Chemistry of Heterocyclic Compounds, Vol. 32, No. 8, 1996

SYNTHESIS AND TRANSFORMATIONS OF 6-AMINO-3,5-DICYANO-4-ETHYLPYRIDINE-2(1H)-THIONE

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The condensation of propionaldehyde with cyanothioacetamide gives 6-amino-3,5-dicyano-4-ethylpyridine-2(1H)-thione, which was used to obtain substituted 2-alkylthiopyridines, 2-ethylthio-6- ethylaminopyridine, and pyrazolo[3,4-b]pyridine.

Pyridine-2-(1H)-thiones containing two cyano groups and other substituents on the pyridine ring in addition to the thione moiety are promising synthones in organic synthesis, in particular, for obtaining biologically active compounds and other derivatives with practical importance [1, 2]. In order to develop synthetic methods for such compounds with an alkyl substituent at $C_{(4)}$ of the pyridine ring, we carried out the reaction of propionaldehyde (I) with cyanothioacetamide (II) in ethanol in the presence of excess N-methylmorpholine at 20°C; the I:II ratio was 1:2. This reaction yielded previously unreported 6-amino-3,5-dicyano-4-ethylpyridine-2(1H)-thione (III), probably, through the initial formation of the Knoevenagel condensation product (IV), which is transformed by reaction with a second equivalent of thioamide II to give a Michael adduct (V). Under the reaction conditions, V undergoes cyclocondensation and the elimination of hydrogen sulfide to give salt VI, which, upon treatment with dilute hydrochloric acid, gives thione III.

The alkylation of thione III and its salt VI was studied. Sulfides VIIIa-VIII*l* and IX were obtained from the action of halides VIIa-VII*l* or phenylchloracetamide on salt VI. In the case of excess alkylating agent VIIb, the amino group of thione III is alkylated in addition to the thione group, leading to 6-ethylamino-2-ethylthio-3,5-dicyano-4-ethylpyridine (X) (method A), which is identical to the product obtained by treating sulfide VIIIb with alkyl halide VIIb (method B). The use of dihaloalkanes in this reaction leads to previously unreported di(pyridylthio)ethane (XIa) and di(pyridylthio)butane (XIb). We should note that sulfide VIIIa undergoes nucleophilic exchange with hydrazine, whose product then cyclizes with the formation of pyrazolo[5,4-*b*]pyridine derivative (XII).

The structures of products III, VI, and VIII-XII were confirmed by their spectral data. Thus, the IR spectra of these compounds have stretching bands for a conjugated nitrile group at 2190-2230 cm^{-1} and an NH_2 group at 3160-3420 cm^{-1}. The most characteristic signals in the PMR spectra of these products is for the amino group protons at 7.90-8.00 ppm, ethyl substituent at 2.70 and 1.20 ppm, as well as the signal for the protons of the substituent at the sulfur atom (see Table 2).

EXPERIMENTAL

The PMR spectra were taken on a Bruker WP-100SY spectrometer at 100 MHz in DMSO-d_6 with TMS as the internal standard. The IR spectra were taken on an IKS-29 spectrometer for vaseline mulls. The reaction course and purity of the compounds were monitored by thin-layer chromatography on Silufol UV-254 plates using 3:5 acetone—hexane as the eluent.

N-Methylmorpholinium 6-Amino-3,5-dicyano-4-ethylpyridine-2-thiolate (VI). A mixture of 10 mmoles propionaldehyde I, 20 mmoles cyanothioacetamide II and 20 mmoles N-methylmorpholine in 20 ml abs. ethanol was stirred for 8 h at 20°C and then maintained at this temperature for an additional 24 h. The precipitate formed was filtered off and washed with

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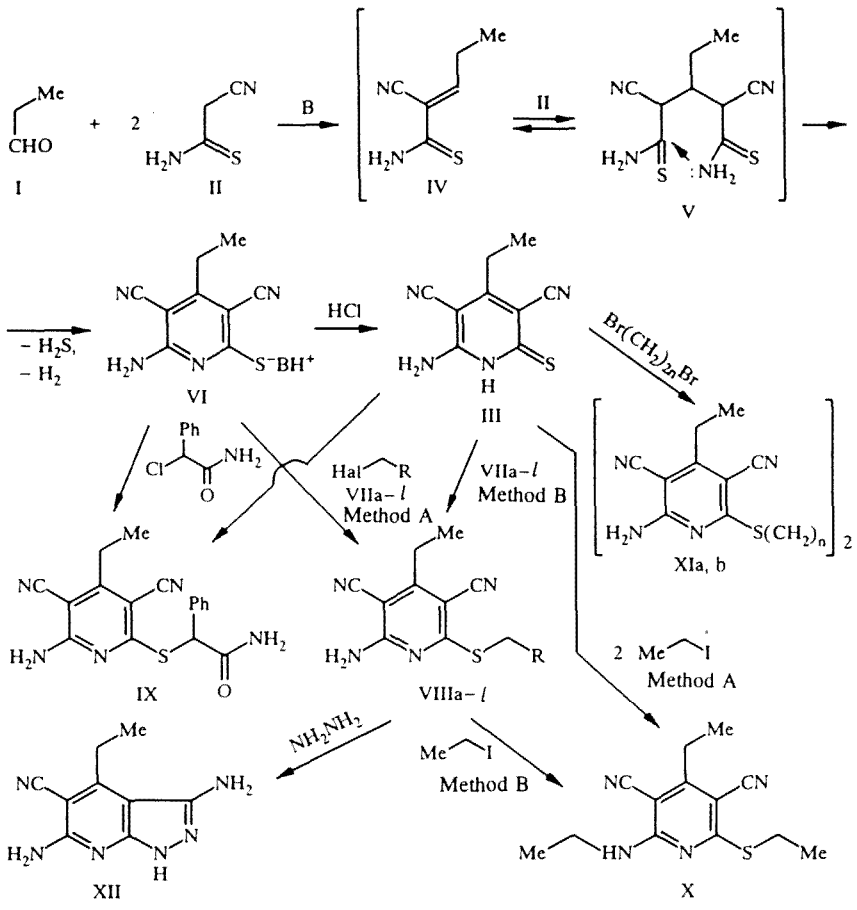
 0009-3122/96/3208-0942 $15.00



B = N-methylmorpholine. VII, VIII a Hal = I, R = H; b Hal = I, R = Me;
c Hal = Br, R = CH=CH$_2$; d Hal = Br, R = Et; e Hal = Cl, R = COOH;
f Hal = Cl, R = Ph; g Hal = Br, R = 2-MeC$_6$H$_4$; h Hal = Br, R = 3-BrC$_6$H$_4$CO;
i Hal = Br, R = 4-Ph-C$_6$H$_4$CO; j Hal = Br, R = 2,4-Me$_2$C$_6$H$_3$CO; k Hal = Br, R = 4-ClC$_6$H$_4$CO;
l Hal = Br, R = 3-coumarinylcarbonyl. XI a a = 1; b n = 2

ethanol to give 2.1 g (70%) salt VI, mp 266-269°C (subl.). PMR spectrum in DMSO-d_6: 8.2 (2H, s, NH_2), 3.68 (4H, t, CH_2OCH_2), 2.85 (4H, t, CH_2NCH_2), 2.60 (2H, q, CH_2), 2.56 (3H, s, N—CH_3), 1.19 ppm (3H, t, CH_3). Found: C, 54.97; H, 6.32; N, 22.85; S, 10.45%. Calculated for $C_9H_8N_4S \cdot C_5H_{11}NO$: C, 55.06; H, 6.27; N, 22.93; S, 10.50%.

6-Amino-3,5-dicyano-4-ethylpyridine-2(1H)thione (III). A suspension of 20 mmoles salt VI in 10 ml ethanol was brought to pH 4 by adding 10% aqueous hydrochloric acid with stirring. The homogeneous solution obtained of salt VI was maintained for 24 h at 20°C. The yellow powder precipitate was filtered off and washed with ethanol and hexane to give 1.5 g (74%) thione III, mp 285-287°C (ethanol). IR spectrum: 3285-3370 (NH_2), 2218 sh (C≡N) cm^{-1}. PMR spectrum in DMSO-d_6: 12.73 (1H. br.s, NH), 7.81 (2H, s, NH_2), 2.65 (2H, q, CH_2), 1.21 (3H, t, CH_3). Found: C, 52.85, H, 27.47; S, 15.68%. Calculated for $C_9H_8N_4S$: C, 52.92; H, 3.95; N, 27.43; S, 15.70%.

6-Amino-2-(R-methylthio)-3,5-dicyano-4-ethylpyridines (VIIIa-VIII*l*) and 6-Amino-2-(α-aminocar-bonylbenzyl-thio)-3,5-dicyano-4-ethylpyridine (IX). A. A sample of halide VIIa-VII*l* or phenylchloracetamide was added to a suspension of 10 mmoles salt VI in 10 ml DMF and stirred for 4 h. The precipitate was filtered off and washed with water and ethanol to give pyridines VIIIa-VIII*l* or IX, respectively. The indices of these compounds are given in Tables 1 and 2.

B. A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added with stirring to a solution of 10 mmoles thione III in 10 ml DMF. After 5 min, alkyl halide VIIa-VII*l* or phenylchloracetamide was added. The reaction mixture was stirred for 4 h and then diluted by adding 10 ml water. Product VIIIa-VIII*l* or IX was filtered off and washed with water and ethanol. These samples of VIIIa-VIII*l* and IX were identical in their melting point and IR spectrum to the samples obtained by method A.

TABLE 1. Physical Indices of Products VIIIa-VIII*l* and IX

Compound	Chemical formula	Found, % / Calculated, %				mp, °C crystallization solvent	Yield, % (method A/B)
		C	H	N	S		
VIIIa	$C_{10}H_{10}N_4S$	54.92 55,03	4.55 4,62	25.71 25,67	14.62 14,69	164...166, ethanol	75/70
VIII b	$C_{11}H_{12}N_4S$	56.73 56,87	5.17 5,21	24.20 24,12	13.74 13,80	115...117, ethanol	80/73
VIII c	$C_{12}H_{12}N_4S$	58.91 58,99	4.88 4,99	22.97 22,93	12.90 13,12	162...164, ethanol	69/71
VIII d	$C_{12}H_{14}N_4S$	58.45 58,51	5.86 5,73	22.68 22,74	12.95 13,02	163...165, ethanol	82/80
VIII e	$C_{11}H_{10}N_4O_2S$	50.28 50,37	3.88 3,84	21.29 21,36	12.17 12,22	225...227, AcOH	69/70
VIII f	$C_{16}H_{14}N_4S$	65.21 65,28	4.69 4,79	18.99 19,03	10.81 10,89	178...180, n-butanol	89/83
VIII g	$C_{17}H_{16}N_4S$	66.15 66,21	5.27 5,23	18.12 18,17	10.35 10,40	157...159, n-butanol	84/77
VIII h	$C_{17}H_{13}BrN_4OS$	50.79 50,88	3.21 3,27	13.88 13,96	7.93 7,99	180...182, n-butanol	91/85
VIII i	$C_{23}H_{18}N_4OS$	69.28 69,33	4.49 4,55	13.87 14,06	8.01 8,05	222...224, n-butanol	85/81
VIII j	$C_{19}H_{18}N_4OS$	65.05 65,12	5.11 5,18	15.89 15,99	9.09 9,15	177...179, n-butanol	80/72
VIII k	$C_{17}H_{13}ClN_4OS$	57.17 57,22	3.59 3,67	15.64 15,70	8.93 8,99	210...212, n-butanol	74/68
VIII *l*	$C_{20}H_{14}N_4O_3S$	61.47 61,53	3.55 3,61	14.29 14,35	8.18 8,21	257...259, n-butanol	72/70
IX	$C_{17}H_{15}N_5OS$	60.29 60,52	4.15 4,48	20.95 20,76	9.64 9,50	236...238, n-butanol	82/72

3,5-Dicyano-4-ethyl-6-ethylamino-2-ethylthiopyridine (X). A. A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added to a stirred solution of 10 mmole thione III and after 10 min, 10 mmole ethyl iodide VIIb was added. After 30 min, 5.6 ml (10 mmoles) 10% aqueous KOH and 10 mmoles ethyl iodide VIIb were added consecutively. Stirring was continued for an additional 30 min. The precipitate was filtered off and washed with water and ethanol to give 2.1 g (81%) pyridine X, mp 116-118°C (ethanol). IR spectrum: 3300-3385 (NH_2), 2218 sh ($C\equiv N$) cm^{-1}. PMR spectrum in DMSO-d_6: 8.11 (1H, t, NH), 3.47 (2H, q, CH_2N), 3.17 (2H, q, CH_2S), 2.67 (2H, q, CH_2), 1.05-1.34 ppm (9H, m, $3CH_3$). Found: C, 59.89; H, 6.13; N, 21.45; S, 12.26%. Calculated for $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52; S, 12.32%.

B. A sample of 5.6 ml (10 mmoles) 10% aqueous KOH and 10 mmoles ethyl iodide were added to a stirred solution of 10 mmoles pyridine VIIIb in 10 ml DMF. The mixture was stirred at 25°C for 4 h and then diluted with 10 ml water. The precipitate was filtered off and washed with water and ethanol to give 2.2 g (85%) X identical in melting point and IR spectrum to the sample obtained according to method A.

3,6-Diamino-5-cyano-3-ethylpyrazolo[5,4-*b*]pyridine (XII). A suspension of 10 mmoles pyridine VIIIa and 30 mmoles hydrazine hydrate in 10 ml ethanol was heated at reflux for 40 min. After cooling, the white flocculent precipitate was filtered off and washed with ethanol and hexane to give 1.7 g (79%) XII, mp 203-205°C (ethanol). IR spectrum: 3210, 3300, 3390 (NH_2), 2220 sh cm^{-1} ($C\equiv N$). PMR spectrum in DMSO-d_6: 8.77 (1H, s, NH), 7.31 (2H, s, NH_2), 4.54 (2H, s, NH_2), 2.62 (2H, q, CH_2), 1.18 ppm (3H, t, CH_3). Found: C, 53.38; H, 4.87; N, 41.47%. Calculated for $C_9H_{10}N_6$: C, 53.46; H, 4.98; N, 41.56%.

1,2-Di(6-amino-3,5-dicyano-4-ethyl-2-pyridylthio)ethane (XIa). A sample of 5.6 ml (10 mmoles) 10% aqueous KOH was added with stirring to a solution of 10 mmoles thione III in 10 ml DMF. After 5 min, 5 mmoles 1,2-dibromoethane was added. The reaction mixture was stirred at 20°C for 4 h, diluted with 10 ml water, and filtered to give 3.3 g (76%) XIa, mp 308-310°C (subl.). IR spectrum: 2240, 3370, 3495 (NH_2), 2220 sh cm^{-1} ($C\equiv N$). PMR spectrum in DMSO-d_6: 7.95 (4H, s, $2NH_2$), 3.47 (4H, s, $2SCH_2$), 2.70 (4H, q, $2CCH_2$), 1.21 ppm (6H, t, $2CH_3$). Found: C, 55.19; H, 4.13; N, 25.71; S, 14.68%. Calculated for $C_{20}H_{18}N_8S_2$: C, 55.28; H, 4.18; N, 25.79; S, 14.76%.

TABLE 2. Spectral Indices of VIIIa-VIII*l* and IX

Compound	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm, SSCC (J), Hz			
	NH_2	C = N	6-NH_2, s	4-CH_2 (q), CH_3 (t)	SCH_2*	R
VIIIa	3185, 3304, 3355	2215	7,94	2,71, 1,21	2,56, s	–
VIIIb	3210, 3305, 3383	2218	7,92	2,72, 1,20	3,18, q	1,30 (3H, t, CH_3)
VIIIc	3162, 3285, 3320	2190	7,96	2,71, 1,20	3,88, d, J = 7	5,14 (1H, d, J_{cis} = 10, CH_2), 5,39 (1H, d, J_{trans} = 17, CH_2), 5,84 (1H, m, CH)
VIIId	3183, 3302, 3324	2198	7,90	2,68, 1,18	3,17, q	1,65 (2H, m, CH_2), 1,18 (3H, t, CH_3)
VIIIe	3375, 3466	2220	7,89	2,71, 1,20	4,08, s	†
VIIIf	3338, 3444	2225, 2214	8,00	2,67, 1,18	4,46, s	7,20...7,55 (5H, m, H_{Ph})
VIIIg	3330, 3435	2218, 2230	7,92	2,70, 1,19	4,50, s	2,34 (3H, s, CH_3), 7,17 (2H, m, H_{Ar}), 7,46 (2H, m, H_{Ar})
VIIIh	3235, 3330, 3415	2220, 2232	7,83	2,71, 1,21	4,96, s	7,62 (2H, m, H_{Ar}), 8,05 (2H, m, H_{Ar})
VIIIi	3375, 3482	2218	7,95	2,75, 1,23	4,98, s	7,48 (2H, d, J = 7, 3-, 5-H_{Ar}), 8,15 (2H, d, J = 7, 2-, 6-H_{Ar}), 7,80 (5H, m, H_{Ph})
VIIIj	3240, 3325, 3420	2220, 2230	7,83	2,71, 1,20	4,81, s	2,35 (3H, s, CH_3), 2,32 (3H, s, CH_3), 7,92 (1H, s, 3-H_{Ar}), 7,15 (2H, m, 5-, 6-H_{Ar})
VIIIk	3240, 3335	2200, 2222	7,84	2,71, 1,22	4,93, s	8,08 (2H, d, J = 8,5, 3-, 5-H_{Ar}), 7,65 (2H, d, J = 8,5, 2-, 6-H_{Ar})
VIII*l*	3400	2215	7,79	2,70, 1,19	4,75, s	8,71 (1H, s, 4-H_{coum}‡), 7,99 (2H, d, 5-, 8-H_{coum}), 7,48 (2H, m, 6-, 7-H_{coum})
IX	3190, 3304, 3391	2217, 2225	7,91	2,68, 1,17	5,56, s	7,31 (5H, m, H_{Ph}), 7,56 (1H, br.s, NH_2), 7,75 (1H, br.s, NH_2)

*SCH_3 for VIIIa, SCH for IX.

†Signal for the proton of the CO_2H proton is not observed due to deuteroexchange.

‡Coum = coumaryl.

1,4-Di(6-amino-3,5-dicyano-4-ethyl-2-pyridylthio)butane (XIb) was obtained as described above for XIa from thione III and 1,4-dibromobutane. The yield of XIb was 3.6 g (78%), mp 265-267°C (dec.). IR spectrum: 2240, 3345, 3435 (NH_2), 2235 cm^{-1} ($C \equiv N$). PMR spectrum in DMSO-d_6: 7.77 (4H, br.s, $2NH_2$), 3.24 (4H, m, $2SCH_2$), 2.72 (4H, q, $2CCH_2$), 1.74 (4H, m, $2SCH_2CH_2$), 1.21 ppm (6H, t, $2CH_3$). Found: C, 57.05; H, 4.15; S, 13.76%. Calculated for $C_{22}H_{22}H_8S_2$: C, 57.12; H, 4.79; N, 24.22; S, 13.86%.

This work was carried out with the financial support of the Russian Basic Research Fund (Project 96-03-32012a).

REFERENCES

1. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, and A. M. Shestopalov, Advances in Science and Technology VINITI, Organic Chemistry, Vol. 17 [in Russian], (1989), p. 72.
2. V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and A. Senning, Sulfur Reports, 13(1), 1 (1992).