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REACTION OF 3-CYANOPYRIDINE-2(1H)-THIONES WITH n-BUTYLLITHIUM

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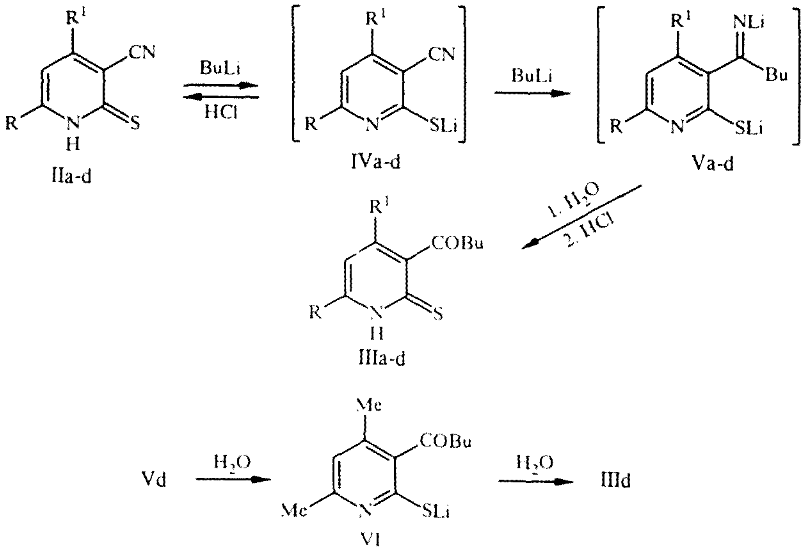
The reaction of 3-cyanopyridine-2(1H)-thiones with BuLi in ether was studied. It was found that the metallation proceeds initially at the sulfur atom. The resulting lithium salts add a second equivalent of n-butyllithium at the CN group. The hydrolysis of the dilithium derivatives leads to 3-pentanoylpyridine-2(1H)-thiones.

Broad investigations of 3-cyanopyridine-2(1H)-thione (I) and its derivatives testify to the detailed study of different aryl(hetaryl)-substituted compounds [1, 2]. However, interest in alkyl-substituted pyridinethiones also increased with the appearance of published data on the anti-speed activity of derivatives of 6-methyl-3-cyano-5-ethylpyridine-2(1H)-one [3].

We previously communicated methods for the synthesis of 6-alkyl(6-alkenyl, 4,6-dialkyl) derivatives of the thione (I) [4, 5]. The present work is the continuation of the investigations indicated and is dedicated to the study of the reaction of alkyl-substituted 3-cyanopyridine-2(1H)-thiones (IIa-d) with BuLi in ether to show possibilities of their functionalization. Products of the last present interest as new compounds with potential biological activity, as well as synthons for obtaining heterocyclic systems. It is known that lithiation is utilized widely in synthetic organic chemistry, however it has not so far been applied in the synthesis of substituted pyridinethiones. Among the examples described in the literature, the closest is that of the synthesis of 3-aroyl-1-methyl-4-methoxypyridin-2-ones based on the Li derivatives of 2(1H)-pyridinones [6].

Scheme 1



II—V a $R = Me$, $R^1 = H$; b $R = n\text{-}Pr$, $R^1 = H$; c $R = i\text{-}Bu$, $R^1 = H$; d $R = R^1 = Me$

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C	Found, % / Calculated, %				Yield, %
			C	H	N	S	
IIIa	$C_{11}H_{15}NOS$	150...152	63,63 63,12	7,44 7,22	6,82 6,67	15,05 15,32	60
IIIb	$C_{13}H_{19}NOS$	90...92	65,77 65,78	8,23 8,07	5,76 5,90	13,54 13,51	90
IIIC	$C_{14}H_{21}NOS$	122...124	66,89 66,87	8,60 8,42	5,51 5,57	12,96 12,76	70
IIId	$C_{12}H_{17}NOS$	150...152	64,21 64,53	7,94 7,67	6,13 6,27	14,66 14,36	80
VI	$C_{12}H_{16}LiNOS$	130...132	—	—	—	—	97
VIIIa	$C_{13}H_{16}N_2OS$	92...93	62,82 62,87	6,58 6,64	11,39 11,28	13,16 12,91	80
VIIIb	$C_{21}H_{25}NO_2S$	124...126	70,81 70,95	6,89 7,09	4,08 3,94	9,16 9,02	45
VIIIc	$C_{14}H_{19}NO_3S$	71...73	59,60 59,76	6,97 6,81	4,81 4,98	11,52 11,39	55
VIIId	$C_{15}H_{20}N_2OS$	119...121	65,31 65,18	7,05 7,29	10,27 10,14	11,35 11,60	60
IX*	$C_{19}H_{18}BrNOS$	92...94	63,51 63,74	4,45 5,06	3,31 3,91	8,36 8,95	94

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*Content of Br was as follows: found 21.91%, and calculated 22.32%.

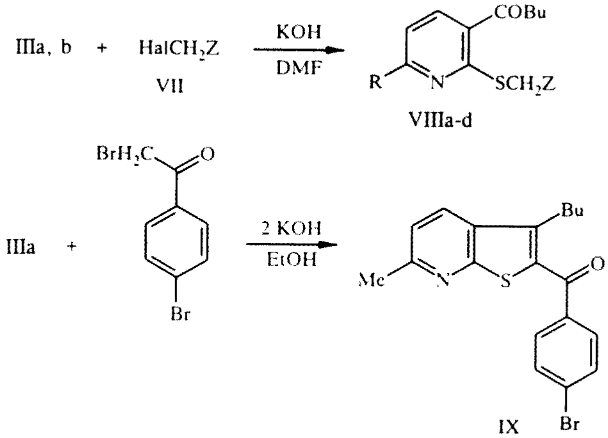
TABLE 2. Data of the IR Spectra and PMR Spectra of the Compounds (IIIa-d), (VI), and (VIIIa-d)

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm				
		R	COBu (CH_3, $\underline{CH_2}CH_3$, $\underline{CH_2}CH_2CH_3$, $COCH_2$)	4-H or R^1	5-H	NH or SCH_2Z
IIIa	1200 (C=S), 1683 (C=O)	2,40 s (CH_3)	0,86 t, 1,32 m, 1,55 m, 3,09 t	7,41 d	6,68 d	13,69 broad · s
IIIb	1190 (C=S), 1694 (C=O)	0,88 m (CH_3), 1,55 m ($\underline{CH_2}CH_3$) 2,60 t (CH_2-Het)	0,88 m, 1,32 m, 1,55 m, 3,04 t	7,40 d	6,60 d	13,98 broad · s
IIIc	1192 (C=S), 1697 (C=O)	0,88 d (2CH_3), 2,50 m (CH), 2,55 d ($\underline{CH_2}$-Het)	0,88 d, 1,30 m, 1,90 m, 3.02 t	8,09 d	6,70 d	14,05 broad · s
IIId	1208 (C=S), 1635 (C=O)	2,29 s (CH_3)	0,86 t, 1,31 m, 1,50 m, 2,63 t	2,02 s (CH_3)	6,55 s	14,00 broad · s
VI	1240 (SLi), 1640 (C=O)	2,30 s (CH_3)	0,89 t, 1,46 m, 1,51 m, 2,69 t	2,08 s (CH_3)	6,70 s	
VIIIa	1670 (C=O), 2236 (CN)	2,58 s (CH_3)	0,90 t, 1,32 m· 1,55 m, 3,05 t	8,49 d	7,29 d	4.07 s
VIIIb	1664 (C=O), 1685 (C=O)	0,89 t (CH_3), 1,57 m ($\underline{CH_2}CH_3$) 2,25 t (CH_2-Het)	0,58 t, 1,29 m ($\underline{CH_2}\underline{CH_2}CH_3$), 2,97 t	8,26 d	7,01 d	4,51 s, 7,56 m (m-H_{Ar}), 7,65 m (n-H_{Ar}), 8,05 m (o-H_{Ar})
VIIIc	1641 (C=O)	2,44 s (CH_3)	0,87 t, 1,31 m, 1,55 m, 2,97 t	8,39 d	7,14 d	3,79 s, 3,61 s (CH_3)
VIIId	1669 (C=O), 2246 (CN)	0,90 m (CH_3), 1,57 m ($\underline{CH_2}CH_3$), 2,80 t (CH_2-Het)	0,90 m, 1,31 m, 1,80 m, 3,02 t	8,41 d	7,29 d	4,05 s

The results obtained by us indicate that the reaction of the thiones (IIa-d) with two equivalents of BuLi in ether at −5 to −3°C with the subsequent hydrolysis by water leads to the production of high yields (60-90%) of their 3-pentanoyl derivatives (IIIa-d). Under analogous conditions, the treatment of the thiones (IIa-d) with one equivalent of BuLi in ether and subsequent hydrolysis gives the initial compounds (IIa-d). It is probable that the indicated thiones are initially metallated at the sulfur atom to give the S-lithium salts (IVa-d); these then add a second equivalent of BuLi at the CN group, forming the dilithium derivatives (Va-d). The hydrolysis of the last goes through in two stages. This is indicated by the fact that the treatment of the dilithium salt (Vd) with a minimal amount of water led to the isolation of the S-lithium salt (VI) (Scheme 1, Table 1) in the form of a white powder, stable on storage. The structure of the salt (VI) is confirmed by PMR and IR spectral data (see Table 2).

The synthesized 6-alkyl-3-pentanoylpyridine-2(1H)-thiones (IIIa-d) are yellow crystalline substances with clear melting temperatures. Their structure is confirmed by PMR and IR spectral data which particularly indicate the occurrence of the compounds (IIIa-d) in the thione tautomeric form. Thus, the IR spectra have intense absorption bands of the C=O group at 1635-1697 cm^{-1} and absorption bands, of moderate intensity, due to the C=S group at 1190-1208 cm^{-1}. The PMR spectra of the thiones (IIIa-d) show broadened singlets of the NH groups in the region of 13.69-14.05 ppm (Tables 1 and 2).

The thiones (IIIa, b) react readily with the halides $HalCH_2Z$ (VII) at the sulfur atom in the presence of the equimolar amount of KOH (the 10% aqueous solution) with the formation of the 6-alkyl-2-(Z-methylthio)pyridines (VIIIa-d). The cyclization product (IX) was obtained in a high yield from compound (IIIa) and p-bromophenacyl bromide when the twofold excess of KOH was utilized (Scheme 2). The structure of the products (VIIIa-d) and (IX) was confirmed by PMR and IR spectral data (see Table 2).



VII Hal – Cl, Br, Z – CN, COPh, COOMe; VIII a R – Me, Z – CN; b R – *n*-Pr, Z – COPh; c R – Me, Z – COOMe; d R – *n*-Pr, Z – CN

EXPERIMENTAL

Melting temperatures were determined on a Kofler stage. The IR spectra were recorded on the UR-20 spectrophotometer in tablets of KBr. The PMR spectra were recorded on the Bruker WM-250 spectrometer (250 MHz, $DMSO-D_6$). Elemental analysis was performed on a Perkin-Elmer instrument.

6-Alkyl-3-pentanoylpyridine-2(1H)-thiones (IIIa-d). To 2 mole of BuLi in 50 ml of ether is added 1 mole of the thione (II) for 10 min in a stream of argon at −5 to −3°C steadily in portions. The suspension which formed is stirred for 1 h at −5 to −3°C, and is further hydrolyzed with 10-20 ml of water until a clear solution results. The aqueous layer is separated, extracted with 3 portions of 20 ml of ether, and neutralized with 17% aqueous HCl to the pH 7. The residue of the product (III) is filtered off and recrystallized from ethyl alcohol.

Lithium Salt of 4,6-Dimethyl-3-pentanoyl-2-pyridinethione (VI). The suspension obtained as described above from the thione (Id) and BuLi is stirred for 1 h prior to the addition of 1-2 ml of water. The precipitated residue of the salt (VI) is filtered off and dried in air.

6-Alkyl-2-(Z-methylthio)pyridines (VIIIa-d). To the solution of 5 mmole of the thione (IIIa, b) in 10 ml of DMF are added 5 mmole of the compound (VII), with the further dropwise addition of 5 mmole of KOH, in the form of the 10% aqueous solution, with stirring. The resulting mixture is maintained for 1-2 min at 60°C and then diluted twofold with water. The residue of the product (VIII) is filtered off and recrystallized from 50% aqueous alcohol.

2-(4-Bromophenacyl)-3-butyl-6-methylthieno[2,3-b]pyridine (IX). To the solution of 0.18 q (5 mmole) of the thione (IIIa) in 10 ml of alcohol is added 0.24 g (5 mmole) of 4-bromophenacyl bromide with the further dropwise addition of 0.96 ml of the 10% aqueous solution of KOH (10 mmole). The mixture is stirred for 1-2 min at 60°C and diluted with an equal volume of water. The precipitated residue is filtered off, washed with alcohol and heptane, and then dried in air and recrystallized from methyl alcohol. The IR spectrum is characterized at 1640 cm^{-1} (C=O). The PMR spectrum is as follows: 1.09 ppm (3H, t, $CH_2\underline{CH_3}$), 1.24 ppm (2H, m, $\underline{CH_2}CH_3$), 1.51 ppm (2H, m, $\underline{CH_2}CH_2CH_3$), 2.64 ppm (3H, s, 6-CH_3), 2.95 ppm (2H, t, $COCH_2$), 7.45 ppm (1H, d, 5-H), 7.78 ppm (4H, s, H_{Ar}), and 8.34 ppm (1H, d, 4-H).

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