α,β-Unsaturated Nitriles in Heterocyclic Synthesis. Novel Synthesis of Pyridines and Thieno[2,3-*b*]pyridine Derivatives

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Arylmethylenecyanothioacetamide reacts with ethyl acetoacetate and acetylacetone to give the corresponding 3-cyano-2(1*H*)-pyridinethione derivatives, which can be alkylated at sulfur atom and cyclized into the corresponding thieno[2,3-*b*]pyridine derivatives.

α,β-Unsaturated nitriles are versatile reagents that have been extensively utilized in heterocyclic synthesis.[1-3] We have previously reported several novel syntheses of azoles,[4] azines,[5] and azoloazines[6] utilizing α,β-unsaturated nitriles as starting components. In continuation of this work, we report here the results of our investigation into the utility of the readily obtainable arylmethylenecyanothioacetamide in heterocyclic synthesis. The investigation have resulted in the development of a novel procedure for the synthesis of pyridines and thieno[2,3-*b*]pyridine derivatives. The compounds obtained seem promising for further chemical transformations and for biological evaluation studies.

Thus, it has been found that benzylidencyanothioacetamide (**1a**) reacted with acetylacetone (**2a**) in boiling ethanol containing catalytic ammounts of piperidine to yield a product with the molecular formula $C_{15}H_{12}N_2OS$ (M^+ 268). Structure **4a** was considered for the product. ^1H NMR spectroscopy was used to confirm this structure for the product. Thus, ^1H NMR revealed two singlets at δ 1.90 and 2.55 assignable for two methyl groups, a broad band at δ 13.86 assignable to NH group, and a multiplet at δ 6.24—

Table 1. Analytical Data of Compounds **4**, **5**, and **6**

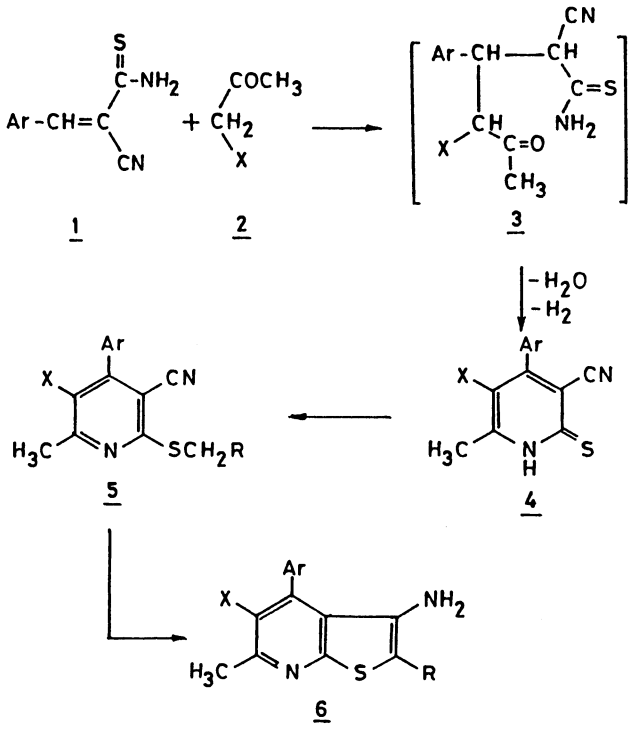
Compound	Ar	X	R	Yield %	Mp θ_m/°C	Found/Calcd (%) C	H	N	*m/z*
4a	C_6H_5	$COCH_3$		75	198—199	67.6	4.1	10.0	268
						67.2	4.5	10.4	
4b	4-$CH_3OC_6H_4$	$COCH_3$		70	235—237	64.0	4.5	9.0	
						64.4	4.7	9.4	
4c	4-$(CH_3)_2NC_6H_4$	$COCH_3$		80	248—250	65.8	5.8	13.2	311
						65.6	5.5	13.5	
4b	2-Furanyl	$COCH_3$		72	145	60.8	3.6	10.6	258
						60.5	3.9	10.9	
4e	C_6H_5	CO_2Et		70	180—182	64.3	4.5	9.0	
						64.4	4.7	9.4	
4f	4-$CH_3OC_6H_4$	CO_2Et		75	193—195	62.1	4.5	8.1	328
						62.2	4.9	8.5	
4g	4-$(CH_3)_2NC_6H_4$	CO_2Et		70	244—245	63.8	5.9	12.0	341
						63.3	5.6	12.3	
4h	2-Furanyl	CO_2Et		80	238—240	58.2	4.4	9.5	288
						58.3	4.2	9.7	
5a	C_6H_5	$COCH_3$	H	77	120—122	67.8	4.9	9.5	
						68.1	5.0	9.9	
5b	4-$CH_3OC_6H_4$	$COCH_3$	H	75	135—136	65.6	5.3	8.6	312
						65.4	5.1	9.0	
5c	4-$(CH_3)_2NC_6H_4$	$COCH_3$	H	75	116—117	66.6	5.5	12.5	
						66.5	5.8	12 9	
5d	2-Furanyl	$COCH_3$	H	70	90—92	62.0	4.0	9.9	
						61.8	4.4	10.3	
5e	C_6H_5	CO_2Et	H	70	87—88	65.7	5.3	8.6	
						65.4	5.1	9.0	
5f	4-$CH_3OC_6H_4$	CO_2Et	H	73	80—82	62.9	5.0	7.8	
						63.2	5.3	8.2	
5g	4-$(CH_3)_2NC_6H_4$	CO_2Et	H	80	138—140	63.8	5.5	11.5	355
						64.2	5.9	11.8	
5h	2-Furanyl	CO_2Et	H	72	85	59.4	4.8	9.6	
						59.6	4.6	9.3	

Table 1. (Continued)

Compound	Ar	X	R	Yield %	Mp θ_m/°C	Found/Calcd (%) C	H	N	m/z
6a	C_6H_5	$COCH_3$	COC_6H_5	70	143—145	71.2	4.5	6.9	
						71.5	4.7	7.2	
6b	4-$CH_3OC_6H_4$	$COCH_3$	COC_6H_5	70	150	69.0	4.7	6.5	416
						69.2	4.8	6.7	
6c	4-$(CH_3)_2NC_6H_4$	$COCH_3$	COC_6H_5	73	190	69.5	5.0	9.5	
						69.9	5.4	9.8	
6d	2-Furanyl	$COCH_3$	COC_6H_5	70	138—140	66.8	4.8	7.2	
						67.0	4.3	7.4	
6e	C_6H_5	CO_2Et	COC_6H_5	75	108—110	69.0	4.5	6.5	
						69.2	4.8	6.7	
6f	4-$CH_3OC_6H_4$	CO_2Et	COC_6H_5	65	99—100	67.0	5.3	6.2	
						67.3	5.3	6.3	
6g	4-$(CH_3)_2NC_6H_4$	CO_2Et	COC_6H_5	60	163—165	68.2	5.0	9.1	
						68.0	5.4	9.2	
6h	2-Furanyl	CO_2Et	COC_6H_5	67	82—83	64.8	4.2	6.6	
						65.0	4.4	6.9	

Table 2. Spectral Data of Compounds **4, 5,** and **6**

Compound	IR (KBr)/cm^{-1}	^1H NMR (DMSO) δ/ppm
4b	3450 (NH); 2225 (CN); 1700 (CO)	1.92 (s, 3H, CH_3); 2.52 (s, 3H, CH_3); 3.80 (s, 3H OCH_3); 6.32—6.92 (m, 4H, C_6H_4); 13.95 (s, br 1H, NH)
4e	3300—3200 (NH); 2220 (CN); 1680 (CO)	0.92 (t, J=7 Hz, 3H, CH_3); 2.66 (s, 3H, CH_3); 4.00 (q, J=7 Hz, 2H, CH_2); 7.27—7.56 (m, 5H, C_6H_5); 13.98 (s, br, 1H, NH)
4f	3400 (NH); 2215 (CN); 1720 (CO)	0.89 (t, J=7 Hz, 3H, CH_3); 2.22 (s, 3H, CH_3); 3.82 (s, 3H, OCH_3); 3.99 (q, J=7 Hz, 2H, CH_2); 7.02—7.42 (m,4H, C_6H_4); 13.8 (s, br 1H, NH)
4h	3250 (NH); 2215 (CN); 1730 (CO)	1.1 (t, J=7 Hz, 3H, CH_3); 2.42 (s, 3H, CH_3); 4.18 (q, J=7 Hz, 2H, CH_2); 6.82 (m, 1H furan H-3); 7.42 (d, J=6 Hz, 1H, furan H-4); 8.18 (d, J=6 Hz, 1H, furan H-5); 13.88 (s, br, 1H, NH)
5a	2220 (CN); 1700 (CO)	1.85 (s, 3H, CH_3); 2.55 (s, 3H, CH_3); 2.65 (s, 3H, SCH_3); 7.32—7.60 (m, 5H, C_6H_5)
5b	2220 (CN); 1690 (CO)	1.66 (s, 3H CH_3); 2.22 (s, 3H, CH_3); 2.68 (s, 3H, SCH_3); 3.42 (s, 3H, OCH_3); 6.5—6.8 (m, 4H, C_6H_4)
5d	2220 (CN); 1700 (CO)	2.22 (s, 3H, CH_3); 2.55 (s, 3H, SCH_3); 2.66 (s, 3H, CH_3), 6.68 (m, 1H, furan H-3); 7.22 (d, J=6 Hz, 1H furan H-4); 7.65 (d, J=6 Hz, 1H, furan H-5)
5f	2220 (CN); 1715 (CO)	0.94 (t, J=7.5 Hz, 3H, CH_3); 2.33 (s, 3H, CH_3); 2.41 (s, 3H, SCH_3); 3.40 (s, 3H, OCH_3); 3.81 (q, J=7.5 Hz, 2H, CH_2); 6.32—6.88 (m, 4H, C_6H_4)
5g	2220 (CN); 1715 (CO)	0.96 (t, J=7.5 Hz, 3H, CH_3); 2.30 (s, 3H, CH_3); 2.35 (s, 3H, SCH_3); 2.68 (s, 6H, $N(CH_3)_2$); 3.88 (q, J=7.5 Hz, 2H, CH_2); 6.44—678 (m, 4H, C_6H_4)
5h	2220 (CN); 1730 (CO)	1.25 (t, J=7.5 Hz, 3H, CH_3); 2.62 (s, 3H, CH_3); 2.68 (s, 3H, SCH_3); 4.22 (q, J=7.5 Hz, 2H, CH_2); 6.60 (m, 1H, furan 3-H); 7.25 (d, J=6 Hz, 1H, furan 4-H); 7.64 (d, J=6 Hz, 1H, furan 5-H)
6a	3400, 3200 (NH_2); 1700 (CO)	2.00 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 6.66 (s, br, 2H, NH_2); 7.22—7.88 (m, 10H, $2C_6H_5$)
6b	3500, 3200 (NH_2); 1700 (CO)	2.00 (s, 3H, CH_3); 2.32 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 6.06—7.23 (m, 11H, C_6H_5, C_6H_4 and NH_2)
6d	3400—3200 (NH_2); 1710 (CO)	2.08 (s, 3H, CH_3); 2.58 (s, 3H, CH_3); 6.68 (m, 2H, furan 3,4-H); 7.08 (s, br, 2H, NH_2); 7.42 (d, J=6.5 Hz, 1H, furan 5-H); 7.48—7.92 (m, 5H, C_6H_5)
6g	3450 (NH_2); 1718 (CO)	1.1 (t, J=7.5 Hz, 3H, CH_3); 2.62 (s, 3H, CH_3); 3.08 (s, 6H, $N(CH_3)_2$); 4.20 (q, J=7.5 Hz, 2H, CH_2); 6.7—7.88 (m, 11H, C_6H_5, C_6H_4 and NH_2)



7.00 assigned for aromatic protons (cf. Table 2). The formation of **4** from the reaction of **1** with **2** is assumed to proceed via Michael type addition of the methylene function in **2** to the activated double bond in **1** to yield acyclic Michael adducts **3** which then loses H_2O and cyclizes into the final isolable stable compounds **4**.

Subjecting the potassium salts of **4** to the action of alkylating agents such as methyl iodide afforded the corresponding *S*-alkyl derivatives **5**. The sturcture of **5** was inferred from analysis, MS and ^1H NMR. When using phenacyl bromide as alkylating agent, the *S*-alkylated derivative can not be isolated, but cyclized into thieno[2,3-*b*]pyridines **6**. The structure of **6a** could be established for the reaction product based on the absence of a CN absorption in the IR spectrum and on ^1H NMR which revealed two singlets at δ 2.00 and 2.26 assignable for two methyl groups, a broad band at δ 6.66 assignable to amino group, and a multiplet at δ 7.22—7.88 assigned for aromatic protons (cf. Table 2). The formation of **6** from reaction of **4** with phenacyl bromide constitutes a new synthesis of thieno[2,3-*b*]pyridine derivatives.

Experimental

All melting points are uncorrected. Analytical data were obtained from the Microanalytical Data Unit at Cairo University. The IR spectra were obtained on a Pye-Unicam SP-1000 spectrophotometer. ^1H NMR spectra were measured in DMSO or $CDCl_3$ on a Varian EM-360-60 MHz using TMS as internal standard and chemical shifts are expressed as δ ppm. Mass spectra were recorded on a Varian MAT 112 spectrometer.

Compounds **1a—d** were prepared following literature procedure.[7]

5-Substituted 4-Aryl-3-cyano-6-methyl-2(1*H*)-pyridinethione (4a—d). General Procedure: To a mixture of arylmethylenecyanothioacetamide **1** (0.01 mol) and acetylacetone **2a** or ethyl acetacetate **2b** (0.01 mol) in ethanol (50 ml), piperidine (a few drops) is added. The mixture is heated under reflux for 3 h, and then allowed to stand overnight. The resultant precipitate is isolated by suction and crystallized.

5-Substituted 4-Aryl-3-cyano-6-methyl-2-(methylthio)pyridines (5a—d). General Procedure. A mixture of **4** (0.01 mol), KOH powder (0.02 mol), and MeI (0.02 mol) in dry CH_2Cl_2 (50 ml) was stirred at room temperature for 3 h and then diluted with cold water (100 ml). The dichloromethane layer was washed several times with water, dried and then evaporated. The resulting solid product was collected by filteration and crystallized.

Thieno[2,3-*b*]pyridine Derivatives (6a—d). General Procedure: A mixture of **4** (0.01 mol), K_2CO_3 (0.02 mol), and phenacyl bromide (0.01 mol) in dry DMF (50 ml) was stirred at room temperature for 3 h and then diluted with cold water (50 ml). The resulting solid product was collected by filteration and crystallized.

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