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Synthesis of 2-Thioxo-6-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile and Ethyl 5-Cyano-6-thioxo-1,6-dihydropyridine-2-carboxylate by the S_NVin Reaction

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Abstract—Ethyl 5-cyano-6-thioxo-1,6-dihydropyridine-2-carboxylate and 2-thioxo-6-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile were obtained by the S_NVin reaction. The latter compound was used in the synthesis of 2-alkylsulfanyl-6-trifluoromethylpyridin-3-carbonitriles, 3-amino-5-trifluoromethylthieno[2,3-*b*]pyridin-2-carboxamide, and 7-thifluoromethyl-2-spirocyclopentane-1,2,3,4-tetrahydropyrido[2',3':2,3]thieno[4,5-*d*]pyrim-idin-4-one.

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Nucleophilic vinyl substitution (S_NVin) is widely used in the synthesis of carbo- and heterocycles, including biologically active compounds [1–3]. These reactions are especially convenient for preparing functionalized 4-unsubstituted derivatives of 6-trifluoromethylpyridine [4, 5] and 5-unsubstituted 4-trifluoromethyl- [6] and 6-trifluoromethylpyridines [7].

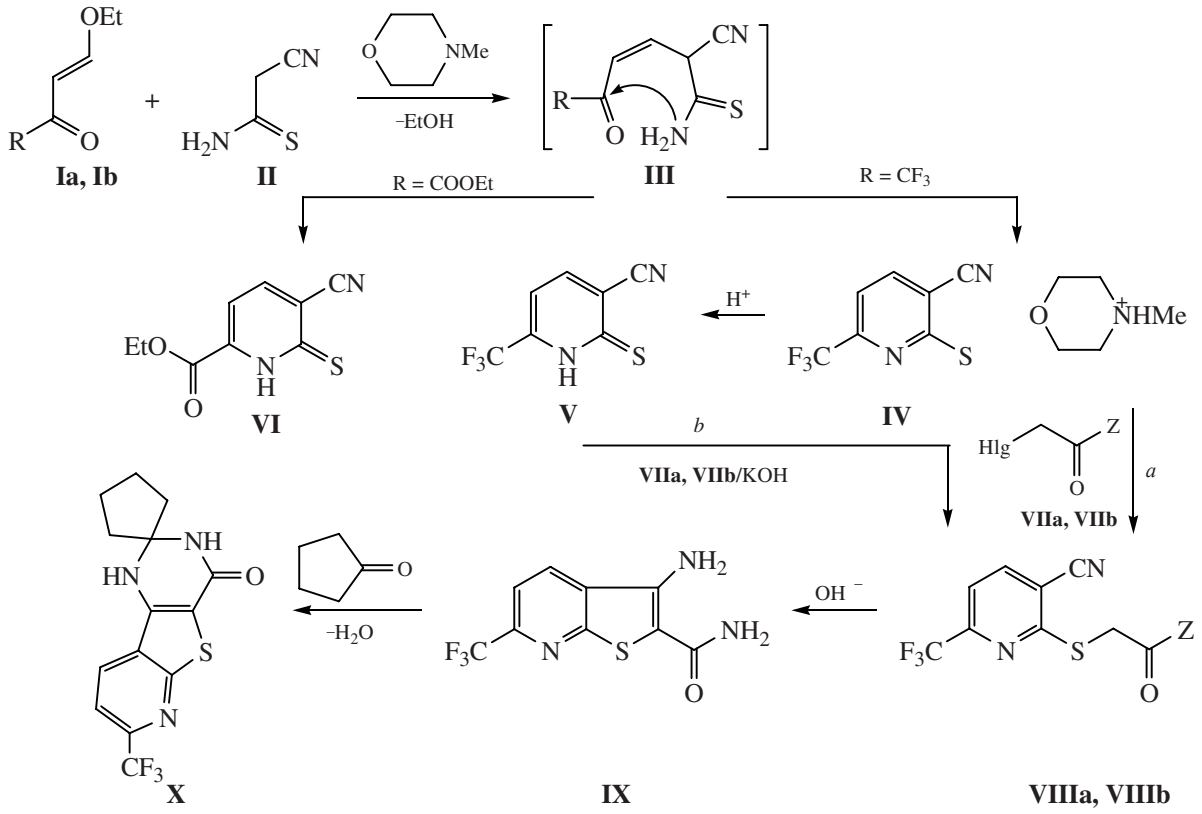
In the present work we synthesized previously unknown 4,5-unsubstituted 6-trifluoromethylpyridines, potential half-products for synthesis of medicinal and agricultural preparations [8]. It was shown that the reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**Ia)** with cyanothioacetamide (**II)** in absolute ethanol at 20°C in the presence of an equimolar amount of *N*-methylmorpholine as nucleophilic vinyl substitution and gives product **III**. The latter is unstable under the reaction conditions and undergoes intramolecular heterocyclization to form *N*-methylmorpholinium 3-cyano-6-trifluoromethylpyridine-2-thiolate (**IV**) which in the acidic medium easily transforms to 2-thioxo-6-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (**V**). Note that compound **Ia** was used previously in the synthesis of trifluoromethyl-substituted spiro-fused pyranes, based on the S_NVin reaction [9].

Introduction of ethyl 4-ethoxy-2-oxobut-3-enoate (**Ib**) as the alkoxyethylene component in condensation with amide **II** did not radically change the S_NVin reaction pathway and resulted in formation of a previously unknown ethyl 5-cyano-6-thioxo-1,6-dihydropyridine-2-carboxylate (**VI**).

The structure of compounds **IV–VI** was confirmed by spectral studies (see Experimental) and chemical transformations. Hence, the presence of the thiolate function in the α position of pyridine **IV** was proved by its reaction with alkylating agents **VIIa** and **VIIb** in DMF, leading to corresponding thioethers **VIIIa** and **VIIIb** (method *a*). The latter compounds were also synthesized from pyridinethione **V** and compounds **VIIa** and **VIIb** (method *b*).

The presence of the vicinal cyano and alkylsulfanyl groups in the pyridinone ring of compound **VIIIa** was easily confirmed by the formation of the thiophene ring under the action of alkali to give 3-amino-6-trifluoromethylthieno[2,3-*b*]pyridine-2-carboxamide (**IX**), which is characteristic of such type structures [10].

The structure of compound **IX** was established, apart from spectral methods (see Experimental), by means of the characteristic reaction of cycloalkanones with vicinal amino and carbamoyl groups [11,12]. The reaction gave 7-thifluoromethyl-2-spirocyclopentane-1,2,3,4-tetrahydropyrido[2',3':2,3]thieno[4,5-*d*]pyrim-idin-4-one with a potential antimicrobial activity [11].



I: R = CF_3 (**a**), COOEt (**b**); **VII**: Hlg = Cl, Z = NH_2 (**a**), Hlg = Br, Z = 3-coumarinyl (**b**); **VIII**: Z = NH_2 (**a**), 3-coumarinyl (**b**).

The ^{1}H NMR spectra of compounds **V** and **VI** show characteristic doublets of the C^4H and C^5H protons of the pyridinone ring. The IR spectra contain a characteristic stretching vibration band of the conjugated cyano group in the range 2225–2231 cm^{-1}.

EXPERIMENTAL

The IR spectra of were recorded on an IKS-40 spectrometer in mineral oil. The ^{1}H NMR spectra were taken on a Bruker DR-500 spectrometer (500.13 MHz) in DMSO-d_6 against internal TMS. The mass spectra were obtained on a Hewlett–Packard 5890/5972 GC–MS spectrometer equipped with an HP-5 MS column (70 eV) in CH_2Cl_2 solutions. The melting points were measured in a Koffler hot stage. The reaction progress and the purity of the compounds were controlled by TLC on Silufol UV-254 plates, elution with a 3:5 acetone–hexane mixture, development in iodine vapor and under UV irradiation.

***N*-Methylmorpholinium-3-cyano-6-trifluoromethylpyridine-2-thiolate (IV).** To a stirred suspension of 1 g of cyanothioacetamide (**II**) in 15 ml of absolute ethanol, 1.1 ml of *N*-methylmorpholine was added, and the mixture was stirred for 8 min until homogenization. After that the reaction mixture was treated with 1.68 g of compound **Ia**, stirred for 20 min and left for a day. The precipitate that formed was filtered off and washed with absolute ethanol and hexane. Yield 2.47 g (81%), mp 102–103°C (from EtOH), yellow crystals. IR spectrum, ν, cm^{-1}: 2219 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.67 s (3H, Me), 3.02 t (4H, CH_2NCH_2, *J* 4.4 Hz), 3.74 t (4H, CH_2OCH_2, *J* 4.4 Hz), 6.92 d (1H, C^4H, *J* 7.5 Hz), 7.72 d (1H, C^5H, *J* 7.5 Hz). The N^+H proton signal does not appear, probably due to a fast exchange with deuterium. Mass spectrum, *m/z* (I_{rel}, %): 205 $[M + 2]^+$ (8), 203 $[M]^+$ (100). Found, %: C 47.11; H 4.58; N 13.68. $C_{12}H_{14}F_3N_3OS$. Calculated, %: C 47.21; H 4.62; N 13.76.

2-Thioxo-6-trifluoromethyl-1,2-dihydropyridine-3-carbonitrile (V). Crystallization of 3.05 g of salt **IV** from 15 ml of glacial acetic acid gave compound **V** as a yellow powder. Yield 1.79 g (88%), mp 107–109°C. IR spectrum, ν, cm^{-1}: 3428 (N–H), 2231 (C=N). ^{1}H NMR spectrum, δ, ppm: 8.08 d (1H, C^4H, *J* 8.0 Hz), 8.76 d (1H, C^5H, *J* 8.0 Hz). The NH proton signal does

not appear, probably due to a fast exchange with deuterium. Mass spectrum, *m/z* (I_{rel}, %): 205 $[M + 1]^+$ (7), 203 $[M - 1]^+$ (100), 106 $[M - H - CF_3^+ - HCN]^+$ (10). Found, %: C 41.04; H 1.33; N 13.60. $C_7H_3F_3N_2S$. Calculated, %: C 41.18; H 1.48, N 13.72.

Ethyl 5-cyano-6-thioxo-1,6-dihydropyridine-2-carboxylate (VI) was obtained similarly to salt **IV** from ethyl 4-ethoxy-2-oxobut-3-enoate (**Ib**). Yield 1.6 g (77%), mp 193–195°C (AcOH), yellow powder. IR spectrum, ν, cm^{-1}: 2225 (C≡N), 1730 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 t (3H, Me, *J* 6.19 Hz), 4.33 q (2H, CH_2, *J* 6.19 Hz), 7.08 d (1H, C^4H, *J* 8.02 Hz), 7.99 d (1H, C^3H, *J* 8.02 Hz), 14.51 br.s (1H, NH). Found, %: C 51.82; H 3.72; N 13.29. $C_9H_8N_2O_2S$. Calculated, %: C 51.91; H 3.87; N 13.45.

2-[(3-Cyano-6-trifluoromethylpyridin-2-yl)sulfanyl]acetamide (VIIIa). *a*. 2-Chloroacetamide (**VIIa**), 0.94 g, was added at 20°C to a stirred solution of 3.05 g of salt **IV** in 10 ml of DMF. The reaction mixture was stirred for 4 h and left for a day. After that in was diluted by half with water, and the precipitate that formed was filtered off, washed with water, ethanol, and hexane. Yield 1.93 g (74%), mp 168°C (AcOH), colorless needles. IR spectrum, ν, cm^{-1}: 3427, 3206 (NH_2), 2232 (C≡N), 1623 (CONH). ^1H NMR spectrum, δ, ppm: 4.00 s (2H, CH_2), 7.13 br.s (1H, NH_2), 7.56 br.s (1H, NH_2), 7.78 d (1H, C^4H, *J* 7.95 Hz), 8.49 d (1H, C^5H, *J* 7.95 Hz). Mass spectrum, *m/z* (I_{rel}, %): 260 $[M - 1]^+$ (91), 242 (59), 203 $[M - CH_2CONH_2]^+$ (100), 143 (8), 106 (11), 84 (19). Found, %: C 41.14; H 2.05; N 15.87. $C_9H_6F_3N_3O_S$. Calculated, %: C 41.38; H 2.31; N 16.09.

b. 2-[2-Oxo-2-(2-oxo-2*H*-chromen-3-yl)ethylsulfanyl]-6-trifluoromethylnicotinonitrile (**VIIIb**) was prepared analogously to amide **VIIIa** from 2.67 g of compound **VIIb**. Yield 3.47 g (89%), mp 170–172°C (AcOH), colorless powder. IR spectrum, ν, cm^{-1}: 2228 (C≡N), 1722 (C=O). ^1H NMR spectrum, δ, ppm: 4.88 s (2H, CH_2), 7.31 d (1H, coumarin C^5H, *J* 9.0 Hz), 7.43 d (1H, coumarin C^8H , *J* 9.0 Hz), 7.50 d (1H, pyridine C^4H, *J* 8.0), 7.77 t (2H, coumarin C^6H and C^7H, *J* 9.0 Hz), 8.51 d (1H, pyridine C^4H, *J* 8.0 Hz), 8.73 s (1H, coumarin C^4). Mass spectrum, *m/z* (I_{rel}, %): 392 $[M + 2]^+$ (15), 390 $[M]^+$ (54), 388 $[M - 2]^+$ (100), 372 (16), 284 (9), 259 (12), 218 (13), 202 (67), 190 (18), 150 (11), 124 (7), 94 (6). Found, %: C 55.20; H 2.14; N 6.99. $C_{18}H_9F_3N_2O_3S$. Calculated, %: C 55.39; H 2.32; N 7.18.

c. Compound **VIIIa**. A stirred solution of 2.04 g of pyridinethione **V** in 10 ml of DMF was treated at 20°C with 5.6 ml of 10% aqueous KOH and 0.94 g of 2-chloroacetamide (**VIIa**). The resulting mixture was stirred for 4 h and left for a day. After that the reaction mixture was diluted by half with water, and the precipitate that formed was filtered off to obtain amide **VIIIa**, yield 1.85 g (71%). Its melting point and R_f were analogous to those of the sample synthesized by method *a*.

d. Compound **VIIIb** was prepared analogously to amide **VIIIa** from 2.67 g of bromoacetylcoumarin **VIIb**. Yield 2.92 g (75%), the melting point and chromatographic data were analogous to those of the sample prepared by method *a*.

3-Amino-4-trifluoromethylthieno[2,3-*b*]pyridine-2-carboxamide (IX). A solution of 2.61 g of amide **VIIIa** in 15 ml of DMF was treated with stirring at 20°C with 5.6 ml of 10% aqueous KOH, and the resulting mixture was stirred for 5 h. After that it was diluted by half with water, and the precipitate that formed was filtered off and washed with water, ethanol, and hexane. Yield 1.98 g (76%), mp 270°C (BuOH), light yellow powder. At 210°C the substance sublimes to form needles, under UV irradiation it fluoresces. IR spectrum, ν, cm^{-1}: 3410, 3390, 3324 (NH_2), 1696 (C=O), 1662 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 7.41 br.s (4H, $2NH_2$), 7.92 d (1H, C^4H, *J* 8.02 Hz), 8.71 d (1H, C^5H, *J* 8.02 Hz). Mass spectrum, *m/z* (I_{rel}, %): 263 $[M + 2]^+$ (14), 262 $[M + 1]^+$ (100), 219 (25), 138 (11), 101 (9), 83 (7). Found, %: C 41.25; H 2.18; N 15.94. $C_9H_6F_3N_3OS$. Calculated, %: C 41.38; H 2.31; N 16.09.

7-Trifluoromethyl-2-spirocyclopentane-1,2,3,4-tetrahydropyrido[2',3':2,3]thieno[4,5-*d*]pyrimidin-4-one (X). A mixture of 2.61 g of compound **IX**, 0.89 g of cyclopentanone, and 25 ml of glacial acetic acid was refluxed for 4 h. After cooling, yellow crystals formed and were filtered off and washed with glacial acetic acid and ether. Yield 2.26 g (69%), mp 220°C. At 170°C the substance sublimes, under UV irradiation it fluoresces. IR spectrum, ν, cm^{-1}: 3324 (N–H), 1714 (C=O). ^1H NMR spectrum, δ, ppm: 1.71 m (4H, $2CH_2$), 1.89 m (4H, $2CH_2$), 7.95 br.s (1H, NH), 7.98 d (1H, C^9H, *J* 8.0 Hz), 8.14 br.s (1H, CONH), 8.65 d (1H, C^8H, *J* 8.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 326 $[M - 1]^+$ (100). Found, %: C 51.29; H 3.55; N 12.74. $C_{14}H_{12}F_3N_3OS$. Calculated, %: C 51.37; H 3.69; N 12.84.

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