## Synthesis of 3-amino-4-methyl-6-trifluoromethylthieno[2,3-b]pyridine-2carboxanilide and its crystal and molecular structure

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4-Methoxy-1,1,1-trifluoropent-3-en-2-one reacts with cyanothioacetamide to give 3-cyano-4-methyl-6-trifluoromethylpyridine-2(1H)-thione, which was transformed into 3-amino-4-methyl-6-trifluoromethylthieno[2,3-b]pyridine-2-carboxanilide by the reaction with chloroacetanilide. The crystal and molecular structure of the amide obtained was studied by X-ray analysis.

Key words: cyanothioacetamide, 3-cyano-4-methyl-6-trifluoromethylpyridine-2(1H)-thione, 3-amino-4-methyl-6-trifluoromethylthieno[2,3-b]pyridine-2-carboxanilide, X-ray analysis.

The results of a study of addition of cyanothioacetamide (1) to trifluoroacetylacetone (TAA) catalyzed by triethylamine were presented in the preceding publication.<sup>1</sup> 3-Cyano-6-methyl-4-trifluoromethylpyridine-2(1H)-thione, the sole product of this reaction, was formed in high yield. The same compound was obtained when TAA was replaced by its O-methyl derivative, viz., 4-methoxy-1,1,1-trifluoropent-3-en-2-one (2), in the presence of KOH. A particular feature of the latter synthesis is that the reagents were introduced into the reaction successively, rather than simultaneously. First, an ethanolic solution of KOH was added to ketone 2, and then amide 1 was added to the resulting solution. Under these conditions, ketone 2 reacts with alkali to generate TAA, and it is this species that reacts with amide 1.

In the present work, we succeeded in carrying out the regioselective synthesis of an isomeric product, viz., 3-cyano-4-methyl-6-trifluoromethylpyridine-2(1*H*)thione (3), using the same initial reagents (amide 1 and ketone 2), but having changed the sequence of operations (Scheme 1). Initially, carbanion (4) is generated from amide 1 under the action of sodium ethoxide and then ketone 2 is introduced into the reaction. Anion 4 adds to the double bond of ketone 2 to give sodium pyridinethiolate 3, from which pyridinethione 3 can be isolated by acidification. Apparently, the reaction involves a stage of formation of intermediate 5, which undergoes cyclization with elimination of  $H_2O$  and MeOH.

The observed difference in the directions of the reactions of TAA and its O-methyl derivative depends



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on the position of the enone fragment in the molecules of these compounds. TAA is enolized in the direction of the trifluoromethyl group, while in the case of ketone 2, the enolization occurs in the opposite direction, which was confirmed by methylation. Both ketone 2 and the enol form of TAA are attacked by anion 4 at the C atom bound with the hydroxy(alkoxy) group, which results in two isomeric pyridinethiones.

The structure of pyridinethione 3 was confirmed by X-ray analysis of 3-amino-4-methyl-6-trifluoromethylthieno[2,3-b]pyridine-2-carboxanilide (7) obtained by the reaction of compound 3 with chloroacetanilide (6)(see Experimental).

The general view of the molecule 7 is shown in Fig. 1. Bond lengths and bond angles are listed in Tables 1 and 2, respectively.

As can be seen from Fig. 1, the thienopyridine fragment of the molecule is planar (the torsion angle between the planes of the heterocycles is equal to  $0.9^{\circ}$ ). In turn, the torsion angle between the thiophene ring and an imaginary plane drawn through the C(2), C(11),

Table 1. Bond lengths (d) in the molecule 7

Bond d/Å		Bond	d/Å		
S(1) - C(2)	1.747(2)	C(2)-C(11)	1.466(3)		
S(1) - C(7a)	1.729(2)	C(3) - C(3a)	1.448(3)		
F(1) - C(8)	1.23(1)	C(3a) - C(4)	1.405(3)		
F(1') - C(8)	1.426(7)	C(3a)-C(7a)	1.411(3)		
F(2) - C(8)	1.300(1)	C(4) - C(5)	1.388(3)		
F(2') - C(8)	1.24(1)	C(4) - C(9)	1.503(4)		
F(3) - C(8)	1.38(1)	C(5) - C(6)	1.384(3)		
F(3')-C(8)	1.210(9)	C(6) - C(8)	1.511(4)		
O(12) - C(11)	1.231(3)	C(14)-C(15)	1.392(4)		
N(7) - C(6)	1.333(3)	C(14) - C(19)	1.381(3)		
N(7) - C(7a)	1.334(3)	C(15)-C(16)	1.379(4)		
N(10)-C(3)	1.371(3)	C(16)-C(17)	1.372(5)		
N(13)-C(11)	1.359(3)	C(17)-C(18)	1.368(5)		
N(13)-C(14)	1.411(3)	C(18)-C(19)	1.391(4)		
C(2)-C(3)	1.376(3)				

**Table 2.** Bond angles  $(\omega)$  in the molecule 7

121.8(2)

125.3(2)

122.9(2)

124.5(2)

112.5(2)

132.2(2)

110.8(2)

117.1(2)

117.0(2)

124.2(2) 118.8(2)

Angle

C(2)-S(1)-C(7a)

C(6) - N(7) - C(7a)

S(1) - C(2) - C(3)

S(1)-C(2)-C(11)

C(3) - C(2) - C(11)

N(10) - C(3) - C(2)

C(2) - C(3) - C(3a)

C(3) - C(3a) - C(4)

C(3) - C(3a) - C(7a)

C(4) - C(3a) - C(7a)C(3a) - C(4) - C(5)

C(3a) - C(4) - C(9)

C(5) - C(4) - C(9)

N(10)-C(3)-C(3a)

C(11) - N(13) - C(14)



S(1)-C(7a)-C(3a)

N(7) - C(7a) - C(3a)

F(1)-C(8)-F(2)

F(1)-C(8)-F(3)

F(2)-C(8)-F(3)

F(1)-C(8)-C(6)

F(1')-C(8)-C(6)

F(1')-C(8)-F(2')

F(1')-C(8)-F(3')

F(2') - C(8) - F(3')

113.0(2)

126.6(2)

112.5(10)

100.2(7)

101.4(8)

104.0(1)

101.8(9)

114.0(8) 117.8(4)

106.3(3)



Fig. 1. The general view of molecule 7.

O(12), N(13), and C(14) atoms is equal to 4.6° (deviations from this plane do not exceed 0.004 Å), while the angle formed by the latter with the phenyl group is 3.1°. Such flattening of the molecule is favored by the intramolecular hydrogen bond N(10)-H(102)...O(12) with the following parameters: N(10)...O(12) 2.764(3) Å, N(10)-H(102) 0.97(3) Å, H(102)...O(12) 2.01(3) Å, the angle N(10)-H(102)...O(12) 133(2)°. In addition, the O atom forms an intramolecular shortened nonvalent contact O(12)...H(19) 2.32(2) Å (the sum of the van der Waals radii of the O and H atoms is equal<sup>2</sup> to 2.72 Å), which, according to the published data,<sup>3,4</sup> can be considered as a hydrogen bond of the C-H...O type (C(19)...O(12) 2.899(3) Å, C(19)-H(19) 0.93(2) Å, theangle  $C(19) - H(19) \dots O(12) 120(3)^{\circ}$ . In the observed mutual arrangement of the atoms in the molecule, the S(1) and H(13) atoms are close to each other at a distance of 2.49(3) Å (N(13)...S(1) 2.990(3) Å, N(13)-H(13) 0.85(3) Å, the angle  $N(13) - H(13) ... S(1) 118(2)^{\circ}$ . The molecule of compound 7 is thus markedly flattened.

The planar structure of the molecule is favorable for the conjugation between the thiophene and benzene rings through a chain of the C(2)-C(11)-N(13)-C(14)atoms, which is confirmed by a certain disproportionation of the bond lengths compared to the standard

Angle	ω/deg
F(2)-C(8)-C(6)	111.9(7)
F(2')-C(8)-C(6)	115.3(5)
F(3) - C(8) - C(6)	109.6(4)
F(3')-C(8)-C(6)	114.9(8)
O(12) - C(11) - N(13)	122.6(2)
0(12) - C(11) - C(2)	121.7(2)
N(13) - C(11) - C(2)	115.7(2)
N(13) - C(14) - C(15)	116.4(2)
N(13) - C(14) - C(19)	124.2(2)
C(15)-C(14)-C(19)	119.4(2)
C(14) - C(15) - C(16)	120.5(3)
C(15)-C(16)-C(17)	120.0(3)
C(16) - C(17) - C(18)	119.9(3)
C(17) - C(18) - C(19)	121.1(3)
C(14) - C(19) - C(18)	119.2(3)

Table 3. Atomic coordinates ( $\times 10^3$  for the hydrogen atoms and  $\times 10^4$  for the other atoms) in the molecule 7

Atom	x	у	Ζ	Atom	x	у	z	Atom	x	у	ζ
S(1)	6048(1)	2434(1)	4445(1)	$\overline{C(3a)}$	7404(2)	4285(2)	4037(1)	C(19)	5574(2)	4349(3)	6154(1)
F(1)	6305(11)	686(9)	2824(2)	C(4)	7970(2)	4820(3)	3668(1)	H(101)	819(2)	670(3)	449(1)
F(1')	7297(10)	277(6)	2907(2)	C(5)	7815(2)	3989(3)	3274(1)	H(102)	785(2)	631(3)	497(1)
F(2)	7847(10)	1546(23)	2630(4)	C(6)	7117(2)	2710(3)	3254(1)	H(13)	543(2)	258(3)	523(1)
F(2')	7539(11)	2200(11)	2518(3)	C(7a)	6720(2)	2965(2)	3972(1)	H(5)	819(2)	430(2)	302(1)
F(3)	6377(15)	2771(8)	2513(3)	C(8)	6924(3)	1829(4)	2822(1)	H(91)	931(3)	608(4)	390(1)
F(3')	5960(6)	1670(27)	2702(4)	C(9)	8701(3)	6238(4)	3673(1)	H(92)	904(3)	634(4)	341(1)
O(12)	6769(2)	5475(2)	5402(1)	C(11)	6388(2)	4328(2)	5202(1)	H(93)	831(3)	714(4)	374(1)
N(7)	6558(2)	2164(2)	3594(1)	C(14)	5278(2)	3288(3)	5824(1)	H(15)	436(2)	141(3)	570(1)
N(10)	8022(2)	6012(3)	4668(1)	C(15)	4545(2)	2091(3)	5917(1)	H(16)	365(3)	109(4)	640(1)
N(13)	5687(2)	3310(2)	5392(1)	C(16)	4129(3)	1948(4)	6336(1)	H(17)	412(3)	289(4)	693(1)
C(2)	6662(2)	3982(2)	4742(1)	C(17)	4424(3)	3005(4)	6662(1)	H(18)	538(2)	497(3)	679(1)
C(3)	7373(2)	4835(2)	4493(1)	C(18)	5129(3)	4200(4)	6571(1)	H(19)	609(2)	512(3)	611(1)

values.<sup>5</sup> In the crystal, the second hydrogen atom of the NH<sub>2</sub> group forms a weak intermolecular nonvalent contact (H(101)...O(12) 2.45(3) Å) comparable with the sum of their van der Waals radii.<sup>1</sup>

## Experimental

The IR spectra were obtained with a Perkin-Elmer 457 instrument (KBr). The <sup>1</sup>H and <sup>19</sup>F NMR spectra were recorded on a Bruker WM-250 instrument (250 and 235.3 MHz, respectively), and the <sup>13</sup>C NMR spectra were recorded on a Bruker AM-300 instrument (75.5 MHz). DMSO-d<sub>6</sub> was used as the solvent.

3-Cyano-4-methyl-6-trifluoromethylpyridine-2(1*H*)-thione (3). Compound 2 (16.6 g, 0.1 mol) was added dropwise with stirring to a solution of cyanothioacetamide 1 (10 g, 0.1 mol) and EtONa (6.8 g, 0.1 mol) in 80 mL of EtOH for 20 min. The reaction mixture was kept at 20 °C for 30 min and then neutralized at 0 °C with 10% HCl until pH 6. The precipitate was filtered off and washed with ethanol and hexane. The yield of pyridinethione 3 was 20.5 g (94%), m.p. 129–131 °C. <sup>1</sup>H NMR,  $\delta$ : 2.45 (s, 3 H, Me); 7.00 (s, 1 H, C(5)H); 14.2 (s, NH). <sup>19</sup>F NMR,  $\delta$ : -63.44. <sup>13</sup>C NMR,  $\delta$ : 159.12 (s, C=S); 111.40 (s, C(3)); 158.4 (q, C(4)); 120.00 (dq, C(5), <sup>1</sup>J<sub>CH</sub> = 165.30 Hz,  $J_{CF}$  = 2.90 Hz); 148.00 (q, C(6), <sup>2</sup>J<sub>CF</sub> = 35.0 Hz); 19.85 (q, Me); 120.2 (q, CF<sub>3</sub>, <sup>1</sup>J<sub>CF</sub> = 275.00 Hz); 112.4 (s, CN). IR, v/cm<sup>-1</sup>: 2240 (CN); 1610 ( $\delta$ NH). Found (%): C, 44.55; H, 2.10; N, 12.77. C<sub>8</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>S. Calculated (%): C, 44.04; H, 2.29; N, 12.34.

3-Amino-4-methyl-6-trifluoromethylthieno[2,3-b]pyridine-2carboxanilide (7). Chloroacetanilide 6 (1.7 g, 0.01 mol) and 10% KOH (5.6 mL) were successively added to a solution of pyridinethione 3 (2.18 g, 0.01 mol) in 15 mL of DMF. The reaction mixture was stirred at 20 °C for 10 min, and an additional 15 mL of DMF and 3 mL of 10% KOH was added. The resulting solution was stirred at 20 °C for 3 h, and the precipitate that formed was filtered off and recrystallized from EtOH. The yield of amide 7 was 2.98 g (85%), m.p. 110– 112 °C. <sup>1</sup>H NMR,  $\delta$ : 2.75 (s, 3 H, Me); 6.75 (s, 2 H, NH<sub>2</sub>); 7.1–7.9 (m, 6 H, Ph, C(5)H); 9.7 (s, 1 H, NH). IR, v/cm<sup>21</sup>: 3500, 3340, 3280, 1600, 1630 ( $\delta$ NH). Found (%): C, 54.65; H, 3.64; N, 11.68. C<sub>16</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>OS. Calculated (%): C, 54.65; H, 3.44; N, 11.95.

X-ray study of compound 7. The crystals of compound 7 (C16H12F3N3OS, molecular weight 351.29) are monoclinic,  $a = 12.064(6), b = 8.592(2), c = 30.03(1) \text{ Å}, \beta = 92.52(3)^{\circ}, V$ = 3110(3) Å<sup>3</sup> (25 °C),  $d_{calc} = 1.501 \text{ g cm}^{-3}$ , Z = 8, space group C2/C. The cell parameters and intensity data from 4210 independent reflections were measured on a Siemens P3/PC four-circle automatic diffractometer (Mo-Ka radiation, graphite monochromator,  $\theta/2\theta$  scanning until  $\theta_{max} = 26^{\circ}$ ). The structure was solved and all nonhydrogen atoms were located by the direct method. The full-matrix least-squares refinement was performed in the anisotropic approximation for nonhydrogen atoms from 2431 reflections with  $l > 3\sigma(l)$ . All hydrogen atoms were located in an objective manner by differential Fourier syntheses and refined isotropically. The trifluoromethyl group was disordered at two positions with equal occupancy (1 : 1). Final residuals are  $\hat{R} = 0.039$  and  $R_{w} = 0.039$  (S = 1.250). All computations were performed with the SHELXTL PLUS program<sup>6</sup> (PC version). Atomic coordinates are listed in Table 3.

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