SYNTHESIS OF PYRIDINE-2(1H)-THIONE AND THIENO[2,3-b]-PYRIDINE DERIVATIVES

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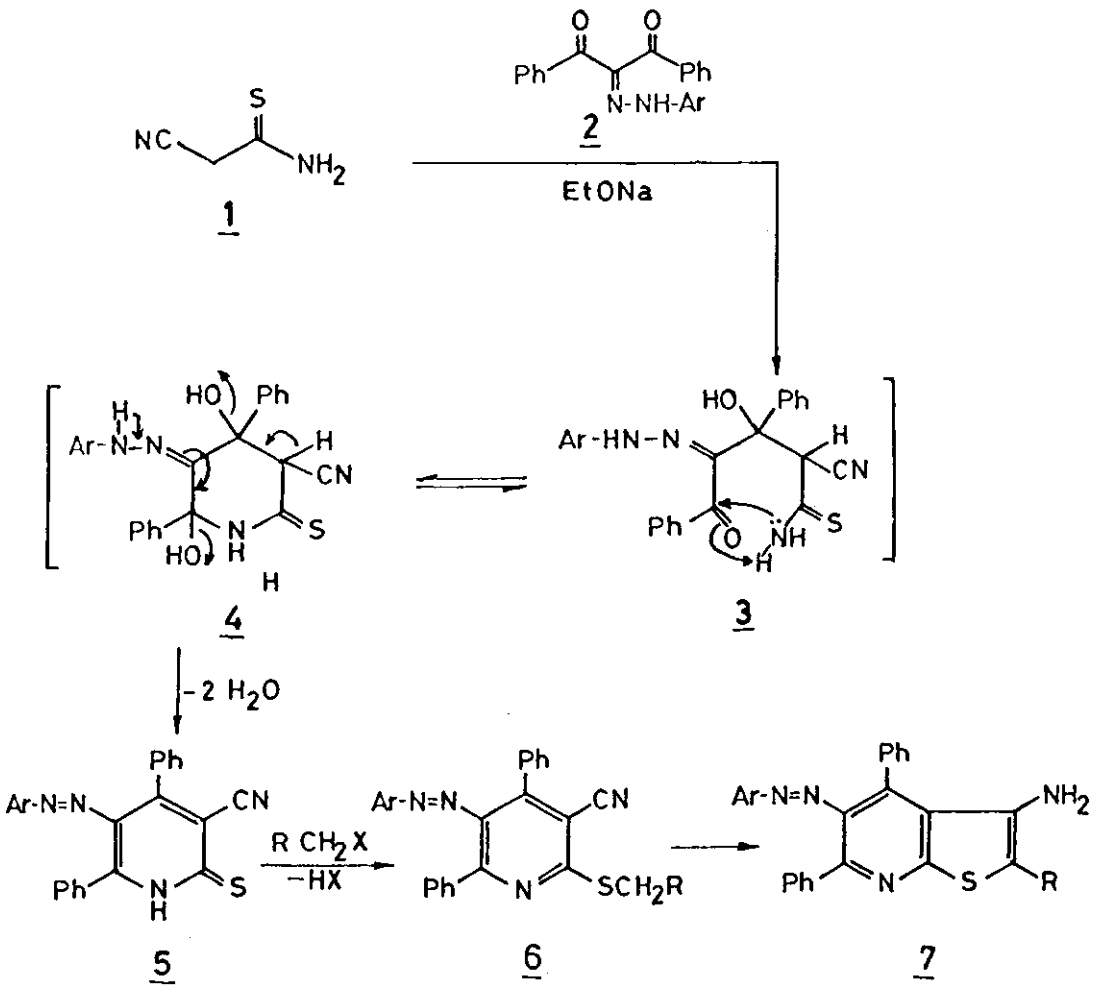
Abstract- A synthesis of pyridine-2(1H)-thiones and thieno-[2,3-b]pyridines utilizing cyanothioacetamide and 2-aryl-hydrazono-1,3-diphenylpropane-1,3-diones as starting components is described.

Activated nitriles are reactive reagents that have been extensively utilized in heterocyclic synthesis.[1,2] As a part of our program directed toward development of new simple and efficient procedures for the synthesis of pyridines,[3,4] we have recently reported a new procedure for the synthesis of pyridine-2(1H)-thiones via the reaction of arylmethylenecyanothioacetamides with active methylene reagents.[5,6] The importance of the synthesized compounds, as intermediates for the synthesis of the biologically active deaza and folic acid ring systems, prompted our interest in the synthesis and chemistry of this class of compounds.[7] In the present paper we report reactions of cyanothioacetamide with arylhydrazones of dibenzoylmethane and related reactions for the synthesis of several substituted pyridine-2(1H)-thiones and their condensed derivatives. Thus, it has been found that dibenzoylmethane coupled with aryldiazonium chlorides in ethanol containing sodium acetate to afford the corresponding monoarylhydrazone derivatives (2) in good yields. Compounds (2) react with cyanothioacetamide in reflux-



		Ar
2 / 5	a,	4-Cl-C_6H_4
	b,	2-Cl-C_6H_4
	c,	4-Br-C_6H_4
	d,	4-H_3C-C_6H_4
	e,	2-H_3C-C_6H_4
	f,	4-H_3CO-C_6H_4
	g,	3-H_3CO-C_6H_4
	h,	2-H_3CO-C_6H_4
	i,	4-O_2N-C_6H_4
	j,	2-O_2N-C_6H_4

		Ar	R
6	a,	4-Cl-C_6H_4	CH_3
	b,	4-Br-C_6H_4	CH_3
	c,	4-H_3C-C_6H_4	CH_3
	d,	4-H_3CO-C_6H_4	CH_3
	e,	4-O_2N-C_6H_4	CH_3

		Ar	R
7	a,	4-Cl-C_6H_4	COC_6H_5
	b,	4-Br-C_6H_4	COC_6H_5
	c,	4-H_3C-C_6H_4	COC_6H_5
	d,	4-H_3CO-C_6H_4	COC_6H_5
	e,	4-O_2N-C_6H_4	COC_6H_5

ing ethanol-sodium ethoxide for 5 h to give the 3-cyanopyridine-2(1H)-thiones (5). The structure of 5 was established on the basis of their elemental analysis and spectral data. Thus, structure (5a) is supported by its mass spectrum which showed a molecular formula $C_{24}H_{15}N_4ClS$ (M^+ 426). ^{1}H-Nmr spectroscopy was used to confirm this structure for the product. ^{1}H-Nmr spectrum revealed a broad band at δ 14.5 ppm assignable to NH group and a multiplet at δ 6.8-7.6 ppm assigned for aromatic protons (cf. Table 2). Compound (5) with its latent functional substituent was found useful for the synthesis of fused pyridines. Thus, compound (5) reacted with ethyl iodide in methylene chloride-sodium hydroxide to afford the corresponding S-ethyl derivatives (6). The ^{1}H-nmr of 6a revealed a triplet at δ 1.4 ppm and a quartet at δ 3.4 ppm assignable to SEt group. When 5 were treated with phenacyl bromide in ethanol-sodium ethoxide, S-alkylated derivatives could not be isolated, but their cyclization products, thieno[2,3-b]pyridine derivatives (7) were obtained. The ir spectrum of 7a revealed the absence of a CN band, the mass spectrum was compatible with the molecular formula $C_{32}H_{21}N_4OClS$ (M^+ 544) and ^{1}H-nmr spectrum showed besides the aromatic proton signals, a broad band at δ 7.2 ppm assignable to an amino function. These results indicate that the reaction of 2 with cyanothioacetamide can be utilized as an excellent route for the synthesis of several, otherwise difficultly accessible, pyridine-2(1H)-thiones and their condensed derivatives.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were obtained (KBr) on a Nicolet Instrument or on a Shimadzu IR 200. ^{1}H-Nmr spectra were measured on a Varian 400 MHz in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed as δ ppm. Mass spectra were measured on a Mass Spectrometer MS 30 (AEI) at 70 ev. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

2-Arylhydrazono-1,3-diphenylpropane-1,3-diones (2a-j)

A solution of dibenzoylmethane (2.24 g, 0.01 mol) in ethanol (100 ml) containing sodium acetate (3.0 g) was cooled to 0°C, stirred and treated gradually with a cooled solution of aryldiazonium chloride (prepared from 0.01 mol of amine and the appropriate quantities of HCl and $NaNO_2$). The solid product formed on standing was collected and crystallized from the appropriate solvent.

Pyridine-2(1H)-thiones (5a-j)

A mixture of 2a-j (0.01 mol) and cyanothioacetamide (1 g, 0.01 mol) was dissolved in ethanol (30 ml) containing sodium ethoxide (0.68 g, 0.01 mol). The mixture was refluxed for 5 h, and then allowed to cool to room temperature and acidified with cold dilute hydrochloric acid. The resulting solid product was collected by filtration and crystallized from the appropriate solvent (cf. Table 1).

2-Ethylthiopyridines (6a-e)

A mixture of 5 (0.01 mol), NaOH (0.4 g, 0.01 mol) and ethyl iodide (1.56 g, 0.01 mol) in dry DMF (50 ml) was stirred at room temperature for 24 h and then diluted with cold water (100 ml), and the resulting solid product was collected by filtration and crystallized from the appropriate solvent (cf. Table 1)

Thieno[2,3-b]pyridines (7a-e)

A mixture of 5 (0.01 mol), sodium ethoxide (0.68 g, 0.01 mol), and phenacyl bromide (2.09 g, 0.01 mol) in dry ethanol (50 ml) was refluxed for 3 h, and then allowed to cool to room temperature and acidified with cold dilute hydrochloric acid. The resulting solid product was collected by filtration and crystallized from the appropriate solvent (cf. Table 1)

Table 1: Characterization data for compounds 5a-j, 6a-e and 7a-e

Compd.	Recryst. solv.	mp °C	Yield (%)	Mol. formula	Found/Calcd (%) C	H	N	M^+ m/z
5a	EtOH	210	80	$C_{24}H_{15}N_4ClS$	67.7	3.6	12.8	426
					67.5	3.5	13.1	
5b	EtOH-DMF	213	65	$C_{24}H_{15}N_4ClS$	67.2	3.3	12.8	
					67.5	3.5	13.1	
5c	DMF	187	60	$C_{24}H_{15}N_4BrS$	61.0	3.5	11.6	471
					61.1	3.2	11.9	
5d	Dioxane	225	85	$C_{25}H_{18}N_4S$	74.1	4.5	13.5	406
					73.9	4.4	13.8	
5e	MeOH-DMF	177	55	$C_{25}H_{18}N_4S$	73.6	4.2	13.7	
					73.9	4.4	13.8	
5f	EtOH	163	78	$C_{25}H_{18}N_4OS$	70.8	4.0	12.9	422
					71.1	4.3	13.3	
5g	EtOH	175	70	$C_{25}H_{18}N_4OS$	71.0	4.5	13.5	
					71.1	4.3	13.3	
5h	DMF	185	50	$C_{25}H_{18}N_4OS$	71.2	4.1	13.0	
					71.1	4.3	13.3	
5i	DMF	194	80	$C_{24}H_{15}N_5O_2S$	65.7	3.5	16.2	
					65.9	3.4	16.0	
5j	DMF	180	70	$C_{24}H_{15}N_5O_2S$	65.6	3.7	15.7	
					65.9	3.4	16.0	
6a	Dioxane	128	85	$C_{26}H_{19}N_4ClS$	68.4	4.4	12.0	454
					68.6	4.2	12.3	
6b	EtOH	152	80	$C_{26}H_{19}N_4BrS$	62.3	4.1	10.9	499
					62.5	3.8	11.2	
6c	MeOH	138	76	$C_{27}H_{22}N_4S$	74.5	4.9	12.6	434
					74.7	5.1	12.9	

Table 1: Contd.

Compd.	Recryst. solv.	mp °C	Yield (%)	Mol. formula	Found/Calcd (%) C	H	N	M^+ m/z
6d	$CHCl_3$	99	77	$C_{27}H_{22}N_4OS$	71.7	5.2	12.1	450
					72.0	4.9	12.4	
6e	CH_2Cl_2	143	60	$C_{26}H_{19}N_5O_2S$	66.8	4.3	14.8	
					67.1	4.1	15.1	
7a	DMF	228	90	$C_{32}H_{21}N_4OClS$	70.1	4.2	10.0	544
					70.5	3.9	10.3	
7b	MeOH-DMF	218	88	$C_{32}H_{21}N_4OBrS$	64.9	3.8	9.4	589
					65.2	3.6	9.5	
7c	DMF	237	82	$C_{33}H_{24}N_4OS$	75.2	4.8	10.3	524
					75.6	4.6	10.7	
7d	DMF	215	77	$C_{33}H_{24}N_4O_2S$	73.0	4.6	10.2	540
					73.3	4.4	10.4	
7e	DMSO	241	80	$C_{32}H_{21}N_5O_3S$	69.0	4.1	12.3	
					69.2	3.8	12.6	

Table 2: Ir and ^{1}H-nmr data for compounds listed in Table 1

Compd.	Ir, νmax/cm^{-1}	^{1}H-Nmr, δ
5a	3350, 3300 (NH), 2220 (CN)	6.82-7.61 (m, 14H, 2 C_6H_5 and C_6H_4), 14.50 (s, br, 1H, NH)
5c	3380, 3350 (NH), 2222 (CN)	6.77-7.59 (m, 14H, 2 C_6H_5 and C_6H_4), 14.66 (s, br, 1H, NH)
5d	3300 (NH), 2220 (CN)	2.28 (s, 3H, CH_3), 6.70-7.50 (m, 14H, 2 C_6H_5 and C_6H_4), 14.60 (s, br, 1H, NH)
5f	3350 (NH), 2220 (CN)	3.95 (s, 3H, OCH_3), 6.80-7.70 (m, 14H,

Table 2: Contd.

Compd.	Ir, νmax/cm^{-1}	^{1}H-Nmr, δ
		2 C_6H_5 and C_6H_4), 14.48 (s, br, 1H, NH)
6a	2225 (CN)	1.40 (t, 3H, J=4.6 Hz, CH_3), 3.42 (q, 2H, J=4.4 Hz, CH_2), 7.18-7.60 (m, 14H, 2 C_6H_5 and C_6H_4)
6c	2230 (CN)	1.42 (t, 3H, J=4.6 Hz, CH_3), 2.36 (s, 3H, CH_3), 3.40 (q, 2H, J=4.3 Hz, CH_2), 7.20-7.58 (m, 14H, $2C_6H_5$ and C_6H_4)
6d	2225 (CN)	1.37 (t, 3H, J=4.5 Hz, CH_3), 3.36 (q, 2H, J=4.2 Hz, CH_2), 3.86 (s, 3H, OCH_3), 7.32-7.67 (m, 14H, 2 C_6H_5 and C_6H_4)
7a	3400, 3350 (NH_2), 1680 (CO)	7.20 (s, br, 2H, NH_2), 7.32-7.90 (m, 19H, 3 C_6H_5 and C_6H_4)
7c	3420, 3380 (NH_2), 1665 (CO)	2.30 (s, 3H, CH_3), 7.11 (s, br, 2H, NH_2), 7.23-7.84 (m, 19H, 3 C_6H_5 and C_6H_4)
7d	3380, 3320 (NH_2), 1670 (CO)	3.85 (s, 3H, OCH_3), 7.18 (s, br, 2H, NH_2), 7.25-7.70 (m, 19H, 3 C_6H_5 and C_6H_4)

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