Zag. J. Pharm. Sci., Vol. 3, No. 2, August 1994

SYNTHESIS OF NEW THIENO-[2,3-b]-PYRIDINE AND PYRAZOLO-[5,4-b]-PYRIDINE DERIVATIVES

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ABSTRACT

3-Cyano-4,6-dimethyl-2-pyridinethiol **1** was allowed to react with chloroacetone and hydrazine hydrate to give the corresponding thienopyridine derivative **2** and pyrazolopyridine derivative **5**, respectively. Compound **2** reacted with aldehydes to yield **3a-3c**. Reaction of compound **5** with thionyl chloride and arylidinemalononitriles gives **6** and **8a,b**, respectively. Compound **6** reacted with benzil and p,p-dichlorobenzil to yield the corresponding benzilimine derivatives **7a,b.**

INTRODUCTION

Studies were conducted on pyridones as synthons to prepare fused nitrogen heterocyclic compounds[1]. We have synthesized some pyridinethione, thienopyridine and pyrazolopyridine derivatives. Synthesis of these compounds was of additional interest, since some of the thienopyridine family showed biology activity, e.g., treatment of diabetes millitus, as analgesics, as anti-inflammatories and as anticoagulants[2].

In the present investigation, 3-cyano-4,6-dimethyl-2-pyridinethiol **1** has been prepared as described[3] and used as starting material for the synthesis of several new thienopyridine and pyrazolopyridine derivatives.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra (KBr) were measured on a Perkin Elmer 137 spectrophotometer. ^{1}HNMR spectra on a Varian A 60 equipment using TMS as an internal standard and $CDCL_3$ as a solvent. The mass spectra were run at 70 ev on a Varian Mat 711 mass spectrometer.

6-Acetyl-5-amino-2,4-dimethylthieno [2,3-b]pyridine 2:

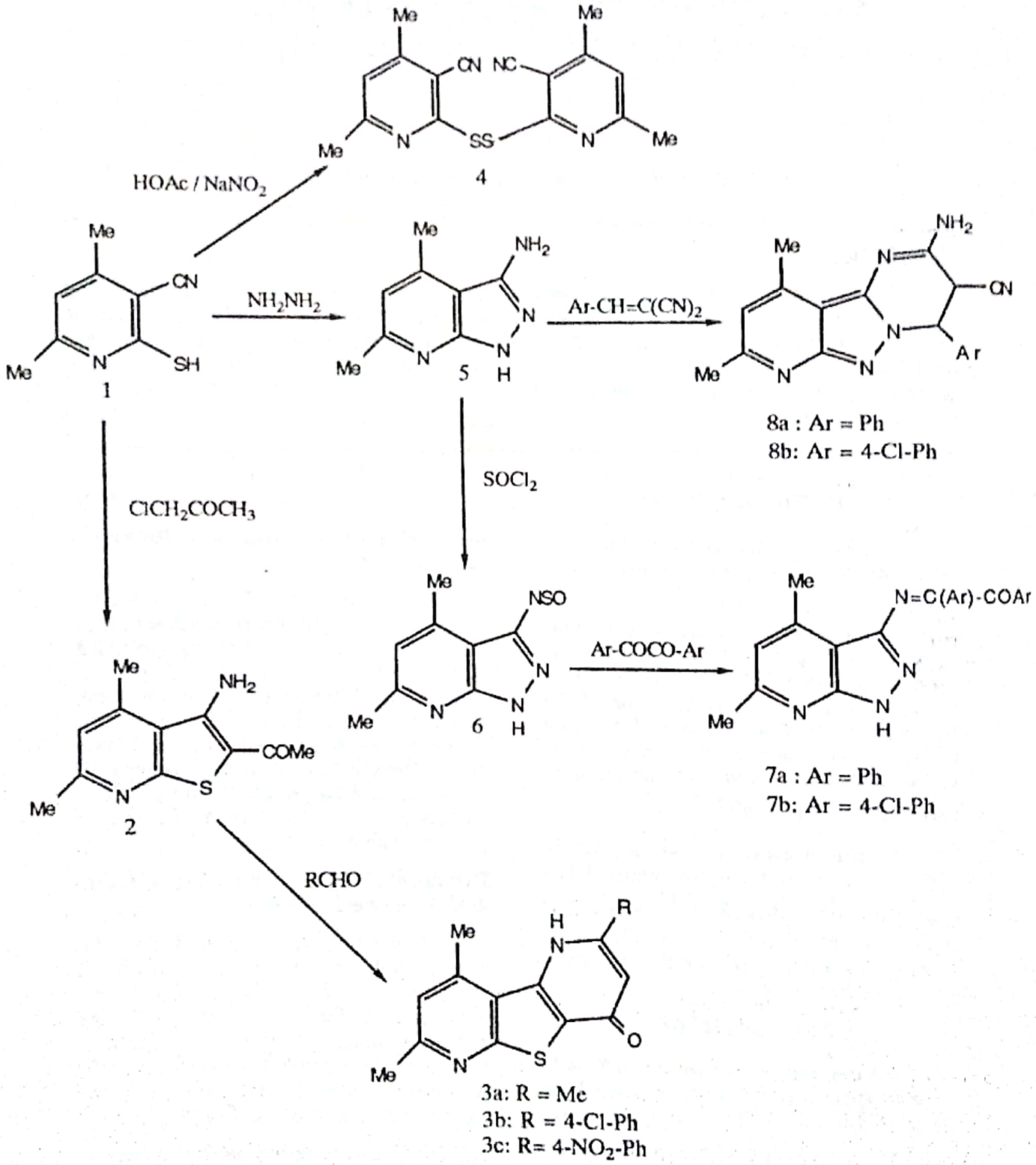
A mixture of chloroacetone (0.1 mol 9.3 ml) anhydrous potassium carbonate (0.1 mol), 10.6 g and compound **1** (0.1 mol) in dry acetone (100 ml) was refluxed for 10 hours. The excess acetone was distilled and the obtained solid was dissolved in water and extracted with ether. The ethereal solution was separated, dried and evaporated. The obtained solid was crystallized from the proper solvent (Table 1).

Pyrido[3',2' : 4,5]thieno[3,2-b]pyridin-4(1H)-one derivatives 3a-3c:

A mixture of compound **2** (0.002 mol), 0.4 g, aldehydes, namely (acetaldehyde,4-chlorobenzaldehyde and 4-nitrobenzaldehyde) (0.002 mol) and sodium ethoxide (0.015 mol) in ethanol (30 ml) was heated for one hour. The formed solid was filtered and crystallized from the proper solvent (Table 1).

2,2'-Bis(3-cyano-4,6-dimethylpyridyl) disulphide 4:

A solution of **1** (0.005 mol), 0.8 g in acetic acid (20 ml) and sodium nitrite (0.04 mol) was left at room temperature


HOAc / NaNO2
NH2NH2
Ar-CH=C(CN)2
ClCH2COCH3
SOCl2
Ar-COCO-Ar
RCHO
1
2
4
5
6
8a : Ar = Ph
8b: Ar = 4-Cl-Ph
7a : Ar = Ph
7b: Ar = 4-Cl-Ph
3a: R = Me
3b: R = 4-Cl-Ph
3c: R= 4-NO2-Ph

Scheme (1)

for 3 hours. The reaction mixture was poured on water (30 ml) and the solid was filtered and crystallized from the proper solvent (Table 1).

4,6-Dimethyl-3-amino-1H-pyrazolo [5,4-b]pyridine 5:

A mixture of **1** (0.01 mol), 1.6 g and hydrazine hydrate (0.02 mol) in n-butanol (30 ml) was heated under reflux for 30 hours. The separated solid formed after concentration and cooling was filtered and crystallized from the proper solvent (Table 1).

4,6-Dimethyl-3-sulfinylamino-1H-pyrazolo[5,4-b]pyridine 6:

A mixture of compound **5** (0.005 mol), 0.8 g and thionyl chloride (0.006 mol) in dry benzene (10 ml) was stirred at room temperature for 5 hours. The formed solid was filtered and crystallized from the proper solvent (Table 1).

4,6-Dimethyl-3-benzilimino-1H-pyrazolo[4,5-b]pyridine derivatives 7a,b :

Dry benzil and/or p,p'-dichlorobenzil (0.01 mol) and $AlCl_3$, 0.5 g are added to **6** (0.01 mol) in 15 ml of benzene. The mixture was heated for 2 hours under anhydrous condition. Small quantities of $AlCl_3$ were added at half hour intervals. The mixture was cooled, the benzene was removed by distillation under vacuum, and the residue was extracted by boiling with 150 ml of a mixture of petroleum ether and CCl_4 (2:1 v/v). The mixture was filtered and the filtrate was cooled. The benzilimine derivatives **7a,b** were precipitated and recrystallized from the proper solvent (Table 1).

2-Amino-3-cyano-8,10-dimethyl-4-aryl-3,4-dihydro-pyrido[3',2':4,5] pyrazolo[2,3-a] pyrimidines 8a,b:

A mixture of compound **5** (0.001 mol), 0.16 g and arylidinemalononitriles, namely (benzylidinemalononitrile and p-chlorobenzylidinemalononitrile) (0.001 mol) in 30 ml pyridine was refluxed for 6 hours. The solid was collected and crystallized from n-butanol to give compounds **8a,b** (Table 1).

RESULTS AND DISCUSSION

Alkylation of **1** with chloroacetone in the presence of potassium carbonate in dry acetone gives the corresponding thieno[2,3-b]pyridine derivative **2**. IR spectrum of compound **2** showed absorption bands at 3200 cm^{-1} (NH_2), 1690 cm^{-1} (C = O) and the absence of any band at 2220 cm^{-1} due to the absence of C ≡ N group. ^{1}HNMR gave signals at δ 2.5-2.8 (9 H of $3CH_3$ groups), δ 6.4 (s NH_2) and δ 7.8 (1H of pyridine) ppm. Also, mass spectrum gives the correct molecular weight 220, which agrees with the molecular formula $C_{11}H_{12}N_2SO$.

As a point of interest, the reaction of **2** with aldehydes[4], such as (acetaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde) gave compounds **3a-3c.** IR spectra of compounds **3a-3c** showed absorption bands at the regions 1660-1700 cm^{-1} (C = O), 3200-3300 cm^{-1} (NH) and 1590-1610 cm^{-1} (C = N). Mass spectrum of compound **3c** gave the correct molecular weight 353. ^{1}HNMR of compound **3c** gvce signals at δ 11.4 (NH proton), δ 2.7-3.1 (6H of 2 CH_3 groups). δ 6.9-7.4 (m 5H aromatic and pyridone protons) and at δ 9.3 (1H of pyridine) ppm.

Oxidation of compound **1** with acetic acid/sodium nitrite[5] gave 2,2'-bis[3-cyano-4,6-dimethylpyridyl] disulphide **4**. IR spectrum of compound **4** showed absorption bands at 1610 cm^{-1} (C = N) and at 2220 cm^{-1} (C ≡ N), while, ^{1}HNMR gave signals at δ 8.4 (s 2H of 2 pyridine rings) and at δ 2.5-2.8 (12 H of 4 CH_3 groups) ppm.

Table (1): Physical and analytical data of synthesized compounds.

Compd No.	Solvent	m.p.°C (Yield%)	Mol.Formula (Mol. wt)	% Analysis calcd/found				
				C	H	N	S	Cl
2	Ethanol	170-1 (69)	$C_{11}H_{12}N_2SO$ (220.26)	59.98 59.73	5.48 5.38	12.71 12.57	14.55 14.42	
3_a	Methanol	270-2 (71)	$C_{13}H_{14}N_2SO$ (246.29)	63.39 62.93	5.72 5.46	11.37 11.21	13.01 12.88	
3_b	Methanol	235 (74)	$C_{18}H_{15}ClN_2SO$ (342.71)	63.08 61.82	4.37 4.19	8.17 7.89	9.35 9.17	10.34 10.21
3_c	Methanol	281 (74)	$C_{18}H_{15}N_3SO_3$ (353.24)	61.20 60.59	4.24 4.11	11.89 11.73	9.07 8.79	
4	Ethanol	215 (41)	$C_{16}H_{14}N_4S_2$ (326.4)	58.57 57.80	4.31 4.11	17.16 16.53	19.64 19.52	
5	Methanol	250-1 (55)	$C_8H_{10}N_4$ (162.17)	59.24 59.03	6.20 5.72	34.54 34.38		
6	Toluene	162 (57)	$C_8H_8N_4SO$ (208.2)	46.14 45.13	3.86 3.65	26.90 26.79	15.39 15.19	
7_a	Methanol	174-5 (66)	$C_{22}H_{18}N_4O$ (354.37)	74.56 74.39	5.11 5.6	15.80 15.51		
7_b	Methanol	149 (58)	$C_{22}H_{16}Cl_2N_4O$ (423.26)	62.42 62.23	3.80 3.69	13.21 13.11		
8_a	n. Butanol	189 (53)	$C_{18}H_{16}N_6$ (316.33)	68.34 67.93	5.09 4.89	26.56 26.08		
8_b	n. Butanol	211 (61)	$C_{18}H_{15}ClN_6$ (350.78)	61.63 60.71	4.30 4.01	10.10 9.73	23.95 23.58	

Furthermore, compound **1**, when reacted with hydrazine hydrate in n-butanol gave aminopyrazolopyridine derivative **5**[6]. IR spectrum of compound **5** showed absorption bands at 1610 cm^{-1} (C=N), a broad band at 3200-3300 cm^{-1} (NH_2 and NH) and the absence of any band at 2200 cm^{-1} due to the absence of C ≡ N group. Also, mass spectrum gives molecular ion peak at m/z 162, which agrees with the molecular formula $C_8H_{10}N_4$.

Compound **5** was reacted with thionyl chloride in dry benzene[7] to give the sulfinylaminopyrazolopyridine derivative **6**. IR spectrum of compound **6** showed absorption bands at 1100 cm^{-1} (NSO), 1595 cm^{-1} (C = N), and at 3300 cm^{-1} (NH_2). ^{1}HNMR gave signals at δ 8.9 (s 1H pyridyl), δ 2.6-2.9 (6H of 2 CH_3) and at δ 9.9 (s NH of pyrazole) ppm.

Compound **6** reacted with benzil and p,p'-dichlorobenzi[8] to yield benzilimine and p,p'-dichlorobenziimine derivatives **7a,b**. IR spectra of **7a,b** showed absorption bands at 1600 cm^{-1} (C = N), 1690 cm^{-1} (C = O) and at 3300 cm^{-1} (NH) and the absence of any band at 1100 cm^{-1} due to the absence of -NSO group.

Compound **5** was allowed to react with arylidinemalononitrile[2], namely, (benzylidinemalonitrile and 4-chlorobenzylidinemalononitrile) in pyridine to yield compounds **Sa,b**. The structure of **Sa,b** was confirmed from analytical and spectral data. IR spectra showed bands at the regions 1550-1600 cm^{-1} (C = N), 2230 cm^{-1} (C ≡ N) and 3300-3350 cm-1 (NH and NH_2) ^{1}HNMR of compound **Sa** gave signals at δ 2.5-2.8 (s 6H of CH_3), δ 8.1 (1H pyridyl), δ 3.2 (m 2H, 2CH proton) and δ 7.4-6.9 (m 5H, aromatic) ppm.

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تخليق بعض مشتقات الثيينوبيريدين والبيرازولوبيريدين الجديده

جمال عبد اللطيف أحمد

قسم الكيمياء - كلية العلوم - جامعة الزقازيق

عند تفاعل المركب ٣-سيانو ٤،٦-داى ميثيل-٢ بيريدين ثيول (١) مع كل من كلوريد الأسيتون والهيدرازين هيدريت أعطى مشتق الثيينوبيريدين (٢) ومشتق البيرازولوبيريدين (٥) على التوالى. المركب (٢) تفاعل مع الألدهيدات وأعطى المركبات (٣ أ - ٣جـ). وعند تفاعل المركب (٥) مع كل من كلوريد الثيونيل ومركبات الأريليدين مالونونيتريل أعطى المركبان (٦)، (٨ أ و ب) على التوالى. وعند تفاعل مركب (٦) مع البنزل ٤،٤' ثنائى كلوريد البنزل فقد تكونت مشتقات البنزل (٧ أ ، ب).