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Novel Method of 4,6-Dimethyl-2-thioxo-1,2-dihydronicotinonitrile Synthesis

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Abstract—Condensation of acetaldehyde with cyanothioacetamide and 1-(prop-1-en-2-yl)pyrrolidine has afforded 4,6-dimethyl-2-thioxo-1,2-dihydronicotinonitrile. Alkylation of the latter with α-haloketones yields substituted 2-alkylsulfanyl-4,6-dimethylnicotinonitriles and thieno[2,3-*b*]pyridines.

Keywords: acetaldehyde, cyanothioacetamide, 1-(prop-1-en-2-yl)pyrrolidine, 2-thioxo-1,2-dihydronicotinonitrile, 2-alkylsulfanylnicotinonitriles, thieno[2,3-*b*]pyridines

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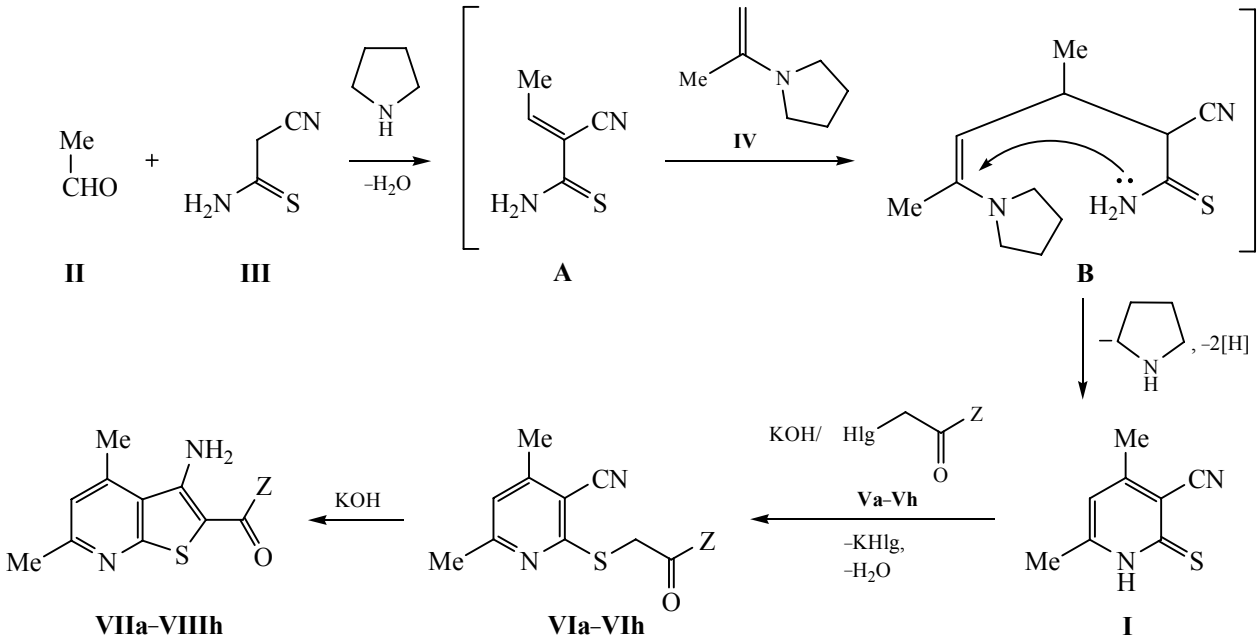
Alkyl-substituted 2-thioxo(oxo)-1,2-dihydronicotinonitriles are intermediates in the synthesis of anti-inflammatory [1] and antineoplastic [2] drugs. They are components of medicines for Alzheimer's disease treatment [3, 4], herbicides [5], and azo dyes [6, 7]. The known methods of their synthesis are based on condensation of acetylacetone with cyanoacetamide or cyanothioacetamide [8], nucleophilic substitution of the chlorine atom in 2-thioureachloronicotinonitrile [9], and the Michael reaction via the methylene components exchange [10].

In this work, we propose a new method of 4,6-dimethyl-2-thioxo-1,2-dihydronicotinonitrile **I** synthesis:

Scheme 1.



V–VII, Hlg = Br, Z = 3,4-$Cl_2C_6H_3$ (**a**); Br, 4-BuC_6H_4 (**b**); Br, 4-PhC_6H_4 (**c**); Cl, 4-BrC_6H_4NHCO (**d**); Br, 2,4-$Me_2C_6H_3$ (**e**); Br, 4-BrC_6H_4 (**f**); Br, 3-BrC_6H_4 (**g**); Cl, $PhCH_2O$ (**h**).

Table 1. Yields, melting points, and elemental analysis data for 2-alkylsulfanyl-4,6-dimethylnicotinonitriles **VIa–VIh** and 3-amino-4,6-dimethyl-2-*Z*-thieno[2,3-*b*]pyridines **VIIa–VIIh**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
VIa	89	118–120 (AcOH)	54.60	3.32	7.85	$C_{16}H_{12}Cl_2N_2OS$	54.71	3.44	7.98
VIb	75	80–81 (MeCN)	70.86	6.41	8.14	$C_{20}H_{22}N_2OS$	70.97	6.55	8.28
VIc	81	156–158 (BuOH)	73.69	4.92	7.77	$C_{22}H_{18}N_2OS$	73.72	5.06	7.81
VId	77	199–201 (AcOH)	50.95	3.66	11.02	$C_{16}H_{14}BrN_3OS$	51.07	3.75	11.17
VIe	70	116–118 (MeOH)	69.51	5.70	8.95	$C_{18}H_{18}N_2OS$	69.65	5.85	9.02
VIf	82	125–127 (EtOH)	53.14	3.58	7.65	$C_{16}H_{13}BrN_2OS$	53.20	3.63	7.75
VIg	76	138–140 (AcOH)	53.11	3.55	7.61	$C_{16}H_{13}BrN_2OS$	53.20	3.63	7.75
VIh	73	81–83 (PrOH)	65.19	5.00	8.86	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97
VIIa	85	211–213[a] (BuOH)	54.69	3.38	7.87	$C_{16}H_{12}Cl_2N_2OS$	54.71	3.44	7.98
VIIb	70	113–114 (MeOH)	70.89	6.46	8.19	$C_{20}H_{22}N_2OS$	70.97	6.55	8.28
VIIc	74	195–197 (PrOH)	37.61	4.88	7.74	$C_{22}H_{18}N_2OS$	37.72	5.06	7.81
VIId	82	230–232[b] (AcOH)	50.99	3.65	11.08	$C_{16}H_{14}BrN_3OS$	51.07	3.75	11.17
VIIe	76	173–175 (AcOH)	69.57	5.70	8.94	$C_{18}H_{18}N_2OS$	69.65	5.85	9.02
VIIf	71	180–182 (AcOH)	53.07	3.50	7.60	$C_{16}H_{13}BrN_2OS$	53.20	3.63	7.75
VIIg	80	191–192 (AcOH)	53.14	3.49	7.62	$C_{16}H_{13}BrN_2OS$	53.20	3.63	7.75
VIIh	72	113–115 (MeOH)	65.25	5.07	8.81	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97

[a] Sublimated at 170°C. [b] Sublimated at 200°C.

a three-component condensation of acetaldehyde **II**, cyanothioacetamide **III**, and 1-(prop-1-en-2-yl)pyrrolidine **IV** in anhydrous ethanol at 20°C. The probable reaction scheme included the Knöevenagel alkene **A** formation that further alkylated the enamine **IV** via the Stork reaction [11] to give the adduct **B.** The latter underwent intramolecular transamination [12] and oxidation (apparently with air oxygen) yielding the nicotinonitrile **I** (Scheme 1).

Alkylation of compound **I** with α-haloketones **Va–Vh** in an alkaline DMF solution proceeded regioselectively at the sulfur atom to form the corresponding thioethers **VIa–VIh**. The latter underwent intramolecular cyclization to give the substituted 3-amino-4,6-dimethylthieno[2,3-*b*]pyridines **VIIa–VIIh**, promising components of antidotes of hormonal action herbicide [13, 14], sunflower growth promoters [15] and inhibitors of the *C*-terminal hydrolase L1 (UCH-L1) [16].

The determined physico-chemical and spectral parameters confirmed the structures of all the synthesized compounds (Tables 1 and 2). Their IR spectra contained characteristic absorption bands of stretching vibrations at 2218–2225 (C≡N) and 1667–1714 cm^{-1} (C=O). The ^1H NMR spectra contained the signals of methyl groups (2.14–2.79 ppm), pyridine H^5 proton (7.00–7.09 ppm), and SCH_2 fragment (for compound **VI**, 4.15–4.84 ppm).

^1H NMR spectra of compounds **VIIa–VIIh** contained the signal of amino group (6.81–8.08 ppm) instead of that of SCH_2 protons, thus confirming the occurred intramolecular cyclization [17–19]. In addition, absorption bands at 3180–3385 and 1638–1648 cm^{-1} appeared in the IR spectra of thienopyridines **VII**, assigned to stretching and deformation vibrations of the amino group; no absorption bands of the nitrile group stretching was registered.

In summary, the three-component condensation of acetaldehyde, cyanothioacetamide, and 1-(prop-1-en-2-yl)pyrrolidine yields 4,6-dimethyl-2-thioxo-1,2-dihydronicotinonitrile that can be further converted into potentially biologically active substituted 2-alkyl-

Table 2. IR, ^{1}H NMR and gas chromatography–mass spectrometry data for 2-alkylsulfanyl-4,6-dimethylnicotinonitriles **VIa–VIh** and 3-amino-4,6-dimethyl-2-*Z*-thieno[2,3-*b*]pyridines **VIIa–VIIh**

Comp. no.	ν, cm^{-1}		*m*/*z* $[M+1]^+$	δ, ppm (*J*, Hz)		
	C≡N or NH_2	C=O, δ(NH_2)		Me	SCH_2 or NH_2, H^5	other signals
VIa	2219	1714	352	2.14, 2.38	4.78, 7.03	7.83 d (1H, H_{Ar}, *J* 7.5), 8.01 d (1H, H_{Ar}, *J* 7.5), 8.29 s (1H, H_{Ar})
VIb	2222	1703	339	2.17, 2.38	4.80, 7.03	0.84 t (3H, Me, *J* 6.5), 1.11–1.72 m (4H, $2SH_2$), 2.67 t (2H, SH_2, *J* 6.4), 7.36 d (2H, H_{Ar}, *J* 8.2), 7.98 d (2H, H_{Ar}, *J* 8.2)
VIc	2220	1710	359	2.18, 2.37	4.84, 7.01	7.45 d (2H, H_{Ar}, *J* 6.6), 7.51 t (1H, H_{Ar}, *J* 6.9), 7.72 t (2H, H_{Ar}, *J* 7.0), 7.84 d (2H, H_{Ar}, *J* 8.4), 8.14 d (2H, H_{Ar}, *J* 8.4)
VId	2224	1699	377	2.39 (2Me)	4.15, 7.07	7.42 d (2H, H_{Ar}, *J* 7.1), 7.62 d (2H, H_{Ar}, *J* 7.1), 10.36 br. s (1H, NH)
VIe	2223	1705	295	2.22, 2.35	4.63, 7.02	2.15 s (3H, Me), 2.18 s (3H, Me), 6.88–7.00 m (2H, H_{Ar}), 7.83 d (1H, H_{Ar}, *J* 7.6)
VIf	2220	1702	362	2.16, 2.38	4.78, 7.03	7.75 d (2H, H_{Ar}, *J* 7.5), 8.00 d (2H, H_{Ar}, *J* 7.5)
VIg	2218	1714	362	2.32, 2.39	4.15, 7.07	7.32 s (5H, Ph)
VIh	2225	1699	313	2.16, 2.39	4.82, 7.04	7.43–7.72 m (2H, H_{Ar}), 8.04 d (2H, H_{Ar}, *J* 8.1)
VIIa	3322, 3211, 3190	1695, 1648	352	2.56, 2.79	8.06, 7.05	7.68–7.79 m (2H, H_{Ar}), 7.89 s (1H, H_{Ar})
VIIb	3316, 3284, 3202	1699, 1645	339	2.52, 2.76	8.00, 7.09	0.91 t (3H, Me, *J* 6.4), 1.12–1.81 m (4H, $2SH_2$), 7.34 d (2H, H_{Ar}, *J* 8.3), 7.69 d (2H, H_{Ar}, *J* 8.3)
VIIc	3315, 3294, 3202	1695, 1646	359	2.51, 2.77	8.08, 7.09	7.45 d (2H, H_{Ar}, *J* 8.4), 7.72 d (2H, H_{Ar}, *J* 8.4), 7.84 s (5H, Ph)
VIId	3300, 3280, 3195	1667, 1642	377	2.52, 2.73	7.00, 7.05	7.48 d (2H, H_{Ar}, *J* 7.8), 7.66 d (2H, H_{Ar}, *J* 7.8), 9.52 br. s (1H, NH)
VIIe	3385, 3309, 3214	1708, 1647	295	2.54, 2.72	7.20, 7.07	2.16 s (3H, Me), 2.22 s (3H, Me), 6.71–6.84 m (2H, H_{Ar}), 7.88 d (1H, H_{Ar}, *J* 7.7)
VIIf	3322, 3277, 3180	1690, 1638	362	2.52, 2.75	8.08, 7.09	7.65 d (2H, H_{Ar}, *J* 7.2), 7.78 d (2H, H_{Ar}, *J* 7.2)
VIIg	3319, 3295, 3200	1711, 1640	362	2.48, 2.70	6.81, 7.01	5.30 s (2H, OSH_2), 7.40 s (5H, Ph)
VIIh	3333, 3298, 3213	1693, 1646	313	2.44, 2.73	8.05, 7.04	7.45–7.61 m (2H, H_{Ar}), 7.68–7.82 m (2H, H_{Ar})

sulfanyl-4,6-dimethylnicotinonitriles and thieno[2,3-*b*]-pyridines.

EXPERIMENTAL

IR spectra (KBr pellets) were recorded with an UR-20 spectrometer. ^{1}H NMR spectra (DMSO-d_6) were registered with a Bruker AM-300 instrument (300.13 MHz) relative to internal TMS reference. Elemental analysis was performed with a EuroVector EA-3000 analyzer. Gas chromatography–mass spectra (CF_3COOH solution, CI) were obtained using a Hewlett-Packard 5890/5972 Chrommass GC/MS instrument equipped with an HP5-MS column. Melting points were determined with a Kofler bench. The reaction progress was monitored by TLC using Silufol

UV-254 plates, eluting with acetone–hexane (3 : 5) mixture and developing with iodine vapor and UV irradiation.

4,6-Dimethyl-2-thioxo-1,2-dihydronicotinonitrile (I). 0.6 mL (10 mmol) of freshly distilled anhydrous acetaldehyde and 2–3 drops of triethylamine were added at 20°C to a stirred suspension of 1.0 g (10 mmol) cyanothioacetamide in 20 mL of anhydrous ethanol. The mixture was stirred during 15 min until complete homogenization. 1.1 g (10 mmol) of enamine **IV** was then added. The reaction mixture was stirred during 1 h and then incubated during 24 h. Next, the mixture was diluted with 10% hydrochloric acid to pH 5 and incubated during 5 h; the formed precipitate was filtered off and washed with ethanol and hexane. Yield 1.2 g (72%), yellow crystals, mp 263–265°C (EtOH) (mp 264°C [8]).

2-Alkylsulfanyl-4,6-dimethylnicotinonitriles (VIa–VIh) *(general procedure)*. 5.6 mL (10 mmol) of 10% aqueous KOH and the corresponding α-haloketone **Va–Vh** were added to a stirred solution of 1.7 g (10 mmol) of nicotinonitrile **I** in 10 mL of DMF; the mixture was stirred during 2 h and then diluted with an equal volume of water. The resulting precipitate was filtered off and washed with water, ethanol, and hexane. Parameters of the products **VIa–VIh** are given in Tables 1 and 2.

3-Amino-4,6-dimethyl-2-*Z*-thieno[2,3-*b*]pyridines (VIIa–VIIh) *(general procedure)*. 5.6 mL (10 mmol) of 10% aqueous KOH solution was added to a stirred solution of 10 mmol of the appropriate sulfide **VI** in 15 mL of DMF; the mixture was stirred during 4 h and then diluted with an equal volume of water. The resulting precipitate was filtered off and washed with water, ethanol, and hexane. Parameters of the products **VIIa–VIIh** are given in Tables 1 and 2.

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