

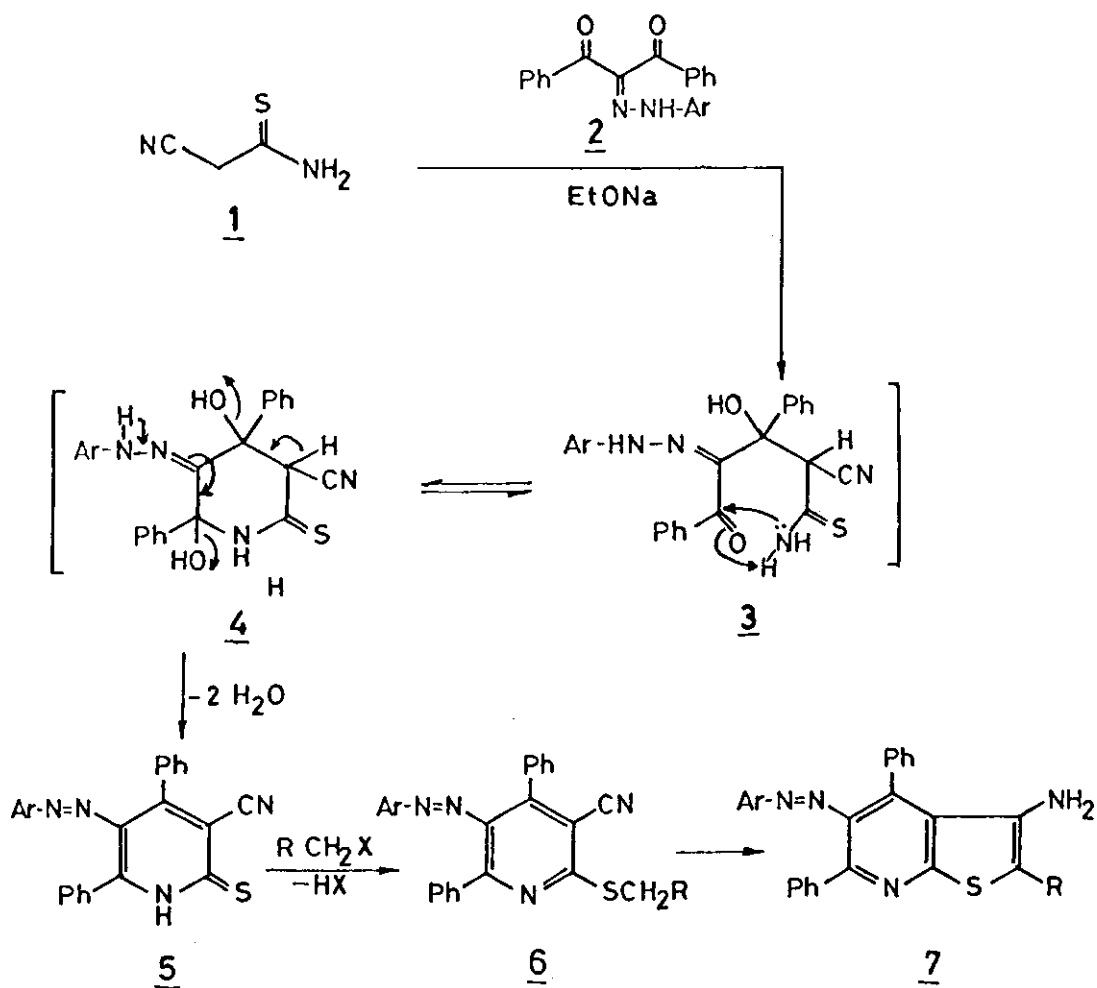
SYNTHESIS OF PYRIDINE-2(1H)-THIONE AND THIENO[2,3-b]-
PYRIDINE DERIVATIVES

Galal E. H. Elgemeie^{*}, Ibrahim S. Alnaimi, and Hafsa F.
Alarab

Chemistry Department, Faculty of Science, Qatar University,
Doha, State of Qatar

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 compo-
nents is described.

Activated nitriles are reactive reagents that have been extensively uti-
lized 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 arylmethylenecyanothioaceta-
mides 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 di-
benzoylmethane 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-



<u>2</u> / <u>5</u>	Ar
a	4-Cl-C ₆ H ₄
b	2-Cl-C ₆ H ₄
c	4-Br-C ₆ H ₄
d	4-H ₃ C-C ₆ H ₄
e	2-H ₃ C-C ₆ H ₄
f	4-H ₃ CO-C ₆ H ₄
g	3-H ₃ CO-C ₆ H ₄
h	2-H ₃ CO-C ₆ H ₄
i	4-O ₂ N-C ₆ H ₄
j	2-O ₂ N-C ₆ H ₄

<u>6</u>	Ar	R
a	4-Cl-C ₆ H ₄	CH ₃
b	4-Br-C ₆ H ₄	CH ₃
c	4-H ₃ C-C ₆ H ₄	CH ₃
d	4-H ₃ CO-C ₆ H ₄	CH ₃
e	4-O ₂ N-C ₆ H ₄	CH ₃

<u>7</u>	Ar	R
a	4-Cl-C ₆ H ₄	COC ₆ H ₅
b	4-Br-C ₆ H ₄	COC ₆ H ₅
c	4-H ₃ C-C ₆ H ₄	COC ₆ H ₅
d	4-H ₃ CO-C ₆ H ₄	COC ₆ H ₅
e	4-O ₂ N-C ₆ H ₄	COC ₆ H 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). 1H -Nmr spectroscopy was used to confirm this structure for the product. 1H -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 1H -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 1H -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. 1H -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 Micro-analytical Data Centre at Cairo University.

2-Aryldiazono-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 NaNO₂). 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 (%)			M ⁺
					C	H	N	m/z
<u>5a</u>	EtOH	210	80	C ₂₄ H ₁₅ N ₄ ClS	67.7	3.6	12.8	426
					67.5	3.5	13.1	
<u>5b</u>	EtOH-DMF	213	65	C ₂₄ H ₁₅ N ₄ ClS	67.2	3.3	12.8	
					67.5	3.5	13.1	
<u>5c</u>	DMF	187	60	C ₂₄ H ₁₅ N ₄ BrS	61.0	3.5	11.6	471
					61.1	3.2	11.9	
<u>5d</u>	Dioxane	225	85	C ₂₅ H ₁₈ N ₄ S	74.1	4.5	13.5	406
					73.9	4.4	13.8	
<u>5e</u>	MeOH-DMF	177	55	C ₂₅ H ₁₈ N ₄ S	73.6	4.2	13.7	
					73.9	4.4	13.8	
<u>5f</u>	EtOH	163	78	C ₂₅ H ₁₈ N ₄ OS	70.8	4.0	12.9	422
					71.1	4.3	13.3	
<u>5g</u>	EtOH	175	70	C ₂₅ H ₁₈ N ₄ OS	71.0	4.5	13.5	
					71.1	4.3	13.3	
<u>5h</u>	DMF	185	50	C ₂₅ H ₁₈ N ₄ OS	71.2	4.1	13.0	
					71.1	4.3	13.3	
<u>5i</u>	DMF	194	80	C ₂₄ H ₁₅ N ₅ O ₂ S	65.7	3.5	16.2	
					65.9	3.4	16.0	
<u>5j</u>	DMF	180	70	C ₂₄ H ₁₅ N ₅ O ₂ S	65.6	3.7	15.7	
					65.9	3.4	16.0	
<u>6a</u>	Dioxane	128	85	C ₂₆ H ₁₉ N ₄ ClS	68.4	4.4	12.0	454
					68.6	4.2	12.3	
<u>6b</u>	EtOH	152	80	C ₂₆ H ₁₉ N ₄ BrS	62.3	4.1	10.9	499
					62.5	3.8	11.2	
<u>6c</u>	MeOH	138	76	C ₂₇ H ₂₂ N ₄ S	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 (%)			M ⁺ m/z
					C	H	N	
<u>6d</u>	CHCl ₃	99	77	C ₂₇ H ₂₂ N ₄ O ₃ S	71.7 72.0	5.2 4.9	12.1 12.4	450
<u>6e</u>	CH ₂ Cl ₂	143	60	C ₂₆ H ₁₉ N ₅ O ₂ S	66.8 67.1	4.3 4.1	14.8 15.1	
<u>7a</u>	DMF	228	90	C ₃₂ H ₂₁ N ₄ OClS	70.1 70.5	4.2 3.9	10.0 10.3	544
<u>7b</u>	MeOH-DMF	218	88	C ₃₂ H ₂₁ N ₄ OBrS	64.9 65.2	3.8 3.6	9.4 9.5	589
<u>7c</u>	DMF	237	82	C ₃₃ H ₂₄ N ₄ O ₃ S	75.2 75.6	4.8 4.6	10.3 10.7	524
<u>7d</u>	DMF	215	77	C ₃₃ H ₂₄ N ₄ O ₂ S	73.0 73.3	4.6 4.4	10.2 10.4	540
<u>7e</u>	DMSO	241	80	C ₃₂ H ₂₁ N ₅ O ₃ S	69.0 69.2	4.1 3.8	12.3 12.6	

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

Compd.	Ir, $\nu_{\max}/\text{cm}^{-1}$	¹ H-Nmr, δ
<u>5a</u>	3350, 3300 (NH), 2220 (CN)	6.82-7.61 (m, 14H, 2 C ₆ H ₅ and C ₆ H ₄), 14.50 (s, br, 1H, NH)
<u>5c</u>	3380, 3350 (NH), 2222 (CN)	6.77-7.59 (m, 14H, 2 C ₆ H ₅ and C ₆ H ₄), 14.66 (s, br, 1H, NH)
<u>5d</u>	3300 (NH), 2220 (CN)	2.28 (s, 3H, CH ₃), 6.70-7.50 (m, 14H, 2 C ₆ H ₅ and C ₆ H ₄), 14.60 (s, br, 1H, NH)
<u>5f</u>	3350 (NH), 2220 (CN)	3.95 (s, 3H, OCH ₃), 6.80-7.70 (m, 14H,

Table 2: Contd.

Compd.	Ir, $\nu_{\max}/\text{cm}^{-1}$	$^1\text{H-Nmr}$, δ
<u>6a</u>	2225 (CN)	2 C ₆ H ₅ and C ₆ H ₄), 14.48 (s, br, 1H, NH) 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 ₆ H ₅ and C ₆ H ₄)
<u>6c</u>	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 ₆ H ₅ and C ₆ H ₄)
<u>6d</u>	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 ₆ H ₅ and C ₆ H ₄)
<u>7a</u>	3400, 3350 (NH ₂), 1680 (CO)	7.20 (s, br, 2H, NH ₂), 7.32-7.90 (m, 19H, 3 C ₆ H ₅ and C ₆ H ₄)
<u>7c</u>	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 ₆ H ₅ and C ₆ H ₄)
<u>7d</u>	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 ₆ H ₅ and C ₆ H ₄)

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Received, 3rd April, 1992