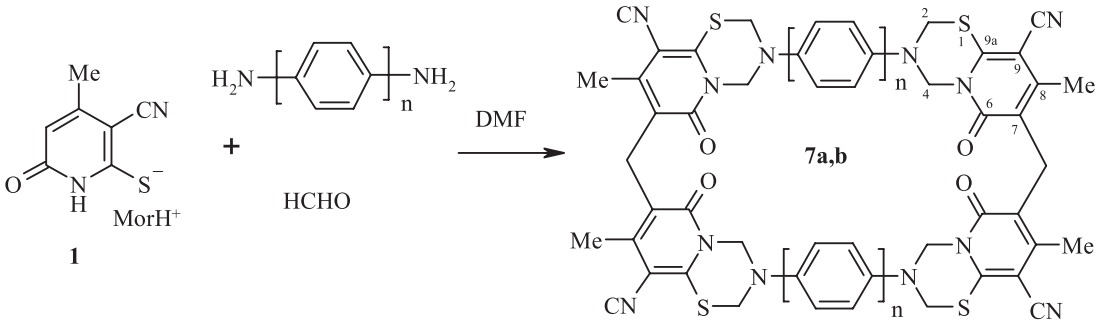
Scheme 1.



Scheme 2.



Scheme 3.



7a ***n*** **=** ***1***; **b** ***n*** **=** ***2***.

Scheme 4.

in hot DMF, amorphous solids were obtained for which we have assigned the structure **7a,b** (Scheme 4)¶.

The compounds **7a,b** are beige powders which are insoluble in any common organic solvents, including DMF, DMSO, acetone, $CHCl_3$ and TFA. Therefore we have failed to characterize the compounds by LCMS and NMR ^1H /^{13}C spectroscopy. In order to confirm the structure, solid state CP/MAS ^{13}C NMR experiments have been performed (Figure 1)[#]. IR spectra of the obtained products are similar to those of compounds **2** and show the absorption bands of C=C (ν 1650-1645 cm^{-1}) and conjugated C≡N (ν 2205 cm^{-1}). No absorption bands of N–H or O–H bands were observed. In the CP/MAS ^{13}C NMR spectra two peaks at δ=18-29 ppm corresponding to CH_3 and methylene bridge carbons were observed, while resonance peaks of SCH_2NCH_2N carbon atoms were observed at δ=52–65 ppm. Elemental analysis data do not contradict the proposed structures.[#]

Notes and References

[§] *Morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate (1). Method A.* A mixture of cyanothioacetamide **5** (1.88 g, 18.77 mmol), ethyl acetoacetate (2.5 ml, 19.73 mmol) and

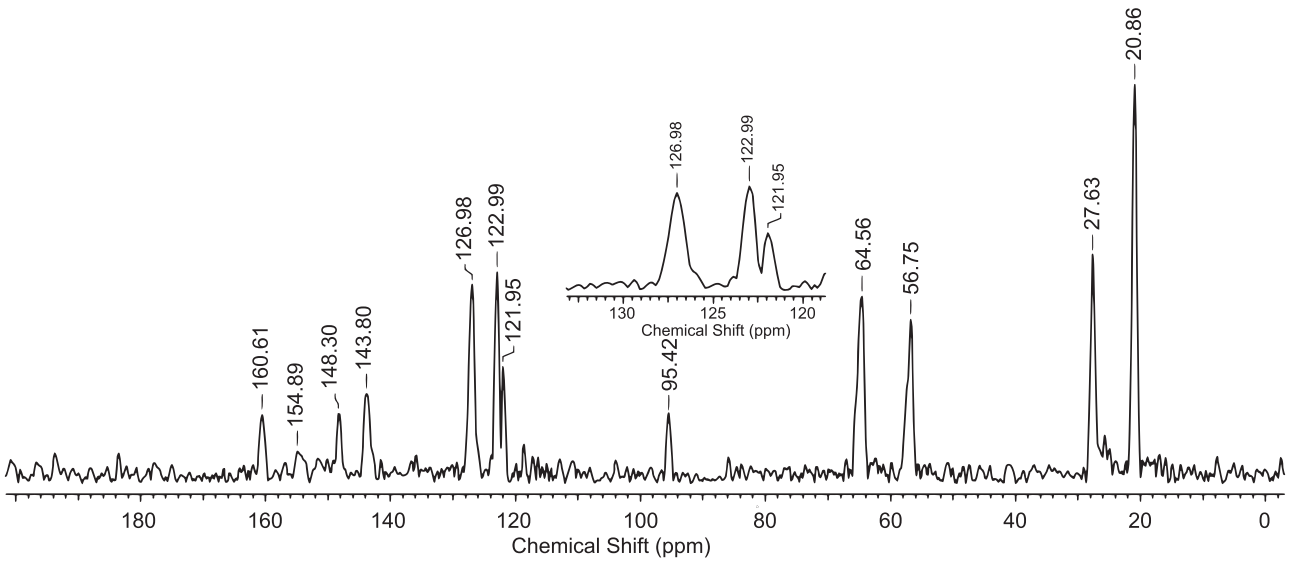


Figure 1. NMR CP/MAS ^{13}C spectrum (101 MHz, ns = 256, 10 kHz) of compound **7a**.

morpholine (1.7 ml, 19.5 mmol) was stirred at 20 °C. A slightly exothermic reaction was observed and the solution was solidified within 10 minutes. Acetone (15 ml) was added and thereafter the obtained slurry was filtered off, washed with acetone and dried at 60 °C. The product **1** (2.59 g, 55 %) was obtained as a beige powder, m.p. 224-227 °C (Lit.: 226-228 °C,[10,11] 224-226 °C[13]). IR ν cm^{-1}: 2205 s (C≡N); 1640 s (NHC(O)). ^{1}H NMR ([D_6]DMSO) δ_H ppm: 2.00 (3H, s, CH_3); 3.12 (4H, m, $(CH_2)_2N$); 3.76 (4H, m, $(CH_2)_2O$); 5.40 (1H, s, H-5); 8.69 (2H, br.s, H_2N^+); 10.40 (1H, br.s, NH). Found, %: C, 52.36; H, 6.00; N, 16.61. $C_{11}H_{15}N_3O_2S$. Calculated, %: C, 52.16; H, 5.97; N, 16.59.

Method B. A mixture of cyanothioacetamide **5** (1.52 g, 15.17 mmol), ethyl acetoacetate (2.1 ml, 16.57 mmol) and morpholine (1.5 ml, 17.22 mmol) was stirred at 20 °C until the starting material dissolved, then it was slowly heated until an exothermic reaction began. Heating was immediately discontinued and acetone (20-25 ml) was added to the red melt under vigorous stirring. The melt was solidified immediately, the precipitate was ground, filtered off and washed with acetone to give thiolate **1** (2.54 g, 66 %) which was identical to the sample obtained by Method A.

Method C. To a mixture of ethyl acetoacetate (5.0 ml, 39.46 mmol) and morpholine (3.8 ml, 43.62 mmol), formic acid (8-10 drops) was added; the mixture was stirred at 30-40 °C for 20 min, then cyanothioacetamide **5** (3.90 g, 38.95 mmol) was added. The formed red solution was slowly heated until an exothermic reaction began (2-3 min). Heating was immediately discontinued and acetone (50 ml) was added to the red melt under vigorous stirring. The melt had solidified immediately, the precipitate was ground, filtered off and washed with acetone to give thiolate **1** (7.46 g, 76 %) as beige powder.

[¶] *The reaction of thiolate **1** with p-phenylenediamine (benzidine) and HCHO.* Thiolate **1** (465 mg, 1.82 mmol) and the corresponding diamine (0.92–0.93 mmol, 101 mg of *p*-phenylenediamine or 175 mg of benzidine) were dissolved in hot DMF (5 ml) and then excess HCHO (37 % aq. soln., 1.5 ml) was added. The product had separated almost immediately. The mixture was gently boiled for 1-3 min under vigorous stirring, allowed to cool, the precipitated solid was filtered off and washed with EtOH and acetone.

*The product **7a*** was obtained as a heavy beige powder (333 mg, 72.5 %), m.p. > 300 °C. IR ν cm^{-1}: 2205 s (C≡N), 1640 m (C=O). ^{13}C NMR CP/MAS δ_C ppm: 20.9 (CH_3); 27.6 (methylene bridge CH_2); 56.8 (SCH_2N); 64.6 (NCH_2N); 95.4 (C-9); 122.0 (C≡N); 123.0 (C-7); 127.0 (CH of the phenylene spacer); 143.8 (C-8); 148.3 (C–N phenylene); 154.9 (C-9a); 160.6 (C=O). Found, %: C, 59.83; H, 4.19; N, 16.88. $C_{50}H_{40}N_{12}O_4S_4$. Calculated, %: C, 59.98; H, 4.03; N, 16.79.

*The product **7b*** was obtained as a sand-coloured powder (459 mg, 86.5 %), m.p. > 300 °C. IR ν cm^{-1}: 2205 s (C≡N); 1650 m (C=O). ^{13}C NMR CP/MAS δ_C ppm: 18.3 (CH_3); 28.8 (methylene bridge CH_2); 51.9 (SCH_2N); 59.0 (NCH_2N); 110.8 (C-9); 117.6 (C≡N); 117.9 (C benzidine); 123.4 (C-7); 125.9 (C benzidine); 128.2 (C benzidine); 144.1 (C-8); 148.3 (C–N benzidine); 151.6 (C-9a); 161.5 (C=O). Found, %: C, 64.43; H, 4.30; N, 14.70. $C_{62}H_{48}N_{12}O_4S_4$. Calculated, %: C, 64.56; H, 4.19; N, 14.57

[#] The solid state CP/MAS ^{13}C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (101 MHz, ns=256, 10 kHz). ^{1}H NMR spectra of thiolate **1** were recorded on Bruker DRX-500 spectrometer (500 MHz) in [D_6]DMSO with TMS as an internal standard. IR spectra were taken in Nujol mulls on an IKS-29 (LOMO, USSR) spectrometer. Elemental analysis was performed on Carlo Erba Strumentazione 1106 device.

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