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SYNTHESIS OF SUBSTITUTED 2-ALKYL(ARYL)THIO-3-CYANOPYRIDINES AND 3-AMINOTHIENO[2,3-b]PYRIDINES

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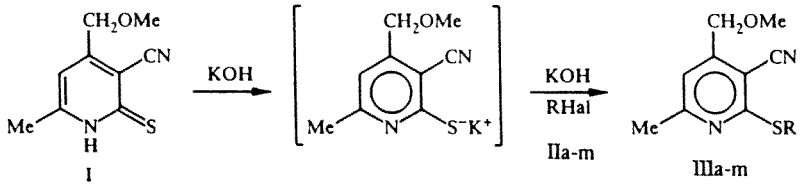
The alkylation of 6-methyl-4-methoxymethyl-3-cyano-2(1H)pyridinethione by halogen derivatives in the presence of KOH proceeds regioselectively with the formation of S-alkyl derivatives. By cathodic electrolysis of the thiols in the presence of 6-methyl-4-methoxymethyl-2-chloro-3-cyanopyridine, 2-arylthiopyridines are obtained. By Thorpe-Ziegler cyclization of 2-alkylthiopyridines having an active methylene group, 2-aminothieno[2,3-b]pyridines have been synthesized.

2-Substituted thiopyridines are of interest as potential biologically active substances and as reagents for fine organic synthesis [1]. The known paths for obtaining these compounds are based on the interaction of 2-halopyridines with thiols, or on the alkylation of 2(1H)-pyridinethiones with halogen derivatives [2]. The alkylation of 3-cyano-2(1H)pyridinethiones proceeds by an S_N2 mechanism through a stage of formation of pyridine-2-thiolates, the interaction of which with halogen derivatives leads to the desired products [3-5].

In a continuation of our studies [6] of the synthesis of substituted 2-thiopyridines, we have investigated the alkylation of 6-methyl-4-methoxymethyl-3-cyano-2(1H)-pyridinethione (I) by halides (IIa-m). The reaction was performed in dimethylformamide or alcohol, in the presence of potassium hydroxide with a reactant ratio I−KOH−II = 1−1−1.

It was established that regardless of the nature of the halogen derivative, the solvent, or the temperature, the reaction proceeds with high regioselectivity and leads to S-substituted thiopyridines IIIa-m with yields of 70-95% (Table 1).



I IIa-m IIIa-m

II, IIIa) R = Me; b) R = Et; c) R = n-C_6H_{13}; d) R = CH_2CONH_2; e) R = $CH_2CONHPh$; f) R = CH_2CH_2COOH; g) R = CH_2CH_2COOEt; h) R = CH_2COPh; i) R = $CH_2COC_6H_3Me_2$-3,5; j) R = $CH_2COC_6H_3Me_2$-2,4; k) R = $CH_2COC_6H_4NO_2$-4; l) R = CH_2COAr^1; m) R = $CH_2COC_6H_3(OH)_2$-3,4

The decisive factor in the regioselectivity is apparently the complete localization of negative charge on the sulfur atom through the formation of a close ion pair in the potassium pyridinethiolate, as indicated by an analysis of x-ray diffraction data on similar salts [5]. For the synthesis of the 2-arylthiopyridines IIIn,o, the traditional alkylation reaction proved to be unsuitable. These compounds were obtained by an electrochemical method [6] from chloropyridine (IV) and thiols (Va,b), respectively.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found % / Calculated %				mp, °C	Yield, %
		C	H	N	S		
IIIa	$C_{10}H_{12}N_2OS$	57.43 57,67	5.74 5,81	13.38 13,45	15.28 15,39	63...64	93
IIIb	$C_{11}H_{14}N_2OS$	59.47 59,43	6.39 6,35	12.54 12,60	14.41 14,42	52...53	92
IIIc	$C_{15}H_{22}N_2OS$	64.64 64,71	7.89 7,96	10.01 10,06	11.47 11,52	Oil	84
IIId	$C_{11}H_{13}N_3O_2S$	52.44 52,57	5.16 5,21	16.62 16,72	12.73 12,76	168...169	95
IIIe	$C_{17}H_{17}N_3O_2S$	62.28 62,36	5.16 5,24	12.75 12,83	9.71 9,79	215...216	92
IIIf	$C_{12}H_{14}N_3O_2S$	54.07 54,12	5.25 5,30	10.46 10,52	11.97 12,04	88,5...89,5	70
IIIg	$C_{14}H_{18}N_2O_3S$	57.07 57,12	6.08 6,16	9.44 9,52	10.75 10,89	66...65	75
IIIh	$C_{17}H_{16}N_2O_2S$	65.28 65,36	5.12 5,16	8.83 8,97	10.18 10,26	123...125	95
IIIi	$C_{19}H_{20}N_2O_2S$	66.92 67,03	5.85 5,92	8.16 8,23	9.37 9,42	121...122	89
IIIj	$C_{19}H_{20}N_2O_2S$	67.01 67,03	5.87 5,92	8.21 8,23	9.28 9,42	95...96	86
IIIk	$C_{17}H_{15}N_3O_4S$	57.03 57,13	4.17 4,23	11.66 11,76	8.85 8,97	128...130	81
IIIl	$C_{21}H_{26}N_2O_2S$	67.98 68,07	7.02 7,07	7.79 7,56	8.56 8,56	103...104	87
IIIm	$C_{17}H_{16}N_2O_4S$	59.19 59,29	4.62 4,68	8.07 8,14	9.25 9,31	200...201	78
IIIn	$C_{15}H_{14}N_2OS$	66.52 66,64	5.07 5,22	10.21 10,37	11.73 11,86	65...67	82
IIIo	$C_{19}H_{22}N_2OS$	69.77 69,90	6.69 6,79	8.55 8,58	9.78 9,82	66...63	93
VIa	$C_{11}H_{13}N_3O_2S$	52.51 52,57	5.14 5,21	16.65 16,72	12.69 12,76	189...191	75
VIb	$C_{17}H_{17}N_3O_2S$	62.31 62,36	5.18 5,24	12.83 12,88	9.68 9,72	179...180	82
VIc	$C_{17}H_{16}N_2O_2S$	65.25 65,36	5.08 5,16	8.85 8,97	10.16 10,26	136...137	80
VId	$C_{19}H_{20}N_2O_2S$	66.95 67,03	5.84 5,92	8.17 8,23	9.38 9,42	132...133	81
VIe	$C_{17}H_{15}N_3O_4S$	57.04 53,13	4.14 4,23	11.62 11,76	8.88 8,97	>210 (decomp.)	76
VIf	$C_{21}H_{26}N_2O_2S$	67.98 68,07	7.01 7,07	7.46 7,56	8.54 8,65	174...175	88
VIg	$C_{17}H_{16}N_2O_4S$	59.15 59,29	4.58 4,68	8.05 8,14	9.22 9,31	210	79
VIh*	$C_{17}H_{15}ClN_2O_2S$	58.79 58,87	4.25 4,36	8.01 8,08	9.14 9,24	118...119	82
VIi †	$C_{17}H_{15}BrN_2O_2S$	52.07 52,18	3.75 3,86	7.11 7,16	8.15 8,20	134...135	81

*Cl found 10.13%, calculated 10.22%.

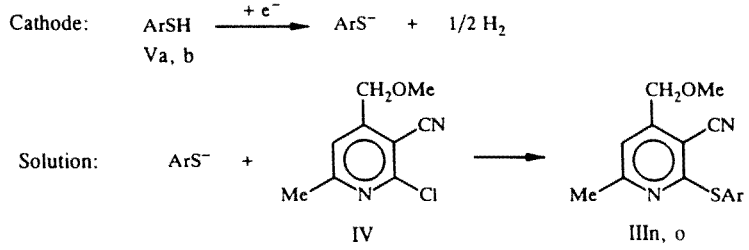
†Br found 20.33%, calculated 20.42%.

Cathodic electrolysis of the thiols V in the presence of chloropyridine was carried out on a Pt cathode in a 0.3 N solution of tetraethylammonium bromide in absolute acetonitrile. The thiolate anions generated on the cathode [7], reacting with the chloropyridine IV, form the sulfides IIIn,o with high yields (Table 1). The electrolysis was performed in a diaphragm cell in an argon atmosphere at 20-25°C, while holding the system in the galvanostatic regime and passing in no more than 1.05-1.10 F/mole.

TABLE 2. IR Spectra of Synthesized Compounds

Compound	ν,* cm^{-1}				
	CN	C=C,C=N	C—O—C	CO	N—H
IIIa	2200	1560	1115, 1105	—	—
IIIb	2180	1550	1105, 1080	—	—
IIIc	2195	1560	1105, 1090	—	—
IIId	2210	1570	1120, 1100	1655 (Amide I)	3350, 3170
IIIe	2210	1570	1120, 1105	1650 (Amide I)	3350, 3170
IIIf	2210	1560	1105, 1070	1670	—
IIIg	2195	1555	1150, 1100, 1080	1690	—
IIIh	2190	1560	1020, 1080, 1110	1670	—
IIIi	2195	1590, 1570	1020, 1090, 1110	1660	—
IIIj	2195	1580, 1570	1020, 1090, 1110	1655	—
IIIk	2195	1530	1105, 1080, 1040	1660	—
IIIl	2200	1580	1140, 1120, 1070, 1015	1700	—
IIIm	2205	1595	1150, 1115	1650	—
IIIn	2200	1640, 1560	1105, 1090	—	—
IIIo	2195	1560	1110, 1095	—	—
VIa	—	1580	1120, 1070	1630	3440, 3360, 3260, 3150
VIb	—	1580	1130, 1070	1670	3360, 3270
VIc	—	1570	1095	1620	3460, 3255
VId	—	1560	1105, 1080	1650	3360, 3270
VIe	—	1600	1150	1620	3320, 3210
VIf	—	1580	1080	1690	3370, 3250
VIg	—	1570	1095	1640	3500...3300 br.sh.
VIh	—	1580	1120, 1080	1650	3370, 3260
VIt [sic]	—	1570	1070	1680	3340, 3230

*ν N–O 1365, 3400 (IIIk); ν OH 3190, 3510 (IIIm), 1365 (VIe), 3400 cm^{-1} (VIg).



Va, IIIn) Ar = Ph; Vb, IIIo) Ar = $C_6H_4(t\text{-Bu})$-4

The structure of the 2-alkyl(aryl)-3-cyanothiopyridines IIIa-o was confirmed by PMR data and IR spectra (Tables 2 and 3).

By Thorpe–Ziegler cyclization of the pyridines IIId,e,h,j,k-m, which have an active methylene group in the substituent R, the corresponding 3-amino-thieno[2,3-b]pyridines (VIa-i) were synthesized (method A).

The present results and those reported in [6] show that the cyclization rate depends on the electronegativity of the substituent on the sulfur atom, decreasing in the series

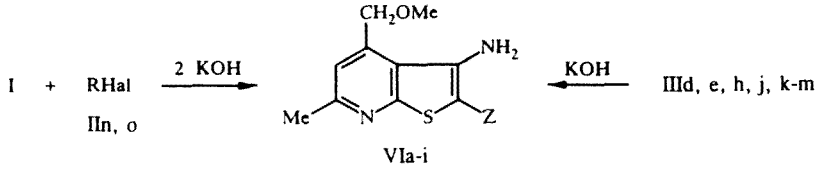
$$COAr > COOEt > CONH_2 > COOH$$

In the example of the compounds VIa,i, we also demonstrated the possibility of obtaining 3-aminothieno[2,3-b]pyridines from the pyridinethione I and halides IIa,o in a single stage without segregating the product III (method B).

TABLE 3. PMR Spectra of Certain Synthesized Compounds

Compound	Chemical shifts δ, ppm, and SSCC (J), Hz					
	CH_3-Het c	OCH_3	SCH_2*	OCH_2	H-Het c	other protons (see R, Z)
IIIa	2,57	3,46 s	2,62 s	4,55 s	7,17	—
IIId	2,59	3,50 s	3,91 s	4,58 s	7,17	5,52 and 6,76 (2H, two br.s, NH_2)
IIIe	2,68	3,51 s	4,01 s	4,59 s	7,10	7,20...7,47 (5H, m, C_6H_5); 9,10 (1H, br.s, NH)
IIIf	2,57	3,49...3,54 (5H, m, J = 6,7)		4,56 s	7,10	2,88 (2H, d, J = 6,7, CH_2COOH)
IIIg	2,56	3,48...3,54 (5H, m)		4,55s	7,08	1,28 (3H, t, J = 7,18, CH_3); 2,78 (2H, t, J = 7,5, $\underline{CH_2}$, COOEt); 4,17 (2H, q, J = 7,18, OCH_2)
IIIh	2,32	3,48 s	4,55 s	4,67 s	7,05	7,27...8,09 (5H, m, C_6H_5)
IIIi	2,46	3,48 s	4,56	(4H, s)	7,05	2,39 (6H, c, $2CH_3$—Ar); 7,75 (2H, m, 2 o-H_{Ar}); 7,79 (1H, d, J = 2,7, n-H_{Ar})
IIIj	2,46	3,47 s	4,55...4,58 (4H, m)		7,05	2,38 и 2,40 (6H, tow s, 2 CH_3—Ar); 7,10 (2H, m, o-, m-H_{Ar}); 7,78 (1H, d, m-H_{Ar})
IIIk	2,31	3,48 s	4,64 s	4,56 s	7,08	7,27...8,37 (4H, m, C_6H_4)
IIIn	2,42	3,50 s	—	4,59 s	7,16	7,40...7,57 (5H, m, C_6H_5)
IIIo	2,43	3,49 s	—	4,58 s	7,11	1,35 (9H, s, 3 CH_3); 7,41...7,52 (4H, m, C_6H_4)
VIa	2,65	3,41 s	—	4,67 s	7,00	5,34 (2H, br. s, NH-Het); 7,10 (2H, br. s, $CONH_2$)
VIc	2,66	3,45 s	—	4,80 s	7,00	7,27...7,89 (5H, m, C_6H_5); 8,12 (2H, br. s, NH_2)
VIe	2,67	3,46 s	—	4,81 s	7,01	7,98...8,32 (6H, m, C_6H_4, NH_2)
VIf	2,80	3,48 s	—	4,62 s	7,13	1,80...2,18 (15H, m, Ad); 8,10 (2H, br. s, NH_2)
VIh	2,66	3,45 s	—	4,80 s	6,99	7,44...7,83 (4H, m, C_6H_4); 8,14 (2H, br. s, NH_2-Het)
VIi	2,66	3,44 s	—	4,79 s	7,00	7,59...7,77 (4H, m, C_6H_4); 8,17 (2H, NH_2)

*SCH_3 in the case of IIIa.



VIa) Z = $CONH_2$; b) Z = CONHPh; c) Z = COPh; d) Z = $COC_6H_3Me_2$-2,4; e) Z = $COC_6H_4NO_2$-4; f Z = $COAr^1$; g Z = $COC_6H_3(OH)_2$-3,4. IIn, VIh) Z = COC_6H_4Cl-4. IIo, VIi) Z = COC_6H_4Br-4

The IR spectra of the compounds VI do not contain any band $\nu C \equiv N$, and a series of bands appears in the 3150-3500 cm^{-1} interval pertaining to stretching and bending vibrations of the amino group. In the PMR spectra, in place of signals of protons of the SCH_2 group, characteristic singlets of the amino group appear in the interval 7.10-8.32 ppm.

EXPERIMENTAL

PMR spectra were registered in a Bruker WM-250 RF spectrometer in $CDCl_3$, but for compounds VIa-c in $(CD)_3CO$. IR spectra were obtained in a Specord 75-IR spectrophotometer on suspensions in white mineral oil. The course of the reaction and the purities of the products were monitored by TLC on Silufol UV-254 plates, eluent 1:2 hexane–acetone, development by iodine vapor or $KMnO_4$ solution.

The characteristics of the synthesized compounds are listed in Tables 1-3.

6-Methyl-4-methoxymethyl-2-R-3-cyanothiopyridines (IIIa-i). A mixture of 10 mmoles of the pyridinethione I in 20-25 ml of DMF, 10 mmoles of a halide II, and 10 mmoles of 10% aqueous potassium hydroxide was held for 1-5 h at room temperature, after which 5-10 ml of water was added. The resulting precipitate of the product III was separated, washed with water, and recrystallized from alcohol.

6-Methyl-4-methoxymethyl-2-phenylthio-3-cyanopyridine (IIIn). The cathode section of an electrolysis cell with a glass diaphragm was charged with 60 ml of a 0.3 M solution of tetraethylammonium bromide in absolute acetonitrile (background solution), containing an equimolar mixture (0.01 mole each) of 6-methyl-4-methoxymethyl-2-chloro-3-cyanopyridine and the thiophenol Va. The anolyte was 50 ml of the background solution. The cathode was a platinum strip ($S = 35$ cm^2); the anode was a magnesium rod with a 1×1 cm section. The electrolysis was performed in an argon atmosphere at 20-25°C in the galvanostatic regime with a current density of 63-65 mA/cm^2. The catholyte was mixed by means of a magnetic stirrer. After passing 1.05-1.15 F/mole, the catholyte was poured off, and the solvent was removed under vacuum. The residue was treated with water. The resulting crystals were filtered off and recrystallized from alcohol. Obtained 1.12 g of the product IIIn. Analogously, from the thiophenol Vb, compound IIIo was synthesized.

3-Amino-2-R-6-methyl-4-methoxymethylthieno[2,3-b]pyridines (VIa-m). ***A***. A mixture of 10 mmoles of the thiopyridine IIId,e,h,k-m in 20-25 ml of DMF and 20 ml of potassium hydroxide (10% aqueous solution) was held for 3-7 h at room temperature. The mixture was diluted with 2-3 times its volume of water, and the precipitate was filtered off. The products VIa-g were recrystallized from alcohol.

B. A mixture of 10 mmoles of the pyridinethione I in 20-25 ml of DMF, 10 mmoles of the halide IIn,o, and 10 mmoles of potassium hydroxide (10% aqueous solution) was stirred for 30 min at room temperature. Then, 10 mmoles of KOH (10% aqueous solution) was added, and the mixture was held at room temperature for 3-7 h. Obtained the product VIh,i. For the synthesis of compounds VIa,b, an additional 5 h of holding the reaction mass was necessary. The products were then recovered as described above.

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