Synthesis of 4,5,6-trisubstituted 3-cyanopyridine-2(1*H*)-thiones based on α -substituted β -diketones

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5-Substituted 3-cyano-4,6-dimethylpyridine-2(1*H*)-thiones were synthesized by the reaction of α -substituted β -diketones with cyanothioacetamide in the presence of triethylamine. The compounds synthesized were converted into thieno[2,3-*b*]pyridines by treatment with organic halides and KOH.

Key words: 5-substituted 3-cyano-4,6-dimethylpyridine-2(1H)-thiones, cyanothio-acetamide, cyclization, thieno[2,3-b]pyridines.

4,5,6-Trisubstituted 3-cyanopyridine-2(1*H*)-thiones and their derivatives are known as intermediates in syntheses of medicinal preparations, in particular, antiallergens.¹ However, only a few examples of the use of α -substituted β -diketones for the preparation of 4,5,6-trisubstituted 3-cyanopyridine-2(1*H*)-thiones have been reported.^{1,2}

In the present work we studied the interaction of 3-substituted 2,4-pentanediones $(1\mathbf{a}-\mathbf{d})$ with cyanothioacetamide (CTA). It was shown that acetylacetone derivatives $1\mathbf{a}-\mathbf{d}$ react with CTA in anhydrous ethanol in the presence of an organic base to give 5-substituted 3-cyano-4,6-dimethylpyridine-2(1*H*)-thiones $(2\mathbf{a}-\mathbf{d})$ (Scheme 1). The starting compounds $1\mathbf{a}-\mathbf{d}$ were synthesized in 50–60% yields by alkylation of Na or K salts of acetylacetone with halides HalCH₂Z using known procedures.^{3,4}

Pyridinethiones 2a-d are yellow crystalline substances. Their structures were confirmed by the data of



elemental analysis and spectroscopy (Tables 1 and 2). Their IR spectra exhibit intense bands in the 2215– 2234 cm⁻¹ region (CN); the spectra of compounds **2a**,**b** also contain signals at 1678–1684 cm⁻¹ (CO). The ¹H NMR spectra exhibit a broadened singlet corresponding to NH in the 13.68–13.77 ppm region, which

Com- pound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found Calculated (%)				Molecular formula
				С	Н	N	S	
2a	282	40	271–273 (AcOH)	<u>68.24</u> 68.06	<u>4.80</u> 4.99	<u>9.81</u> 9.92	<u>11.16</u> 11.36	C ₁₆ H ₁₄ N ₂ OS
2b*	361	92	283—285 (AcOH)	<u>53.27</u> 53.19	<u>3.45</u> 3.63	<u>7.88</u> 7.76	<u>8.95</u> 8.88	$C_{16}H_{13}BrN_2OS$
2c	204	30	203—205 (EtOH)	<u>64.51</u> 64.67	<u>5.74</u> 5.92	<u>13.77</u> 13.71	<u>15.81</u> 15.70	$C_{11}H_{12}N_2S$
2d	218	56	228—230 (EtOH)	<u>65.89</u> 66.02	<u>6.30</u> 6.46	<u>12.71</u> 12.83	<u>14.58</u> 14.69	C ₁₂ H ₁₄ N ₂ S
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Table 1. Characteristics of 5-substituted 3-cyano-4,6-dimethylpyridine-2(1H)-thiones 2a-d

• The content of Br: found 21.70%; calculated 22.12%.

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Cor po- und	m- IR spectrum I (KBr), v/cm ⁻¹	Mass spectrum, m/z (1 (%))	¹ H NMR spectrum (DMSO-d ₆ , δ)
2a	1678(CO) 2234(CN)	282 (20.22), 177 (8.98), 106 (40.26), 105 (57.81)	2.27 (s, 3 H, Me); 2.32 (s, 3 H, Me); 4.45 (s, 2 H, CH ₂ CO); 7.59 (t, 2 H, H _{arom}); 7.70 (t, 1 H, H _{arom}); 8.1 (d, 2 H, H _{arom}); 13.70 (br.s, 1 H, NH)
2b	1684(CO) 2230(CN)	362 (4.93), 185 (43.79), 183 (42.94), 177 (7.39), 156 (16.01), 154 (15.41), 105 (37.27)	2.27 (s, 3 H, Me); 2.32 (s, 3 H, Me); 4.41 (s, 2 H, CH_2CO); 7.8 (d, 2 H, H_{arom}); 8.0 (d, 2 H, H_{arom}); 13.74 (br.s, 1 H, NH)
2c	2213(CN)	204 (53.49), 203 (17.91), 189 (37.19), 177 (41.87), 162 (13.12)	2.38 (s, 6 H, Me); 3.28* (m, 2 H, \underline{CH}_2 -Het); 5.0 (m, 2 H, \underline{CH}_2 =CH); 5.85 (m, 1 H, \underline{CH} =CH ₂); 13.77 (br.s, 1 H, NH)
2đ	2215(CN)	218 (100, M ⁺), 203 (36.51), 188 (24.95), 177 (16.37), 170 (15.71)	1.55 (d, 3 H, <u>Me</u> -CH=CH); 2.33 (s, 6 H, Me); 3.20* (m, 2 H, CH ₂ -Het); 5.35 (m, 2 H, CH=CH); 13.68 (br.s, 1 H, NH)

 Table 2. Spectral characteristics of 5-substituted 3-cyano-4,6-dimethylpyridine-2(1H)-thiones 2a-d

*The signal overlaps with the signal of H_2O .

indicates that these compounds exist in the thione tautomeric form. The molecular ions found in the mass spectra of the pyridinethiones 2a-d synthesized correspond to the calculated values (Table 2). A typical feature of the mass spectra of compounds 2a,b is the presence of low-intensity molecular ions M⁺. One of the basic routes for the decomposition of the molecular ions is the elimination of the C₆H₅CO[•] radical (in the case of 2a) or the *p*-BrC₆H₄CO[•] radical (for **2b**). A different mass-spectral pattern is observed for thiones **2c**,d. These mass spectra have molecular ion peaks M⁺ with high intensities.

A study of the chemical properties of the thiones 2a-d synthesized showed that these compounds are readily alkylated at the sulfur atom by halides HalCH₂Z (**3a**-c) and can serve as a base for the synthesis of new heterocyclic systems.

For example, the reaction of compound 2a with methyl iodide (3a) in ethanol in the presence of an equimolar amount of KOH (a 10% aqueous solution) gave 3-cyano-4,6-dimethyl-2-methylthio-5-phenacylpyridine (4) (Scheme 2) in a quantitative yield; the structure of this compound was confirmed by the data of ¹H NMR and IR spectra (Tables 3 and 4). The IR spectrum of compound 4 exhibits an intense absorption





3: Hal = 1, Z = H (**a**); Hal = Br, Z = Bz (**b**); Hal = Br, Z = $COC_6H_4Br-\rho$ (**c**); **4:** R = $CH_2COC_6H_5$, Z = H; **5:** R = CH_2COPh , Z = Bz (**a**); R = $CH_2COC_6H_4Br-\rho$, Z = $COC_6H_4Br-\rho$ (**b**); R = $CH_2CH=CHMe$, Z = $COC_6H_4Br-\rho$ (**c**)

band at 1690 cm⁻¹ (v(CO)) and an absorption band at 2133 cm⁻¹ (v(CN)). A typical feature of the ¹H NMR spectrum of compound **4** is the presence of a singlet in the region of 2.6 ppm corresponding to the protons of the SMe group.

In the presence of a twofold excess of KOH, thiones 2a,b,d readily react with halides 3b,c; these reactions involve the sulfur atom and give 5-substituted 3-amino-4,6-dimethylthieno[2,3-b]pyridines (5a-c) (Scheme 2), whose structure was confirmed by the spectral data (Tables 3 and 4).

Experimental

IR spectra were recorded on a UR-20 spectrophotometer in pellets with KBr. ¹H NMR spectra were obtained on a Bruker WM-250 spectrometer (250 MHz, DMSO-d₆), and mass spectra were run on a Varian MAT-313 A mass spectrometer.

3-Acetyl-1-phenylpentane-1,4-dione (1a) and 3-(*p*-bromophenacyl)pentane-2,4-dione (1b) were prepared in 60% yields by a known procedue, ³ and 3-allylpentane-2,4-dione (1c) and 3-crotylpentane-2,4-dione (1d) were synthesized in 50-60 % yields by a previously described method.⁴

5-Substituted 3-cyano-4,6-dimethylpyridine-2(1*H*)-thiones (2a-d). Cyanothioacetamide (5 mmol) and an equimolar amount of Et₃N were added to α -substituted acetylacetone **la**-d (5 mmol) in 20 mL of anhydrous ethanol. The mixture was brought to boiling, cooled, and acidified with a 17% aqueous solution of HCl to pH 2. The precipitate that formed was filtered off and recrystallized. The characteristics of compounds 2a-d are presented in Tables 1 and 2.

3-Cyano-4,6-dimethyl-2-methylthio-5-phenacylpyridine (4). A 10% aqueous solution of KOH (2.8 mL, 5 mmol) and then methyl iodide (0.78 g, 5.5 mmol) were added dropwise with stirring to a solution of thione 2a (1.41 g, 5 mmol) in 10 mL

Com- pound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found (%) Calculated				Molecular formula
				C.	H.	N	S	
4	296	100	193—195 (EtOH)	<u>68.80</u> 68.89	<u>5.23</u> 5.44	<u>9.32</u> 9.45	<u>10.91</u> 10.82	C ₁₇ H ₁₆ N ₂ OS
5 a	400	68	234—235 (EtOH)	<u>71.86</u> 71.97	<u>5.16</u> 5.03	<u>6.85</u> 6.99	<u>8.18</u> 8.01	$C_{24}H_{20}N_2O_2S$
5 b *	558	62	230—231 (CHCl ₃)	<u>51.43</u> 51.63	<u>3.02</u> 3.25	<u>5.00</u> 5.02	<u>5.79</u> 5.74	C ₂₄ H ₁₈ Br ₂ N ₂ O ₂ S
5c**	415	50	171—173 (EtOH)	<u>57.66</u> 57.83	<u>4.38</u> 4.61	<u>6.61</u> 6.75	<u>7.80</u> 7.72	$C_{20}H_{19}BrN_2OS$

Table 3. Characteristics of 3-cyano-4,6-dimethyl-2-methylthio-5-phenacylpyridine (4) and 5-substituted 3-amino-4,6-dimethylthion[2,3-b]pyridines (**5a**-c)

* The content of Br: found 28.19%; calculated 28.63%.

** The content of Br: found 18.82%; calculated 19.24%.

Table 4. Spectral characteristics of 3-cyano-4,6-dimethyl-2-methylthio-5-phenacylpyridine 4 and 5-substituted 3-amino-4,6-dimethylthieno[2,3-b]pyridines (**5a**-c)

Com po- und	- IR spectrum (KBr), v/cm ⁻¹	¹ H NMR spectrum (DMSO-d ₆ , δ)
4	1690 (CO) 2133 (CN)	2.32 (s, 3 H, Me); 2.44 (s, 3 H, Me); 2.6 (s, 3 H, SMe); 4.6 (s, 2 H, CH_2CO); 7.58 (t, 2 H, H_{arom}); 7.7 (t, 1 H, H_{arom}); 8.12 (d, 2 H, H_{arom})
5a	1690 (CO)	2.45 (s, 3 H, Me); 2.63 (s, 3 H, Me); 4.62 (s, 2 H, CH ₂ CO); 7.55, 7.75, 8.15 (10 H, H _{arom} + 2 H, NH ₂)
5b	1695 (CO)	2.43 (s, 3 H, Me); 2.62 (s, 3 H, Me); 4.7 (s, 2 H, CH ₂ CO); 7.68 (s, 2 H, NH ₂); 7.8 (d, 4 H, H _{aron}); 8.1 (d, 4 H, H _{aron})
5c	1690 (CO)	1.6 (d, 3 H, <u>Me</u> -CH=CH); 2.5* (s, 3 H, Me); 2.49 (s, 3 H, Me); 3.4 (s, 2 H, CH ₂ -Het); 5.28 (m, 1 H, CH=CH); 5.52 (m, 1 H, CH=CH); 7.65 (d, 2 H, H _{arom}); 7.75 (d, 2 H, H _{arom}); 8.18 (s, 2 H, NH ₂)

* The signal overlaps with the signal of DMSO.

of ethanol. The mixture was kept for 1-2 min at 60 °C and diluted with an equal volume of water. The precipitate that formed was filtered off and recrystallized. The characteristics of compound **4** are listed in Tables in 3 and 4.

5-Substituted 3-amino-4,6-dimethylthieno[2,3-b]pyridines (5a-c). A 10% aqueous solution of KOH (10 mmol) and compound 3b,c (5 mmol) were added to a solution of thione 2a,b,d in 10 mL of DMF or ethanol. The mixture was stirred for 10-15 min at 60 °C and diluted with an equal volume of water. The precipitate that formed was filtered off and recrystallized. The characteristics of compounds 5a-c are listed in Tables 3 and 4.

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