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SYNTHESIS, STRUCTURE, AND ALKYLATION OF N-METHYL-MORPHOLINIUM 5-THENOYL- AND 5-BENZOYL-3-CYANO-6-TRIFLUOROMETHYL-PYRIDINE-2-THIOLATES

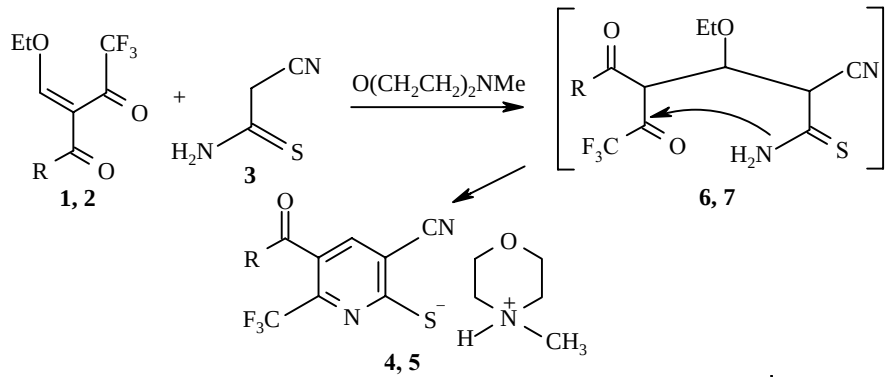
Ya. Yu. Yakunin[1], V. D. Dyachenko[1], and V. P. Litvinov[2]

By reaction of ethoxymethylene derivatives of trifluorothenoyl- and trifluorobenzoylacetone with cyanothioacetamide in the presence of excess N-methylmorpholine, we have obtained the corresponding N-methylmorpholinium 5-acyl-3-cyano-6-trifluoromethylpyridine-2-thiolates and have studied their alkylation.

Keywords: N-methylmorpholine, pyridine, thieno[2,3-*b*]pyridine, cyanothioacetamide, ethoxyethylene, alkylation.

In the literature, we find descriptions of trifluoromethyl-substituted pyridinethiones obtained by reaction of cyanothioacetamides with activated olefins or 1,3-dicarbonyl compounds [1-4]. Trifluoromethyl-substituted aromatic and heterocyclic compounds [5] and also 4-unsubstituted pyridine-2(1H)-thiones [6-8] are known to have biological activity. Continuing studies in this direction, we have developed a method for synthesis of 5-thenoyl- and 5-benzoyl-3-cyano-6-trifluoromethylpyridine-2-thiolates.

Reaction of ethoxymethylene derivatives of trifluorothenoyl- (**1**) or trifluorobenzoylacetone (**2**) with cyanothioacetamide (**3**) in the presence of a two-fold excess of N-methylmorpholine at room temperature leads to N-methylmorpholinium 5-thenoyl- (**4**) or 5-benzoyl-3-cyano-6-trifluoromethylpyridine-2-thiolate (**5**) in 85% and 51% yields respectively. The reaction probably occurs with formation of adducts **6**, **7**, undergoing ring closure to salts **4** and **5** respectively.



1, 4, 6 R = thienyl-2; **2, 5, 7** R = Ph

[1] Taras Shevchenko Lugansk State Pedagogical University, Lugansk 348011, Ukraine. [2] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 117913.Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1667-1673, December, 2000. Original article submitted April 12, 1999; revision submitted January 7, 2000.

The structure of the latter has been confirmed by the results of elemental analysis and spectroscopic studies (Tables 1 and 2), and also is consistent with literature data on condensation of 1,1,1-trifluoroacetylacetone with cyanothioacetamide [2]. In the IR spectra of salts **4, 5** we see absorption bands for the stretching vibrations of the carbonyl group in the 1600-1630 cm^{-1} region and the conjugated nitrile group in the 2190 cm^{-1} region.

In the ^1H NMR spectra of compounds **4, 5**, we observe triplets in the 3.17-3.80 ppm region typical for protons of the N-methylmorpholinium cation, and also a singlet signal from the proton of the 4-H pyridine ring in the 7.27-7.74 ppm region. The signals from protons of the thenoyl moiety of salt **4** have the form of a triplet and two doublets in the 7.16 ppm and 7.70 ppm, 7.89 ppm region respectively. The benzoyl moiety of thiolate **5** appears as a multiplet at 7.34-8.04 ppm.

Treatment of salts **4** and **5** with equimolar amounts of halides **8a-f** in DMF in the presence of KOH (method A) leads to formation of the alkylthio derivatives **9a-f** and **10a-f** respectively. When treating thiolates **4** and **5** with 4-bromophenacyl bromide **7g** or α-chloroacetamide **8h** according to method **A**, in all cases we see formation of the linear product **9g,h** or **10g,h** with the corresponding thienopyridine **11g,h** and **12g,h**. By briefly heating the indicated reagents in DMF without KOH (method B), we were able to obtain pure linear derivatives **9h** and **10g,h**. We should note that the relatively high capacity of product **9g** for cyclization did not allow us to isolate it as a pure compound under the conditions of methods A and B.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
4	$C_{17}H_{16}F_3N_3O_2S_2$	49.03 / 49.15	3.71 / 3.88	10.32 / 10.11	15.54 / 15.44	128-130	85
5	$C_{19}H_{18}F_3N_3O_2S$	55.90 / 55.74	4.21 / 4.43	10.11 / 10.26	7.99 / 7.83	114-116	51
9a	$C_{13}H_7F_3N_2OS_2$	47.70 / 47.56	2.31 / 2.15	8.39 / 8.53	19.40 / 19.53	145-147	72
9b	$C_{14}H_9F_3N_2OS_2$	49.01 / 49.12	2.42 / 2.65	8.30 / 8.18	18.84 / 18.73	124-126	56
9c	$C_{15}H_{11}F_3N_2OS_2$	50.33 / 50.55	3.00 / 3.11	7.99 / 7.86	17.32 / 17.19	103-105	52
9d	$C_{16}H_{13}F_3N_2OS_2$	51.92 / 51.88	3.70 / 3.54	7.41 / 7.56	17.22 / 17.31	76-78	53
9e	$C_{15}H_9F_3N_2OS_2$	50.77 / 50.84	2.33 / 2.56	7.74 / 7.91	18.25 / 18.10	107-109	52
9f	$C_{19}H_{11}F_3N_2OS_2$	56.55 / 56.43	2.82 / 2.74	6.80 / 6.93	15.71 / 15.86	126-128	58
9h	$C_{14}H_8F_3N_3O_2S_2$	45.10 / 45.28	2.34 / 2.17	11.50 / 11.32	17.12 / 17.27	130-132 subl.	61
10a	$C_{15}H_9F_3N_2OS$	55.76 / 55.90	2.59 / 2.81	8.81 / 8.69	9.85 / 9.95	105-107	84
10b	$C_{16}H_{11}F_3N_2OS$	57.30 / 57.14	3.18 / 3.30	8.12 / 8.33	9.66 / 9.53	86-88	55
10c	$C_{17}H_{13}F_3N_2OS$	58.11 / 58.28	3.55 / 3.74	8.25 / 8.00	9.06 / 9.15	83-85	53
10d	$C_{18}H_{15}F_3N_2OS$	59.41 / 59.33	4.39 / 4.15	7.54 / 7.69	8.62 / 8.80	74-76	52
10e	$C_{17}H_{11}F_3N_2OS$	58.50 / 58.62	3.11 / 3.18	8.33 / 8.04	9.40 / 9.20	97-99	52
10f	$C_{21}H_{13}F_3N_3OS$	63.14 / 63.31	3.12 / 3.29	7.22 / 7.03	8.13 / 8.05	75-77	56
10g	$C_{22}H_{12}BrF_3N_2O_2S$	52.42 / 52.29	2.11 / 2.39	5.34 / 5.54	6.60 / 6.35	80-82	58
10h	$C_{16}H_{10}F_3N_3O_2S$	52.43 / 52.60	2.59 / 2.76	11.71 / 11.50	8.92 / 8.78	108-110	61
11g	$C_{20}H_{10}BrF_3N_2O_2S_2$	46.76 / 46.98	1.80 / 1.97	5.59 / 5.48	12.61 / 12.54	88-90	58
11h	$C_{14}H_8F_3N_3O_2S_2$	45.51 / 45.28	2.32 / 2.17	11.14 / 11.32	17.10 / 17.27	73-75	56
12g	$C_{22}H_{12}BrF_3N_2O_2S$	52.14 / 52.29	2.22 / 2. 39	5.61 / 5.54	6.49 / 6.35	134-136	54
12h	$C_{16}H_{10}F_3N_3O_2S$	52.71 / 52.60	2.92 / 2.76	11.41 / 11.50	8.55 / 8.78	70-73	57

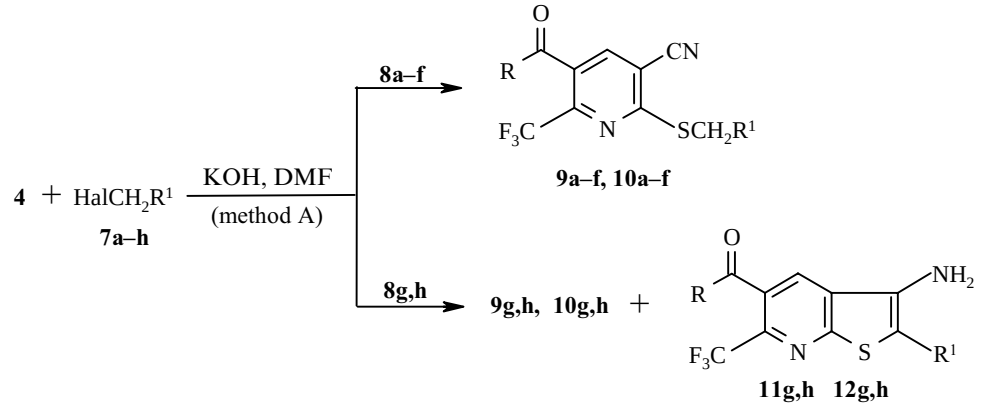
TABLE 2. Spectral Characteristics of Synthesized Compounds

Compound	IR spectrum, cm^{-1}		^1H NMR spectrum, δ, ppm; spin–spin coupling constant (J), Hz		
	$C\equiv N$	C=O, NH_2	4-H pyridine ring (1H, s)	R ($H_{thienyl}$ or H_{phenyl})	protons of methylmorpholinium or SCH_2, R^1, NH_2
1	2	3	4	5	6
4	2190	1635	7.27	7.16 (1H, t, J = 4.6, 4-H); 7.70 (1H, d, J = 5.0, 3H); 7.89 (1H, d, J = 4.6, 5-H)	2.80 (3H, s, CH_3); 3.80 (4H, t, J = 5.0, CH_2NCH_2); 3.78 (4H, t, J = 5.0, CH_2OCH_2)
5	2190	1660	7.74*	7.34-8.04 (5H, m)*	2.79 (3H, s, CH_3); 3.17 (4H, t, J = 5.0, CH_2NCH_2); 3.78 (4H, t, J = 5.0, CH_2COCH_2)
9a	2220	1660	8.12	7.26 (1H, t, J = 4.6, 4-H); 7.91 (1H, d, J = 5.0, 3-H); 8.24 (1H, d, J = 4.6, 5-H)	2.69 (3H, s, CH_3)
9b	2224	1570	8.11	7.26 (1H, t, J = 4.6, 4-H); 7.91 (1H, d, J = 5.0, 3-H); 8.23 (1H, d, J = 4.6, 5-H)	1.34 (3H, t, J = 7.5, CH_3); 3.31 (2H, q, J = 7.5, SCH_2)
9c	2210	1680	8.13	7.26 (1H, t, J = 4.6, 4-H); 7.93 (1H, d, J = 5.0, 3-H); 8.24 (1H, d, J = 4.6, 5-H)	1.04 (3H, t, J = 7.5, CH_3); 1.75 (2H, m, $\underline{C}H_2CH_3$); 3.29 (2H, t, J = 7.5, SCH_2)
9d	2210	1640	8.15	7.28 (1H, t, J = 4.6, 4-H); 7.95 (1H, d, J = 5.0, 3-H); 8.26 (1H, d, J = 4.6, 5-H)	0.93 (3H, t, J = 7.5, CH_3); 1.62 (4H, m, $CH_2(\underline{C}H_2)_2$); 3.29 (2H, t, J = 7.5, SCH_2)
9e	2210	1650	8.15	7.27 (1H, t, J = 4.6, 4-H); 7.92 (1H, d, J = 5.0, 3-H); 8.25 (1H, d, J = 4.6, 5-H)	4.01 (2H, d, J = 7.5, SCH_2); 5.14 and 5.41 (2H, two d, J = 7.5, CH_2=); 5.98 (1H, m, CH=)
9f	2200	1670	8.18	7.48 (1H, t, J = 4.6, 4-H); 7.95 (1H, d, J = 5.0, 3-H); 8.27 (1H, d, J = 4.6, 5-H)	4.65 (2H, s, SCH_2); 7.30 (5H, m, Ph)
9h	2230	1600, 1660, 3400	8.14	7.22 (1H, m, 4-H and 1-H, NH_2)*; 7.96 (1H, d, J = 5.0, 3-H); 8.26 (1H, d, J = 4.6, 5-H)	4.07 (2H, s, SCH_2); 7.64 (1H, br. s, NH_2)

TABLE 2 (continued)

1	2	3	4	5	6
10a	2235	1600	8.18	7.58 (3H, m, 3-, 4- and 5-H); 8.31 (2H, m, 2- and 6-H)	2.77 (3H, s, SCH_3)
10b	2225	1670	8.17	7.58 (3H, m, 3-, 4- and 5-H); 8.28 (2H, m, 2- and 6-H)	1.40 (3H, t, J = 7.5, CH_3); 3.39 (2H, q, J = 7.5, SCH_2)
10c	2200	1670	8.15	7.57 (3H, m, 3-, 4- and 5-H); 8.28 (2H, m, 2- and 6-H)	1.03 (3H, t, J = 7.5, CH_3); 1.76 (2H, m, $CH_3\underline{CH_2}$); 3.35 (2H, m, SCH_2)
10d	2290	1665	8.15	7.60 (3H, m, 3-, 4- and 5-H); 8.24 (2H, m, 2- and 6-H)	0.92 (3H, m, CH_3); 1.28-1.88 (4H, m, $2CH_2$); 3.38 (2H, t, J = 7.5, SCH_2)
10e	2235	1600	8.17	7.58 (3H, m, 3-, 4- and 5-H); 8.29 (2H, m, 2- and 6-H)	4.09 (2H, d, J = 7.5, SCH_2); 5.21 and 5.46 (2H, two d, J = 7.5, CH_2=); 6.01 (1H, m, CH=)
10f	2210	1630	8.21	7.21-7.68 (8H, m, 3-, 4-, 5-H, and CH_2Ph)*; 8.31 (2H, m, 2- and 6-H)	4.74 (2H, s, SCH_2)
10g	2210	1660	8.16	7.81-8.03 (10H, m, 2Ph)	5.10 (2H, s, SCH_2)
10h	2220	1640, 3410	8.20	7.58 (3H, m, 3-, 4- and 5-H); 8.32 (2H, m, 2- and 6-H)	4.12 (2H, s, SCH_2); 7.25 (1H, s, NH_2); 7.75 (1H, s, NH_2)
11g	—	1585, 1600, 3510	8.29	7.24 (1H, t, J = 4.6, 4-H); 7.76-7.90 (3H, m, 3-H and NH_2); 8.25 (1H, d, J = 4.6, 5-H)	7.74 (4H, br. s, C_6H_4)
11h	—	1600, 1660, 3330, 3440	8.24	7.24 (1H, t, J = 4.6, 4-H); 7.81 (1H, d, J = 5.0, 3-H); 8.18 (1H, d, J = 4.6, 5-H)	6.66 (2H, br. s, NH_2); 7.45 (2H, br. s, $CONH_2$)
12g	—	1600, 1680, 3340	8.13-8.28 (3H, m, 4-, 2-, 6-H Ph)	7.39-7.92 (5H, m, 3-, 4-, 5-H, and NH_2)*	7.75 (4H, br. s, C_6H_4)*
12h	—	1600, 1680, 3360, 3480	8.21 (3H, m, 4-H, 2-, 6-H Ph)	7.49 (5H, m, 3-, 4-, 5-H, and $CONH_2$)	6.68 (2H, br. s, NH_2)

* The signals overlap.



9,11 R = thienyl-2; **10, 12** R = Ph; **8-11 a** R^1 = H, **b** R^1 = Me, **c** R^1 = Et, **d** R^1 = Pr, **e** R^1 = CH_2 =CH, **f** R^1 = Ph, **g** R^1 = 4-BrC_6H_4CO, **h** R^1 = H_2NCO

The structure of the obtained alkyl derivatives **9a-f,h** and **10a-h**, and also thienopyridines **11g,h** and **12g,h** is confirmed by the results of elemental analysis (Table 1), IR and ^{1}H NMR spectra (Table 2).

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on an IKS-29 instrument for a suspension in vaseline oil. The ^{1}H NMR spectra were recorded on a Bruker WP-100 SY spectrometer (100 MHz) for solutions in DMSO-d_6, internal standard TMS. The course of the reaction and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in a 3:5 acetone–heptane system, with iodine as the visualizing agent.

N-Methylmorpholinium 3-Cyano-5-thenoyl-6-trifluoromethylpyridine-2-thiolate (4). N-methylmorpholine (10 ml, 0.09 mol) was added with stirring to a mixture of ethoxyethylene **1** (12.5 g, 45 mimol) and cyanothioacetamide **3** (4.5 g, 45 mmol) in absolute ethanol (20 ml) at 20°C. After the starting compounds were completely dissolved, the reaction mixture was filtered through a pleated filter. The filtrate was stirred for 4 h. The precipitate of product formed was filtered off and washed with acetone. Yield of compound **4** 15.9 g.

N-Methylmorpholinium 5-Benzoyl-3-cyano-6-trifluoromethylpyridine-2-thiolate (5) was obtained similarly to compound **4**, from amide **3** and ethoxyethylene **2**.

2-Alkylthio- and 2-Benzylthio-3-cyano-5-thenoyl-6-trifluoromethylpyridines (9a-f). 10% KOH (1.3 ml, 2.4 mmol) was added with stirring to a solution of salt **4** (1 g, 2.4 mmol) in DMF (8 ml). After 10 min, the corresponding alkyl halide **8a-f** (2.4 mmol) was added to the reaction mass, the reaction mixture was filtered through a pleated filter, and the filtrate was stirred for 4 h. The precipitate of product formed was filtered off and washed with alcohol.

2-Alkylthio- and 5-Benzoyl-2-benzylthio-3-cyano-6-trifluoromethylpyridines (10a-f) were obtained similarly to compounds **9a-f**, from salt **5** (1 g, 2.4 mmol) and the corresponding alkyl halide **8a-f** (2.4 mmol).

2-Carbamoylmethylthio-3-cyano-5-thenoyl-6-trifluoromethylpyridine (9h). α-Chloroacetamide **8h** (0.22 g, 2.4 mmol) was added with stirring to a solution of salt **4** (1 g, 2.4 mmol) in DMF (8 ml). The reaction mixture was heated to boiling and filtered hot through a pleated filter. The filtrate was held for 12 h at room temperature. The precipitate formed was filtered off and washed with alcohol.

2-(4-Bromophenylcarbonylmethylthio)- and 5-Benzoyl-2-carbamoylmethylthio-3-cyano-6-trifluoromethylpyridines (10g,h) were obtained similarly to compound **9h**, from salt **5** and 4-bromophenacyl bromide **8g** or amide **8h** respectively.

3-Amino-2-(4-bromophenylcarbonyl)- and 3-Amino-2-carbamoyl-5-thenoyl-6-trifluoromethylthieno[2,3-*b*]pyridines (11g,h). 10% KOH (1.3 ml, 2.4 mmol) was added with stirring to a solution of salt **4** (1 g, 2.4 mmol) in DMF (8 ml), and after 10 min an equimolar amount of compound **8g** or **8h** was also added. The

reaction mass was stirred for 0.5 h, then 10% KOH (1.3 ml) was added and the mixture was stirred for 4 h. The precipitate of product formed was filtered off and washed with alcohol.

3-Amino-2-(4-bromophenylcarbonyl)- and 3-Amino-5-benzoyl-2-carbamoyl-6-trifluoromethyl-thieno[2,3-*b*]pyridines (12g,h) were obtained similarly to compounds **11g,h**, from salt **5** and compound **8g** or **8h** respectively.

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