One-pot synthesis of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones and their transformation to substituted thieno[2,3-*b*;4,5-*b*]dipyridines and pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidines

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4,6-Diaryl-3-cyanopyridine-2(1*H*)-thiones were synthesized in one step by the reaction of elemental sulfur, malononitrile, and 2-aryl-1-aroylethylenes in the presence of excess triethylamine. The products were used in one-pot syntheses of substituted thieno[2,3-*b*;4,5-*b*]dipyridines and pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidines.

Key words: malononitrile, α,β-unsaturated ketones, elemental sulfur, pyridine-2(1*H*)-thiones, thienodipyridines, pyridothienopyrimidines.

4,6-Diaryl-3-cyanopyridine-2(1*H*)-thiones are used for the synthesis of antioxidants, biocides, dyes, and other practically valuable substances.[1—3] In most cases, pyridinethiones are prepared by condensation of cyanothioacetamide with α,β-unsaturated ketones, 1,3-diketones, and 1,3-ketoenamines; by the reaction of elemental sulfur with 1,4-ketonitriles; or by replacement of the halogen atom in 2-halopyridines by sulfur.[1,4—6] The main drawback of these methods is the fact that they require preliminary synthesis of rather complex starting compounds. Moreover, the reactions are not always regioselective and often give target products in relatively low yields.

This study is devoted to the development of an improved one-pot method for the synthesis of 4,6-diaryl-3-cyanopyridine-2(1*H*)-thiones starting from simple and readily available chemicals, namely, elemental sulfur, malononitrile, and α,β-unsaturated ketones. The resulting pyridine-2(1*H*)-thiones served as the starting compounds in one-pot methods for the synthesis of annelated heterocycles, namely, thienodipyridines and pyridothienopyrimidines, difficult to obtain by other methods.

The strategy used to prepare pyridine-2(1*H*)-thiones is as follows: first, finely ground sulfur is refluxed in ethanol in the presence of a slight excess of triethylamine to cleave the S_8 ring giving betaine **1**; then a mixture of α,β-unsaturated ketone **2a—n** and malononitrile (**3**) is added to the hot solution (Scheme 1). Apparently, under the action of excess base, ketonitrile **4** is formed, which is then thiolated at the C(2)—H bond to afford intermediate **5**. The subsequent transformation of intermediate **5** can follow two pathways. The first pathway includes elimination of hydrogen sulfide, which then adds to a nitrile group of unsaturated nitrile **6** to yield unsaturated thioamide **7**, whose intramolecular condensation leads to pyridine-2(1*H*)-thiones **8a—n**. The other reaction pathway does not include elimination of hydrogen sulfide but goes through thiirene ring **9** and also gives rise to compounds **8a—n**.

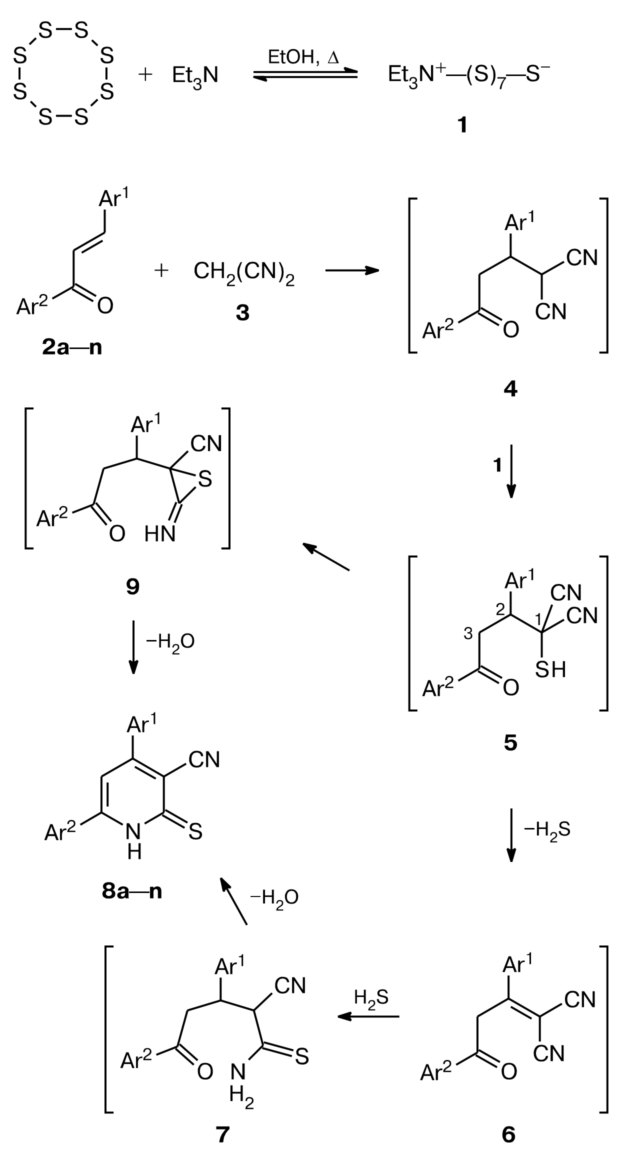
This reaction scheme is confirmed to a certain extent by earlier experimental data. Cyclic sulfur is known to react with organic bases to give betaines **1**.[7] The high probability of the formation of ketonitriles **4** in the reaction medium is confirmed by the fact that these compounds and elemental sulfur have already been used to synthesize pyridine-2(1*H*)-thiones.[4,6] Thiolation of the C—H bond giving intermediate **5** is also probable, as 3-cyano-4,6-diphenylpyridine-2(1*H*)-thione has previously been prepared by the reaction of 1-bromo-1,1-dicyano-2,4-diphenylbutan-4-one with sodium hydrogen sulfide.

The structure of pyridine-2(1*H*)-thiones **8a—n** obtained in this way was confirmed by instrumental methods and by comparing their IR spectra and melting points with those of known pyridine-2(1*H*)-thiones (Table 1, Experimental).

Substituted pyridine-2(1*H*)-thiones **8b**,**l**,**m** were used in one-pot syntheses of thienobipyridines **10a—c**. The products were obtained in 46—73% yields by refluxing the corresponding pyridine-2(1*H*)-thiones **8** with ethyl 4-chloroacetoacetate (**11**) in ethanol in the presence of excess sodium ethoxide (in 1 : 2.5 ratio). Compounds **10** are produced (after acidification of the reaction mixture) in a domino reaction or cascade heterocyclization according to a previously reported pattern.[8]

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 2087—2090, October, 2003.

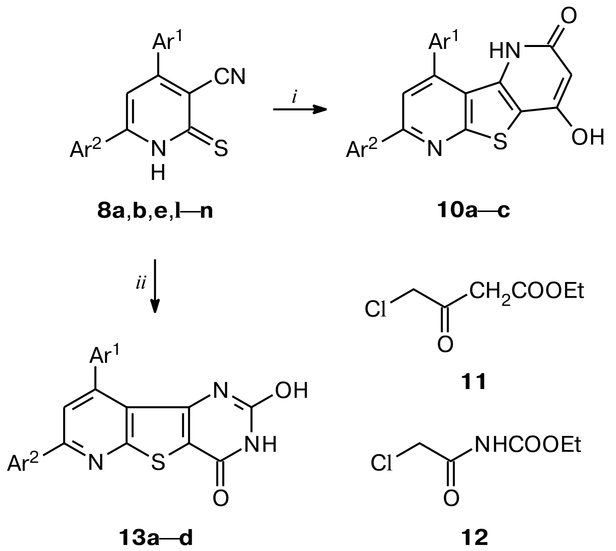
Scheme 1



8	Ar^1	Ar^2
a	4-MeOC$_6$H$_4$	Ph
b	4-F-C$_6$H$_4$	Ph
c	2-Thienyl	4-FC$_6$H$_4$
d	2-Thienyl	4-MeOC$_6$H$_4$
e	4-MeOC$_6$H$_4$	2-Thienyl
f	3,4-(MeO)$_2$C$_6$H$_3$	2-Thienyl
g	3-Thienyl	2-Thienyl
h	Ph	2-Furyl
i	4-FC$_6$H$_4$	2-Thienyl
j	Ph	4-MeOC$_6$H$_4$
k	4-ClC$_6$H$_4$	2-Thienyl
l	4-ClC$_6$H$_4$	Ph
m	2-MeOC$_6$H$_4$	Ph
n	Ph	Ph

By using *N*-(ethoxycarbonyl)chloroacetamide (chloroacetourethane) (**12**) in the reaction with pyridinethiones **8**, we developed a new one-pot synthetic route to pyridothienopyrimidines (**13**). Heating of pyridinethiones **8a**,**b**,**e**,**n** with urethane **12** in a ethanol—dimethylformamide (1 : 1) mixture in the presence of excess sodium ethoxide gave compounds **13a—d** in one step (Scheme 2).

Scheme 2



i. 1) **11**, 2.5 *M* EtONa, EtOH, Δ; 2) HCl.
ii. 1) **12**, 2.5 *M* EtONa, EtOH/DMF, Δ; 2) HCl.

Compound	10		13	
	Ar^1	Ar^2	Ar^1	Ar^2
a	4-ClC$_6$H$_4$	Ph	Ph	Ph
b	4-FC$_6$H$_4$	Ph	4-FC$_6$H$_4$	Ph
c	2-MeOC$_6$H$_4$	Ph	4-MeOC$_6$H$_4$	Ph
d	—	—	4-MeOC$_6$H$_4$	2-Thienyl

These products are apparently formed *via* a sequence of nucleophilic substitution (S_N2) and the Thorpe—Ziegler and Guareschi—Thorpe reactions, similar to the sequence involved in the previously studied reactions between vicinal mercaptonitriles and ethyl 4-chloroacetoacetate or *N*-cyanochloroacetamidine.[8,9]

The structures of compounds **10** and **13** were confirmed by the data of elemental analysis and IR and NMR spectroscopy (Table 2). The absorption bands in the IR spectra and the chemical shifts in the ^{1}H NMR spectra of thienodipyridines **10** were assigned by analogy with known data.[8] It is noteworthy that the IR spectra of compounds **13c**,**d** exhibit a narrow absorption band at 3580 cm^{-1}, typical of compounds containing an OH group.[10]

Experimental

IR spectra were recorded on a Specord M-82 instrument in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument (250 and 63 MHz, respectively)

Table 1. 3-Cyanopyridine-2(1*H*)-thiones **8**

Compound	Yield (%)	M.p. /°C	Molecular formula	Found/Calculated (%)			IR, ν/cm^{-1}		^{1}H NMR, δ			
				C	H	N	CS	CN	Ar^1	Ar^2	C(5)H	NH (s, 1 H)
8c	93	202—203	$C_{16}H_9FN_2S_2$	61.29 61.54	2.87 2.88	8.85 8.97	1205	2230	7.10 (t, 1 H, *J* = 3.9, *J* = 4.6); 7.93 (br.s, 1 H); 8.12 (d, 1 H, *J* = 4.6)	7.60 (m, 2 H); 7.74 (m, 2 H)	7.05	14.26
8d	89	214—216	$C_{17}H_{12}N_2OS_2$	62.71 62.96	3.67 3.70	8.58 8.64	1202	2224	7.08 (t, 1 H, *J* = 3.9, *J* = 4.6); 7.95 (d, 1 H, *J* = 3.9); 8.10 (d, 1 H, *J* = 4.6)	3.85 (s, 3 H, OMe); 7.44 (d, 2 H, *J* = 8.5); 7.68 (d, 2 H, *J* = 8.5)	7.04	14.18
8e	92	234—236	$C_{17}H_{12}N_2OS_2$	63.05 62.96	3.68 3.70	8.56 8.64	1205	2225	3.87 (s, 3 H, OMe); 7.40 (d, *J* = 8.5); 7.57 (d, *J* = 8.5)	7.02 (t, 1 H, *J* = 3.7, *J* = 4.8); 7.84 (d, 1 H, *J* = 3.7); 8.02 (d, 1 H, *J* = 4.8)	7.02	14.09
8f	84	238—240	$C_{18}H_{14}N_2O_2S_2$	60.83 61.02	3.94 3.95	7.52 7.61	1204	2226	3.72 (s, 3 H, 3-OMe); 3.83 (s, 3 H, 4-OMe); 7.12 (s, 1 H); 7.38 (d, *J* = 8.4); 7.52 (d, *J* = 8.4)	7.08 (t, 1 H, *J* = 3.9, *J* = 5.2); 7.82 (d, 1 H, *J* = 3.9); 8.04 (d, 1 H, *J* = 5.2)	7.06	14.04
8g	90	245—246	$C_{14}H_8N_2S_3$	55.66 56.00	2.65 2.67	9.26 9.33	1195	2220	7.03—8.14 (m, 6 H)		7.08*	14.30
8h	93	224—226	$C_{16}H_{10}N_2OS$	68.61 69.06	3.59 3.60	10.00 10.07	1204	2228	6.98—7.98 (m, 6 H)		7.06*	14.02
8i	82	203—205	$C_{16}H_9FN_2S_2$	62.01 61.52	2.87 2.90	8.86 8.97	1200	2217	7.48 (m, 2 H); 7.60 (m, 2 H)	7.22 (t, 1 H, *J* = 3.7, *J* = 4.9); 7.89 (d, 1 H, *J* = 3.7); 8.13 (d, 1 H, *J* = 4.9)	7.01	14.32
8k	94	220—222	$C_{16}H_9FN_2S_2$	58.92 58.44	2.71 2.76	8.64 8.52	1204	2213	7.42 (d, 2 H, *J* = 8.5); 7.50 (d, 2 H, *J* = 8.5)	7.18 (t, 1 H, *J* = 4.3, *J* = 4.8); 7.73 (d, 1 H, *J* = 4.3); 8.12 (d, 1 H, *J* = 4.8)	6.96	14.29

* The proton signals overlap.

Note. The physicochemical characteristics of compounds **8a**,**b**,**j**,**l**—**n** were reported previously.[5,6]

Table 2. 4-Hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*]dipyridin-2-ones **10** and pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidin-2,4-diols (**13**)

Compound	Yield (%)	Molecular formula	Found/Calculated (%)			IR, ν/cm^{-1} CONH, OH	^{1}H NMR, δ				
			C	H	N		Ar^1	Ar^2	C(8)H	C(3)H	NH (OH) (s, 1 H)
10a	54.32	$C_{22}H_{13}ClN_2O_2S$	65.04 65.26	3.15 3.24	6.70 6.92	1632, 3384, 3408, 3464	7.61 (d, 2 H, *J* = 8.1); 7.76 (d, 2 H, *J* = 8.1)	7.52 (m, 3 H); 8.25 (d, 2 H, *J* = 7.4)	7.90	6.10	11.66
10b	46.15	$C_{22}H_{13}FN_2O_2S$	67.87 68.03	3.21 3.37	7.08 7.21	1628, 3400, 3468	7.39 (t, 2 H, *J* = 8.8); 7.78 (m, 2 H)	7.53 (m, 3 H); 8.26 (d, 2 H, *J* = 6.6)	7.90	6.10	11.71

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	Molecular formula	Found/Calculated (%)			IR, ν/cm^{-1} CONH, OH	^{1}H NMR, δ				
			C	H	N		Ar^1	Ar^2	C(8)H	C(3)H	NH (OH) (s, 1 H)
10c	72.50	$C_{23}H_{16}N_2O_3S$	68.73 68.98	3.92 4.03	6.83 7.00	1632, 3388, 3408, 3468	2.50 (s, 1 H, Me); 7.21 (t, 1 H, *J* = 7.4); 7.31 (d, 1 H, *J* = 8.1); 7.55 (m, 1 H); 7.63 (t, 1 H, *J* = 7.4, *J* = 8.1)	7.51 (m, 3 H); 8.23 (d, 2 H, *J* = 5.9)	7.91	5.90	11.71
13a	62.10	$C_{21}H_{13}N_3O_2S$	68.12 67.91	3.68 3.53	11.54 11.31	1642, 1704 sh, 3408	7.44—7.80 (m, 6 H); 8.17—8.35 (m, 4 H)		8.01	—	11.64
13b	54.36	$C_{21}H_{12}FN_3O_2S$	64.95 64.77	3.36 3.11	10.92 10.79	1668, 1702 sh, 3408	7.35 (t, 2 H, *J* = 7.5, *J* = 8.5); 7.76 (t, 2 H, *J* = 7.2, *J* = 5.9)	7.54 (m, 3 H); 8.25 (d, 2 H, *J* = 6.6)	7.87	—	9.94 (br.s)
13c	85.41	$C_{22}H_{15}N_3O_3S$	65.64 65.82	3.54 3.77	10.24 10.47	1644, 1704 sh, 3404, 3580	3.87 (s, 3 H, MeO); 7.01 (d, 2 H, *J* = 8.1); 7.66* (d, 2 H, *J* = 8.1)	7.51 (m, 3 H); 8.21 (d, 2 H, *J* = 7.4)	7.68*	—	9.67 (br.s)
13d	81.48	$C_{20}H_{13}N_3O_3S_2$	58.67 58.95	3.17 3.22	10.02 10.31	1640, 1684 sh, 3400, 3580	3.86 (s, 3 H, Me); 7.01 (d, 2 H, *J* = 8.1); 7.62* (d, 2 H, *J* = 8.1)	7.18 (t, 1 H, *J* = 4.4); 7.68 (d, 1 H, *J* = 5.2); 7.94 (br.s, 1 H)	7.63*	—	9.49 (br.s)

* The proton signals overlap. The melting points of compounds **10** and **13** are higher than 300 °C.

in DMSO-d$_6$. Elemental analysis was carried out on a Perkin—Elmer C,H,N-analyzer.

4,6-Diaryl-3-cyanopyridine-2(1*H*)-thiones 8a—n (general procedure). A mixture of finely dispersed sulfur (3.5 g, 0.11 mol) and morpholine (8.7 g, 0.1 mol) in 100 mL of ethanol was refluxed for 20 min. Malononitrile (6.6 g, 0.1 mol) and α,β-unsaturated ketone **2** (0.1 mol) were added and the mixture was refluxed for 2 h. Then the mixture was cooled to ~20 °C, and 10% HCl was added to reach pH 5—6. The precipitate was filtered off and washed with water. The product was recrystallized from ethanol.

4-Hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*]dipyridin-2-ones 10a—c (general procedure). A mixture of the required pyridine-2(1*H*)-thione **8** (10 mmol), sodium ethoxide (25 mmol), and ethyl 4-chloroacetoacetate (10 mmol) in 50 mL of ethanol was refluxed for 0.5 h, cooled to 20 °C, and acidified with 2.5 mL of 10% HCl. The precipitate was filtered off and washed with water, ethanol, and hexane.

Pyrido[3´,2´:4,5]thieno[3,2-*d*]pyrimidine-2,4-diols (13a—d) (general procedure). The required pyridine-2(1*H*)-thione **8** (10 mmol), *N*-ethoxycarbonylchloroacetamide (10 mmol), and sodium ethoxide (25 mmol) were placed in a solvent mixture consisting of 25 mL of ethanol and 25 mL of DMF. The reaction mixture was refluxed for 2 h, cooled to 20 °C, and acidified with 2.5 mL of 10% HCl. The precipitate was filtered off and washed with water, ethanol, and hexane.

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Received March 6, 2003;
in revised form June 11, 2003