Synthesis and alkylation of *N*-methylmorpholinium 6-amino-3,5-dicyano-4-methylpyridine-2-thiolate

V. D. Dyachenko,[a] S. G. Krivokolysko,[a] and V. P. Litvinov[b]*

[a]*T. G. Shevchenko Lugansk State Pedagogical Institute, 348011 Lugansk, Ukraine*
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: 007 (095) 135 5328*

The condensation of acetaldehyde with a twofold excess of cyanothioacetamide and *N*-methylmorpholine gives *N*-methylmorpholinium 6-amino-3,5-dicyano-4-methylpyridine-2-thiolate. This compound is also formed by recyclization of 2,6-diamino-3,5-dicyano-4-methyl-4*H*-thiopyran. From this pyridinethiolate, several substituted 2-alkylthiopyridines and 3,6-diamino-5-cyano-4-methyl-2-methoxycarbonylthieno[2,3-*b*]pyridine were obtained.

Key words: acetaldehyde, cyanothioacetamide, *N*-methylmorpholine, pyridine, thiopyran, condensation, recyclization.

Previously[1] we described a method for the synthesis of 6-amino-4-aryl-3,5-dicyanopyridine-2(1*H*)-thiones and their hydrogenated analogs by the reaction of arylmethylenecyanothioacetamides with cyanothioacetamide. 4-Alkyl-containing analogs of these pyridine derivatives cannot be obtained by this procedure, because alkyl-substituted acrylonitriles easily dimerize.[2] Recently, an original method for the synthesis of 4-alkyl-2,6-amino-3,5-dicyanopyridine-2(1*H*)-thiones has been developed. This method involves recyclization of 4-alkyl-6-amino-3,5-dicyano-4*H*-thiopyrans, which are, in turn, prepared by three-component cyclization of aliphatic aldehydes, cyanothioacetamide, and malononitrile.[3] This procedure made it possible to minimize side processes and to increase the yield of the target product.

In continuation of the studies dealing with the synthesis of functionally substituted 3-cyanopyridine-2(1*H*)-chalkogenones, which are excellent synthons for the preparation of many biologically active compounds,[4] we developed a method for the synthesis of *N*-methylmorpholinium 6-amino-3,5-dicyano-4-methylpyridine-2-thiolate according to Scheme 1.

When acetaldehyde (**1**) is made to react with a twofold excess of cyanothioacetamide (**2**) in the presence of *N*-methylmorpholine, Knoevenagel condensation occurs in the first step to give substituted acrylonitrile **3**. This product reacts with the second equivalent of thioamide **2** to give Michael adduct **4**, which undergoes intramolecular condensation under the reaction conditions to yield salt **5**. Elimination of hydrogen sulfide and hydrogen from **5** affords stable *N*-methylmorpholinium

Table 1. Characteristics of compounds **10a—e**

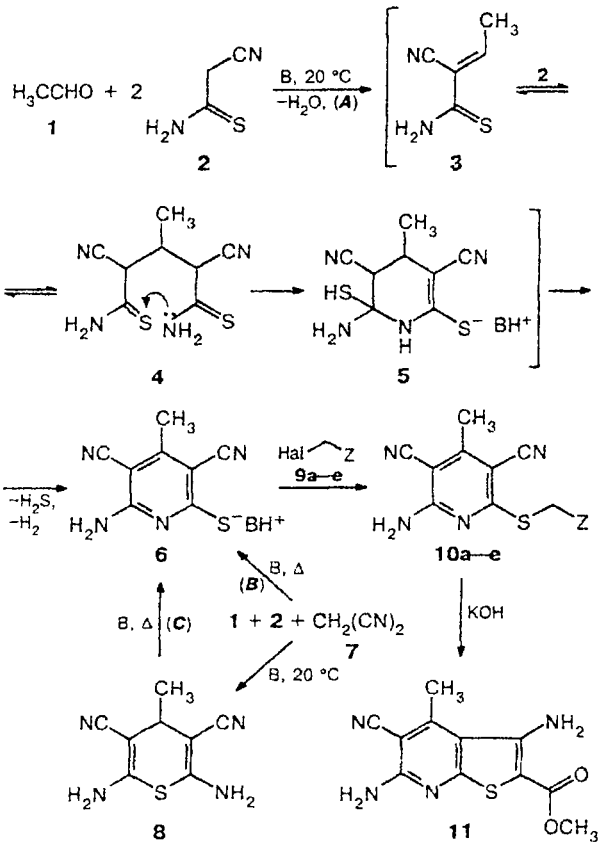
Compound	Yield (%)	M.p./°C	Solvent for crystallization	Found / Calculated (%) C	H	N	S	Molecular formula
10a	73	150—152	Methanol	50.42	3.66	21.40	12.11	$C_{11}H_{10}N_4O_2S$
				50.37	3.84	21.36	12.22	
10b	74	239—240*	Ethanol	53.05	3.80	27.55	15.60	$C_9H_8N_4S$
				52.92	3.95	27.43	15.70	
10c	80	172—174	Ethanol	57.35	4.41	24.10	14.14	$C_{11}H_{10}N_4S$
				57.37	4.38	24.33	13.92	
10d	82	255—257	AcOH	48.41	3.50	28.48	13.07	$C_{10}H_9N_5OS$
				48.57	3.67	28.32	12.97	
10e	71	222—224	DMF	55.85	3.15	16.45	9.41	$C_{16}H_{11}ClN_4OS$
				56.06	3.23	16.34	9.35	

* At 140 °C, sublimation of this compound starts.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2013—2015, November, 1997.

1066-5285/97/4611-1909 $18.00 © 1997 Plenum Publishing Corporation

Scheme 1



B = *N*-methylmorpholine.

9, 10	**a**	**b**	**c**	**d**	**e**
Hal	Cl	I	Br	Cl	Br
Z	COOMe	H	$CH{=}CH_2$	$CONH_2$	4-ClC_6H_4CO

6-amino-3,5-dicyano-4-methylpyridine-2-thiolate (**6**) (method *A*). Salt **6** can also be obtained by the condensation of acetaldehyde (**1**), cyanothioacetamide (**2**), and malononitrile (**7**) in the presence of *N*-methylmorpholine in boiling ethanol (method *B*) and by recyclization of 2,6-diamino-3,5-dicyano-4-methyl-4*H*-thiopyran (**8**) upon refluxing in ethanol in the presence of *N*-methylmorpholine (method *C*).

The structure of thiolate **6** is fully confirmed by the results of spectral studies (see Experimental) and by its chemical transformations. For example, its interaction with halides **9** yields sulfides **10**, which apparently indicates that the negative charge is localized on the sulfur atom. In addition, compound **10a** was converted into a substituted thieno[2,3-*b*]pyridine **11** according to Thorpe—Ziegler; this confirms the structure of sulfides **10**, which is consistent with their physicochemical and spectral characteristics (Tables 1 and 2).

Experimental

^{1}H NMR spectra were recorded on a Bruker WP-100 SY (100 MHz) instrument in DMSO-d_6 using tetramethylsilane as the standard. IR spectra were recorded on an IKS-29 spectrophotometer in Vaseline oil. The individuality of compounds was checked by TLC on Silufol UV-254 plates using the acetone—heptane system (3 : 5).

***N*-Methylmorpholinium 6-amino-3,5-dicyano-4-methylpyridine-2-thiolate (6). Method *A*.** A suspension of acetaldehyde (**1**) (0.56 mL, 10 mmol), cyanothioacetamide (**2**) (2 g, 20 mmol), and *N*-methylmorpholine (2.2 mL, 10 mmol) in 15 mL of anhydrous ethanol was stirred at 20 °C for 4 h. The precipitate was filtered off and washed with anhydrous ethanol and acetone. Yield 2.3 g (79%), m.p. 300 °C (decomp.). Found (%): C, 53.44; H, 5.72; N, 23.86; S, 11.18. $C_{13}H_{17}N_5OS$. Calculated (%): C, 53.59; H, 5.88; N, 24.04; S, 11.00. IR, ν/cm^{-1}: 3300—3470 (NH_2); 2216 sh. (CN); 1680 (δ NH_2). ^{1}H NMR, δ: 7.53 (br.s, 2 H, NH_2); 3.68 (m, 4 H, CH_2OCH_2); 2.83 (m, 4 H, CH_2NCH_2); 2.54 (s, 3 H, NCH_3); 2.31 (s, 3 H, CH_3).

Method *B*. A mixture of acetaldehyde (**1**) (0.56 mL, 10 mmol), cyanothioacetamide (**2**) (1 g, 10 mmol), malononitrile (**7**) (0.66 g, 10 mmol), and *N*-methylmorpholine (2.2 mL, 20 mmol) in 10 mL of anhydrous ethanol was refluxed for 1 h and cooled to 20 °C. After 5 h, the precipitate that formed was filtered off and washed with anhydrous ethanol and acetone to give salt **6** in a yield of 1.9 g (66%). Judging from its melting point and TLC, this sample was identical to that prepared by method *A*.

Method *C*. A suspension of thiopyran **8** (3.84 g, 20 mmol) and *N*-methylmorpholine (4.4 mL, 40 mmol) in 10 mL of anhydrous ethanol was refluxed for 1 h. After 5 h, the precipitate was filtered off and washed with anhydrous ethanol and acetone. The yield of compound **6** was 2.1 g (71%).

2,6-Diamino-3,5-dicyano-4-methyl-4*H*-thiopyran (8). A mixture of acetaldehyde (**1**) (0.56 mL, 10 mmol),

Table 2. Spectral characteristics of compounds **10a—e**

Compound	IR, ν/cm^{-1}			^{1}H NMR, δ			
	NH_2	C≡N	δNH_2	NH_2 (br.s)	4-SH_3 (s)	SCH_2	Z
10a	3335, 3450	2218 sh	1657	7.86	2.42	4.14 s	3.66 (s, 3 H, OCH_3)
10b	3340, 3450	2220 sh	1670	7.83	2.40	2.52 s	—
10c	3210, 3330, 3472	2218 sh	1654	7.89	2.40	3.85 d	5.10—5.55 (m, 2 H, CH_2=); 5.85 (m, 1 H, CH=)
10d	3190, 3300, 3402	2223 sh	1670	7.85	2.41	3.83 s	7.45 and 7.20 (both br.s, 1 H, $CONH_2$)
10e	3345, 3464	2217 sh	1677	7.78	2.44	4.92 s	8.05 and 7.62 (both d, 2 H, C_6H_4)

cyanothioacetamide (2) (1 g, 10 mmol), and malononitrile (7) (0.66 g, 10 mmol), and 3 drops of *N*-methylmorpholine in 10 mL of ethanol was stirred at 20 °C for 6 h. Then the precipitate was filtered off and washed with ethanol and hexane. The yield of thiopyran **8** was 1.6 g (83%), m.p. 153—155 °C (ethanol). Found (%): C, 50.10; H, 4.12; N, 29.00; S, 16.68. $C_8H_8N_4S$. Calculated (%): C, 49.98; H, 4.19; N, 29.14; S, 16.78. IR, ν/cm^{-1}: 3346, 3440, 3480 (NH_2); 2175 (CN); 1640 (δ NH_2). ^1H NMR, δ: 6.79 (br.s, 4 H, $(NH_2)_2$); 3.03 (q, 1 H, H(4)); 1.15 (d, 3 H, CH_3).

6-Amino-3,5-dicyano-4-methyl-2-Z-methylthiopyridines (10a—e). Halide **9** (10 mmol) was added at 20 °C to a suspension of salt **6** (2.9 g, 10 mmol) in 8 mL of DMF, and the mixture was stirred for 4 h and then diluted with 10 mL of water. The precipitate was separated and washed with water, ethanol, and hexane to give sulfides **10a—e**, whose characteristics are listed in Tables 1 and 2.

3,6-Diamino-5-cyano-4-methyl-2-methoxycarbonylthieno[2,3-*b*]pyridine (11). A 10% aqueous solution of KOH (5.6 mL, 10 mmol) was added to a solution of sulfide **10a** (2.6 g, 10 mmol) in 10 mL of DMF, and the mixture was stirred at 20 °C for 3 h and then diluted with 10 mL of water. The resulting precipitate was filtered off and washed with water, ethanol, and hexane. The yield of compound **11** was 1.9 g (71%), m.p. 304—306 °C (AcOH). Found (%): C, 50.50; H, 3.90; N, 21.20; S, 12.15. $C_{11}H_{10}N_4O_2S$. Calculated (%): C, 50.37; H, 3.84; N, 21.36; S, 12.22. IR, ν/cm^{-1}: 3165, 3333, 3400, 3505 (NH_2); 2220 (CN); 1680 (C=O); 1625 (δ NH_2). ^1H NMR, δ: 7.23 (br.s, 2 H, 6-NH_2); 6.75 (br.s, 2 H, 3-NH_2); 3.73 (s, 3 H, OCH_3); 2.75 (s, 3 H, CH_3).

This work was carried out with the financial support of the Russian Foundation for Basic Research (Project No 96-03-32012a).

References

1. Yu. A. Sharanin, S. G. Krivokolysko, and V. D. Dyachenko, *Zh. Org. Khim.*, 1994, **30**, 581 [*J. Org. Chem.*, 1994, **30** (Engl. Transl.)].
2. F. Freeman, *Chem. Rev.*, 1969, **69**, 591.
3. N. G. Frolova, V. K. Zav'yalova, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 938 [*Russ. Chem. Bull.*, 1996, **45**, 893 (Engl. Transl.)].
4. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, *Sulfur Reports*, 1992, **13**, 1.

Received March 3, 1997