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Synthesis of 2,3-Bis[amino(benzylsulfanyl)methylidene]butanedinitrile and 2-(Benzylsulfanyl)pyridine-3-carbonitrile derivatives

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Abstract—The alkylation of cyanothioacetamide with benzyl chloride in DMF in the presence of 10% aqueous potassium hydroxide afforded 2,3-bis[amino(benzylsulfanyl)methylidene]butanedinitrile. Analogous reaction with addition of acetylacetone or its 3-methyl derivative led to the formation of 2-benzylsulfanyl-4,6-dimethyl- or -4,5,6-trimethylpyridine-3-carbonitrile.

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Cyanothioacetamide (**1**) is widely used in organic synthesis as an active methylene compound for the preparation of 2-thioxo-3-cyanopyridine derivatives [1]. There are a few published data on the alkylation of cyanothioacetamide. In particular, we previously studied its alkylation with allyl bromide, which led to the formation of 2,3-bis[allylsulfanyl(amino)methylidene]butanedinitrile [2].

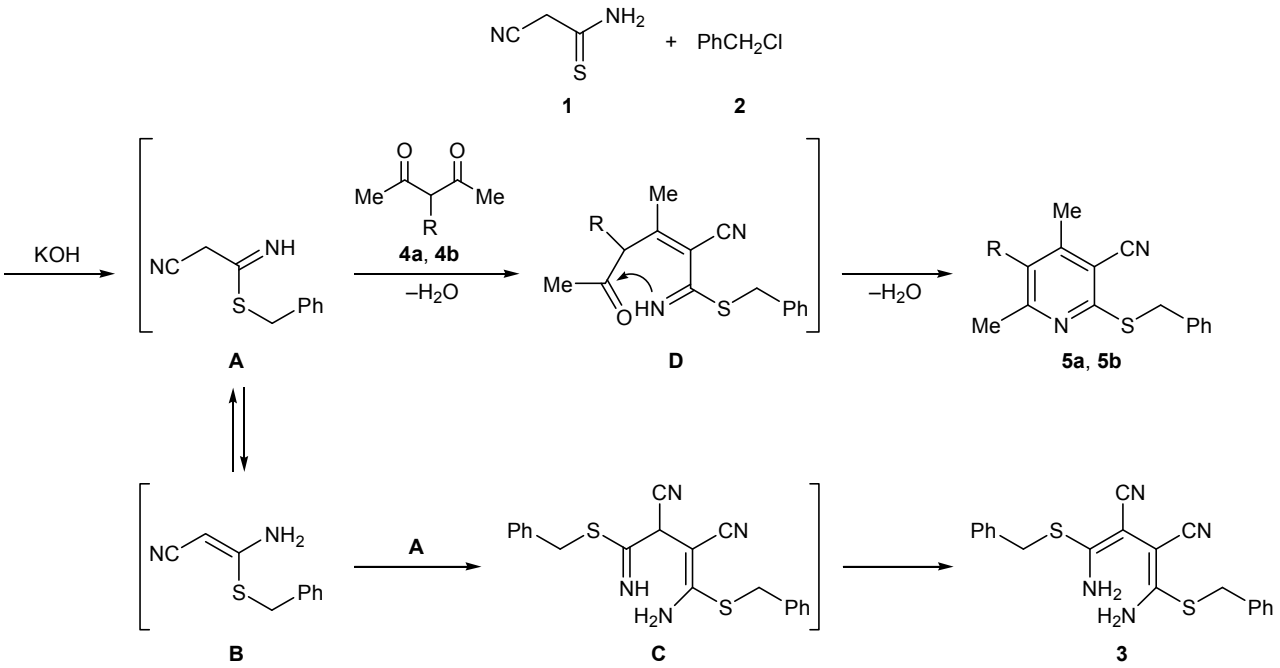
Herein we report the alkylation of **1** with benzyl chloride (**2**) in DMF in the presence of 10% aqueous potassium hydroxide at 20°C. The reaction afforded 2,3-bis[amino(benzylsulfanyl)methylidene]butanedinitrile (**3**) (Scheme 1). Presumably, the reaction involves intermediate formation of imidothioate **A** which tautomerizes to enamino nitrile **B**, and the subsequent Michael addition gives adduct **C** which is stabilized via tautomerization to substituted buta-1,3-diene **3**. The latter is a promising building block for various heterocyclizations [3, 4].

When a third component, acetylacetone **4a** or its 3-methyl derivative **4b**, was added to the reaction mixture, we isolated 2-(benzylsulfanyl)-4,6-dimethyl- and -4,5,6-trimethylpyridine-3-carbonitriles **5a** and **5b**, respectively. The reaction is likely to proceed through the same intermediate imidothioate **A** whose condensation with 1,3-dicarbonyl component **4** gives intermediate **D** (Guareschi–Torpe reaction), and intramolecular cyclization of the latter yields stable final structure **5**. Compounds **5a** and **5b** attract interest as intermediate products for the synthesis of compounds possessing anti-inflammatory [5], antitumor [6], and growth-regulating activity [7].

The structures of condensation products **5a** and **5b** were unambiguously determined by X-ray analysis (Fig. 1). The polymethylpyridinecarbonitrile fragments of molecules **5a** and **5b** are almost planar. Deviations of non-hydrogen atoms from the mean-square planes do not exceed 0.022 (**5a**) or 0.020 Å (**5b**). However, the conformations of 2-benzylsulfanyl substituents in **5a** and **5b** are different. In particular, the torsion angles $C^2S^1C^7C^8$ are –86.30(12) and –79.63(17)°, the angles $S^1C^7C^8C^9$ are –76.65(13) and –59.36(17)°, and the dihedral angles between the pyridine and benzene ring planes are 79.07(6) and 83.36(6)°, respectively.

Molecules of both compounds in crystal form double stacks along the *a* crystallographic axis. In

Scheme 1.



R = H (**a**), Me (**b**).

these stacks, molecules are displaced alternately in parallel planes passing through the pyridine rings by ~1.4 (**5a**) and ~1.6 Å (**5b**) (Fig. 2).

In the crystal structure of **5a**, molecules in the stacks are oriented at a dihedral angle of 21.3(3)° with respect to the 0*YZ* plane and are linked to each other through π–π stacking interactions [the distance between the pyridine ring planes is 3.396(5) Å, and the shortest distance between the C^2 and C^4 (–*x*, 1 – *y*, 1 – *z*) or C^4 and C^2 atoms (–*x*, 1 – *y*, 1 – *z*) is 3.392(2) Å]. The presence of an additional methyl group in position *5* of the pyridine ring of **5b** not only leads to greater displacement of molecules in the double stacks relative to each other but also increases the distance between the pyridine rings of the neighboring molecules to 3.574(5) Å. Furthermore, mole-

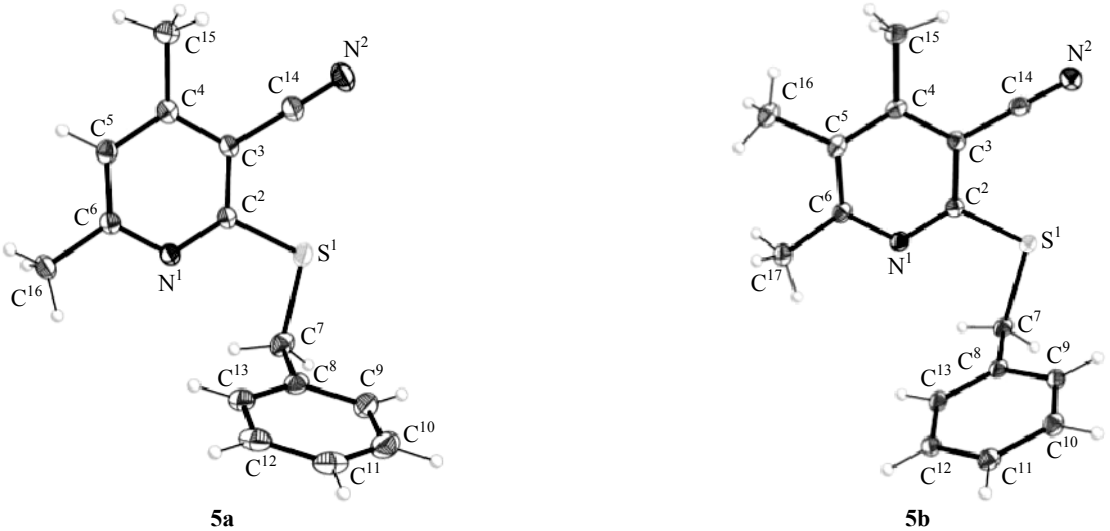


Fig. 1. Molecular structures of 2-(benzylsulfanyl)-4,6-dimethylpyridine-3-carbonitrile (**5a**) and 2-(benzylsulfanyl)-4,5,6-trimethylpyridine-3-carbonitrile (**5b**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as anisotropic displacement ellipsoids with a probability of 50%.

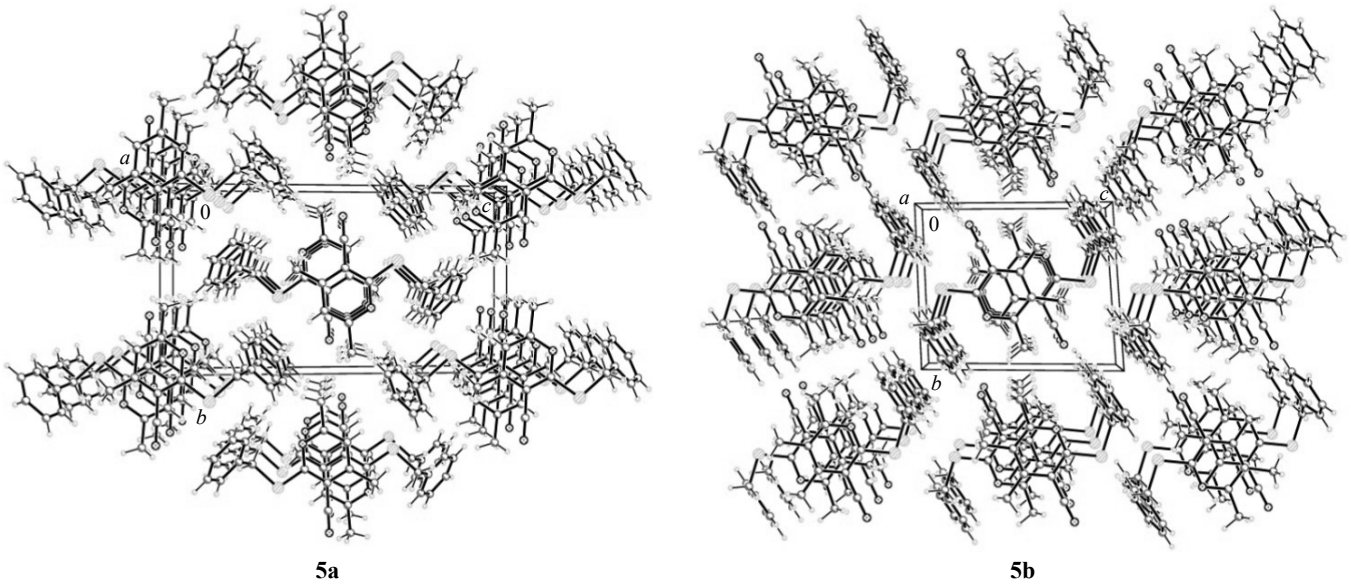


Fig. 2. Crystal packings of 2-(benzylsulfanyl)-4,6-dimethylpyridine-3-carbonitrile (**5a**) and 2-(benzylsulfanyl)-4,5,6-trimethylpyridine-3-carbonitrile (**5b**).

cules **5b** in the stacks are oriented at a smaller angle with respect to the 0*YZ* plane [12.9(3)°] than in the crystal structure of **5a**. Thus, molecules **5b** in crystal are located at van der Waals distances from each other.

EXPERIMENTAL

The X-ray diffraction data for compounds **5a** and **5b** were obtained on a BELOK synchrotron station (National Research Center "Kurchatov Institute") with a Rayonix SX165 CCD two-coordinate detector (temperature 100 K, λ 0.96990 Å, φ-scanning with a step of 1.0°). The data were processed by iMOSFLM program implemented in CCP4 package [8]. A correction for absorption was applied using SCALA program [9]. The principal crystallographic data and structure refinement parameters are given in Table 1. The structures were solved by the direct method and were refined against F^2 by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions and were refined with fixed positional parameters (riding model) and isotropic displacement parameters [U_{iso}(H) = 1.5 U_{eq}(C) for methyl groups, U_{iso}(H) = 1.2 U_{eq}(C) for the other hydrogens]. All calculations were performed using SHELXTL [10]. The tabulated coordinates of atoms, bond lengths, bond and torsion angles, and anisotropic displacement parameters for compounds **5a** and **5b** were deposited to the Cambridge Crystallographic Data Centre; CCDC entry nos. 1868569 (**5a**) and 1868570 (**5b**).

The IR spectra were recorded on an IKS-40 spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Varian VXR-400 instrument at 399.97 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The high-resolution mass spectra of **5a** and **5b** were recorded on an Orbitrap Elite instrument; samples were dissolved in 1 mL of DMSO, and the solutions were diluted by a factor of 100 with 1% formic acid in acetonitrile and introduced into the ESI source at a flow rate of 40 μL/min using a syringe pump with the gas supply being turned off; capillary voltage 3.5 kV, capillary temperature 275°C; positive and negative ion detection using an orbital trap with a resolution of 480000; internal calibration against [2DMSO + H]$^+$ (*m*/*z* 157.03515, positive ions) and dodecyl sulfate anion (*m*/*z* 265.14789; negative ions). The mass spectrum of **3** (electron impact, 70 eV) was obtained on an Agilent 1100 Series LC/MSD instrument (a sample was introduced as a solution in AcOH). Elemental analysis was performed on a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of the isolated compounds were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were visualized by treatment with iodine vapor and under UV light.

2,3-Bis[amino(benzylsulfanyl)methylidene]-butanedinitrile (3). Cyanothioacetamide (**1**), 1.0 g (10 mmol), was dissolved in 15 mL of DMF, and 5.6 mL (10 mmol) of 10% aqueous potassium hydrox-

Table 1. X-Ray diffraction data for compounds **5a** and **5b**

Parameter	**5a**	**5b**
Formula	$C_{15}H_{14}N_2S$	$C_{16}H_{16}N_2S$
Molecular weight	254.34	268.37
Single crystal dimensions, mm	0.05×0.05×0.20	0.15×0.15×0.20
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	P-1
a, A	7.1803(14)	7.2950(15)
b, A	10.040(2)	9.1851(18)
c, A	18.690(4)	10.815(2)
α, deg	90	85.13(3)
β, deg	98.68(3)	81.63(3)
γ, deg	90	77.31(3)
V, A^3	1331.9(5)	698.4(3)
Z	4	2
d_{calc}, g/cm^3	1.268	1.276
$F(000)$	536	284
μ, mm^{-1}	0.522	0.505
$2\theta_{max}$, deg	76.92	76.58
Total number of reflections	23735	12066
Number of independent reflections (R_{int})	2756 (0.088)	2497 (0.089)
Number of reflections with $I > 2\sigma(I)$	2351	2244
Number of variables	166	176
R_1, wR_2 [reflections with $I > 2\sigma(I)$]	0.048, 0.120	0.056, 0.153
R_1, wR_2 (independent reflections)	0.056, 0.126	0.062, 0.161
Goodness of fit (F^2)	1.080	0.993
Extinction coefficient	0.011(1)	0.035(5)
T_{min}, T_{max}	0.890, 0.970	0.890, 0.920

ide and 1.2 mL (10 mmol) of benzyl chloride (**2**) were added in succession with stirring at 20°C. The mixture was stirred for 2 h and left to stand for 3 days. The mixture was then slowly diluted with an equal volume of water under stirring and was left to stand for 3 days at room temperature. The precipitate was filtered off and washed with water and methanol. Yield 1.6 g (43%), white powder, mp 179–180°C (from EtOH). IR spectrum, ν, cm^{-1}: 3280–3450 (NH_2), 2200 (C≡N), 1638 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 4.29 s (4H, CH_2), 6.69 br.s (4H, NH_2), 7.35 br.s (10H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 36.0 (2C), 71.5 (2C), 120.7 (2C), 127.9 (2C), 129.2 (4C), 129.4 (4C), 134.0 (2C), 156.6 (2C). Mass spectrum: m/z 379.0 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 63.35; H 4.68; N 14.72. $C_{20}H_{18}N_4S_2$. Calculated, %: C 63.46; H 4.79; N 14.80. M 378.5.

2-(Benzylsulfanyl)-4,6-dimethylpyridine-3-carbonitrile (5a). Cyanothioacetamide (**1**), 1.0 g (10 mmol), was dissolved in 15 mL of DMF, and 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide and 1.2 mL (10 mmol) of benzyl chloride (**2**) were added in succession with stirring at 20°C. The mixture was stirred for 2 h, 1.23 mL (10 mmol) of acetylacetone (**4a**) was added, and the mixture was heated to 50°C, left to stand for 2 days, and diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane. Yield 1.7 g (68%), colorless needles, mp 80–82°C (from AcOH) [11]. ^{13}C NMR spectrum, δ_C, ppm: 20.1, 24.7, 33.7, 104.2, 115.4, 120.9, 127.6, 128.8 (2C), 129.5 (2C), 138.1, 152.9, 160.7, 161.8. Found: m/z 255.0951 $[M + H]^+$. $C_{15}H_{14}N_2S$. Calculated: M + H 255.0878.

2-(Benzylsulfanyl)-4,5,6-trimethylpyridine-3-carbonitrile (5b) was synthesized in a similar way using 1.2 mL (10 mmol) of 3-methylpentane-2,4-dione (**4b**). Yield 1.9 g (71%), colorless crystals, mp 120–122°C (from EtOH) [12]. ^{13}C NMR spectrum, δ_C, ppm: 14.6, 18.6, 24.0, 33.6, 105.0, 116.0, 125.5 (2C), 127.3, 127.5, 128.8 (2C), 138.4, 150.7, 156.9, 160.4. Found: m/z 269.1108 $[M + H]^+$. $C_{16}H_{16}N_2S$. Calculated: M + H 269.1034.

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