Chemistry of Heterocyclic Compounds, Vol. 43, No. 5, 2007

REACTION OF DIKETENE WITH CYANOTHIOACETAMIDE: A CONVENIENT AND REGIOSELECTIVE METHOD FOR THE PREPARATION OF NEW 4(1H)-PYRIDONE DERIVATIVES

V. V. Dotsenko[1], S. G. Krivokolysko[1], B. P. Litvinov[2†], and A. N. Chernega[2]

The reaction of diketene with cyanothioacetamide in dry dioxane in the presence of triethylamine gives triethylammonium 3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinethiolate. The regioselective S-alkylation of this thiolate is a convenient method for the preparation of substituted 4(1H)-pyridones and also derivatives of thiazolo[3,2-a]pyridine and thieno[2,3-b]pyridine. The action of 2-amino-1,1,3-tricyanopropene on this thiolate leads to its transformation into a new heterocyclic system, namely, 5H-pyrido[2',3':4,5]thiopyrano[2,3-b]pyridine; treatment with iodine yields the oxidation product, namely, the corresponding bis(2-pyridyl) disulfide. The structure of isopropyl (3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thioacetate was confirmed by X-ray diffraction structural analysis.

Keywords: diketene, 4(1H)-pyridones, 5H-pyrido[2',3':4,5]thiopyrano[2,3-*b*]pyridines, thiazolo-[3,2-*a*]pyridines, thieno[2,3-*b*]pyridines, cyanothioacetamide, S-alkylation, X-ray diffraction structural analysis, Thorpe-Ziegler cyclization, cyclocondensation.

As a consequence of its extremely high chemical activity, diketene **1** has found use as efficient reagent in heterocyclic chemistry [1, 2]. In recent years, diketene has been employed to obtain derivatives of such heterocyclic systems as cyclopropanespiro-β-lactones [3], benzofurans [4], pyrazolidines [5], pyrido[2,3-*d*]pyrimidines [6], and condensed isoquinoline analogs [7]. We found special interest in the reaction of diketene with active methylene reagents such as Meldrum's acid [8, 9], malononitrile and ethyl cyanoacetate [10], ethyl acetoacetate [11], diethyl 3-ketoglutarate [12], diethyl malonate [13], and 2-nitromethylimidazole derivatives [14] since C-acetoacetylation in these cases is usually accompanied by further cyclization of the initially formed linear intermediates [1]. Hence, such reactions may be seen as an easy preparative and convenient general method for obtaining various functionally-substituted derivatives of pyran and pyridine.

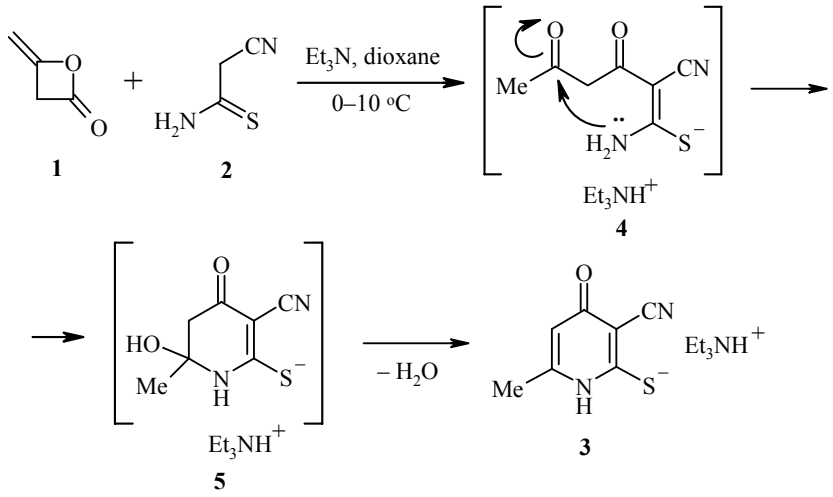
In the past few years, we have been interested in the chemistry of cyanothioacetamide **2**. Since this reagent was first described by Howard et al. in the mid-1950's, it has attracted attention as an readily available and convenient reagent and has found use in heterocyclic synthesis [17-20].

†Deceased.

[1]"ChemEx" Laboratory, Vladimir Dal East-Ukrainian National University, 91034 Lugansk, Ukraine; e-mail: ksg@lep.lg.ua. [2]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russia; e-mail: vpl@mail.ioc.ac.ru. [2]Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02094 Kiev, Ukraine; e-mail: xray@bpci.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 716-725, May, 2007. Original article submitted April 3, 2006.

Cyanothioacetamide **2** has three nucleophilic sites, which may potentially undergo initial attack by the diketene molecule: the methylene group carbon and the thioamide group nitrogen and sulfur atoms. On the whole, under cyclocondensation or cycloaddition conditions, thioamide **2** acts as a C,N-, C,S-, or S,N-binucleophile [17-20]. In the course of our study of the synthetic scope of cyanothioacetamide **2**, we investigated its reaction with diketene as well as the structure and transformations of the reaction products.

Scheme 1



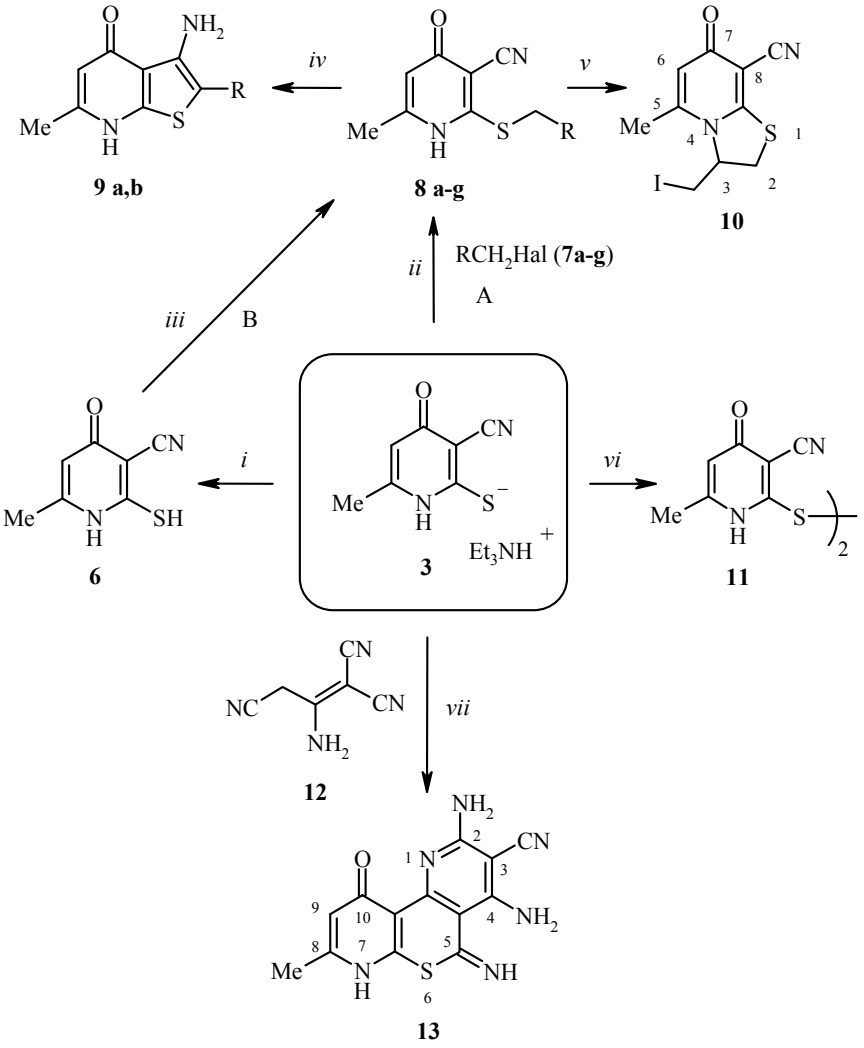
Diketene was found to react very vigorously with thioamide **2** (in 1:1 mol ratio) in the presence of excess triethylamine in dry dioxane with cooling to give triethylammonium 3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinethiolate (**3**) in 46% yield. We assume that the low yield of thiolate **3** is a result of an unavoidable side-reaction promoted by Et_3N, namely, the decomposition of diketene by water eliminated during the course of the reaction. Thus, about half of the total amount of diketene is lost as acetone and CO_2 due to the decomposition of the unstable hydrolysis product, namely, acetoacetic acid. The yield of the desired thiolate **3** can be increased to 80% by carrying out the reaction of diketene and thioamide **2** in 2:1 mol ratio. The formation of thiolate **3** may be explained by the mechanism shown in Scheme 1. In the first step of the cascade reaction, the attack of the diketene molecule apparently occurs highly selectively at the methylene group carbon atom as in previous cases [1, 8-14] to give exclusively the product of C-acetoacetylation **4**. Adduct **4** immediately cyclizes to give intermediate **5**, which, in turn, loses a water molecule and converts to the final thiolate **3**. We should stress that thiolate **3** is the only isolated reaction product. In light of the high yield of this reaction, it may be considered highly regioselective.

Since it possesses both electrophilic and nucleophilic fragments, thiolate **3** holds high promise for use in various transformations. In this regard, we studied the properties of **3** (Scheme 2). Firstly, the acidification of thiolate **3** with dilute hydrochloric acid gave 2-mercapto-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (**6**) in virtually quantitative yield. Treatment of thiolate **3** with alkyl halides **7** under mild conditions provided products of the regioselective S-alkylation, namely, sulfides **8** (method A). Also, sulfides **8** are formed with somewhat higher yields starting from mercaptopyridine and halides **7** in the presence of aqueous KOH (method B). The action of a strong base (KOH) on **8f, 8g** gave a Thorpe-Ziegler cyclization and formation of thieno[2,3-*b*]pyridine derivatives **9a**,**b** in good yields. We should note that 2-{[2-(4-bromophenyl)-2-oxoethyl]thio}-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (**8g**) is spontaneously and completely converted in the molten state into isomeric thienopyridine **9b** in the absence of solvent or any catalyst. To our knowledge, this is the first example of such a noncatalyzed synthesis of thienopyridines under Thorpe-Ziegler reaction conditions [21]. A Hansch reaction-type cyclocondensation occurs during the reaction of

2-(allylthio)-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (**8b**) with molecular iodine to give thiazolo[3,2-*a*]pyridine derivative **10**. Then, mild oxidation of thiolate **3** by iodine yields bis(3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridyl) disulfide (**11**) in 93% yield. In previous work [20, 22], we were the first to report the unusual cascade reaction of partially hydrogenated 3-cyano-2-pyridinethiolates with malononitrile dimer (2-amino-1,1,2-tricyanopropene (**12**)) leading to derivatives of 5H-pyrido[2',3':4,5]thiopyrano-[2,3-*b*]pyridine, whose structures were determined by X-ray diffraction structural analysis. We have discovered that thiolate **3** reacts similarly under analogous conditions with dimer **12** to give tricyclic product **13** in 41% yield.

All the products were characterized by ^{1}H NMR and IR spectroscopy as well as elemental analysis (Table 1). These results indicate that all the products obtained exist exclusively in the 4(1H)-pyridone tautomeric form and not in the 4-hydroxypyridine form both in the solid state and in solution in DMSO-d_6.

Scheme 2



i HCl, EtOH–H_2O; *ii* EtOH–H_2O, Δ; *iii* RCH_2Hal (**7a-g**), 10% KOH, EtOH;
iv 10% KOH, EtOH, Δ, or melting (for **8g**); *v* I_2, EtOH–dioxane, Δ;
vi I_2, EtOH–H_2O, Δ; *vii* EtOH, boiling;
7,8 a R = H, Hal = I; **b** R = CH=CH_2, Hal = Br; **c** R = COOEt, Hal = Cl; **d** R = COOPr-*i*, Hal = Cl; **e** R = 3,4-$Me_2C_6H_3NHC(O)$, Hal = Cl; **f** R = 4-$MeC_6H_4NHC(O)$, Hal = Cl; **g** R = 4-$BrC_6H_4C(O)$, Hal = Br; **9 a** R = 4-$MeC_6H_4NHC(O)$, **b** R= 4-$BrC_6H_4C(O)$

TABLE 1. Elemental Analysis Data of Products Obtained

Compound	Empirical formula	*M*	Found, % / Calculated, %			mp, °C	Yield, % (Method)
			C	H	N		
3	$C_7H_6N_2OS$	267.40	57.39 / 58.39	8.00 / 7.92	15.55 / 15.71	204-206 (dec.)	80
6	$C_7H_6N_2OS$	166.20	49.89 / 50.59	3.70 / 3.64	16.66 / 16.85		94
8a	$C_8H_8N_2OS$	180.23	52.65 / 53.31	4.51 / 4.47	15.39 / 15.54	236-238 (EtOH)	40 (A) 55.5 (B)
8b	$C_{10}H_{10}N_2OS$	206.27	57.50 / 58.23	4.95 / 4.89	13.39 / 13.58	170-171	45 (A) 58 (B)
8c	$C_{11}H_{12}N_2O_3S$	252.29	51.51 / 52.37	4.86 / 4.79	10.93 / 11.10	160-161	59 (B)
8d	$C_{12}H_{14}N_2O_3S$	266.32	53.22 / 54.12	5.39 / 5.30	10.42 / 10.52	171-173	64 (B)
8e	$C_{17}H_{17}N_3O_2S$	327.41	62.88 / 62.37	5.28 / 5.23	12.70 / 12.83	230-232	56 (A) 62 (B)
8f	$C_{16}H_{15}N_3O_2S$	313.38	62.00 / 61.32	4.87 / 4.82	13.40 / 13.41	227-230 (dec.)	73 (B)
8g	$C_{15}H_{11}BrN_2O_2S$	363.24	49.94 / 49.60	3.10 / 3.05	7.60 / 7.71	206-208	76 (B)
9a	$C_{16}H_{15}N_3O_2S$	313.38	61.86 / 61.32	4.79 / 4.82	13.37 / 13.41	292-294 (dec.)	70
9b	$C_{15}H_{11}BrN_2O_2S$	363.24	49.78 / 49.60	3.07 / 3.05	7.66 / 7.71		69
10	$C_{10}H_9IN_2OS$	332.16	36.64 / 36.16	2.73 / 2.73	8.48 / 8.43	204-206 (dec.)	74.5
11	$C_{14}H_{10}N_4O_2S_2$	330.39	51.09 / 50.90	3.10 / 3.05	16.80 / 16.96		93
13	$C_{13}H_{10}N_6OS$	298.33	51.67 / 52.34	3.41 / 3.38	27.75 / 28.17	>350	41

Thus, the ^{1}H NMR spectra of **3, 6, 8, 9,** and **11** shows signals for the NH proton as very broad, partially exchanging singlets at δ 12.90-11.12 ppm. Furthermore, the signals for C(5)H appear as narrow singlets at δ 6.58-5.53 ppm, indicating the nonaromatic nature of these protons. The IR spectra of the products show bands at 3240-3180 (NH) and 1640-1620 cm^{-1} (pyridone C=O). The structure of thiazolo[3,2-*a*]pyridine **10** was supported by comparative analysis of the spectrum with the corresponding data (in particular the δ C(2)H and C(3)H values in the ^{1}H NMR spectra) for related compounds [23]. The ^{1}H NMR spectrum of **10** at 200 MHz lacks a signal for the NH group and shows a doublet at δ 3.55 (^3J = 6.7 Hz) and a broad doublet at δ 3.68 ppm (^2J = 11.8 Hz) assigned to the CH_2I and *cis*-C(2)H protons, respectively. The signal for the *trans*-C(2)H proton appears as a doublet of doublets at δ 3.93 ppm (^3J = 6.9, ^3J = 11.8 Hz). Finally, the multiplet at δ 5.38 ppm should be assigned to the C(3)H proton. The ^{1}H NMR spectrum of dipyridothiopyran **13** is in good accord with the spectra of other similar compounds [22]. Thus, the spectrum of **13** shows two broad singlets at δ 11.34 and 10.17 ppm, which should be assigned to the C(5)NH proton and one of the two protons of the C(4)NH_2 amino group, which participated in intramolecular hydrogen bonding [22]. As a consequence, its signal is shifted downfield, while the signal of the other proton of the C(4)NH_2 amino group appears at δ 7.56 Hz and partially overlaps with the broad singlet of the C(2)NH_2 amino group protons. Furthermore, the ^{1}H NMR spectrum of dipyridothiopyran **13** shows two singlets at δ 6.47 (C(9)H) and δ 2.32 ppm (CH_3).

In order unequivocally to establish the direction of the acetoacetylation reaction and confirm the structure of the products of the chemical transformations, the structure of isopropyl (3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thioacetate (**8d**) was studied by X-ray diffraction structural analysis. Two symmetrically independent molecules **A** and **B** exist in the crystal of **8d** with extremely similar

geometry (Fig. 1). The six-membered ring N(1)C(1-5) is planar (the deviations of the atoms from the mean-square plane in both molecules does not exceed 0.010 Å). The C(5)S(1)C(8) group is almost orthogonal to this ring and the corresponding dihedral angle is 77.4° in molecule **A** and 75.1° in molecule **B**. The bond lengths and angles in both independent molecules of **8d** are ordinary and fall within the reported values [24]. Molecules **A** and **B** in the crystal of **8d** are linked by rather strong intermolecular hydrogen bonds into infinite chains: N(1**A**)-H···O(1**B**) (N···O, 2.707(3); N–H, 0.90(3); O···H, 1.82(3) Å, NHO, 167(2)°) and N(1**B**)-H···O(1**A**) (N···O, 2.701(3); N–H, 0.90(3); O···H, 1.81(3) Å, NHO, 174(2)°) (Fig. 2). The corresponding crystallographic data and the details of the structure are given in the Experimental.

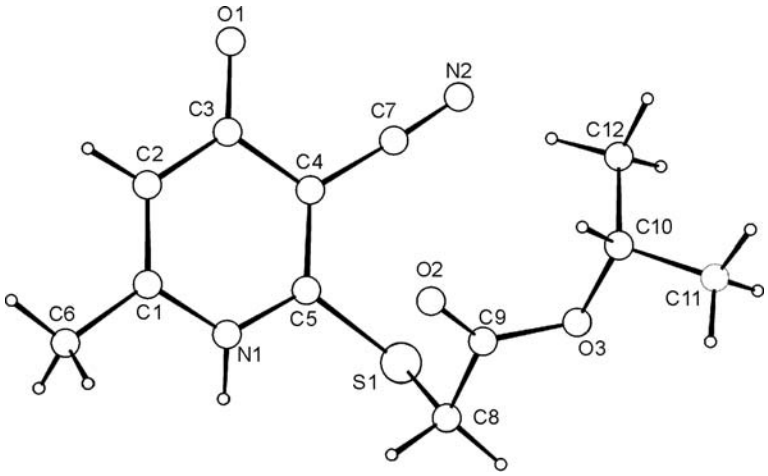


Fig. 1. General view of molecule of **8d**. The major bond lengths and valence angles given as the average of the two independent molecules **A** and **B**: S(1)–C(5), 1.766(2); S(1)–C(8), 1.814(3); N(1)–C(1), 1.368(3); N(1)–C(5), 1.350(3); N(2)–C(7), 1.142(3) Å; C(5)S(1)C(8), 100.7(1), C(1)N(1)C(5), 122.1(2)°.

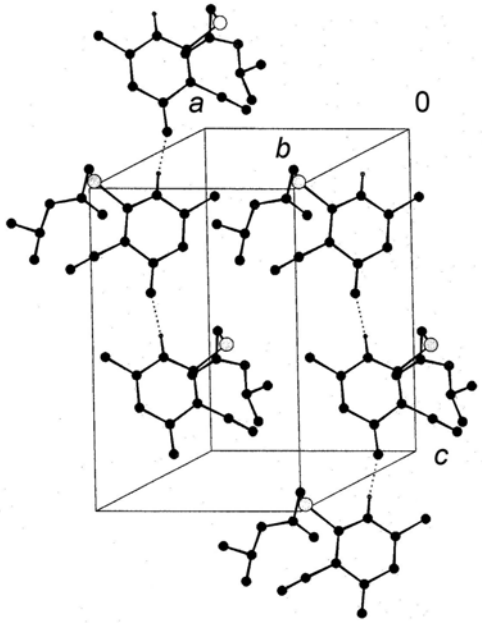


Fig. 2. Crystal packing of **8d** (the intermolecular N-H···O hydrogen bonds are indicated by the dotted lines).

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian Gemini 200 spectrometer at 200 MHz in DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on an IKS-29 spectrophotometer in vaseline mull. The elemental analyses were carried out on a Perkin–Elmer C,H,N-Analyzer. The reaction course and purity of the products were checked by thin-layer chromatography on Silufol UV-254 plates using 1:1 acetone-heptane as the eluent. The plates were developed with iodine vapor a UV detector. The melting points were taken on a Koefler block and not corrected. Dioxane and triethylamine were dried over sodium.

A commercially sample of diketene supplied by Fluka was used. Samples of cyanothioacetamide [26] and 2-amino1,1,3-tricyanopropene (**12**) [27] were prepared according to reported procedures.

X-Ray Diffraction Study of a spherical monocrystal of **8d** (d = 0.48 Å) grown from solution in 2-propanol was carried out at room temperature on an Enraf-Nonius CAD-4 automatic four-circle diffractometer using CuK_α radiation, λ = 1.54178 Å, scanning rate ratio $2\theta/\omega$= 1.2, θ_{max} = 68°, sphere segment $0 \le h \le 11$, $-14 \le k \le 14$, $-16 \le l \le 16$. A total of 4349 reflections were recorded, from which 4220 were symmetrically independent (R_{int} = 0.015). The unit cell data for triclinic crystals of **8d** are: a = 8.571(5), b = 12.028(7), c =13.371(11) Å, α = 87.86(7), β = 89.67(7)°, γ = 76.55(7)°, V = 1340(2) Å^3, M = 266.3, Z = 4 (two independent molecules), d_{calc} = 1.32g/cm^3, μ = 21.36 cm^{-1}, $F(000)$ = 562.8, space group $P\bar{1}$ (N 2). The structure was solved by the direct method and refined by the method of least squares in the full-matrix anisotropic approximation using the CRYSTALS program package [28]. A total of 3507 reflections were used in the refinement with $I > 3\sigma(I)$ (333 refinable parameters, the number of reflections per parameter was 10.5). All the hydrogen atoms were revealed in the electron density difference map and refined with fixed positional and temperature parameters (only H(1) and H(3) involved in hydrogen bonding were refined isotropically). The Chebyshev weighting system [29] with three parameters: 3.55, 2.15, and 2.55 was used in the refinement. The final R = 0.041 and R_w = 0.051, GOF = 1.040. The residual electron density from the Fourier difference map was 0.23 and -0.26 e/Å^3. Absorption in the crystal was considered using an azimuthal scanning procedure [30].

The complete set of X-ray diffraction data for **8d** has been deposited in the Cambridge Structural Data Bank (CCDC 615170).

Triethylammonium 3-Cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinethiolate (3). A solution of amide **2** (3.0 g, 30 mmol) in absolute dioxane (20 ml) was cooled to about 10°C and dry triethylamine (6.3 ml, 45 mmol) was added. Then, diketene (4.6 ml, 60 mmol) was added carefully dropwise with vigorous stirring and ice cooling. A thick red oil remained at the end of the exothermal reaction. The reaction mixture was heated at reflux with stirring until the reagents were completely converted, then stirred for an additional 8 h at ~20°C, and left overnight. The oily product solidified upon adding a nucleation crystal or further stirring to give a light-yellow fine-crystalline powder. Filtration and washing twice with acetone gave 6.4 g thiolate **3**. IR spectrum, ν, cm^{-1}: 3180 (N–H), 2207, 2265 (shoulder) (C≡N), 1625 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 11.12 (1H, s, NH, partially exchanged); 5.53 (1H, s, C(5)H); 3.10 (2H, q, J = 7.2, C$\underline{H}_2$CH$_3$); 2.07 (3H, s, C$\underline{H}_3$); 1.22 (3H, t, J = 7.2, CH$_2$C$\underline{H}_3$).

2-Mercapto-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (6). A stirred suspension of thiolate **3** (3.0 g, 11.2 mmol) in ethanol (20 ml) was treated with excess 10% hydrochloric acid (5 ml, 14.4 mmol). The mixture was stirred for 2 h, diluted with water (5 ml), and left in a refrigerator for 12 h. The precipitate formed was filtered off and washed with ethanol to give pyridine **6** (1.75 g) as a beige fine-crystalline powder, which decomposed at 250-260°C. This product was used without further purification. IR spectrum, ν, cm^{-1}: 3200 (N–H), 2227 (C≡N), 1635 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.90 (1H, br. s, NH, partially exchanged); 6.17 (1H, s, C(5)H); 2.27 (3H, s, CH$_3$). The signal for SH was not found, probably due to deuterium exchange.

Synthesis of 8a-g (General Method). A. A solution of the corresponding alkyl halide **7** (1.9 mmol) in ethanol (5 ml) was added to a solution of thiolate **3** (0.5 g, 1.87 mmol) in hot 70% aq. ethanol (15 ml). The mixture was heated to reflux, stirred for 8 h at ~20°C, and left stand for 72 h. The precipitate formed of the corresponding pyridine **8a-g** was filtered off and washed with ethanol.

B. A suspension of mercaptopyridine **6** (0.5 g, 3 mmol) in hot ethanol (15 ml) was treated with 10% aq. KOH (1.6 ml, 3 mmol). The potassium salt solution formed was passed through a paper filter into a solution of the corresponding halide **7** in ethanol (5 ml). The mixture was heated to reflux and then treated as in Procedure A.

6-Methyl-2-methylthio-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (8a). Yield 0.22 g (Method A) and 0.30 g (Method B). IR spectrum, ν, cm^{-1}: 3210 (N–H), 2218 (C≡N), 1635 (C=O). ^{1}H NMR spectrum, δ, ppm: 12.07 (1H, br. s, NH); 6.51 (1H, s, C(5)H); 2.52 (3H, s, SC$\underline{H}_3$); 2.27 (3H, s, C$\underline{H}_3$).

2-Allylthio-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (8b). Yield 0.28 g (Method A) and 0.36 g (Method B). IR spectrum, ν, cm^{-1}: 3195 (N–H), 2223, 2258 (shoulder) (C≡N), 1628 (C=O). ^{1}H NMR spectrum, δ, ppm (*J,* Hz): 6.50 (1H, s, C(5)H); 5.87 (1H, m, C$\underline{H}$=C); 5.27 (1H, br. d, *J* = 17.2, *trans*-HC=C$\underline{H}_2$); 5.08 (1H, br. d, *J* = 10.2, *cis*-HC=C$\underline{H}_2$); 3.86 (2H, d, *J* = 7.0, SC$\underline{H}_2$); 2.38 (3H, s, C$\underline{H}_3$). The signal for NH was not seen, probably due to deuterium exchange.

Ethyl (3-Cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thioacetate (8c). Yield 0.45 g (Method B). IR spectrum, ν, cm^{-1}: 3200 (N–H), 2218 (C≡N), 1725 (C=O_{ester}), 1633 (C=$O_{pyridone}$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.58 (1H, s, C(5)H); 4.11 (2H, q, *J* = 7.2, C$\underline{H}_2$CH$_3$); 3.97 (2H, s, SC$\underline{H}_2$); 2.34 (3H, s, C$\underline{H}_3$); 1.21 (3H, t, *J* = 7.2, CH$_2$C$\underline{H}_3$). The signal for NH was not seen, probably due to deuterium exchange.

Isopropyl (3-Cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thioacetate (8d). Yield 0.69 g (Method B). IR spectrum, ν, cm^{-1}: 3195 (N–H), 2223, 2258 (shoulder) (C≡N), 1723 (C=O_{ester}), 1635 (C=$O_{pyridone}$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.20 (1H, br. s, NH); 6.56 (1H, s, C(5)H); 4.94 (1H, m, C$\underline{H}$(CH$_3$)$_2$); 3.92 (2H, s, SC$\underline{H}_2$); 2.37 (3H, s, C$\underline{H}_3$); 1.23 (6H, d, *J* = 6.2, CH(C$\underline{H}_3$)$_2$).

N-(3,4-Dimethylphenyl)-2-[(3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thio]acetamide (8e). Yield 0.55 g (Method A) or 0.61 g (Method B). IR spectrum, ν, cm^{-1}: 3510, 3390, 3210 (2N–H), 2225 (C≡N), 1665 (C=$O_{carbamoyl}$), 1630 (C=$O_{pyridone}$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.03 (1H, br. s, $NH_{pyridine}$); 9.86 (1H, br. s (C(O)N$\underline{H}$); 7.30 (1H, s, C(2)H_{aryl}); 7.23 (1H, d, *J* = 7.9, C(6)H_{aryl}); 6.96 (1H, d, *J* = 7.9, C(5)H_{aryl}); 6.52 (1H, s, C(5)$H_{pyridine}$); 4.00 (2H, s, SC$\underline{H}_2$); 2.40 (3H, s, C(6)C$\underline{H}_{3\ pyridine}$); 2.22 and 2.19 (3H each, both s, C(3)C$\underline{H}_{3\ aryl}$ and C(4)C$\underline{H}_{3\ aryl}$).

N-(4-Methylphenyl)-2-[3-cyano-6-methyl-4-oxo-1,4-dihydro-2-pyridinyl)thio]acetamide (8f). Yield 0.69 g (Method B). IR spectrum, ν, cm^{-1}: 3460, 3330, 3240 (2N–H), 2213 (C≡N), 1650 (C=$O_{carbamoyl}$), 1626 (C=$O_{pyridone}$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.05 (1H, br. s, $NH_{pyridine}$); 9.96 (1H, br. s, C(O)N$\underline{H}$); 7.40 (2H, d, *J* = 8.2, C(2)H_{aryl} and C(6)H_{aryl}); 7.01 (2H, d, *J* = 8.2, C(3)H_{aryl}) and C(5)H_{aryl}); 6.51 (1H, s, C(5)$H_{pyridine}$); 4.00 (2H, s, SC$\underline{H}_2$); 2.37 (3H, s, C(6)C$\underline{H}_{3\ pyridine}$); 2.27 (3H, s, C(4)C$\underline{H}_{3\ aryl}$).

2-{[2-(4-Bromophenyl)-2-oxoethyl]thio}-6-methyl-4-oxo-1,4-dihydro-3-pyridinecarbonitrile (8g). Yield 0.83 g (Procedure B); mp 206-208°C (converts to **9b**). IR spectrum, ν, cm^{-1}: 3240 (N–H), 2215 (C≡N), 1675 C=$O_{phenacyl}$), 1640 (C=$O_{pyridone}$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.99 (1H, br. s, NH, partially exchanged); 7.92 (2H, d, *J* = 8.6, C(2)H_{aryl} and C(6)H_{aryl}); 7.62 (2H, d, *J* = 8.6, C(3)H_{aryl} and C(5)H_{aryl}); 6.45 (1H, s, C(5)$H_{pyridine}$); 4.60 (2H, s, SC$\underline{H}_2$); 2.12 (3H, s, C$\underline{H}_3$).

Thorpe-Ziegler Cyclization of 8 Promoted by KOH (General Method). A two-fold excess of 10% aq. KOH (3.1 ml, 6 mmol) was added to a stirred suspension of corresponding pyridine **8f** or **8g** (3 mmol). The mixture was heated at reflux for 5 min, cooled, stirred for 2 h at ~20°C, and then acidified by adding acetic acid. The precipitate formed was filtered off and washed twice with ethanol to give thieno[2,3-*b*]pyridines **9a,b**.

3-Amino-6-methyl-2-N-(4-methylphenyl)carbamoyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine (9a). **Y**ield 0.66 g. IR spectrum, ν, cm^{-1}: 3450, 3375, 3330, 3190 (NH_2, 2N–H), 1650 ($C=O_{carbamoyl}$), 1620 ($C=O_{pyridone}$). ^1H NMR spectrum, δ, ppm (*J*, Hz): 12.10 (1H, br. s, $NH_{pyridine}$, partially exchanged); 8.83 (1H, s, C(O)N<u>H</u>); 7.50 (4H, m, superposition of signals of NH_2, $C(2)H_{aryl}$ and $C(6)H_{aryl}$); 7.02 (2H, d, $J = 8.1$, $C(3)H_{aryl}$ and $C(5)H_{aryl}$); 5.93 (1H, s, $C(5)H_{pyridine}$); 2.32 and 2.28 (each 3H, both s, $C(4)C\underline{H}_{3\ aryl}$ and $C(6)C\underline{H}_3$).

3-Amino-2-(4-bromobenzoyl)-6-methyl-4-oxo-4,7-dihydrothieno[2,3-*b*]pyridine (9b). Yield 0.75 g; mp 330-332°C (dec., acetic acid). IR spectrum, ν, cm^{-1}: 3440, 3325 (NH_2), 3230 (N–H), 1650 ($C=O_{benzoyl}$), 1625 ($C=O_{pyridone}$). ^1H NMR spectrum, δ, ppm: 12.39 (1H, br. s, NH); 8.32 (2H, br. s, NH_2); 7.62 (4H, m, 4-BrC_6H_4); 5.86 (1H, s, C(5)H); 2.30 (3H, s, CH_3).

Noncatalyzed Thermal Isomerization of Pyridine 6g to Thieno[2,3-*b*]pyridine 9b. A sample of **8g** (0.3 g, 0.83 mmol) was heated rapidly in an open vessel to the melting point (~210°C). The melt was converted within a few seconds into a solid mass of thieno[2,3-*b*]pyridine **9b** (0.3 g), mp 320-330°C (dec.), in quantitative yield. Recrystallization from acetic acid gave 0.24 g (80%) **9b** as fine yellow crystals, mp 330-332°C (dec.). The analytical data agree with the data for a sample obtained in the cyclization promoted by KOH.

3-(Iodomethyl)-5-methyl-7-oxo-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carbonitrile (10). Crystalline iodine **(**0.5 g, 1.97 mmol) was added in a single batch to a hot solution of pyridine **8b** (0.4 g, 1.94 mmol) in 2:1 ethanol-dioxane (15 ml). The mixture was heated at reflux for 5 min and then stirred for 24 h at ~20°C. The precipitate formed was filtered off and recrystallized from 1:1 AcOH-DMF to give 0.48 g **10**, (dec.) IR spectrum, ν, cm^{-1}: 2224 (C≡N), 1630 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.09 (1H, s, C(6)H); 5.38 (1H, m, C(3)H); 3.93 (1H, dd, $^3J = 6.9$, $^2J = 11.8$, *trans*-C(2)H); 3.68 (1H, br. d, $^2J = 11.8$, *cis*-C(2)H); 3.55 (2H, d, $^3J = 6.7$, $C\underline{H}_2I$); 2.43 (3H, s, CH_3).

Bis(3-cyano-6-methyl-4-oxo--1,4-dihydro-2-pyridinyl) Disulfide (11). A solution of thiolate **3** (0.4 g, 1.5 mmol) in hot aqueous ethanol (20 ml) was treated with a hot solution of iodine (0.19 g, 0.75 mmol) in ethanol (15 ml). The mixture was heated at reflux with vigorous stirring for 5 min and cooled. The precipitate was filtered off and washed with ethanol to give 0.23 g disulfide **11** (dec. >250°C). IR spectrum, ν, cm^{-1}: 3200 (2N–H), 2223 (2 C≡N), 1638 (2 C=O). ^1H NMR spectrum, δ, ppm: 12.50 (2H, br. s, 2NH, partially exchanged); 6.56 (2H, s, 2C(5)H); 2.35 (6H, s, $2CH_3$).

2,4-Diamino-5-imino-8-methyl-10-oxo-7,10-dihydro-5H-pyrido[2',3':4,5]thiopyrano-[2,3-*b*]pyridine-3-carbonitrile (13). 2-Amino-1,1,3-tricyanopropene (**12**) (0.48 g, 3.6 mmol) and five drops of Et_3N were added to a suspension of thiolate **3** (0.5 g, 1.8 mmol) in ethanols (20 ml). The mixture was heated at reflux for 10 h and cooled. The precipitate was filtered off and recrystallized from 1:1 AcOH-DMF to give 0.23 g **13** as light-brown crystals. IR spectrum, ν, cm^{-1}: 3555, 3420, 3350-3190 ($2NH_2$, 2N–H), 2203 (C≡N), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 11.34 (1H, br. s, $C(4)N\underline{H}_2$ or C(5)N<u>H</u>); 10.17 (1H, s, C(5)N<u>H</u> or $C(4)N\underline{H}_2$); 7.56 (3H, m, superposition of signals for $C(4)N\underline{H}_2$ (1H) and $C(2)N\underline{H}_2$ (2H)); 6.47 (1H,s, C(9)H), 2.32 (3H, s, $C\underline{H}_3$). The proton for endocyclic NH was not seen, probably due to deuterium exchange.

This work was carried out with the financial support of the Russian Basic Research Fund (RFFI) (Project 05-03-32031).

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