Synthesis of 3-cyano-5-ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1*H*)-thione by three-component condensation

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Condensation of isovaleraldehyde with cyanothioacetamide and ethyl acetoacetate (or its enamine) gives 3-cyano-5-ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1*H*)-thione. This compound was used in the synthesis of substituted 1,4-dihydropyridin-2-yl sulfides.

Key words: isovaleraldehyde, cyanothioacetamide, ethyl acetoacetate, pyridine, condensation.

Up to now, literature data on the synthesis of alkyl-substituted 3-cyano-3,4-dihydropyridine-2(1*H*)-thiones are lacking.[1,2] In studying this problem, we elaborated convenient methods for the preparation of 3-cyano-5-ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1*H*)-thione (**1**). These methods involve condensation of isovaleraldehyde (**2**) with cyanothioacetamide (**3**) and ethyl acetoacetate (**4**) (method *A*) or its enamine **5** (method *B*) in ethanol at 20 °C in the presence of morpholine (Scheme 1). Apparently, the above reactions proceed *via* intermediates **6** or **7**, which undergo regioselective cyclocondensation into salt **8**.

Scheme 1

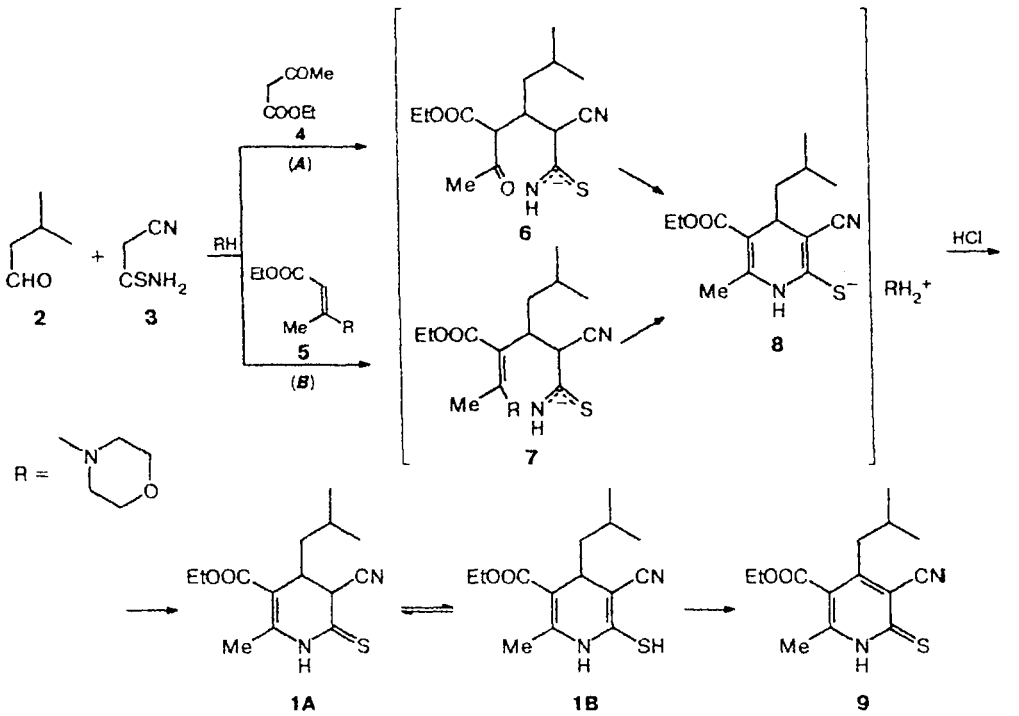

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Table 1. Main physicochemical characteristics of compounds **11a—e**

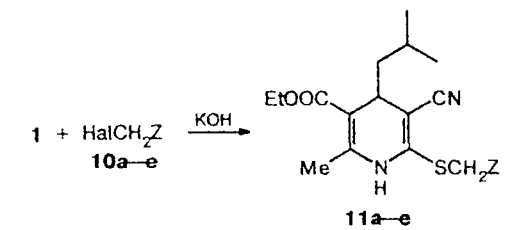
Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	S	Molecular formula
11a	83	107—109	61.01 61.19	7.58 7.53	9.44 9.51	10.82 10.89	$C_{15}H_{22}N_2O_2S$
11b	74	174—176	56.85 56.95	6.94 6.87	12.33 12.45	9.46 9.50	$C_{16}H_{23}N_3O_3S$
11c	76	172—173	66.24 66.31	6.59 6.58	7.14 7.03	7.91 8.05	$C_{22}H_{26}N_2O_3S$
11d	85	161—163	63.31 63.44	5.89 6.05	6.64 6.73	7.65 7.70	$C_{22}H_{25}FN_2O_3S$
11e	66	153—155	60.89 61.03	5.72 5.82	6.41 6.47	7.32 7.41	$C_{22}H_{25}ClN_2O_3S$

Dilution of the reaction mixtures with 10% HCl results in the formation of thione **1**, which is dehydrogenated to the stable compound **9** upon treatment with boiling glacial acetic acid on air access.

^{1}H NMR spectroscopic data suggest that pyridinethione **1** in DMSO exists as a 1 : 1 tautomeric mixture of thione **1A** and thiol **1B**, which is evidenced by doubled signals for the protons of the Me(C6) group and the NH group. The IR spectrum of a suspension of thione **1** in Vaseline oil exhibits two absorption bands at 2254 and 2195 cm^{-1} corresponding to the stretching vibrations of the cyano group, which indicates that the above-mentioned tautomerism is also valid in the crystalline state.

The reaction of compound **1** with halides **10** in an alkaline medium yields sulfides **11** (Scheme 2), whose structures were confirmed by physicochemical methods (Tables 1 and 2).

Scheme 2



	a	b	c	d	e
Hal	I	Cl	Br	Br	Br
Z	H	$CONH_2$	PhCO	4-FC_6H_4CO	4-ClC_6H_4CO

Experimental

IR spectra were recorded on an IKS-29 spectrophotometer (Vaseline oil). ^{1}H NMR spectra were recorded on a Bruker WP-100 SY instrument (100 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The course of reaction and the individuality of compounds were monitored by TLC on Silufol UV-254 plates (acetone—heptane (3 : 5) as the eluent).

Table 2. Spectral characteristics of compounds **11a—e**

Compound	IR ν/cm^{-1}	^{1}H NMR, δ
11a	3290 (NH); 2186 (CN); 1698 (CO)	0.88 (t, 6 H, 2 CH_3); 1.22 (t, 5 H, CH_2, OCH_2CH_3);[a] 1.65 (m, 1 H, CH); 2.24 (s, 3 H, 6-Me); 2.48 (s, 3 H, SCH_3); 3.32 (m, 1 H, C(4)H); 4.08 (q, 2 H, OCH_2CH_3); 9.43 (br.s, 1 H, NH)
11b	3375, 3180, 3075 (NH, NH_2); 2192 (CN); 1698, 1620 (CO)	0.86 (t, 6 H, 2 CH_3); 1.21 (t, 5 H, CH_2, OCH_2CH_3);[a] 1.64 (m, 1 H, CH); 2.22 (s, 3 H, 6-Me); 3.38 (m, 1 H, C(4)H); 3.65 (q, 2 H, SCH_2); 4.08 (q, 2 H, OCH_2CH_3); 7.53, 7.85 (both br.s, 2 H, $CONH_2$)[b]
11c	3290 (NH); 2176 (CN); 1690, 1625 (CO)	0.84 (t, 6 H, 2 CH_3); 1.20 (t, 5 H, CH_2, OCH_2CH_3);[a] 1.60 (m, 1 H, CH); 2.21 (s, 3 H, 6-Me); 3.37 (m, 1 H, C(4)H); 4.08 (q, 2 H, OCH_2CH_3); 4.68 (s, 2 H, SCH_2); 7.61—7.98 (m, 5 H, Ph); 9.51 (br.s, 1 H, NH)
11d	3290 (NH); 2191 (CN); 1697, 1635 (CO)	0.85 (t, 6 H, 2 CH_3); 1.21 (t, 5 H, CH_2, OCH_2CH_3);[a] 1.60 (m, 1 H, CH); 2.21 (s, 3 H, 6-Me); 3.37 (m, 1 H, C(4)H); 4.09 (q, 2 H, OCH_2CH_3); 4.64 (s, 2 H, SCH_2); 7.37 (t), 8.04 (q) (each 2 H, Ar); 9.51 (br.s, 1 H, NH)
11e	3315 (NH); 2195 (CN); 1693, 1634 (CO)	0.86 (t, 6 H, 2 CH_3); 1.23 (t, 5 H, CH_2, OCH_2CH_3);[a] 1.61 (m, 1 H, CH); 2.23 (s, 3 H, 6-Me); 3.38 (m, 1 H, C(4)H); 4.10 (q, 2 H, OCH_2CH_3); 4.65 (s, 2 H, SCH_2); 7.61, 7.99 (both d, each 2 H, Ar); 9.52 (br.s, 1 H, NH)

[a] The proton signals are overlapped.
[b] No signal for the NH proton; probably, due to deuterium exchange.

3-Cyano-5-ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyridine-2(1*H*)-thione (1). *A.* A mixture of isovaleraldehyde (**2**) (5.38 mL, 50 mmol), cyanothioacetamide (**3**) (5 g, 50 mmol), ethyl acetoacetate (**4**) (6.35 mL, 50 mmol), and morpholine (6.54 mL, 75 mmol) in 75 mL of ethanol was stirred at 20 °C for 3 h and diluted with 10% HCl to pH 5. The precipitate that formed after 24 h was filtered off and washed with ethanol and hexane to give thione **1** (10.94 g, 78%), m.p. 128—130 °C. IR, ν/cm^{-1}: 3300 (NH); 2254, 2195 (CN); 1690 (C=O). ^{1}H NMR, δ: 0.85 (m, 6 H, 2 CH_3); 1.25 (m, 5 H, CH_2, OCH_2CH_3); 1.57 (m, 1 H, CH); 2.29, 2.35 (both s, 3 H, 6-Me); 3.12 (m, 1 H, C(4)H); 4.15 (q, 2 H, OCH_2CH_3); 4.70 (d, 1 H, C(3)H); 11.95, 12.22 (both br.s, 1 H, NH). Found (%): C, 59.88; H, 7.08; N, 9.91; S, 11.32. $C_{14}H_{20}N_2O_2S$. Calculated (%): C, 59.97; H, 7.19; N, 9.99; S, 11.44.

B. Morpholine (3 drops) and ethyl 3-morpholinobut-2-enate (**5**) (9.96 g, 50 mmol) were added with stirring to a mixture of isovaleraldehyde (**2**) (5.38 mL, 50 mmol) and cyanothioacetamide (**3**) (5 g, 50 mmol) in 75 mL of ethanol at 20 °C. After 3 h, the reaction mixture was diluted with 10% HCl to pH 5 and left for 24 h. The precipitate that formed was filtered off and washed with ethanol and hexane to give thione **1** (9.81 g, 70%) spectrally identical to the compound synthesized by method *A*.

3-Cyano-5-ethoxycarbonyl-4-isobutyl-6-methylpyridine-2(1*H*)-thione (9). Substituted pyridinethione **1** (2.8 g,

10 mmol) was recrystallized by dissolving it in 15 mL of boiling glacial acid in air and subsequent cooling. The precipitate that formed after 24 h was filtered off and washed with ethanol and hexane to give compound **9** (1.84 g, 66%), m.p. 172—174 °C. IR, ν/cm^{-1}: 3180 (NH); 2214 (CN); 1620 (C=O). ^1H NMR, δ: 0.90 (d, 6 H, 2 CH_3); 1.30 (t, 3 H, OCH_2CH_3); 1.70 (m, 1 H, CH); 2.42 (s, 3 H, 6-Me); 2.69 (d, 2 H, CH_2); 4.33 (q, 2 H, OCH_2CH_3); 14.20 (br.s, 1 H, NH). Found (%): C, 60.30; H, 6.44; N, 9.01; S, 11.44. $C_{14}H_{18}N_2O_2S$. Calculated (%): C, 60.41; H, 6.52; N, 10.06; S, 11.52.

3-Cyano-5-ethoxycarbonyl-4-isobutyl-6-methyl-2-Z-methylthio-1,4-dihydropyridines (11a—e). A 10% aqueous solution of KOH (5.6 mL, 10 mmol) and, after 1 min, the corresponding halide **10** (10 mmol) were added with stirring to a suspension of thione **1** (2.8 g, 10 mmol) in 20 mL of ethanol. The precipitate that formed after 4 h was filtered off, washed with ethanol and hexane, and recrystallized from butan-1-ol to give compounds **11a—e** (see Tables 1 and 2).

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