Synthesis of 6-substituted 3-cyano-5-nitropyridine-2(1*H*)-thiones

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The reactions of 1-substituted 2-nitro-3-phenylaminoprop-2-en-1-ones with cyanothioacetamide afforded the corresponding 6-substituted 3-cyano-5-nitropyridine-2(1*H*)-thiones, which were used for the synthesis of 6-substituted 3-cyano-2-methylthio-5-nitropyridines and 7-substituted 4-hydroxy-8-nitropyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-2(1*H*)-ones.

Key words: cyanothioacetamide, 1-substituted 2-nitro-3-phenylaminoprop-2-en-1-ones, 3-cyano-5-nitropyridine-2(1*H*)-thiones, 3-cyano-2-methylthio-5-nitropyridines, pyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-2(1*H*)-ones.

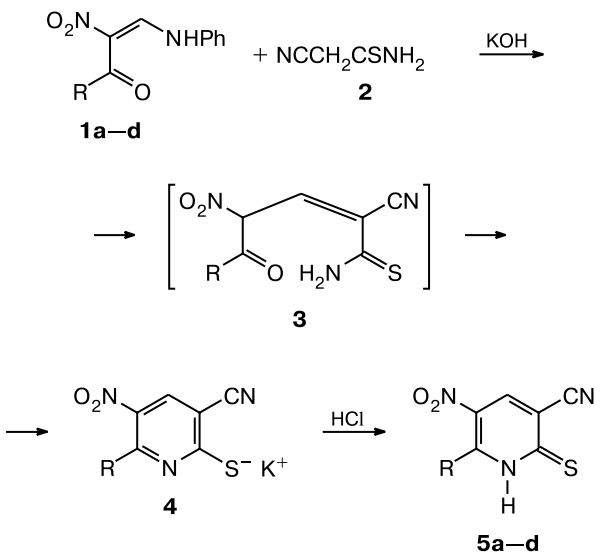
The use of substituted 3-cyanopyridinethiones in the synthesis of practically important compounds, *viz.*, dyes, drugs, pesticides, *etc.*, gives impetus to the extensive development of procedures for their preparation.[1—3] β-Enaminocarbonyl compounds serve as convenient reagents for the regioselective synthesis of substituted 3-cyanopyridine-2(1*H*)-thiones and their hydrogenated analogs.[4,5] Thus, the reactions of β-enaminocarbonyl compounds with cyanothioacetamide afforded various 3-cyanopyridine-2(1*H*)-thiones containing the acetyl, alkoxycarbonyl, or cyano group at position 5. The reaction of the sodium salt of nitromalondialdehyde with cyanothioacetamide[6] was the only example of the synthesis of 3-cyano-5-nitropyridine-2(1*H*)-thiones published in the literature. Because of this, the chemical properties of nitro-substituted 3-cyanopyridine-2(1*H*)-thiones remained virtually unknown.

In the present study, we carried out the regioselective synthesis of substituted 3-cyano-5-nitropyridine-2(1*H*)-thiones based on β-enaminocarbonyl compounds and studied some chemical transformations of nitro-containing pyridinethiones.

We used 1-substituted 1-nitro-2-phenylaminoethylenes **1a—d** as β-enaminocarbonyl compounds. These enamines were prepared according to a known procedure[7] by condensation of the corresponding α-nitrocarbonyl compounds, trimethyl orthoformate, and aniline. We chose compounds **1a—d** as enamines because they are more stable and can be more easily isolated than free nitrodicarbonyl compounds.

We found that the reactions of enamines **1a—d** with cyanothioacetamide **2** in water in the presence of a 10% KOH solution (Scheme 1) followed by acidification of the reaction mixture with hydrochloric acid afforded 6-substituted 3-cyano-5-nitropyridine-2(1*H*)-thiones **5a—d** in 95—98% yields. The reactions proceeded regioselectively at 40—45 °C through, apparently, the formation of intermediate **3** followed by cyclization to give thiolate **4**.

Scheme 1



R = EtO (**1a**), OH (**5a**), Ph (**1b**, **5b**), 4-MeC_6H_4 (**1c**, **5c**), 4-$MeOC_6H_4$ (**1d**, **5d**)

The structures of the compounds thus synthesized were confirmed by ^{1}H NMR and IR spectroscopy and elemental analysis. The ^{1}H NMR spectra of compounds **5a—d** have characteristic singlets for the H(4) protons of the pyridine ring at δ 8.26—8.67. The IR spectra have absorp-

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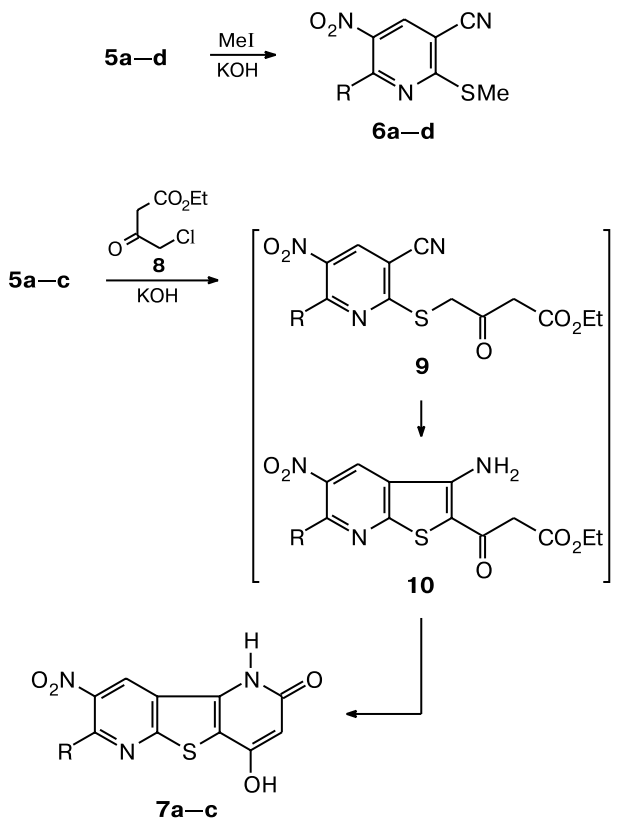
Scheme 2



6, 7: R = OH (**a**), Ph (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**)

tion bands of the cyano groups at 2224—2240 cm^{-1}, which are characteristic of 3-cyanopyridine-2(1*H*)-thiones, and intense absorption bands at 1564—1592 and 1324—1328 cm^{-1} corresponding respectively to symmetrical and asymmetrical vibrations of the nitro group.

Compounds **5a—d** undergo chemical transformations (Scheme 2) typical of 3-cyanopyridine-2(1*H*)-thiones. The reactions of compounds **5a—d** with iodomethane in ethanol in the presence of an equivalent amount of KOH produced substituted 2-(methylthio)pyridines **6a—d**. 3-Cyano-5-nitropyridine-2(1*H*)-thiones **5a—c** were used also in the synthesis of difficultly accessible annelated nitropyridines **7a—c** according to a procedure described earlier.[8] This procedure involved alkylation of ethyl 4-chloroacetoacetate (**8**) followed by cyclization of intermediate ethyl 4-(pyridylthio)acetoacetates **9** and ethyl 3-(3-aminothieno[2,3-*b*]pyrid-2-yl)-3-oxopropionates **10** in the presence of an excess of KOH.

The ^{1}H NMR spectra of compounds **7a—c** have singlets at δ 5.69—5.85 belonging to the C(3)H protons and singlets at δ 12.10—12.25 belonging to the N(1)H protons. These signals are characteristic of 4-hydroxypyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-2(1*H*)-ones.[1,8] The assignment of the signals of the hydroxy groups in the ^{1}H NMR spectra of compounds **7a—c** presented difficulties due, apparently, to association of these compounds with water, deuterium exchange in DMSO-d_6, and low solubility in other solvents used in NMR spectroscopy.

Experimental

The melting points were measured on a Kofler hot-stage apparatus. The IR spectra were recorded on a Perkin—Elmer 577 instrument (in KBr). The ^{1}H NMR spectra were measured on a Bruker WM-250 instrument in DMSO-d_6. The mass spectra were obtained on a MAT INCOS-50 Finnigan instrument (energy of ionizing electrons was 70 eV). Elemental analysis was performed on a Perkin—Elmer C,H,N analyzer.

Synthesis of compounds 5a—d (general procedure). A 10% aqueous solution of KOH (2.35 mL) was added dropwise with stirring to a suspension of compounds **1a—d** (3 mmol) and cyanothioacetamide (**2**) (0.31 g, 3.1 mmol) in water (3 mL) at 30—35 °C for 5 min. The resulting solution was stirred at 40—45 °C for 20 min, cooled to 20 °C, and acidified with concentrated HCl (0.5 mL). The precipitate that formed was filtered off, washed with water and hexane, and recrystallized from

Table 1. Characteristics of 6-substituted 3-cyano-5-nitropyridine-2(1*H*)-thiones **5a—d**

Compound	R	Yield (%)	Found / Calculated (%)				Molecular formula	IR, ν/cm^{-1}		^{1}H NMR, δ, ^3J/Hz		MS $[M]^+$ *m/z*
			C	H	N	S		CN	NO_2	H(4) (s, 1 H)	Other signals	
5a	OH	98	36.71 36.55	1.56 1.53	21.10 21.31	16.12 16.26	$C_6H_3N_3O_3S$	2224	1328, 1564	8.26	11.78 (s, 1 H, NH, OH)	—
5b	Ph	97	56.14 56.02	2.82 2.74	16.69 16.33	12.23 12.46	$C_{12}H_7N_3O_2S$	2240	1328, 1584	8.67	7.56 (m, 5 H, Ph)	257
5c	4-MeC_6H_4	96	57.68 57.56	3.45 3.32	15.78 15.49	11.78 11.82	$C_{13}H_9N_3O_2S$	2232	1324, 1588	8.65	2.41 (s, 3 H, Me); 7.29, 7.36 (both d, 2 H each, J = 8.2)	271
5d	4-$MeOC_6H_4$	95	54.63 54.35	3.17 3.16	14.79 14.63	11.23 11.16	$C_{13}H_9N_3O_3S$	2224	1324, 1592	8.57	3.85 (d, 3 H, MeO); 7.02, 7.43 (both d, 2 H each, J = 8.3)	287

Table 2. Characteristics of 6-substituted 3-cyano-2-methylthio-5-nitropyridines **6a—d**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula	IR, ν/cm^{-1}		^{1}H NMR, δ, ^3J/Hz			MS [M]$^+$ *m/z*
			C	H	N	S		CN	NO_2	H(4) (s, 1 H)	SMe (s, 3 H)	Other signals	
6a	40	271 (decomp.)	40.09 39.81	2.42 2.39	19.70 19.90	15.08 15.18	$C_7H_5N_3O_3S$	2224	1304, 1576	8.13	2.41	11.65 (s, 1 H, NH, OH)	211
6b	50	129—130	57.51 57.56	3.44 3.34	15.61 15.49	11.69 11.82	$C_{13}H_9N_3O_2S$	2224	1340, 1540	8.36	2.75	7.56 (m, 5 H, Ph)	271
6c	63	130—131	59.11 58.94	4.01 3.89	14.78 14.73	11.36 11.24	$C_{14}H_{11}N_3O_2S$	2224	1336, 1584	8.87	2.71	2.39 (s, 3 H, Me); 7.31 (d, 2 H, C_6H_4, J = 8.4); 7.52 (d, 2 H, C_6H_4, J = 8.4)	285
6d	76	132—133	55.79 55.81	3.73 3.84	14.12 13.95	10.78 10.64	$C_{14}H_{11}N_3O_3S$	2224	1340, 1568	8.81	2.72	3.85 (s, 3 H, MeO); 7.05 (d, 2 H, C_6H_4, J = 8.4); 7.62 (d, 2 H, C_6H_4, J = 8.4)	301

Table 3. Characteristics of 7-substituted 4-hydroxy-8-nitropyrido[2′,3′:4,5]thieno[2,3-*b*]pyridin-2(1*H*)-ones **7a—c**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula	IR, ν/cm^{-1}		^{1}H NMR, δ, ^3J/Hz			
			C	H	N	S		CONH, OH, *etc.*	NO_2	H(3)	H(9)	NH (OH)	Other signals
										s, 1 H			
7a	40	>300	42.97 43.02	1.78 1.80	14.82 15.05	11.32 11.48	$C_{10}H_5N_3O_5S$	1656, 3648, 3632	1380, 1548	5.69	9.31	12.10	7.91 (s, 1 H, OH)
7b	86	>300	56.69 56.63	2.72 2.67	12.29 12.38	9.32 9.45	$C_{16}H_9N_3O_4S$	1640, 3592, 3376, 3056	1372, 1540	5.85	9.32	12.25	7.61 (m, 5 H, Ph)
7c	88	>300	57.90 57.79	3.17 3.14	11.78 11.89	9.11 9.07	$C_{17}H_{11}N_3O_4S$	1640, 3056, 3240, 3580	1344, 1544	5.82	9.32	12.22	2.39 (s, 3 H, Me); 7.29 (d, 2 H, C_6H_4, J = 8.2); 7.47 (d, 2 H, C_6H_4, J = 8.2)

EtOH. The characteristics of compounds **5a—d** are given in Table 1.

Synthesis of compounds 6a—d (general procedure). A 10% aqueous solution of KOH (0.56 mL) and MeI (0.1 mL, 1.4 mmol) were successively added dropwise to a suspension of compounds **5a—d** (1 mmol) in EtOH (3 mL). After 1 h, the precipitate that formed was filtered off and recrystallized from hexane. The characteristics of compounds **6a—d** are given in Table 2.

Synthesis of compounds 7a—c (general procedure). A 10% aqueous solution of KOH (0.56 mL) was added dropwise with stirring to a suspension of compounds **5a—c** (1 mmol) in EtOH (3 mL). Then ethyl 4-chloroacetoacetate (**8**) (0.14 mL, 1 mmol) was added and the reaction mixture was kept for 5 min, after which a precipitate formed. A 10% aqueous solution of KOH (0.84 mL) was added to the resulting mixture and the mixture was heated until a transparent solution was obtained. The solu-

tion was cooled to ~20 °C and then concentrated HCl (0.15 mL) was added. The precipitate that formed was filtered off and washed successively with EtOH, water, and hexane. The characteristics of compounds **7a—d** are given in Table 3.

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