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NEW HETEROCYCLIC SYNTHESIS FROM CYANOPYRIDINE DERIVATIVES

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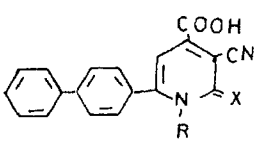
ABSTRACT

Reaction of 4-carboxy-3-cyano-pyrid-2-one **1a** with $SOCl_2$ afforded the corresponding acid chloride 2. Treatment of **2** with different alcohols formed ester **3a,b**. Condensation of **3a** with hydrazine hydrate yielded the pyridazinone derivative **4**. Reaction of N-acetyl pyridone **1b** with thiosemicarbazide and hydroxylamine hydrochloride gave thiosemicarbazone **5** and oxime **7** derivatives. Condensation of 4-carboxy-3-cyano-pyrid-2-thione **1c** with ethyl chloroacetate and thiourea gave ester derivative **8** and pyrido **[2,3-d]** pyrimidine derivative **10**. Quinazolone derivative **11** was prepared by reaction of **1d** with anthranilic acid. The reaction of **11** with several reagents was reported. The structure of the new compounds were established by analytical and spectroscopic measurements. Some new compounds showed interesting antimicrobial activities in vitro.

INTRODUCTION

In a previous paper[1] we have described an easy method for the synthesis of some 4-carboxy-3-cyanopyridine derivatives to be evaluated as antimicrobial agents. In continuation of our previous work, the pyridine derivatives proved to be useful precursor for the synthesis of new fused heterocycles.

Scheme 1



1

	R	X
a	H	O
b	$COCH_3$	O
c	H	S
d	S=C-NHph	O

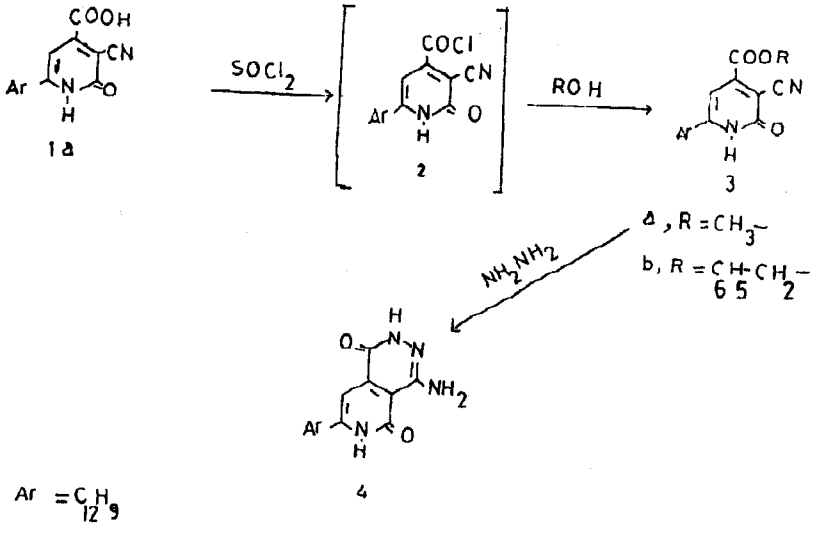
Table 1. Spectral data of prepared compounds

Compd.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
3a	1720 (C=O), 3200 (HN) 2225 (CN), and 1675 (C=O ring amide).	3.15 (3H,s, $COOCH_3$)10.11 (1H,br,NH) and 6.91-7.11 (10H,m,aromatic H and CH heterocycl)
3b	1710 (C=O), and 3225 (NH)	6.41-7.11 (15H,m,aromatic H and CH heterocycl), 3.71 (2H,s,CH_2-COO) and 10.21 (1H,br,NH)
4	1670 (C=O), 1610 (C=N), 1653 (C=O ring amide), and 3350-3200 (NH, NH_2)	5.81 (2H,s,NH_2), 6.91-7.31 (10H,m, aromatic H and CH heterocycl), 8.11 (1H,br,NH), and 10.12 (1H,br,NH)
5	3500-3300 (NH, NH_2) 1120 (–N–C=S amide) 1610 (C=N), 1580 (C–N). and 3210 (OH)	2.31 (3H,s,CH_3–C=N), 5.52 (2H,s,NH_2), 6.197.13 (10H,m,aromatic H and CH heterocycl), 10.12 (1H,br,NH), and 11.21 (1H,br,OH)
6	1718 (C=O), 1620 (C=N) and 3200 (NH)	2.51 (3H,s,CH_3–C=N), 3.81 (2H,d,CH_2 C=O) 10.11 (1H,br,NH), 6.91-7.31 (10H,m,aromatic H and CH heterocycl), and 10.11 (1H,br,OH)
7	1675 (C=O), 3250 (OH) and 2220 (CN)	2.53 (3H,s,CH_3), 6.91-7.31 (10H,m,aromatic H and CH heterocycl), 9.91 (1H,br,OH) and 11.31 (1H,br,OH)
8	2210 (CN), 1620 (C=N) 1710 (C=O), 3230 (OH)	3.41 (3H,t,CH_2–CH_3), 4.11 (2H,q,CH_3–CH_2), 4.31 (2H,s,S–CH_2), 6.92-7.91(10H,m,aromatic H and CH heterocycl), and 11.11 (1H,br,OH)
9	3478, 3344 (NH_2), and 1672 (C=O)	3.40 (3H,t,CH_3-CH_2), 4.11 (2H,q,CH_2–CH_3), 5.81 (2H,br,NH_2), 6.91-7.91 (10H,m,aromatic H and CH heterocycl), and 11.31 (1H,br,OH)
10	3400-3300 (NH,NH_2) 1240 (C=S), 1630 (C=N)	5.51 (2H,br,NH_2), 8.51 (1H,br,NH) 6.91-7.84 (10H,m,aromatic H and CH heterocycl) and 11.22 (1H,br,OH)
11	1700 (C=O), 1620 (C=N) 2220 (CN), 1675 (C=O)	6.91-7.91 (19H,m,aromatic H and CH heterocycl) and 11.12 (1H,br,OH)
12	3400, 3344 (NH_2) 1620 (C=N)	5.11 (2H,br,NH_2), 6.91-7.91 (19H,m, aromatic H and CH heterocycl), and 11.13 (1H,br,OH)
13	3340 (NH), 1240 (C=S) 1620 (C=N)	10.11 (2H,br,2NH), 6.91-7.91 (24H,m, aromatic H and CH heterocycl), 11.31 (1H,br,OH)

RESULTS

Reaction of 4-carbox-3-cyano-6-biphenylpyrid-2-one **la** with $SOCl_2$[2] afforded the corresponding acid chloride **2**. Compound **2** could not be isolated however its formation was proved by reaction with various alcohols resulting in the formation of ester, **3a,3b**. When **3a** reacted with hydrazine hydrate,[3] it yielded the pyridazinone derivative **4** (Scheme 2). The analytical and spectral data of **2** and **3** were in accordance with the proposed structures.

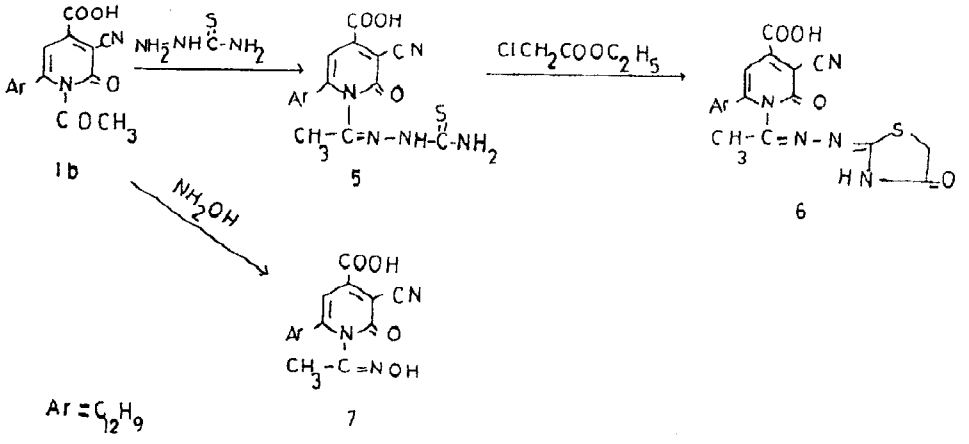
Scheme 2



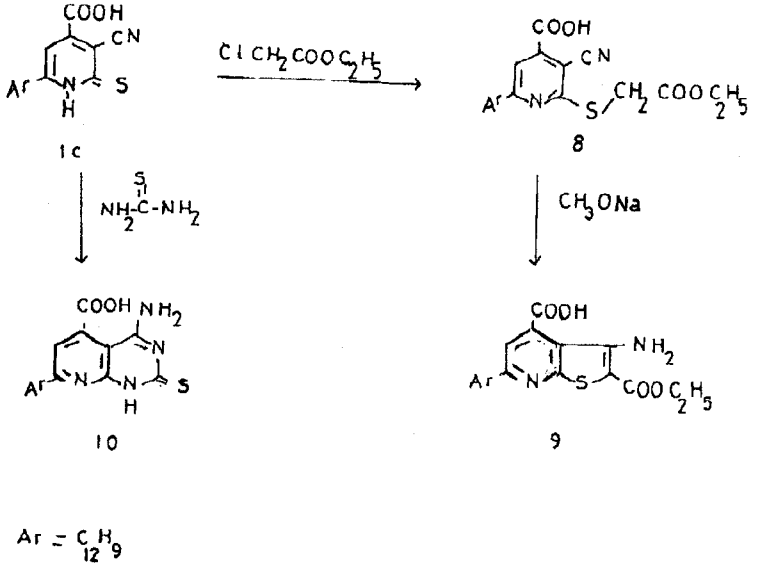
Treatment of N-acetyl-4-carboxy-3-cyano-6-biphenylpyrid-2-one **1b** with thiosemicarbazide[4] in refluxing AcOH yielded thiosemicarbazone **5**. This latter compound was cyclized with ethylchloroacetate in refluxing ethanol in the presence of AcONa, and the 4-oxothiazole derivative **6** was obtained. Morever, reaction **1b** with hydroxylamine hydrochloride to gave the corresponding oxime **7** (Scheme 3).

4-carboxy-3-cyano pyridin-2-thione **1c** was condensed with ethyl chioroacetate[5] in dimethyl formamide in the presence of potassium carbonate gave the corresponding ethylmercapto derivative 8 (Scheme 4).

Scheme 3



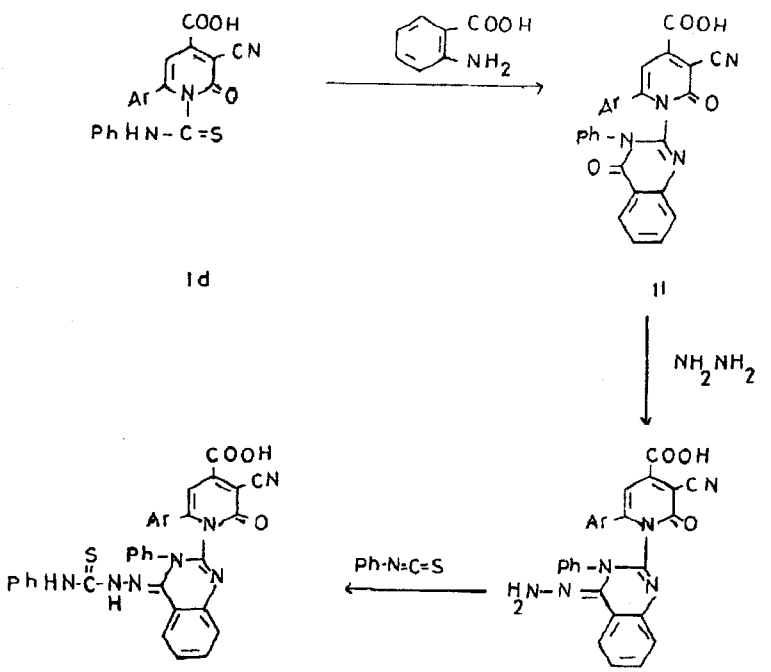
Scheme 4



Cyclization[6] of **8** with CH_3ONa afforded the corresponding thieno [2,3-bJ pyridine derivative **9**. On the other hand, treatment of (**1c** with thiourea afforded the corresponding pyrido [2,3-d] pyrimidine derivative **10**. The quinazolone derivatives **11** were prepared by the reaction of anthranilic

acid[7,8] with N-phenylthiocarbamoyl-4-carboxy-3-cyano-6-biphenylpyrid-2-one **1d**. Treatment of **11** with hydrazine hydrate[9] gave hydrazino derivatives **12** Compound **12** reacted with phenylisothiocyanate to afford 4-[N^2-phenyl-thiocarbamoyl) hydrazino] quinoline derivatives **13** (Scheme 5).

Scheme 5



Biological activity

Some of the synthesized compounds were evaluated for their antimicrobial activities (minimium inhibition concentration MIC) against Gram positive bacteria (*staphylococcus aureus* ATCC-65 38-p and *Bacillus cereus* NRRL-B-569) and Gram negative bacterial (*serratia marcesens* IMRU-70 and *proteus merabitis* NTC-289) using the nutrient agar pour plate method[10] at the 125 ug/ml and 175 ug/ml levels against the microorganisms used. The antifungal activity of same compounds were tested against *Aspergillus fumgytus* (pp.29) to determine the MIC using

turbidmetric method.[11] Ofloxacin was used as a drug reference. The results are listed in Table 2. Results indicated that compound **6** posses highest activity at low concentration level [125 ug/ml] against all microorganisms used to compared to the drug ofloxacin. Compound **9** also has the same activity against staphylococcus *aureus* at the same concentration Compounds **3,5,6** and **9** posses highest activity against *Bacillus cereus* at concentration level (175 ug/ml) compared to ofloxac in. Compounds **6** and **9** show highest anti fungal activity at 175 ug/ml concentration.

EXPERIMENTAL

All mp.'s are uncorrected. IR spectra (cm^{-1}) were recorded on a pye-Unicam spectrophotometer using KBr Wafer technique. ^{1}H-NMR spectra were obtained on a Varian EM-390 (90 MHz) spectrometer using TMS as internal standared and DMSO-d_6 as solvent Chemical shifts were expressed in δ (ppm) values. Elemental analyses were determined using Perkin-Elmer 240 C Microanalyser.

General synthesis of ester (3)

Dry acid **1a** (0.01 mol) and $SOCl_2$ (30 ml) were refluxed for 2h. The excess of $SOCl_2$ was completely removed under pressure, to the residual yellow solid (**2**) suitable alcohol (15 ml) were added and the reaction mixture was again refluxed for 3h. Then the excess of alcohol was distilled off, the dry residue was treated under cooling with $NaHCO_3$ and the formed precipitate was filtered offf and crystallized from ethanol.

3a, (R = CH_3): yellow crystals, m.p. 185-187°C; yield, 80% (Found: C, 72.74; H, 4.3; N, 8.50. $C_{20}H_{14}N_2O_3$ required C, 72.71; H, 4.27; N, 8.47%).

3b, (R = $C_6H_5CH_2$–): brown crystals, m.p. 90-95°C; yield 60% (Found: C, 76.85; H, 4.49; N, 6.91 $C_{26}H_{18}N_2O_3$ required C, 76.83; H, 4.46; N, 6.89%.

Table 2. Antimicrobial activity of some compounds at different concentration (M1C in μg/ml)

Compd.	*Straphylococcus aureus* (ATCC-6538-p)		*Bacillus cereus* (NRRL-B-569)		*Serratia marcesens* (1MRU-70)		*Proteus mirabitis* (NTC-289)		*Aspergillus fumgytus* (pp-29)	
	125	175	125	175	125	175	125	175	125	175
3	++	+++	+	+++	++	++	+	+++	+	+
5	++	++	++	+++	++	++	++	++	+	++
6	+++	+++	+++	+++	+++	+++	++	++	++	+++
8	++	++	+	++	+	++	+	++	+	++
9	+++	+++	++	+++	++	++	+	++	+	+++
10	+	++	+	++	+	++	+	++	+	++
Ofloxacin	++	+++	++	++	++	+++	++	+++	-	++

Diameter of the zome of inhibition – < 1 cm; + = 1 to 1.5 cm; ++ = 1.5 cm to 2 cm ; +++ > 2 cm

4-Amino-7-biphenylpyrido [4,3-d] pyridazin-1,5-dion (4)

A mixture of compound **3a** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 6 h, then allowed to cool. The solid product was collected and crystallized from acetone as yellow crystals; m.p. 146-148°C; yield 72% (Found: C, 69.10; H, 4.30; N, 16.97. $C_{19}H_{14}N_4O_2$ requires C, 69.08; H, 4.27; N, 16.95%).

1-(Acetylthiosemicarbazone)-4-carboxy-3-cyanopyrid-2-one(5)

A mixture of **1b** (0.01 mol) and thiosemicarbazide (0.01 mol) in acetic acid (30 ml) was refluxed for 2 h, then allowed to cool. the solid product was filtered off and crystallized from ethanol as brown needles, m.p. 145-148°C; yield 70% (Found: C, 61.26; H, 3.99; N, 16.24; S, 7.45. $C_{22}H_{17}N_5O_3S$ requires C, 61.24; H, 3.97; N, 16.22; S, 7.43%).

1-[1-4-oxothazolidine-2-yl)hydrazonoethyl]-4-carboxy-3-cyano-6-biphenylpyrid-2-one (6)

A mixture of **5** (0.01 mol), ethylchloroacetate (0.01) and sodium acetate (0.02 ol)in ethanol was refluxed for 2 h, then allowed to cool. The solid product was filtered off and washed well with water and crystallized from ethanol as brown crystals, m.p. 220-223°C; yield 70% (Found: C, 61.16; H, 3.66; N, 14.88; S, 4.93. $C_{24}H_{17}N_5O_4S$ requires C, 61.14; H, 3.63; N, 14.85; S, 4.89%).

1-Acetyloxime-4-carboxy-3-cyano-6-biphenylpyrid-2-one (7)

A mixture of **1b** (0.01 mol), hydroxylarnine hydrochloride (0.01 mol in 2 ml H_2O) and sodium acetate (0.12 mol) in ethanol (30 ml) was refluxed for 2 h, then the mixture was allowed to cool and poured into cold water. The solid product was crystallized from acetic acid as brown crystals, m.p. 110-112°C; yield 70% (Found: C, 67.58; H, 4.08; N, 11.27. $C_{21}H_{15}N_3O_4$ requires C, 67.55; H, 4.04 ; N, 11.25%).

4-carboxy-3-cyano-6-biphenyl-2-ethylthioglycolyl-pyridine (8)

To a stirred solution of **1c** (0.01 mol) in DMF (10 ml), and K_2CO_3 (0.04 mol) was added and stirring was continued at 60°C for 30 min. Ethyl chloroacecate (0.02 mol) was dropwisely added and stirring was

continued for 1 h. After cooling, the reaction mixture was poured into an ice-cold water. The product was crystallized from acetone as brown crystals, rn.p. 120-123°C; yield 45% (Found: C, 66.04; H, 4.35; N, 6.72; S, 7.68; $C_{23}H_{18}N_2O_4S$ requires C, 66.0l; H, 4.33; N, 6.69; S, 7.66%).

3-Amino-2-carboethoxy-6-biphenylthieno[2,3-b] pyridine (9)

To a stirred suspension of **8** (0.01 mol) in ethanol (10 ml), sodium methoxide (1 ml sodium methoxide, 2%) was added and the reaction mixture was heated on water bath under stirring for 15 min. The solid colour changed from orange to greenish yellow After cooling, the solid was separated by filtration and crystallized from dioxane. m.p. 230-233°C; yield 50% (Found: C, 66.04; H, 4.35; N, 6.72; S, 7.68 $C_{23}H_{18}N_2O_4S$ requires C, 66.01; H, 4.33; N, 6.69; S, 7.66%).

4-Amino-S-carboxy-7-biphenylpyrido [2,3-d] pyrimidin-2-thione (10)

A mixture of 1c (0.01 mol) and thiourea (0.01 mol) was refluxed in ethanol (50 ml) containing few drops of piperidine (2 ml) for 5h. The reaction mixture was allowed to cool and the solid product was filtered off and crystallized from ethanol as yellow crystals, m.p. 135-139°C; yield 65% (Found: C, 64.18; H, 3,78; N, 14,99; S, 8.59. C20 $H_{14}N_4O_2S$ requires C, 64.16 ; H, 3.76; N, 14.96; S, 8.56%).

2-[4-carboxy-3-cyano-6-biphenyl-2-oxo-pyrid-1-yl]-3-phenyl-4-quinazolone (11)

To a solution of anthranilic acid (0.01 mol) in n-butanol (50 ml), **1d** (0.01 mol) was added and the resulting solution was heated under reflux for 48 solvent was then evaporated under reduced pressure, and the solid product was collected by filtration and crystallized from acetone, m.p 230-233°C; yield 80% (Found: C, 73.89, H, 3.77, N, 10.48. $C_{33}H_{20}N_4O_4$ requires C, 73.87; H, 3.75; N, 10.44%)

2-[4-Carboxy-3-cyano-6-biphenyl-2-oxo-pyridin-1-yl]-3-phenyl-4 hydrazinoquin-azoline (12)

A mixture of 11 (0.01 mol) and hydrazine hydrate (0.01 mol) in abs. ethanol (30 ml) was refluxed for 6h. After cooling the precipiated product

was filtered off and crystallized by dioxane, m.p. 200-202°C; yield: 60% (Found : C, 72.01; H, 4.04; N, 15.29 $C_{33}H_{22}N_6O_3$ requires, 71.99; H, 4.02; N, 15.26%)

2-[4-Carboxe-3-cyano-6-biphenyl-2-oxo-pyrid-1-yl]-3-phenyl-4-(N^1-phenylthioc-arbamoyl hydrazino)-quinazoline (13)

A mixture of 12 (0.01 mol) and phenylisothiocyanate (0.01 mol) in abs. ethanol (50 ml) was refluxed for 6 h and then allowed to cool. The solid product was collected and crystallized from ethanol, m.p: 180-182°C; yield: 80% (Found: C, 70.09; H, 3.99; N, 14.31; S, 4.09. $C_{40}H_{27}N_7O_3S$ requires C, 70.06; H, 3.96; N, 14.29; S, 4.67%)

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