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New Approach to the Synthesis of 2-Alkylsulfanyl-4,5,6-trimethylnicotinonitriles

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Abstract—Multicomponent condensation of acetaldehyde, cyanothioacetamide, 1-(but-2-en-2-yl)pyrrolidine, and alkyl halides afforded 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles. Their structure was confirmed by IR, ^{1}H NMR spectroscopy, and chromatography-mass spectrometry.

Keywords: acetaldehyde, cyanothioacetamide, 1-(but-2-en-2-yl)pyrrolidine, alkyl halides, 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles

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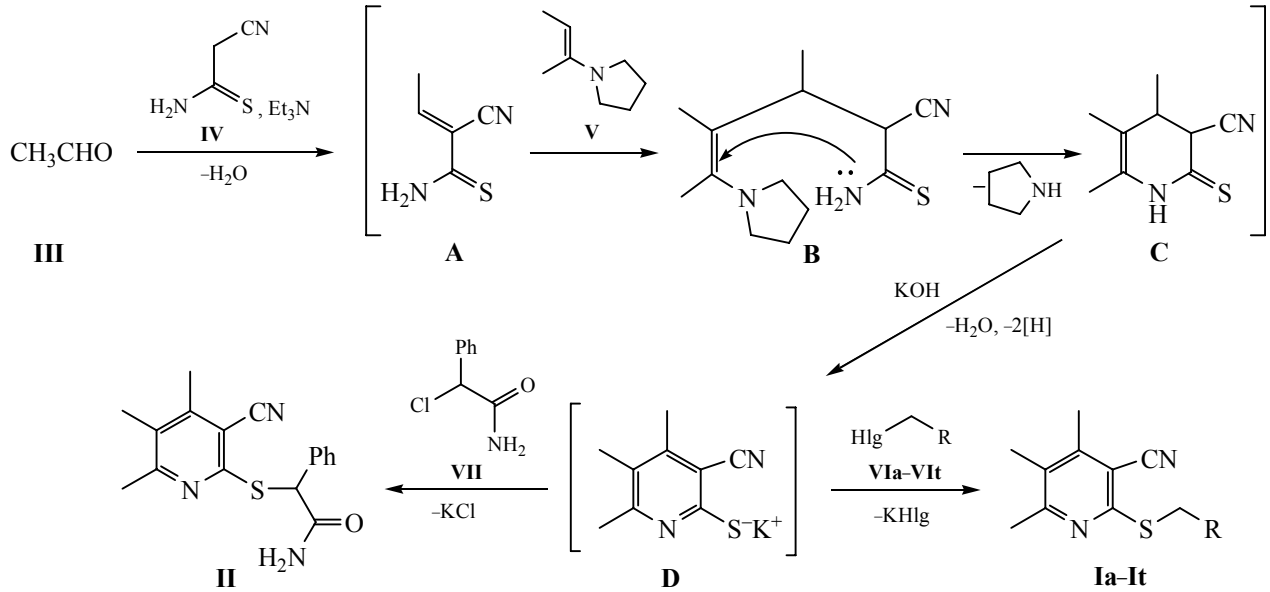
Some alkyl-substituted derivatives of 2-oxo(thioxo)-1,2-dihydronicotinonitrile possess anti-inflammatory [1], cardiovascular protecting [2], and fungicidal [3] properties. Compounds of this series are also promising for designing drugs against Alzheimer's disease [4]. The synthesis of these compounds is preferably based on condensation of 1,3-dicarbonyl compounds with cyanoacetyl(thio)amide in the presence of bases [5–8].

Scheme 1.



I, **VI**, Hlg = Cl, R = 2-MeOC$_6$H$_4$NHCO (**a**); Br, 3-oxo-3*H*-benzo[*f*]chromen-2-ylcarbonyl (**b**); Cl, thiazol-2-ylcarbamoyl (**c**); Cl, quinolin-8-ylcarbamoyl (**d**); Cl, Ph (**e**); I, Me (**f**); I, *n*-Bu (**g**); I, Et (**h**); Br, 5,7-dibromo-3-oxo-3*H*-benzo[*f*]chromen-2-ylcarbonyl (**i**); Br, 7-bromo-3-oxo-3*H*-benzo[*f*]chromen-2-ylcarbonyl (**j**); Cl, COOH (**k**); Br, 4-NO$_2$C$_6$H$_4$CO (**l**); Br, 3,4-Cl$_2$C$_6$H$_3$CO (**m**); Br, 3-BrC$_6$H$_4$CO (**n**); Br, 4-ClC$_6$H$_4$ (**o**); Br, 4-BuC$_6$H$_4$CO (**p**); Cl, PhCH$_2$OCO (**q**); Br, 2,4-Me$_2$C$_6$H$_3$ (**r**); Cl, PrOCO (**s**); Br, 4-ClC$_6$H$_4$CO (**t**).

Table 1. Yields, melting points, and elemental analysis data for 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles **Ia**–**It** and **II**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Ia	84	195–196 (AcOH)	63.18	5.49	12.22	$C_{18}H_{19}N_3O_2S$	63.32	5.61	12.31
Ib	78	225–227 (BuOH)	69.40	4.27	6.66	$C_{24}H_{18}N_2O_3S$	69.55	4.38	6.76
Ic	73	219–221 (AcOH)	52.75	4.31	17.49	$C_{14}H_{14}N_4OS$	52.81	4.43	17.60
Id	77	206–208[a] (AcOH)	66.14	4.89	15.33	$C_{20}H_{18}N_4OS$	66.28	5.01	15.46
Ie	82	103–105(MeOH)	71.50	5.88	10.32	$C_{16}H_{16}N_2S$	71.61	6.01	10.44
If	76	86–87 (MeOH)	63.92	6.70	13.44	$C_{11}H_{14}N_2S$	64.04	6.84	13.58
Ig	71	77–78 (MeOH)	67.58	8.04	11.09	$C_{14}H_{20}N_2S$	67.70	8.12	11.28
Ih	79	70–71 (MeOH)	65.30	7.18	12.66	$C_{12}H_{16}N_2S$	65.42	7.32	12.71
Ii	83	213–215 (BuOH)	45.88	2.61	5.20	$C_{20}H_{14}Br_2N_2O_3S$	46.00	2.70	5.36
Ij	80	231–233 (BuOH)	54.03	3.28	6.19	$C_{20}H_{15}BrN_2O_3S$	54.19	3.41	6.32
Ik	69	175–177 (AcOH)	55.87	5.02	11.73	$C_{11}H_{12}N_2O_2S$	55.91	5.12	11.86
Il	71	132–134 (AcOH)	59.78	4.33	12.18	$C_{17}H_{15}N_3O_3S$	59.81	4.43	12.31
Im	70	146–148 (AcOH)	55.81	3.76	7.57	$C_{17}H_{14}Cl_2N_2OS$	55.90	3.86	7.67
In	81	119–121 (EtOH)	54.32	3.91	7.35	$C_{17}H_{15}BrN_2OS$	54.41	4.03	7.46
Io	72	125–127 (PrOH)	63.31	4.84	9.13	$C_{16}H_{15}ClN_2S$	63.46	4.99	9.25
Ip	76	92–93 (MeOH)	71.44	6.75	7.88	$C_{21}H_{24}N_2OS$	71.56	6.86	7.95
Iq	85	98–100 (EtOH)	66.11	5.42	8.47	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
Ir	77	144–146 (AcOH)	70.25	6.13	8.49	$C_{19}H_{20}N_2OS$	70.34	6.21	8.63
Is	69	56–57 (PrOH)	60.30	6.42	9.93	$C_{14}H_{18}N_2O_2S$	60.41	6.52	10.06
It	75	136–138 (EtOH)	61.62	4.39	8.35	$C_{17}H_{15}ClN_2OS$	61.72	4.57	8.47
II	80	182–184 (BuOH)	65.40	5.38	13.36	$C_{17}H_{17}N_3OS$	65.57	5.50	13.49

[a] Fluoresced when UV irradiated.

Taking into consideration the practical significance of alkyl-substituted 2-thioxo-1,2-dihydronicotinonitriles and continuing the research on the chemistry of this type of compounds [9–12], we developed a new effective method for the preparation of 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles **Ia**–**It** and **II** based on the condensation of acetaldehyde **III** with cyanothioacetamide **IV**, 1-(but-2-en-2-yl)pyrrolidine **V**, and α-halocarbonyl compounds **VIa**–**VIt**, and **VII**.

The reaction proceeded at 20°C in anhydrous ethanol in the presence of triethylamine to form, presumably, intermediate Knövenagel alkene **A**, which alkylated enamine **V** by Stork reaction [13] to give adduct **B**. The latter underwent intramolecular transamination, which can be regarded as an intramolecular reaction of vinyl substitution ($S_N$vin) [14–16]. The resulting tetrahydropyridine **C** was readily dehydrogenated in an alkaline medium to give salt **D**, which was regioselectively alkylated with compounds **VIa**–**VIt** and **VII** to afford the corresponding thioesters **Ia**–**It** and **II** (Scheme 1).

Physicochemical and spectral characteristics of the synthesized nicotinonitriles **Ia**–**It** and **II** are given in Tables 1–4. Thus, in the mass spectra of the obtained compounds the molecular ion peak $[M + 2]^+$ was present indicating the content of sulfur atom in their molecules, and the numerical value of the molecular ion $[M]^+$ agreed with the "nitrogen rule" [17]. The IR

Table 2. IR and ^{1}H NMR spectral data for 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles **Ia**–**It** and **II**

Comp. no.	ν, cm^{-1}		δ, ppm (^3J, Hz)		
	C≡N, NH	C=O	Me	SCH_2	other signals
Ia	2215, 3311	1668	2.21, 2.45, 2.59	4.08	3.79 s (3H, MeO), 6.82 t (1H, H_{arom}, *J* 8.2), 6.91 d (1H, H_{arom}, *J* 8.2), 6.98 t (1H, H_{arom}, *J* 8.0), 8.11 d (1H, H_{arom}, *J* 8.0), 9.10 br.s (1H, NH)
Ib	2220	1715, 1694	2.13, 2.33, 2.39	4.75	7.56–7.67 m (2H, H_{arom}), 7.76 d (1H, H_{arom}, *J* 7.0), 8.04 d (1H, H_{arom}, *J* 8.1), 8.29 d (1H, H_{arom}, *J* 9.1), 8.55 d (1H, H_{arom}, *J* 8.1), 9.29 s (1H, H^1, benzochromene)
Ic	2218, 3297	1664	2.17, 2.42, 2.45	4.13	6.97 d (1H, H^5, thiazole, *J* 3.4), 7.36 d (1H, H^4, thiazole, *J* 3.4), 12.27 br.s (1H, NH)
Id	2224, 3305	1673	2.17, 2.40, 2.58	4.20	7.41–7.62 m (3H, H_{arom}), 8.25 d (1H, H_{arom}, *J* 8.6), 8.59d (1H, H_{arom}, *J* 7.1), 8.71d (1H, H_{arom}, *J* 7.6), 10.52 br.s (1H, NH)
Ie	2223	–	2.19, 2.39, 2.55	4.43	7.24 t (1H, Ph, *J* 6.8), 7.25 t (1H, Ph, *J* 6.8), 7.39 d (2H, Ph, *J* 7.2)
If	2219	–	2.17, 2.38, 2.49	3.16 q, *J* 6.0	1.33 t (3H, Me, *J* 6.0)
Ig	2216	–	2.16, 2.38, 2.48	3.14 t, *J* 5.5	0.89 t (3H, Me, *J* 7.0), 1.23–1.45 m (4H, $2CH_2$), 1.54–1.67 m (2H, CH_2)
Ih	2222	–	2.18, 2.40, 2.51	3.16 t, *J* 7.1	1.03 t (3H, Me), 1.59–1.82 m (2H, CH_2)
Ii	2225	1714, 1698	2.14, 2.34, 2.39	4.64	8.11 s (1H, H_{arom}), 8.19 s (1H, H_{arom}), 8.61 s (1H, H^4, coumarin)
Ij	2223	1715, 1700	2.16, 2.36, 2.42	4.63	7.40 d (1H, H_{arom}, *J* 8.8), 7.80 d (1H, H_{arom}, *J* 8.8), 8.13 s (1H, H^5, coumarin), 8.62 s (1H, H^4, coumarin)
Ik	2217	1690	2.17, 2.36, 2.47	4.00	12.61 br.s (1H, OH)
Il	2218	1702	2.09, 2.14, 2.37	4.83	8.25 d (2H, H_{arom}, *J* 7.9), 8.45 d (2H, H_{arom}, *J* 7.9)
Im	2220	1696	2.08, 2.17, 2.35	4.75	7.80 d (1H, H_{arom}, *J* 8.1), 8.00 d (1H, H_{arom}, *J* 8.1), 8.23 s (1H, H_{arom})
In	2222	1705	2.14, 2.26, 2.40	4.78	7.45–7.72 m (3H, H_{arom}), 8.05 d (1H, H_{arom}, *J* 7.9)
Io	2224	–	2.15, 2.37, 2.54	4.48	7.35 d (2H, H_{arom}, *J* 6.9), 7.44 d (2H, H_{arom}, *J* 6.9)
Ip	2219	1700	2.13, 2.23, 2.40	4.79	0.93 t (3H, Me, *J* 6.4), 1.15–1.78 m (2H, $2CH_2$), 2.76 t (2H, CH_2, *J* 6.1), 7.40 d (2H, H_{arom}, *J* 7.9), 7.99 d (2H, H_{arom}, *J* 7.9)
Iq	2218	1714	2.13, 2.34, 2.37	4.13	5.14 s (2H, OCH_2), 7.32 s (5H, Ph)
Ir	2221	1695	2.11, 2.33, 2.39	4.64	7.02–7.23 m (2H, H_{arom}), 7.87 d (1H, H_{arom}, *J* 7.4)
Is	2217	1712	2.17, 2.40, 2.46	4.07	0.85 t (3H, Me, *J* 6.5), 1.42–1.76 m (2H, CH_2), 4.03 t (2H, OCH_2, *J* 6.3)
It	2225	1701	2.13, 2.25, 2.39	4.77	7.60 d (2H, H_{arom}, *J* 8.6), 8.07 d (2H, H_{arom}, *J* 8.6)
II	2218, 3208, 3291, 3335	1666	2.14, 2.36, 2.51	5.69	7.18–7.42 m (4H, $3H_{arom}$, NH_2), 7.50–7.68 m (2H, H_{arom}), 7.87 br.s (1H, NH_2)

Table 3. Mass spectrometry data for 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles **II–Ij**

Comp. no.	$[M]^+$ (I_{rel}, %), M	$[M+1]^+$, $[M+2]^+$ (I_{rel}, %)	Other signals
Ia	341 (8), 341.435	342 (2), 343 (1)	219 (94) [M – $MeOC_6H_4NH$]$^+$, 191 (100) [M – $MeOC_6H_4NH$–H_2CN]$^+$, 179 (13), 159 (11), 145 (24), 123 (79) [$MeOC_6H_4NH_2$]$^+$, 118 (21), 108 (30), 92 (19), 77 (17) [Ph]$^+$, 65 (29), 52 (15), 44 (16) [C=S]$^+$
Ib	414 (12), 414.486	415 (3), 416 (2)	386 (17) [M – H_2CN]$^+$, 381 (9), 223 (86) [3-oxo-3*H*-benzo[*f*]chromen-2-ylcarbonyl]$^+$, 191 (100) [M – 3-oxo-3*H*-benzo[*f*]chromen-2-ylcarbonyl]$^+$, 177 (11), 139 (42), 73 (8), 44 (15) [C=S]$^+$
Ic	318 (12), 318.442	319 (3), 320 (2)	219 (73) [M – thiazolyl]$^+$, 192 (100) [M – thiazolyl – HCN]$^+$, 191 (97) [M – thiazolyl –H_2CN]$^+$, 178 (18), 159 (8), 145 (23), 127 (52) [thiazolylcarbamoyl]$^+$, 118 (19), 100 (11), 91 (15), 77 (9), 65 (8), 55 (16), 45 (18) [CHS]$^+$
Id	362 (10), 362.456	363 (2), 364 (1)	218 (32) [M – aminoquinoline]$^+$, 191 (19), 184 (17), 171 (100) [quinolinylcarbamoyl]$^+$, 144 (35), 116 (18), 89 (8), 77 (6), 45 (4) [CHS]$^+$
Ie	268 (100), 68.381	269 (29), 270 (5)	267 (14) [M – 1]$^+$, 253 (5) [M – Me]$^+$, 235 (84) [M – SH]$^+$, 220 (6), 191 (17), 146 (7), 134 (8), 121 (5), 93 (13) [PhMe]$^+$, 91 (95) [$PhCH_2$]$^+$, 65 (32), 45 (8) [CHS]$^+$, 44 (47) [C=S]$^+$, 39 (9)
If	206 (55), 206.312	207 (7), 208 (2)	205 (58) [M – 1]$^+$, 191 (56) [M – Me]$^+$, 178 (28) [M – H_2CN]$^+$, 173 (100) [M – SH]$^+$, 160 (7), 146 (28), 131 (12), 118 (13), 104 (12), 91 (15), 77 (16), 65 (17), 53 (15), 45 (9), 44 (5) [C=S]$^+$, 42 (14), 39 (18)
Ig	248 (19), 248.392	249 (3), 250 (2)	247 (4) [M – 1]$^+$, 233 (3) [M – Me]$^+$, 250 (2), 215 (8) [M – SH]$^+$, 205 (37), 192 (100) [M – C_4H_8]$^+$, 178 (84), 173 (14), 145 (15), 133 (9), 118 (13), 91 (12), 77 (8), 65 (9), 53 (7), 44 (13) [C=S]$^+$, 42 (13), 41 (29) [MeCN]$^+$
Ih	220 (44), 220.339	221 (7), 222 (2)	219 (26) [M – 1]$^+$, 205 (49) [M – Me]$^+$, 192 (70) [M – H_2CN]$^+$, 191 (76) [M – C_2H_5]$^+$, 187 (58) [M – SH]$^+$, 178 (100), 173 (8), 160 (9), 145 (20), 134 (17), 118 (19), 104 (11), 91 (22), 77 (16), 65 (17), 53 (14), 44 (19) [C=S]$^+$, 42 (20), 41 (36), [MeCN]$^+$, 39 (28)
Ii	522 (35), 522.218	523 (12), 524 (19)	521 (20) [M – 1]$^+$, 507 (2) [M – Me]$^+$, 494 (52) [M – H_2CN]$^+$, 346 (13), 331 (50) [M – dibromocoumarinylcarbonyl]$^+$, 247 (49), 191 (100) dibromocoumarinylcarbonyl]$^+$, 177 (13), 145 (14), 118 (11), 87 (9), 77 (5), 65 (5), 53 (4), 45 (5) [CHS]$^+$, 44 (4) [C=S]$^+$, 43 (8), 42 (4)
Ij	443 (6), 443.322	444 (12), 445 (2)	442 (14) [M – 1]$^+$, 428 (2) [M – Me]$^+$, 416 (17) [M – HCN]$^+$, 251 (29), [bromocoumarinylcarbonyl]$^+$, 191 (100) [M – bromocoumarinylcarbonyl + 1]$^+$, 145 (11), 118 (12), 88 (6), 78 (3), 53 (3), 43 (4), 41 (4) [MeCN]$^+$

spectra of compounds **Ia–It** and **II** contained characteristic absorption bands of the stretching vibrations of the conjugated cyano group at 2215–2225 cm^{-1}, and the C=O band at 1666–1715 cm^{-1}. In the ^1H NMR spectra of compounds **Ia–It** and **II** there were characteristic proton signals of the methyl groups (Table 2) and the signal of SCH_2 group in the range of 4.00–4.79 ppm that is typical for this type of compounds [18–20].

In summary, a new method for the synthesis of 2-alkylsulfanyl-3,4,5-trimethylnicotinonitriles was developed based on the multicomponent condensation of acetaldehyde, cyanothioacetamide, 1-(but-2-en-2-yl)pyrrolidine, and alkyl halides.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument from KBr pellets. ^1H NMR spectra (DMSO-d_6) were taken on a Bruker DR 500 (500.13 MHz), internal reference TMS. Elemental analysis was performed on a EuroVector EA-3000 analyzer. Chromatography-mass spectrometry analysis was performed on a KRATOS MS 890A instruments (EI, 70 eV) with direct input of the sample into the ion source (for **Ia–**

Table 4. Chromatography-mass spectrometry data and molecular weight of 2-alkylsulfanyl-4,5,6-trimethylnicotinonitriles **Ik**–**It** and **II**

Comp. no.	*M*	$[M + 1]^+$
Ik	236.295	237
Il	341.392	342
Im	365.284	366
In	375.290	376
Io	302.826	303
Ip	352.501	353
Iq	326.420	327
Ir	324.447	325
Is	278.375	279
It	330.839	331
II	311.408	312

Ij), and Hewlett-Packard 5890/5972 Chrommass GC/MS spectrometer using chemical ionization mode (column HP5-MS) in CF_3COOH solutions. Melting points were determined on a Koeffler heating block. The reaction progress was monitored by TLC using Silufol UV-254 plates and eluting with acetone–hexane (3 : 5), developing with iodine vapor and UV irradiation.

2-Alkylsulfanyl-4,5,6-trimethylnicotinonitriles (Ia–It, II). A mixture of 0.6 mL (10 mmol) of freshly distilled acetaldehyde **III**, 1.0 g (10 mmol) of cyanothioacetamide **IV**, and 1 drop of triethylamine in 20 mL of anhydrous ethanol was stirred for 20 min at 20°C to dissolve compound **IV**. Then 1.24 g (10 mmol) of enamine **V** was added. The mixture was stirred for 2 h and left standing for 24 h. Next, 5.6 mL (10 mmol) of 10% aqueous KOH and 10 mmol of an appropriate alkyl halide **VI** or **VII** in 10 mL of DMF were added in succession, the reaction mixture was stirred for 5 h and diluted with an equal volume of water. The resulting precipitate was filtered off, washed with water, ethanol, and hexane, and dried.

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