Regioselective synthesis and properties of 3-cyano-6-methyl-4-trifluoromethylpyridine-2(1*H*)-thione. Molecular and crystal structure of 3-cyano-2-ethylthio-6-methyl-4-trifluoromethylpyridine

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The reaction of trifluoroacetylacetone with cyanothioacetamide proceeded regioselectively to form 3-cyano-6-methyl-4-trifluoromethylpyridine-2(1H)-thione from which the corresponding 2-alkylthiopyridines and 3-aminothieno[2,3-b]pyridines were obtained. The crystal and molecular structure of 3-cyano-2-ethylthio-6-methyl-4-trifluoromethylpyridine was established by X-ray diffraction analysis.

Key words: cyanothioacetamide. 3-cyano-6-methyl-4-trifluoromethylpyridine-2(1H)-thione, 3-cyano-2-ethylthio-6-methyl-4-trifluoromethylpyridine, 3-aminothieno[2,3-b]pyridines, X-ray diffraction analysis.

Derivatives of 3-cyanopyridine-2(1H)-thione exhibit interesting chemical properties.^{1,2} However, trifluoromethyl-substituted derivatives of this compound are hardly available and remain poorly studied.¹⁻⁴ Pyridinethiones of this type were prepared by the reaction of the corresponding 2-chloropyridine with thiourea³ and by condensation of aroyltrifluoroacetones with cyanothioacetamide although the regioselectivity of the latter reaction was not established.⁴ Only the structure of 3-cyano-6-phenyl-4-trifluoromethylpyridine-2(1H)thione was determined by oxidative desulfurization of this compound to the corresponding pyridone.⁵

In this work, we developed a regioselective procedure for the synthesis of 3-cyano-6-methyl-4-trifluoromethylpyridine-2(1H)-thione (1) and studied its chemical properties. Compound 1 was prepared according to the following procedures: by the reaction of cyanothioacetamide (2) with trifluoroacetylacetone (3) in EtOH in the presence of triethylamine (A) and by the reaction of 1,1,1-trifluoro-4-methoxypent-3-en-2-one (4) with KOH followed by the reaction with amide 2 (B). Both procedures afforded compound 1 in comparable yields (88% and 89%, respectively). However, methoxypentenone 4 is a more readily available reagent.

The structure of compound 1 was confirmed by the spectral data. It was found that only one of two possible isomers was formed. The reaction of compound 1 with





$$\begin{split} \mathsf{R} &= \mathsf{CH}_3 \; (\textbf{a}), \; \mathsf{Ph} \; (\textbf{b}) \\ \mathsf{Ar} &= \mathsf{Ph} \; (\textbf{8}, \; \textbf{11}, \; \textbf{14}); \; 4\text{-}\mathsf{MeC}_6\mathsf{H}_4 \; (\textbf{9}, \; \textbf{12}, \; \textbf{15}); \\ 3\text{-}\mathsf{BuOC}_6\mathsf{H}_4 \; (\textbf{10}, \; \textbf{13}, \; \textbf{16}) \end{split}$$

EtI in the presence of a base yielded 3-cyano-2-ethylthio-6-methyl-4-trifluoromethylpyridine (5a). The latter com-

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Fig. 1. Overall view of molecule 5a

pound was studied by X-ray diffraction analysis with the aim of unambiguously establishing the structure of pyridinethione 1. The overall view of molecule 5a and the bond lengths are shown in Fig. 1. The bond angles are given in Table 1.

The geometric parameters of molecule 5a have standard values.⁶ The N(1)C(2)SC(10) and C(2)SC(10)C(11) torsion angles (1.0° and 78.7°, respectively) are indicative of a substantial twist of the ethyl substituent with respect to the plane of the heterocycle, whose conformation is, apparently, affected by the intramolecular nonbonded N(1)...C(10) and N(1)...H(101) contacts

| Table | 1. | Bond | angles | (w) | in | mol | lecule | : 5a |
|-------|----|------|--------|-----|----|-----|--------|------|
|-------|----|------|--------|-----|----|-----|--------|------|

| Angle | ω/deg | Angle | ω/deg |
|---|--|---|----------------------|
| C(2)-S-C(10) C(2)-N(1)-C(6) S-C(2)-N(1) S-C(2)-C(3) | 102.2(4) | N(1)C(6)C(5) | 122.4(7) |
| | 119.3(6) | N(1)C(6)C(7) | 118.0(7) |
| | 119.2(5) | C(5)C(6)C(7) | 119.6(7) |
| | 118.8(5) | F(1)C(8)F(2) | 106.3(8) |
| N(1)-C(2)-C(3) | 122.0(6) | F(1)-C(8)-F(3) F(2)-C(8)-F(3) F(1)-C(8)-C(4) F(2)-C(8)-C(4) F(3)-C(8)-C(4) F(3)-C(8)-C(4) F(3)-C(8)-C(4) F(3)-C(8)-C(4) F(3)-C(8)-F(3) F(3)-F(3)-F(3) F(3)-F(3)-F(3)-F(3) F(3)-F(3)-F(3)-F(3) F(3)-F(3)-F(3)-F(3) F(3)-F(3)-F(3)-F(3)-F(3) F(3)-F(3)-F(3)-F(3)-F(3)-F(3)-F(3)-F(3)- | 107.1(7) |
| C(2)-C(3)-C(4) | 118.2(6) | | 106.7(8) |
| C(2)-C(3)-C(9) | 118.0(6) | | 112.4(7) |
| C(4)-C(3)-C(9) | 123.7(6) | | 112.5(7) |
| C(3)-C(4)-C(5) | 119.4(7) | | 111.5(7) |
| C(3)-C(4)-C(8) C(3)-C(4)-C(8) C(5)-C(4)-C(8) C(4)-C(5)-C(6) | 119.9(7) 119.9(7) 120.6(7) 118.6(7) | N(2)-C(9)-C(3) S-C(10)-C(11) | 176.4(9) 113.2(7) |

(3.22(1) and 2.47(3) Å, respectively; the sum of the van der Waals radii⁷ of the N and C atoms is 3.25; the sum of the van der Waals radii of the C and H atoms is 2.90 Å). On the whole, the geometric parameters of molecule **5a** are similar to those of the substituted pyridines studied previously.⁸⁻¹⁰

The related 2-benzylthiopyridine 5b was prepared from pyridinethione 1 analogously to compound 5a.

The reactions of 3-cyanopyridine-2(1H)-thiones with halogenocarbonyl compounds are widely used in the synthesis of fused pyridines.^{1,2,4} We found that *N*-arylchloroacetamides **8**–10 readily reacted with pyridinethione 1 to form pyridylthioacetoamides 11–13. When compounds 11–13 were treated with an aqueous KOH solution in DMF, 3-aminothieno[2,3-*b*]pyridinecarboxamides 14–16 were obtained in good yields. The resulting compounds can also be prepared immediately from pyridinethione 1 and amides **8–10** without isolation of compounds 11–13. Alkylthiopyridines **5a** and **5b**, which do not contain the activating carboxyl group, did not undergo cyclization under the above-described conditions. The structures of compounds 11–16 were confirmed by the physicochemical characteristics (Table 2).

Experimental

The ¹H and ¹⁹F NMR spectra were recorded on a Bruker WM-250 instrument operating at 250 and 235.3 MHz, respectively. The ¹³C NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 75.5 MHz (DMSO-d₆ as the solvent). The IR spectra were obtained on a Perkin-Elmer 457 instrument as KBr pellets.

3-Cyano-6-methyl-4-trifluoromethylpyridine-2(1H)-thione (1). A. A mixture of amide 2 (1.0 g, 10 mmol), ketone 3 (1.53 g, 10 mmol), and triethylamine (0.1 mL) in EtOH (80 mL) was boiled for 2 min and then kept at 20 °C for 6 h. The precipitate was filtered off and washed with ethanol and hexane. The yield of pyridinethione 1 was 1.92 g (88%).

B. A solution of KOH (5.6 g, 0.1 mol) in EtOH (50 mL) was added to pentenone 4 (16.6 g, 0.1 mol). The reaction mixture was stirred at 20 °C for 15 min. Then amide 2 (10 g, 0.1 mol) was added. The mixture was stirred for 10 min and then poured into 0.1 N HCl (200 mL). The precipitate was filtered off and recrystallized from EtOH. The yield of pyridinethione 1 was 19.4 g (89%).

Samples of compound 1, which were prepared according to procedures *A* and *B*, have identical IR spectra and melted without depression of the melting temperature. M.p. 213– 215 °C (decomp.). Found (%): C, 44.55; H, 2.10; N, 12.77. C₈H₅F₃N₂S. Calculated (%): C, 44.04; H, 2.29; N, 12.84. ¹H NMR, δ : 2.64 (s, 3 H, CH₃); 7.87 (s, 1 H, C(5)H); 14.5 (s, NH). ¹⁹F NMR, δ : -67.48. ¹³C NMR, δ : 179.00 (s, C-2), 109.6 (s, C-3, ³J = 6.73 Hz); 142.6 (qd, C-4, ²J_{CF} = 32.70 Hz, ²J_{CH} = 2.47 Hz); 109.3 (dq, C-5, ¹J_{CH} = 179.0 Hz); 157.70 (q, C-6); 19.6 (q, CH₃); 121.1 (qd, CF₃, ¹J_{CF} = 276.7 Hz, ³J_{CH} = 4.12 Hz); 113.8 (s, CN). IR, v/cm⁻¹: 2240 (CN), 1590 (NH). The data of elemental analysis are given in Table 2.

Alkylthiopyridines 5a,b and 11-13 (general procedure). The corresponding halide 6a,b or 8-10 (0.01 mol) and a 10% KOH solution (5.6 mL) were added successively with stirring

| Com- pound | Yield (%) | М.р. /°С | Found (%) Calculated | | Molecular formula | IR (v/cm ⁻¹) | ¹ Η NMR (DMSO-d ₆), δ | |
|---------------|--------------|-------------|-------------------------|---------------------|-----------------------|--|---|--|
| | | | C | Н | N | | | |
| 52 | 45 | 50-51 | <u>48.53</u> 48.77 | <u>3.67</u> 3.68 | <u>11.29</u> 11.32 | C ₁₀ H ₉ F ₃ N ₂ S | 2240 (C≞N) | 1.41 (t, 3 H, <u>CH₃CH₂);</u> 2.7 (s, 3 H, CH ₃); 3.3 (q, 2 H, CH ₂ S); 7.15 (s, 1 H, C(5)H) |
| 5b | 68 | 4547 | <u>58.31</u> 58.43 | <u>3.57</u> 3.60 | <u>9.08</u> 9.09 | C ₁₅ H ₁₁ F ₃ N ₂ S | 2230(C=N) | 2.7 (s, 3 H, CH ₃); 4.5 (s, 2 H, CH ₂ S); 7.2 (s, 1 H, C(5)H); 7.25-7.5 (m, 5 H, Ph) |
| 11 | 80 | 156-157 | <u>54.31</u> 54.65 | <u>3.42</u> 3.44 | <u>11.86</u> 11.95 | C ₁₆ H ₁₂ F ₃ N ₃ OS | 1550, 1600, 1660, 2240 (C=N); 3300-3330, | 2.7 (s, 3 H, CH ₃); 4.2 (s, 2 H, CH ₂ S); 7.0–7.5 (m, 6 H, C ₆ H ₅ , C(5)H); 10.3 (s, 1 H, NH) |
| 12 | 91 | 171-172 | <u>55.67</u> 55.88 | <u>3.83</u> 3.86 | <u>11.77</u> 11.50 | C ₁₇ H ₁₄ F ₃ N ₃ OS | 1652 (CONH), 2228 (C=N); 3318, 3336 | 2.3 (s, 3 H, MePh); 2.75 (s, 3 H, CH ₃); 4.05 (s, 2 H, CH ₂ S); 7.2, 7.4 (dd, 4 H, Ph, ${}^{3}J = 7.1$); 7.62 (s, 1 H, C(5)H); 8.4 (s, 1 H, NH) |
| 13 | 73 | 110—111 | <u>56.34</u> 56.73 | <u>4.73</u> 4.76 | <u>9.87</u> 9.92 | $C_{20}H_{20}F_3N_3O_2S$ | 1662 (CONH); 2232 (C≡N); 3320, 3340 (NH) | 0.9 (s, 3 H, CH ₃); 1.35–1.85 (m, 4 H, CH ₂ CH ₂); 2.6 (s, 3 H, CH ₃); 3.9 (t, 2 H, CH ₂ O); 4.1 (s, 2 H, CH ₂ S); 6.65–7.3 (m, 5 H, C ₆ H ₄ , C(5)H); 10.25 (s, 1 H, NH) |
| 14 | 85 | 122-123 | <u>54.83</u> 54.65 | <u>3.55</u> 3.44 | <u>11.72</u> 11.95 | C ₁₆ H ₁₂ F ₃ N ₃ OS | 1600, 1630 (δ, NH, NH ₂); 3280, 3340, 3500 | 2.7 (s, 3 H, CH ₃); 6.7 (s, 2 H, NH ₂); 7.1–7.8 (m, 6 H, Ph, C(5)H); 9.7 (s, 1 H, NH) |
| 15 | 73 | 210212 | <u>55.63</u> 55.88 | <u>3.80</u> 3.86 | <u>11.79</u> 11.50 | C ₁₇ H ₁₄ F ₃ N ₃ OS | 1630 (8, NH ₂); 1642 (CONH); 3342, 3376, 3448 (NH) | 2.6 (s, 3 H, CH ₃); 2.7 (s, 3 H, <u>CH₃C₆H₄);</u> 6.83 (s, 2 H, NH ₂); 7.2, 7.7 (dd, 4 H, C ₆ H ₄ , ${}^{3}J = 7.2$); 7.5 (s, 1 H, C(5)H); 9.7 (s, 1 H, NH) |
| 16 | 68 | 121-124 | <u>56.36</u> 56.73 | <u>4.75</u> 4.76 | <u>9.83</u> 9.92 | C ₂₀ H ₂₀ F ₃ N ₃ O ₂ S | 1632 (8, NH ₂): 1648 (CONH); 3285, 3326, 3400 (NH) | 0.9 (t, 3 H, <u>CH₂CH₂</u>); 1.35-1.85 (m, 4 H, CH ₂ CH ₂); 2.65 (s, 3 H,CH ₃); 3.95 (t, 2 H, CH ₂ O); 6.6 (s, 2 H, NH ₂); 6.65-7.3 (m, 5 H, C ₆ H ₄ , C(5)H); 9.6 (s, 1 H, NH) |

Table 2. Yields, melting temperatures, and data of elemental analysis and IR and ¹H NMR spectra of compounds 5a,b and 11-16

to a solution of pyridinethione 1 (2.18 g, 10 mmol) in DMF (15 mL). The reaction mixture was stirred at 20 °C for 30 min, diluted with water (10-15 mL), and filtered off. After recrystallization from EtOH, compounds 5a,b and 11-13 were obtained. The yields, melting points, and data of elemental analysis and ¹H NMR and IR spectra of the resulting compounds are given in Table 2.

3-Aminothieno [2,3-b] pyridine-2-carboxamides (14-16). A. A 10% KOH solution (3 mL) was added to a suspension of amide 11-13 (0.01 mol) in DMF (15 mL). The reaction mixture was stirred at 20 °C for 3 h and diluted with water (10 mL). The precipitate of thienopyridine 14-16 was filtered off and recrystallized from EtOH.

B. The corresponding halide 6a,b or 8-10 (0.01 mol) and a 10% KOH solution (5.6 mL) were added successively to a solution of pyridinethione 1 (2.2 g, 10 mmol) in DMF (15 mL). The reaction mixture was stirred at 20 °C for 10 min. Then DMF (15 mL) and a 10% KOH solution (3 mL) were added, and the reaction mixture was stirred at 20 $^{\circ}\mathrm{C}$ for 3 h. Compounds 14-16 were filtered off and recrystallized from EtOH.

The yields (according to procedure A), melting points, and data of elemental analysis and ¹H NMR and IR spectra of compounds 14-16 are given in Table 2.

X-ray diffraction analysis of compound 5a. Crystals of compound 5a ($C_{10}H_9F_3N_2S$, M = 246.23) are orthorhombic,

Table 3. Coordinates $(\times 10^4)$ and isotropic equivalent thermal parameters of nonhydrogen atoms in molecule 5a

| Atom | x | у | z | Uiso |
|-------|----------|---------|-----------|-------|
| S | 7417(2) | 3562(1) | 861(5) | 64(1) |
| F(1) | 10381(4) | 866(3) | 3177(14) | 94(2) |
| F(2) | 9709(5) | 1029(3) | -733(13) | 93(2) |
| F(3) | 8784(4) | 752(2) | 2688(15) | 99(2) |
| N(1) | 9057(4) | 3409(3) | 4079(14) | 48(2) |
| N(2) | 7448(6) | 1830(4) | -2413(17) | 79(3) |
| C(2) | 8456(5) | 3076(4) | 2257(17) | 45(2) |
| C(3) | 8626(5) | 2343(4) | 1395(15) | 43(2) |
| C(4) | 9429(5) | 1956(4) | 2588(16) | 46(2) |
| C(5) | 10036(5) | 2300(4) | 4472(17) | 53(3) |
| C(6) | 9829(6) | 3042(4) | 5154(15) | 49(3) |
| C(7) | 10499(6) | 3436(5) | 7183(18) | 66(3) |
| C(8) | 9578(7) | 1147(4) | 1925(22) | 65(3) |
| C(9) | 7965(6) | 2041(4) | -671(19) | 55(3) |
| C(10) | 7536(7) | 4449(4) | 2497(19) | 75(3) |
| C(11) | 8337(8) | 4930(5) | 1189(25) | 90(4) |

at 20 °C: a = 13.104(7), b = 18.082(15), c = 4.819(3) Å, V =1142(1) Å³, $d_{calc} = 1.432 \text{ g cm}^{-3}$, Z = 4, space group $P2_12_12_2$. The unit cell parameters and intensities of 1976 independent reflections were measured on an automated four-circle Siemens P3/PC diffractometer (\lambda MoKa, graphite monochromator, $\theta/2\theta$ scanning technique to $\theta_{max} = 28^{\circ}$). The structure was solved by the direct method, which revealed all nonhydrogen atoms, and refined by full-matrix least squares with anisotropic thermal parameters for nonhydrogen atoms using 765 reflections with $I > 2\sigma(I)$. All hydrogen atoms were located from difference Fourier syntheses. However, hydrogen atoms were included in the refinement with the fixed positional and thermal parameters ($U = 0.08 \text{ Å}^2$) because of their large thermal vibrations. The final values of the R factors were as follows: R = 0.047 and $R_w = 0.047$ (S = 0.9239). All calculations were carried out using the SHELXTL PLUS program¹¹ (PC version). The coordinates and isotropic thermal parameters of nonhydrogen atoms are given in Table 3.

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