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NEW METHOD FOR THE SYNTHESIS OF THIENO[2,3-*d*]PYRIMIDINES

O. B. Ryabova[1], M. I. Evstratova[1], V. A. Makarov[1], V. A. Tafeenko[2], and V. G. Granik[1]

The reaction of 5-formyl-4-thiocyanatopyrimidines with nitromethane was studied under various conditions. The reaction was found unexpectedly to proceed with closure of a thiophene ring to give thieno[2,3-d]pyrimidines. The use of ammonium acetate as the catalyst leads to a side reaction involving closure of an isothiazole ring to give isothiazolo[5,4-d]pyrimidines. X-ray diffraction crystallographic analysis was used to confirm the structure of thieno[2,3-d]pyrimidine.

Keywords: isothiazolo[5,4-*d*]pyrimidine, nitromethane, thieno[2,3-*d*]pyrimidine, 5-formylpyrimidine.

In a continuation of a study of 4-dialkyldithiocarbamoyl-5-nitropyrimidines and some of the chemical and physicochemical properties of these compounds [1], we investigated 4-thiocyanatopyrimidines, which have a nitroethylene group at $C_{(5)}$.

The properties of alkyl- and arylthiocyanates have been studied rather extensively since these compounds have high insecticidal activity [2]. The synthetic methods for thiocyanate derivatives are based, as a rule, on the reaction of the corresponding halides, sulfates, or sulfonates with ammonium or alkali metal thiocyanates [3, 4].

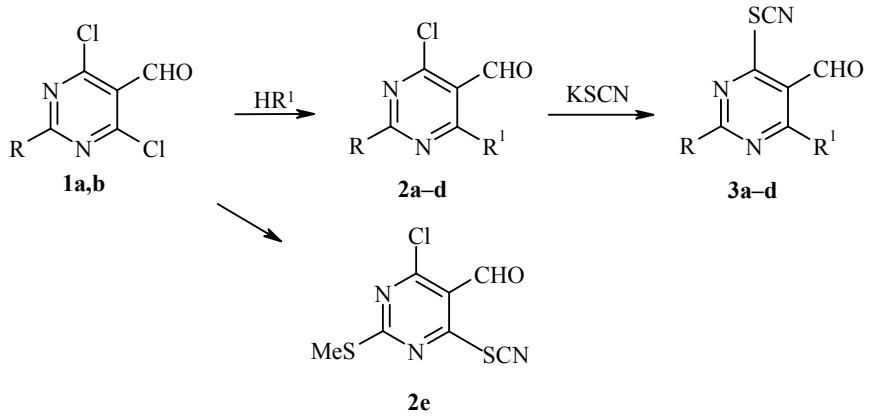
4,6-Dichloro-5-formylpyrimidines **1a**,**b** were prepared according to reported procedures by the Vilsmeier formylation of 4,6-dihydroxypyrimidines with the concurrent replacement of the hydroxy groups by chlorine atoms [5, 6].

In the first stage, we synthesized 6-amino derivatives **2a-d** by treating dichloropyrimidines **1a**,**b** in dioxane with an aqueous solution of amine in the presence of an equimolar amount of acetic acid added to prevent the replacement of the second chlorine atom. The presence of the electron-withdrawing formyl group at $C_{(5)}$ permits us to replace the second chlorine atom in 6-amino-4-chloro derivatives **2a-d** by a thiocyanato group by treating the corresponding chloro derivative with potassium thiocyanate in methanol or DMF. Thiocyanates **3a-d** were obtained in high yield (Scheme 1).

Since the lability of the chlorine atoms in **1a**,**b** is less than in the analogous 5-nitropyrimidines, we were able to replace only one of the chlorine atoms by a thiocyanate group in 2-methylmercapto derivative **1b** [7-9]. The reaction was carried out in methanol at 17°C and monitored by thin-layer chromatography. It proved necessary to stop this reaction when about half of the starting compound still remained in the reaction mixture since the reaction is complicated by the formation of a large amount of impurities. Dilution of the reaction mixture with water and recrystallization of the precipitate gave monothiocyano derivative **2e** in 27% yield.

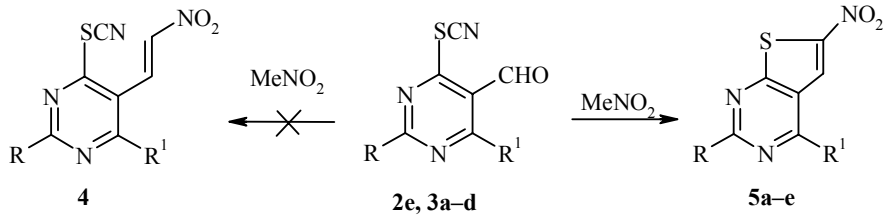
[1] State Antibiotics Research Center, 117105 Moscow, Russia; e-mail: makar-cl@ropnet.ru. [2] M. V. Lomonosov Moscow State University, 119234 Moscow, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1564-1571, October, 2004. Original article submitted June 8, 2004.

Scheme 1



1 a R = H, **b** R = SMe; **2**, **3 a**, **b** R = H, **c**, **d** R = SMe; **a**, **c** $R^1 = NMe_2$, **b**, **d** $R^1 = N(CH_2)_5$

Since aromatic aldehydes condense with nitromethane to give nitroethylene derivatives [10-12], we studied the reaction of formylthiocyanates **2e** and **3a-d** with nitromethane. The reaction of thiocyanate **3a** in nitromethane at reflux in the presence of ammonium acetate led to a tarry mixture of products, from which we were able to obtain a crystalline compound only in 4% yield. The yield was increased to 20% when the reaction was carried out in 2-propanol at reflux.



5 a, b R = H, **c**–**e** R = SMe; **a**, **c** $R^1 = NMe_2$, **b**, **d** $R^1 = N(CH_2)_5$, **e** R^1 = Cl

The IR spectrum of this product lacked the CN group stretching band. NMR spectroscopy, mass spectrometry, and elemental analysis were not in accord with the presumed condensation product **4**. The reaction was found unexpectedly to proceed to give thieno[2,3-*d*]pyrimidine **5a**. The structure of this compound was demonstrated by NMR spectroscopy and X-ray diffraction structural analysis (Fig. 1). Some of the bond lengths and angles in the structure of **5a** are given in Table 1.

The reactions of thiocyanates **2e** and **3b-d** proceed similarly with varying yields (Table 2). Dimethylamino derivative **3a** reacts with nitromethane in the presence of trimethylamine even at 0°C. The pure cyclic product precipitates out of the reaction mixture in 50% yield. The reaction of piperidine derivative **3b** with nitromethane in the presence of Et_3N in 2-propanol is accompanied by tar formation but thiophene derivative **5b** was also obtained in this case in 10% yield.

Breakage of the S–CN bond in thiocyanates may proceed by the action of mild nucleophiles such as CH-acid anions [13]. Hence, we supposed that the nontrivial formation of 6-nitrothieno[2,3-*d*]pyrimidines may be depicted as follows:

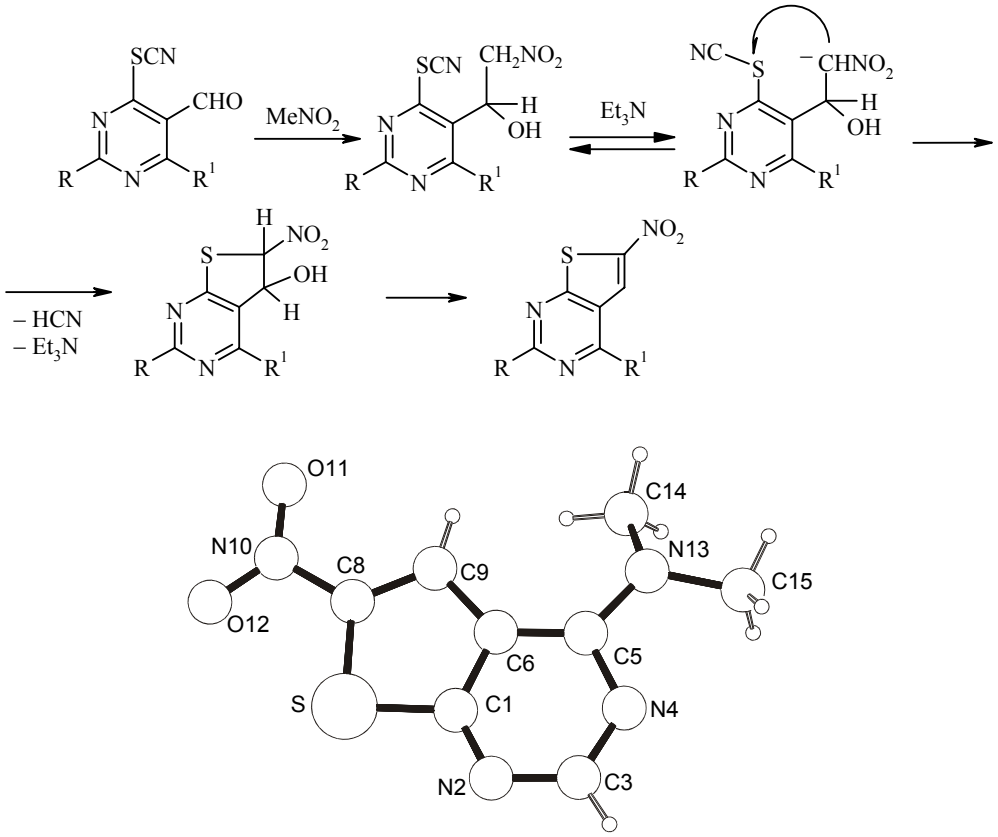


Fig. 1. Molecular structure of **5a** from X-ray diffraction structural data.

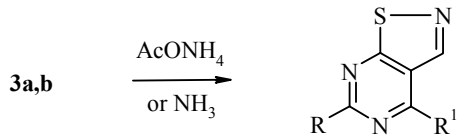
TABLE 1. Bond Lengths (*l*) and bond angles (ω) in **5a**

Bond	*l*, Å	Angle	ω, deg.
$C_{(1)}–N_{(2)}$	1.3021	$C_{(6)}–C_{(1)}–S_{(7)}$	112.59
$C_{(1)}–C_{(6)}$	1.4207	$N_{(2)}–C_{(1)}–S_{(7)}$	118.80
$C_{(1)}–S_{(7)}$	1.7320	$N_{(2)}–C_{(1)}–C_{(6)}$	128.32
$N_{(2)}–C_{(3)}$	1.3635	$C_{(1)}–N_{(2)}–C_{(3)}$	117.07
$C_{(3)}–N_{(4)}$	1.3822	$N_{(2)}–C_{(3)}–N_{(4)}$	118.51
$N_{(4)}–C_{(5)}$	1.3963	$C_{(3)}–N_{(4)}–C_{(5)}$	123.96
$C_{(5)}–C_{(6)}$	1.3948	$N_{(4)}–C_{(5)}–N_{(13)}$	112.36
$C_{(5)}–N_{(13)}$	1.4097	$N_{(4)}–C_{(5)}–C_{(6)}$	117.07
$C_{(6)}–C_{(9)}$	1.4431	$C_{(6)}–C_{(5)}–N_{(13)}$	130.54
$S_{(7)}–C_{(8)}$	1.7514	$C_{(1)}–C_{(6)}–C_{(5)}$	114.38
$C_{(8)}–C_{(9)}$	1.3775	$C_{(5)}–C_{(6)}–C_{(9)}$	132.83
$C_{(8)}–N_{(10)}$	1.4006	$C_{(1)}–C_{(6)}–C_{(9)}$	112.72
$N_{(10)}–O_{(11)}$	1.2422	$C_{(1)}–S_{(7)}–C_{(8)}$	89.44
$N_{(10)}–O_{(12)}$	1.2459	$S_{(7)}–C_{(8)}–N_{(10)}$	118.19
$N_{(13)}–C_{(14)}$	1.5375	$S_{(7)}–C_{(8)}–C_{(9)}$	115.74
$N_{(13)}–C_{(15)}$	1.5082	$C_{(9)}–C_{(8)}–N_{(10)}$	126.04
		$C_{(6)}–C_{(9)}–C_{(8)}$	109.47
		$C_{(8)}–N_{(10)}–O_{(12)}$	113.61
		$C_{(8)}–N_{(10)}–O_{(11)}$	116.74
		$O_{(11)}–N_{(10)}–O_{(12)}$	129.49
		$C_{(5)}–N_{(13)}–C_{(15)}$	122.36
		$C_{(5)}–N_{(13)}–C_{(14)}$	118.13
		$C_{(14)}–N_{(13)}–C_{(15)}$	107.54

TABLE 2. Physicochemical and Mass Spectral Data of Products

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Solvent for crystallization	$[M]^{+\cdot}$	Yield, %
		C	H	N	S				
2e	$C_7H_4ClN_3OS_2$	33.85 / 34.22	1.58 / 1.64	16.72 / 17.10	26.08 / 26.10	177-178	Benzene	245	27
3a	$C_8H_8N_4OS$	46.11 / 46.14	3.66 / 3.87	26.92 / 26.91	15.40 / 15.59	124-126	2-Propanol	208	71
3b	$C_{11}H_{12}N_4OS$	53.35 / 53.20	4.84 / 4.87	22.21 / 22.56	12.88 / 12.91	121-123	Ethanol	248	70
3c	$C_9H_{10}N_4OS_2$	42.35 / 42.50	4.00 / 3.96	22.37 / 22.03	25.00 / 25.22	177-179	Ethanol	254	73
3d	$C_{12}H_{14}N_4OS_2$	48.91 / 48.96	4.82 / 4.97	19.18 / 19.03	21.80 / 21.78	168-171	Ethanol	294	20
5a	$C_8H_8N_4O_2S$	43.07 / 42.85	3.48 / 3.59	24.87 / 24.99	14.47 / 14.30	192-193	2-Propanol	224	50
5b	$C_{11}H_{12}N_4O_2S$	50.49 / 49.98	4.70 / 4.58	21.03 / 21.20	12.13 / 12.62	119-121	Ethanol	264	42
5c	$C_9H_{10}N_4O_2S_2$	40.48 / 40.00	3.80 / 3.73	20.80 / 20.73	23.71 / 23.72	200-202	Acetonitrile	270	67
5d	$C_{12}H_{14}N_4O_2S_2$	46.40 / 46.43	4.12 / 4.56	18.08 / 18.05	20.61 / 20.66	215-218	Benzene	310	54
5e	$C_7H_4ClN_3O_3S_2$	32.31 / 32.13	1.46 / 1.54	15.98 / 16.06		182-184	2-Propanol	261	10
6a	$C_7H_8N_4S$	47.09 / 46.65	4.41 / 4.47	31.00 / 31.09	17.86 / 17.72	169-171	Heptane	180	33

In a study of the mother liquors after separation of the thiophene derivatives when ammonium acetate was used as catalyst, we found side products in addition to the thienopyrimidine major products. These side products were identified as isothiazolo[5,4-*d*]pyrimidines **6a**,**b** using spectral data.



6a,b

6 a, b R = H, **a** $R^1 = NMe_2$; **b** $R^1 = N(CH_2)_5$

To study the process of their formation "blank" experiment was carried out without nitromethane. Thiocyanates **3a,b** were heated at reflux in 2-propanol in the presence of ammonium acetate. As a result the mixture was obtained which after the preparative chromatography gave the main compound **6a,b**. According to spectral characteristics these compounds were identical to those obtained in the reactions with nitromethane.

In the presence of ammonium acetate, ammonia probably adds at the formyl group with subsequent elimination of HCN and closure of the isothiazole ring. Product **6a** was also obtained by treating thiocyanate **3a** with methanolic ammonia. A similar closure of an isothiazole ring starting from *ortho*-formylthiocyanates has been described for derivatives of benzene [14] and pyridine [15].

EXPERIMENTAL

The IR spectra were taken on a Perkin–Elmer spectrometer for vaseline mulls. The NMR spectra were taken on a Bruker AC-200 spectrometer at 200 MHz in DMSO-d_6 with TMS as the internal standard. The mass spectra were obtained on a Varian SSQ-700 mass spectrometer with direct inlet into the ion source and 70 eV ionizing voltage. Purity of the products and the reaction course were monitored by thin-layer chromatography on Merck 60 F-254 plates.

The physicochemical data of the starting compounds **1a,b** [5, 6], **2a** [16], **2b** [17], **2c,d** [18] were in accord with the literature values.

6-Chloro-5-formyl-2-methylthio-4-thiocyanatopyrimidine (2e). A solution of pyrimidine **1b** (3.26 g, 15 mmol) and potassium thiocyanate (1.75 g, 18 mmol) in methanol was stirred for 10 h at 17°C. The reaction mixture was diluted with water and the white precipitate formed was filtered off. The precipitate was dried in vacuum and recrystallized from benzene to give 0.8 g thiocyanate **2e**. Hexane was added to the mother liquor and an additional 0.22 g pyrimidine **2e** was obtained. The total yield of **2e** was 27%.

2-R-5-Formyl-4-thiocyanato-6-R^1-pyrimidines 3a-d. A solution of chloro derivative **2a-d** (15 mmol) and KSCN (16 mmol) in DMF (20 ml) was stirred at 80-85°C (in the case of **2b**, the reaction was carried out in methanol at reflux for 5 h). After cooling to room temperature, the reaction mixture was diluted with water. The precipitate was filtered off, washed with water, and dried.

4-Dimethylamino-6-nitrothieno[2,3-*d*]pyrimidine (5a). A. A solution of pyrimidine **3a** (0.42 g, 2 mmol), nitromethane (0.5 ml, 17 mmol), and ammonium acetate (0.2 g, 2.5 mmol) in 2-propanol (5 ml) was heated at reflux for 2.5 h. The precipitate formed after cooling was filtered off and recrystallized from 2-propanol to give 0.09 g (20%) of cyclic derivative **5a**.

B. Triethylamine (0.8 ml, 6 mmol) was added dropwise to a suspension of pyrimidine **3a** (2.1 g, 1 mmol) in nitromethane (10 ml) cooled to 0°C until starting **3a** had disappeared as indicated by thin-layer chromatography. The precipitate formed during the reaction was filtered off, washed with 2-propanol, and dried to give 1.13 g thienopyrimidine **5a** identical in its physicochemical data to a sample obtained by method A. ^{1}H NMR spectrum, δ, ppm: 8.54 (1H, s, CH pyrimidine); 8.46 (1H, s, H thiophene); 3.40 (6H, s, NMe_2).

Light-yellow crystals of thienopyrimidine **5a** obtained by the slow evaporation of a solution of this compound in 2-propanol were studied on a four-circle automatic CAD4 diffractometer using Mo$K\alpha$ radiation, graphite monochromator, and ω-scanning. The unit cell parameters were determined relative to 25 reflections at θ 7-10° by self-induction and refined relative to 24 reflections at θ 12-15°; a = 9.522(2), b = 15.457(4), c = 13.458(4) Å; β = 106.54(2)°; V = 1904.8(9) Å^3; space group $P2_1/c$; Z = 4. A total of 2997 nonzero reflections were measured in the range θ 2-24°. No correction for absorption was introduced.

The structure was solved by the direct method (MULTAN) using the SDP program package. The positional and temperature parameters of the non-hydrogen atoms were refined in the full-matrix anisotropic approximation using the SHELXL-93 program package. The hydrogen atom coordinates were determined both from the Fourier difference maps and calculations. R_f = 0.059 for 1358 reflections with $I > 2\sigma(I)$ (Table 1, Fig. 1).

6-Nitro-4-piperidinothieno[2,3-*d*]pyrimidine (5b) and 4-Piperidinoisothiazolo[5,4-*d*]pyrimidine (6b). A. A solution of pyrimidine **3b** (1.5 g, 6 mmol), nitromethane (1.5 ml), and ammonium acetate (0.56 g, 7 mmol) in 2-propanol (20 ml) was heated at reflux for 2 h. The solution was cooled and 0.6 g (40%) of starting **3b** was filtered off. The mother liquor was evaporated. The residue was dissolved in methylene chloride, placed on a silica gel column, and eluted with methylene chloride to give a fraction containing 0.28 g (18%) of thienopyrimidine **5b**. The second fraction eluted with methanol gave 0.01 g of isothiazole **6b** with $[M]^{+\cdot}$ 220.

B. Triethylamine was added dropwise to a suspension of **3b** (0.9 g, 36 mmol) and nitromethane (0.5 ml, 10 mmol) in 2-propanol (10 ml) cooled to 0°C until the suspension was at pH 8-9. The reaction mixture was stirred for 7 h at 5-10°C, periodically adding triethylamine to pH 8-9, and then evaporated. The residue was dissolved in chloroform. The solution was passed through a silica gel layer and evaporated to give 0.4 g of thienopyrimidine **5b**, identical in its physicochemical data to the product obtained using method A. ^{1}H NMR spectrum, δ, ppm: 8.51 (1H, s, CH pyrimidine); 8.48 (1H, s, H thiophene); 3.93 (4H, m, $N(CH_2)_2$); 1.69 (6H, br. s, $(CH_2)_3$).

4-Dimethylamino-2-methylthio-6-nitrothieno[2,3-*d*]pyrimidine (5c). Triethylamine was added dropwise to a suspension of 2-methylmercaptopyrimidine **3c** in nitromethane (3 ml) cooled to 0°C. The solution was stirred for 4 h at 7°C. The precipitate formed was filtered off and washed with 2-propanol to give 0.37 g of thienopyrimidine **5c**. ^{1}H NMR spectrum, δ, ppm: 8.43 (1H, s, H thiophene); 3.37 (6H, s, $N(CH_3)_2$); 3.26 (3H, s, SCH_3).

2-Methylthio-6-nitro-4-piperidinothieno[2,3-*d*]pyrimidine (5d). A sample of triethylamine (0.23 g, 22 mmol) was added to a suspension of 2-methylmercaptopyrimidine **3d** (0.65 g, 22 mmol) and nitromethane (1 ml, 22 mmol) in 2-propanol (20 ml) at 15°C. The reaction mixture was stirred for 5 h at 50°C, cooled, and filtered to give 0.54 g of thienopyrimidine **5d**.

4-Chloro-2-methylthio-6-nitrothieno[2,3-*d*]pyrimidine (5e). Triethylamine was added dropwise to a suspension of thiocyanate **2e** (0.79 g, 3 mmol) in nitromethane (6 ml) cooled to 15°C until the suspension was at pH 8-9. The reaction mixture was stirred for 2 h at 15°C, periodically adding triethylamine to pH 8-9, and then evaporated. The residue was dissolved in benzene and placed on a silica gel column. Elution with benzene gave 0.1 g of thienopyrimidine **5e**.

6-Dimethylaminoisothiazolo[5,4-*d*]pyrimidine (6a). A. A solution of thiocyanate **3a** (0.42 g, 2 mmol) and ammonium acetate (0.2 g, 0.3 mmol) in 2-propanol (10 ml) was heated at reflux for 30 h. The reaction mixture was treated with activated charcoal, filtered, and evaporated. The residue was dissolved in methanol and subjected to chromatography on a preparative silica gel plate (Merck 160×160) with elution using 50:1 chloroform–methanol. The zone with R_f 0.6 was separated, extracted with chloroform, and evaporated to give 0.06 g of isothiazole derivative **6a**.

B. A mixture of thiocyanate **3a** (0.45 g, 2.16 mmol) and 20% methanolic ammonia (10 ml) was stirred for 4 h at -10°C and then for 10 h at room temperature. The precipitate of **6a** (0.13 g) was filtered and found identical in its physicochemical data to the sample obtained using method A.

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