β-Ketoaldehydes in the synthesis of 6-alkyl-3-cyano-2(1*H*)-pyridinethiones

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An efficient synthesis of 6-alkyl-3-cyano-2(1*H*)-pyridinethiones by the reactions of the sodium salts of β-ketoaldehydes with cyanothioacetamide was developed. Pyridinethiones undergo selective *S*-alkylation with haloacetonitriles and haloacetophenones followed by cyclization to the corresponding thieno[2,3-*b*]pyridines.

Key words: 6-alkyl-3-cyano-2(1*H*)-pyridinethiones, cyanothioacetamide, cyclization, thieno[2,3-*b*]pyridines.

3-Cyano-2(1*H*)-pyridinethiones are of interest to chemists due to their great synthetic potential. One of the main methods for their synthesis relies on condensation of 1,3-diketones with cyanothioacetamide.[1,2] A significant limitation of this method is that it is applicable mainly to the preparation of 4,6-disubstituted derivatives. Condensation of cyanothioacetamide with sodium salts of β-ketoaldehydes or their enamines has previously been used[3,4,5] for synthesizing 6-substituted 3-cyano-2(1*H*)-pyridinethiones. Using this method, aryl-, hetaryl-, 1-adamantyl-, and cyclopropyl-2(1*H*)-pyridinethiones have been obtained in high yields. Of 6-alkyl-substituted pyridinethiones, only 6-methyl- and 6-propyl-3-cyano-2(1*H*)-pyridinethione have been synthesized.[5,6] The latter was isolated as an admixture formed as a result of opening of the cyclopropane ring.

In the present work, 6-alkyl-3-cyano-2(1*H*)-pyridinethiones (**1a—h**) were synthesized by the condensation of the sodium salts of 3-alkyl-1-hydroxy-1-propen-3-ones (**2a—h**) with cyanothioacetamide in the presence of AcOH under mild conditions (Scheme 1). Sodium salts of **2a—h** were obtained by the reaction of the corresponding ketones (**3a—h**) with ethyl formate in the presence of Na in ether according to the known procedure.[7] It should be noted that in all cases the reactions proceeded rather regioselectively to give 6-substituted pyridinethiones **1b—h**. Ketone **3a** was the only exception; in this case a mixture of products **1a** and **4** in the ratio of 2 : 1 (according to ^{1}H NMR spectral data) was formed. The products were separated by frac-

Scheme 1

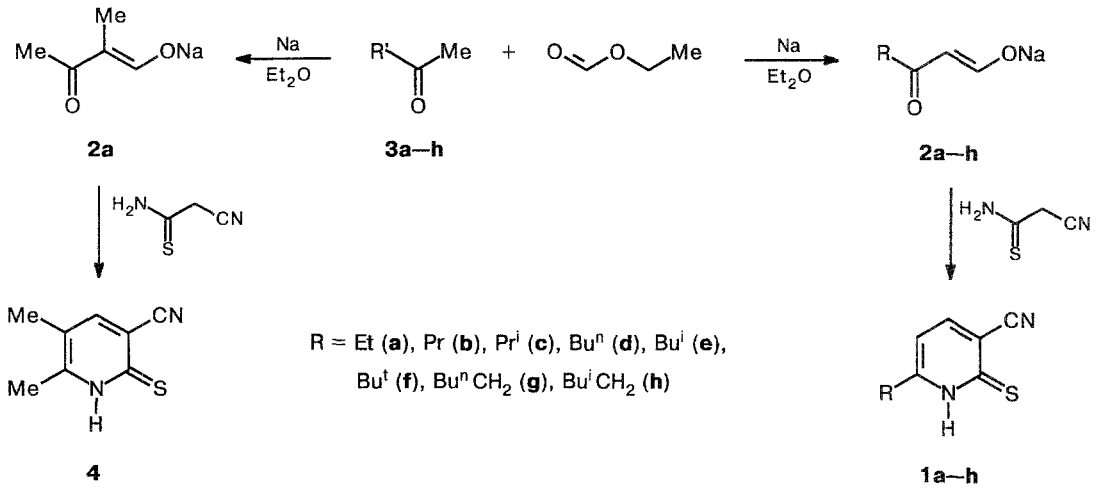

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Table 1. Characteristics of compounds **1a—h** and **4**

Compound	Mol. wt.	Yield (%)	M.p./°C (Solvent)	Found (%) / Calculated				Molecular formula
				C	H	N	S	
1a	164	74*	203—205 (AcOH)	58.62 58.59	4.81 4.92	16.95 17.08	19.40 19.55	$C_8H_8N_2S$
4	164		266—270 (AcOH)	58.60 58.59	4.78 4.92	16.96 17.08	19.63 19.55	$C_8H_8N_2S$
1b	178	96	164—165 (50 % EtOH)	65.88 65.91	6.21 6.15	15.57 15.73	17.92 18.01	$C_9H_{10}N_2S$
1c	178	40	210—212 (EtOH)	65.79 65.91	5.97 6.15	15.77 15.73	17.87 18.01	$C_9H_{10}N_2S$
1d	192	70	130—135 (AcOEt—heptane)	73.01 73.23	7.49 7.38	14.57 14.69	16.53 16.70	$C_{10}H_{12}N_2S$
1e	192	73	150—151 (50 % EtOH)	73.19 73.23	7.28 7.38	14.43 14.59	16.72 16.70	$C_{10}H_{12}N_2S$
1f	192	8	208—210 (EtOH)	73.07 73.23	7.30 7.38	14.63 14.59	16.64 16.70	$C_{10}H_{12}N_2S$
1g	206	90	106—108 (50 % EtOH)	80.67 80.55	8.42 8.60	13.42 13.60	15.37 15.56	$C_{11}H_{14}N_2S$
1h	206	60	126—128 (50 % EtOH)	80.41 80.55	8.59 8.60	13.65 13.60	15.49 15.56	$C_{11}H_{14}N_2S$

* The yield is for a mixture of **1a** and **4** in the ratio of 2 : 1.

Table 2. Spectral characteristics of 6-alkyl-3-cyano-2(1*H*)-pyridinethiones **1a—h** and **4**

Compound	IR, ν(CN)/cm^{-1}	MS, *m/z* (*I*(%))	^{1}H NMR (δ, *J*/Hz)*
1a	2220		1.15 (t, 3 H, MeCH$_2$); 2.65 (q, 2 H, CH$_2$Me); 6.7 (d, 1 H, H(5)); 7.93 (d, 1 H, H(4)); 14.05 (br.s, 1 H, NH)
4	2224		2.05 (s, 3 H, Me); 2.37 (s, 3 H, Me); 7.88 (s, 1 H, H(4)); 14.0 (br.s, 1 H, NH)
1b	2228	178 (51.4), 177 (19.1), 163 (78.4), 152 (10.2), 151 (20.3), 150 (100), 149 (7.9), 69 (12.2)	0.87 (t, 3 H, MeCH$_2$); 1.59 (q, 2 H, CH$_2$Me); 2.13 (t, 2 H, CH$_2$CH$_2$); 6.73 (d, 1 H, H(5)); 7.98 (d, 1 H, H(4)); 14.0 (br.s, 1 H, NH)
1c	2226	178 (84), 177 (56), 165 (13), 164 (30.8), 163 (100), 150 (50)	1.15 (d, 6 H, Me$_2$CH, J = 7); 3.04 (sep, 1 H, CHMe$_2$, J = 7); 6.77 (d, 1 H, H(5)); 8.03 (d, 1 H, H(4)); 13.9 (br.s, 1 H, NH)
1d	2224	192 (30.9), 191 (8.2), 177 (19), 164 (18.3), 163 (72.8), 152 (13.2), 151 (23.4), 150 (100)	0.9 (t, 3 H, MeCH$_2$); 1.29 (m, 2 H, CH$_2$CH$_2$); 1.54 (m, 2 H, CH$_2$CH$_2$); 2.67 (t, 2 H, CH$_2$Me); 6.75 (d, 1 H, H(5)); 8.0 (d, 1 H, H(4)); 14.05 (br.s, 1 H, NH)
1e	2226	192 (21.8), 191 (10.2), 177 (41.8), 152 (11.2), 151 (22.1), 150 (100)	0.85 (d, 6 H, Me$_2$CH, J = 6.75); 1.93 (m, 1 H, CHMe$_2$); 2.55 (d, 2 H, CH$_2$CH, J = 6.75); 6.73 (d, 1 H, H(5)); 8.01 (d, 1 H, H(4)); 14.03 (br.s, 1 H, NH)
1f	2228	192 (87.7), 191 (39.3), 179 (11), 178 (26.6), 177 (100), 150 (54.7), 149 (12.3)	1.3 (s, 9 H, Me$_3$C); 6.73 (d, 1 H, H(5)); 7.94 (d, 1 H, H(4)); 14.0 (br.s, 1 H, NH)
1g	2228	206 (34.3), 205 (5.2), 177 (30.4), 164 (24.5), 163 (80.7), 152 (11.6), 151 (21.9), 150 (100)	0.85 (t, 3 H, MeCH$_2$); 1.26 (m, 4 H, CH$_2$CH$_2$); 1.55 (m, 2 H, CH$_2$CH$_2$); 2.57 (t, 2 H, CH$_2$Me); 6.6 (d, 1 H, H(5)); 7.74 (d, 1 H, H(4)); 14.0 (br.s, 1 H, NH)
1h	2228	206 (6), 205 (6.7), 191 (26), 177 (12), 164 (12) 163 (71.7), 152 (13.3), 151 (29.7), 150 (100)	0.89 (d, 6 H, Me$_2$CH, J = 6.75); 1.5 (m, 3 H, CHMe$_2$); 2.66 (t, 2 H, CH$_2$CH$_2$); 6.77 (d, 1 H, H(5)); 8.0 (d, 1 H, H(4)); 14.0 (br.s, 1 H, NH)

* For all compounds, $J_{4,5}$ = 8 Hz.

Table 3. Characteristics of compounds **6b,d,e** and **7b,d,e,g,h**

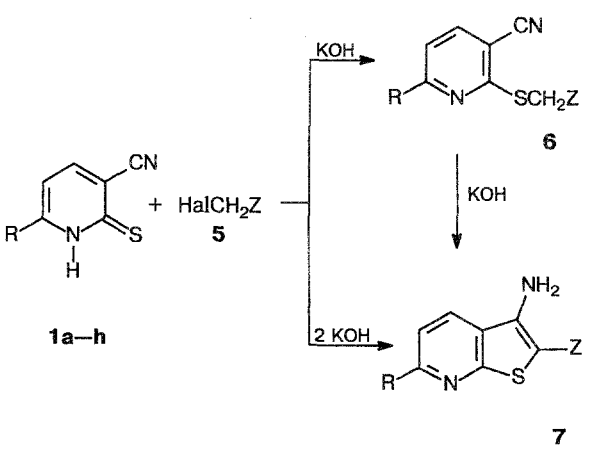
Compound	Z	Mol. wt.	Yield (%)	M.p./°C (Solvent)	Found (%) / Calculated					Molecular formula
					C	H	Br	N	S	
6b	COC_6H_4Br-*p*	375	50	98—100 (heptane)	54.38 54.45	3.89 4.03	21.42 21.31	7.32 7.47	8.60 8.55	$C_{17}H_{15}BrN_2S$
7b	Bz	396	92	118—120 (50 % EtOH)	51.42 51.56	3.95 4.07	—	6.89 7.07	8.01 8.10	$C_{17}H_{16}N_2OS$
7b	CN	217	92	143—145 (50 % EtOH)	60.72 60.88	5.01 5.11	—	19.20 19.37	14.68 14.78	$C_{11}H_{11}N_3S$
7d	COC_6H_4Br-*p*	389	60	166—168 (EtOH)	55.43 55.57	4.35 4.41	20.48 20.54	7.01 7.20	8.01 8.24	$C_{18}H_{17}BrN_2OS$
6d	Bz	310	81	74—76 (heptane)	69.67 69.74	5.60 5.85	—	8.99 9.04	10.22 10.34	$C_{18}H_{18}N_2OS$
7d	CN	231	83	103—105 (50 % EtOH)	62.48 62.39	5.70 5.67	—	18.12 18.19	13.98 13.88	$C_{12}H_{13}N_3S$
6e	COC_6H_4Br-*p*	389.9	41	114—116 (50 % EtOH)	55.50 55.44	4.58 4.65	20.52 20.50	7.22 7.19	8.09 8.22	$C_{18}H_{18}BrN_2OS$
7e	Bz	310	81	74—76 (EtOH)	69.60 69.74	5.77 5.85	—	8.89 9.04	10.42 10.34	$C_{18}H_{18}N_2OS$
7e	CN	231	99	141—142 (50 % EtOH)	62.38 62.39	5.72 5.67	—	18.25 18.19	13.72 13.88	$C_{12}H_{13}N_3S$
7g	COC_6H_4Br-*p*	402.9	45	165—167 (EtOH)	56.59 56.64	4.67 4.75	19.92 19.84	6.72 6.95	7.82 7.96	$C_{19}H_{19}BrN_2OS$
7g	Bz	324	90	116—118 (50 % EtOH)	70.49 70.43	6.01 6.22	—	8.72 8.65	9.72 9.90	$C_{19}H_{20}N_2OS$
7g	CN	261	36	122—124 (heptane)	59.88 59.82	5.82 5.79	—	15.98 16.10	12.32 12.29	$C_{13}H_{15}N_3S$
7h	COC_6H_4Br-*p*	402.9	40	188—190 (50 % EtOH)	56.60 56.64	4.78 4.79	19.77 19.84	6.89 6.95	7.88 7.96	$C_{19}H_{19}BrN_2OS$
7h	Bz	324	60	130—132 (heptane)	70.39 70.43	6.30 6.22	—	8.69 8.65	9.65 9.90	$C_{19}H_{20}N_2OS$
7h	CN	261	65	130—132 (50 % EtOH)	59.94 59.82	5.83 5.79	—	15.87 16.10	12.31 12.29	$C_{13}H_{15}N_3S$

tional crystallization from AcOH. This result is consistent with the data that the condensation of ketone **3a** can occur both at the methyl and the methylene groups.[8]

The structures of pyridinethiones **1a—h** and **4** were confirmed by elemental analysis and spectral data (Tables 1, 2). The IR spectra contain intense bands at 2224—2228 cm^{-1} (ν(CN)). A broadened singlet of NH at 13.9—14.05 ppm is observed in the ^1H NMR spectra, which confirms that the products are in the thione form.

Pyridinethiones **1a—h** and **4** are yellow crystalline substances. They are alkylated by haloacetonitriles and α-haloacetophenones $HalCH_2Z$ (**5**) exclusively at the sulfur atom to give pyridines (**6**), which, according to the general rules,[9] readily close the thiophene ring (Scheme 2). In this case the 6-alkyl-3-aminothieno[2,3-*b*]pyridines (**7**) were isolated and characterized (Table 3). The structure of the product was confirmed by spectral data (Table 4).

Scheme 2



Hal = Cl, Br

Z = Bz, COC_6H_4Br-*p*, CN

Table 4. Spectral characteristics of compounds **6b,d,e** and **7b,d,e,g,h**

Compound	Z	IR, ν/cm^{-1}	^1H NMR, δ, J/Hz*
6b	COC_6H_4Br-*p*	2210 (CN), 1690(CO)	0.66 (t, 3 H, $\underline{Me}CH_2$); 1.35 (sex, 2 H, CH_2Me); 2.4 (t, 2 H, CH_2CH_2); 4.55 (s, 2 H, SCH_2); 6.82 (d, 1 H, H(5)); 7.57 (d, 2 H, H arom); 7.67 (d, 1 H, H(4)); 7.85 (d, 2 H, H arom)
7b	Bz	3260 (NH_2), 3360 (NH_2), 1595 (CO)	0.3 (t, 3 H, $\underline{Me}CH_2$); 1.0 (sex, 2 H, CH_2Me); 2.2 (t, 2 H, CH_2CH_2); 6.85 (d, 1 H, H(5)); 6.95 (t, 3 H, H arom); 7.18 (d, 2 H, H arom); 7.85 (s, 2 H, NH_2); 7.95 (d, 1 H, H(4))
7b	CN	3384 (NH_2), 3332 (NH_2), 2192 (CN)	0.9 (t, 3 H, $\underline{Me}CH_2$); 1.7 (q, 2 H, CH_2CH_2); 2.8 (t, 2 H, CH_2Me); 7.28 (s, 2 H, NH_2); 7.37 (d, 1 H, H(5)); 8.0 (d, 1 H, H(4))
7d	COC_6H_4Br-*p*	3345 (NH_2), 3290 (NH_2), 1600 (CO)	0.9 (t, 3 H, $\underline{Me}CH_2$); 1.3 (m, 2 H, CH_2CH_2); 1.67 (m, 2 H, CH_2CH_2); 2.83 (t, 2 H, CH_2Me); 7.37 (d, 1 H, H(5)); 7.7 (s, 4 H, H arom); 8.44 (s, 2 H, NH_2); 8.55 (d, 1 H, H(4))
6d	Bz	2212 (CN), 1692 (CO)	0.6 (t, 3 H, $\underline{Me}CH_2$); 0.95 (m, 2 H, CH_2CH_2); 1.2 (m, 2 H, CH_2CH_2); 2.41 (t, 2 H, CH_2Me); 4.8 (s, 2 H, SCH_2); 7.09 (d, 1 H, H(5)); 7.51 (m, 3 H, H arom); 8.05 (m, 3 H, H(4) + H arom)
7d	CN	3330 (NH_2), 3415 (NH_2), 2200 (CN)	0.89 (t, 3 H, $\underline{Me}CH_2$); 1.3 (m, 2 H, CH_2CH_2); 1.66 (m, 2 H, CH_2CH_2); 2.82 (t, 2 H, CH_2Me); 7.21 (s, 2 H, NH_2); 7.36 (d, 1 H, H(5)); 8.35 (d, 1 H, H(4))
6e	Bz	2220 (CN), 1690 (CO)	0.55 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 1.57 (m, 1 H, $CHMe_2$); 2.27 (d, 2 H, CH_2CH); 4.8 (s, 2 H, SCH_2); 7.1 (d, 1 H, H(5)); 7.81 (d, 2 H, H arom); 8.03 (d, 2 H, H arom); 8.1 (d, 1 H, H(4))
7e	Bz	3415 (NH_2), 3310 (NH_2), 1590 (CO)	0.89 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 2.1 (m, 1 H, $CHMe_2$); 2.7 (d, 2 H, CH_2CH); 7.34 (d, 1 H, H(5)); 7.55 (m, 3 H, H arom); 7.76 (m, 2 H, H arom); 8.39 (s, 2 H, NH_2); 8.53 (d, 1 H, H(4))
7e	CN	3428 (NH_2), 3328 (NH_2), 2196 (CN)	0.9 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 2.1 (m, 1 H, $CHMe_2$); 2.7 (d, 2 H, CH_2CH); 7.3 (s, 2 H, NH_2); 7.38 (d, 1 H, H(5)); 8.4 (d, 1 H, H(4))
7g	COC_6H_4Br-*p*	3392 (NH_2), 3284 (NH_2), 1596 (CO)	0.27 (t, 3 H, $\underline{Me}CH_2$); 0.75 (m, 4 H, CH_2CH_2); 1.11 (m, 2 H, CH_2CH_2); 2.28 (t, 2 H, $C\underline{H}_2Me$); 6.8 (d, 1 H, H(5)); 7.18 (s, 4 H, H arom); 7.85 (s, 2 H, NH_2); 8.0 (d, 1 H, H(4))
7g	COC_6H_4	3400 (NH_2), 3284 (NH_2), 1592 (CO)	0.83 (t, 3 H, $\underline{Me}CH_2$); 1.28 (m, 4 H, CH_2CH_2); 1.68 (m, 2 H, CH_2CH_2); 2.78 (m, 2 H, $C\underline{H}_2Me$); 7.1 (d, 1 H, H(5)); 7.42 (m, 3 H, H arom); 7.75 (m, 2 H, H arom); 8.15 (s, 2 H, NH_2); 8.36 (d, 1 H, H(4))
7g	CN	3372 (NH_2), 3336 (NH_2), 2192 (CN)	0.85 (t, 3 H, $\underline{Me}CH_2$); 1.26 (m, 4 H, CH_2CH_2); 1.67 (m, 2 H, CH_2CH_2); 2.8 (t, 2 H, CH_2CH_2); 7.23 (s, 2 H, NH_2); 7.36 (d, 1 H, H(5)); 8.45 (d, 1 H, H(4))
7h	COC_6H_4Br-*p*	3280 (NH_2), 2952 (NH_2), 1596 (CO)	0.90 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 1.57 (m, 3 H, CH_2CH); 2.82 (t, 2 H, CH_2CH_2); 7.47 (d, 1 H, H(5)); 7.72 (s, 4 H, H arom); 8.44 (s, 2 H, NH_2); 8.53 (d, 1 H, H(4))
7h	Bz	3380 (NH_2), 3250 (NH_2), 1590 (CO)	0.9 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 1.57 (m, 3 H, $CHCH_2$); 2.82 (t, 2 H, CH_2CH_2); 7.35 (d, 1 H, H(5)); 7.53 (m, 3 H, H arom); 7.77 (m, 2 H, H arom); 8.39 (s, 2 H, NH_2); 8.5 (d, 1 H, H(4))
7h	CN	3410 (NH_2), 3340 (NH_2), 2200 (CN)	0.92 (d, 6 H, $\underline{Me}_2CH$, J = 6.75); 1.6 (m, 3 H, $CHCH_2$); 2.82 (t, 2 H, CH_2CH_2); 7.29 (s, 2 H, NH_2); 7.4 (d, 1 H, H(5)); 8.36 (d, 1 H, H(4))

* For all compounds, $J_{4,5}$ = 8.5 Hz.

Experimental

IR spectra were recorded on a UR-20 spectrophotometer in KBr pellets. ^1H NMR spectra were obtained on a Bruker WM-250 instrument (250 MHz, DMSO-d_6). Mass-spectra were recorded on a Varian MAT-313 A instrument.

The sodium salts of 3-alkyl-1-hydroxy-1-propen-3-ones (**2a—h**) were obtained in 40—90 % yields according to the known procedure.[7]

6-Alkyl-3-cyano-2(1*H*)-pyridinethiones (1a—h, 4). Acetic acid (20 mmol) and cyanothioacetamide (10 mmol) were added to a suspension of salts **2a—h** (10 mmol) in 10—15 mL of EtOH. The mixture was heated to boiling, cooled, and diluted with water. The precipitate that formed was filtered and recrystallized. The characteristics of compounds **1a—h** and **4** are given in Tables 1 and 2.

6-Alkyl-3-cyano-2-(*Z*-methylthio)-pyridines (6). Compound **5** (5 mmol) was added to a solution of thione **1** (5 mmol) in 10 mL of DMF, then 10 % aqueous KOH (5 mmol) was added dropwise with stirring. The mixture was kept for 10—15 min with gentle heating and then diluted with an equal volume of water. The precipitate that formed was filtered and

recrystallized. The characteristics of compounds **6** are given in Tables 3 and 4.

6-Alkyl-3-aminothieno[2,3-*b*]pyridines (7). ***A.*** Compound **5** (5 mmol) was added to a solution of thione **1** (5 mmol) in 10 mL of DMF or ethanol, then 10 % aqueous KOH (10 mmol) was added dropwise. The mixture was stirred for 10—15 min with gentle heating and then diluted with an equal volume of water. The precipitate that formed was filtered and recrystallized.

B. Aqueous 10 % KOH (10 mmol) was added dropwise to a solution of pyridine **6** (5 mmol) in 10 mL of DMF. The mixture was stirred for 10—15 min with gentle heating and diluted with an equal volume of water. The precipitate that formed was filtered and recrystallized. The characteristics of compounds **7** are given in Tables 3 and 4.

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References

1. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, *Sulfur Reports*, 1992, **13**, No. 1, 1.
2. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, and A. M. Shestopalov, *Itogi nauki i tekhniki. Ser. Organicheskaya khimiya* [*Advances in Science and Technology, Organic Chemistry*], VINITI, Moscow, 1989, **17**, 72 (in Russian).
3. L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1988, 805 [*Chem. Heterocycl. Compd.*, 1988 (Engl. Transl.)].
4. V. P. Litvinov, Ye. A. Apyonova, Yu. A. Sharanin, V. N. Nesterov, and V. E. Shklover, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 145 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 131 (Engl. Transl.)].
5. V. P. Litvinov, Ye. A. Apyonova, Ya. A. Sharanin, V. S. Bogdanov, and O. M. Nefedov, *Sulfur Letters*, 1985, **3**, No. 4, 107.
6. V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1965, 334 [*Chem. Heterocycl. Compd.*, 1988 (Engl. Transl.)].
7. R. P. Mariella, *J. Am. Chem. Soc.*, 1947, **69**, 2670.
8. E. E. Royals and K. C. Brannock, *J. Am. Chem. Soc.*, 1953, **75**, 2050.
9. V. P. Litvinov, Yu. A. Sharanin, and F. S. Babichev, *Sulfur Reports*, 1986, **6**, No. 2, 97.

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