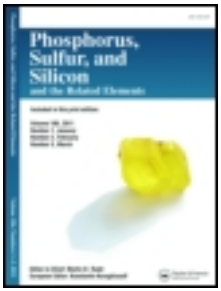

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SYNTHESIS AND REACTIONS OF SOME IMIDAZOPYRIMIDO (PYRIDO)THIENO [2,3-b]QUINOXALINE DERIVATIVES*

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2-Amino-3(4,5-dihydro-1H-imidazol-2-yl)thieno[2,3-b]quinoxaline **2** was prepared and then allowed to react with nitrous acid, triethyl orthoformate, acetic anhydride and carbon disulfide to give the imidazotriazinothienoquinoxaline **3** and imidazopyrimidothienoquinoxaline **4–6** respectively. Starting with thione **6** a series of S-ubstituted mercapto derivatives **7–10** was obtained. Reaction of 2-amino-3-carbonitrile-thieno[2,3-b]quinoxaline **1** with acrylonitrile, malononitrile and/or arylidine malononitrile gave pyridothienoquinoxaline derivatives **11–13**.

Keywords: Ethylenediamine; imidazol; imidazotriazinothienoquinoxaline

INTRODUCTION

Some purines (imidazopyrimidines) are reported to posses biological activity[1] arylquinoxalines were found to have a great antimicrobial potency[2]. Also quinoxaline antibiotics and antiasthmatics are well known[3,4] In this context and in continuation of our investigations upon the synthesis of polyheterocyclic systems containing a quinoxaline moiety[5–7], we report herein the synthesis of some new pyrimido and pyridothienoquinoxalines of potenial biological activity.

RESULTS AND DISCUSSION

Earlier reports described the conversion of the cyano group of *o*-amino nitriles into the corresponding 4,5-dihydro-1H-imidazol-2-yl group by the

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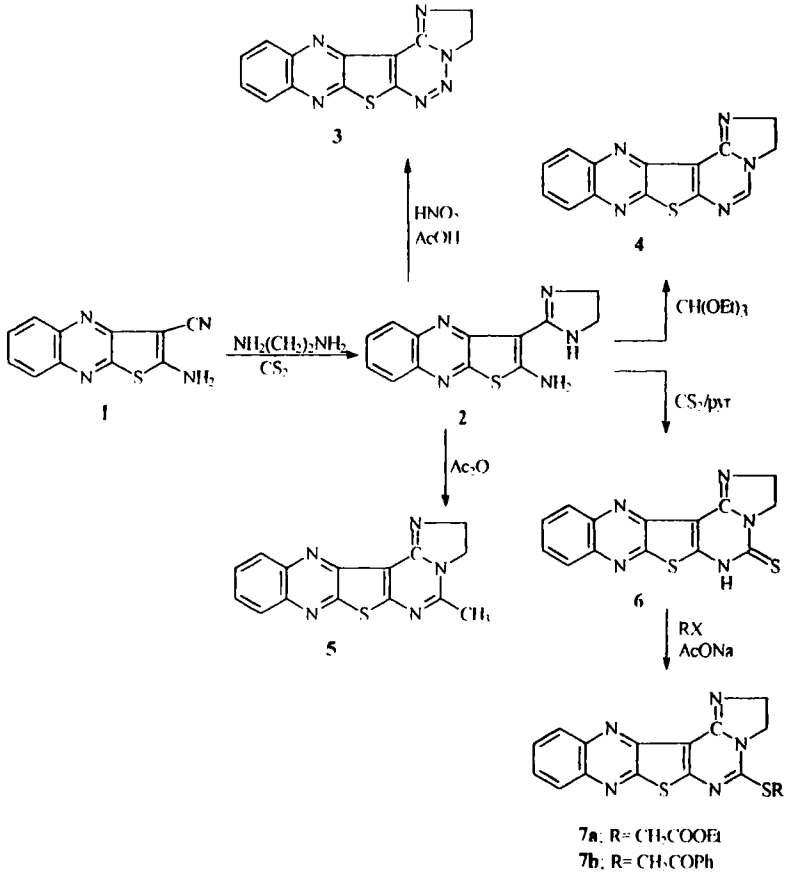
interaction of the aminonitrile with ethylenediamine in the presence of carbon disulfide[8], p-toluenesulfonicacid[9]or phosphorus pentasulfide[10]. Consequently,2-amino-3-carbonitrile-thieno[2,3-b]quinoxaline[11,12]. Compound **1** was allowed to react with ethylenediamine in the presence of carbon disulfide on water bath to give 2-amino-3(4,5-dihydro-1H-imidazol-2-yl)thieno [2,3-b]quinoxaline **2**. The latter compound on treatment with nitrous acid gave 2,3-dihydro-imidazo[1″,2″:1′,6′]triazino [4′,5′:4,5]thieno[2,3-b]quinoxaline **3**, compound **2** was heated under reflux with triethyl orthoformate in presence of a few drops of acetic acid gave 2,3-dihydro- imidazo[1″,2″:1′,6′]-pyrimido[4′,5′:4,5]thieno[2,3-b]quinoxaline **4**. However the 5-methyl derivative **5** was obtained by the interaction of **2** with acetic anhydride. The reaction of **2** with carbon disulfide in ethanolic potassium hydroxide followed by acidifaction gave thione derivative **6** which was alkylated with halocompounds; namely methyl odide, phenacyl bromide to S-substituted-2,3-dihydro-imidazo[1″,2″:1′,6′] pyrimido[4′,5′:4,5]thieno [2,3-b] quinoxalines $7_{a,b}$ (Scheme 1).

The ester function of derivative 7_a was converted into carbohydrazide **8** by the interaction with hydrazine hydrate in boiling ethanol. The latter carbohydrazide **8** was treated with nitrous acid to produce carboazide **9**, condensation of **8** in presence of piperidine with aromatic aldehydes such as benzaldehyde, *p*-anisaldehyde gave arylidine derivatives $\mathbf{10}_{a,b}$, respectively (Scheme 2).

Likewise, compound **1** was readily cyclized to the corresponding pyrido [1′,2′:4,5]-thieno[2,3-b]quinoxaline derivatives **11–13** upon reaction with acrylonitrile, malononitrile and/or arylidine malononitrile through refluxing in pyridine or in sodium ethoxide(Scheme 3).

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. The IR spectra were recorded as KBr disks on a Pye-Unicam SP3–100 spectrometer using KBr wafer technique. ^{1}H-NMR spectra are recorded in suitable deutrated solvent on a Varian 390 90 MHz NMR spectrometer using *TMS* as internal standard. Elemental analyses were obtained on a Perkin-Elmer 240 C microanalyzer. Elemental analysis, Melting points, yields and spectroscopic data are listed in Tables I and II respectively.



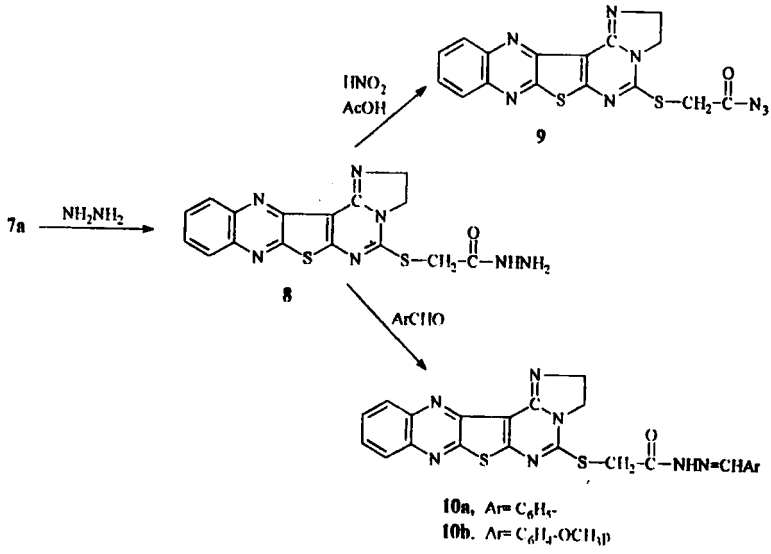
SCHEME 1

2-Amino-3-carbonitrile-thieno(2,3-b)quinoxaline(1)

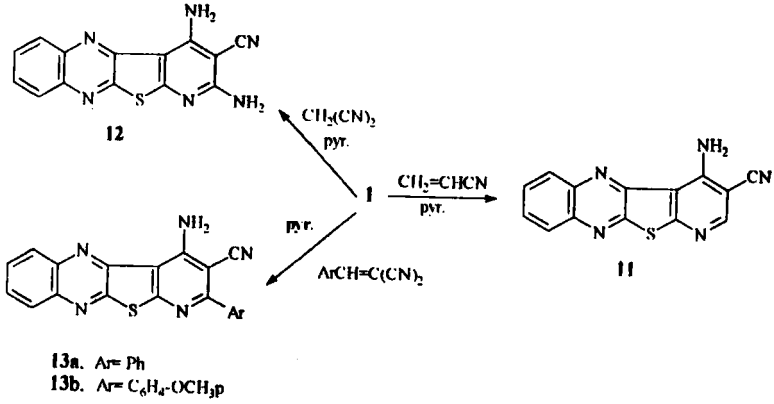
This compound was prepared according to a known procedure[Lit. 11,12]

2-Amino-3(4,5-dihydro-1H-imidazol-2-yl)thieno[2,3-b]quinoxaline (2)

To a mixture of compound **1** (0.01mol) and ethylenediamine (12 ml) was added dropwise carbon disulfide (1 ml). The resulting reaction mixture was heated on a steam bath for 2 hr, the cold reaction mixture was poured



SCHEME 2



SCHEME 3

into cold water, and was left to stand for one hour. The sold precipitate was collected and recrystallized from ethanol as dark brown crystals.

TABLE I Melting points, Yields and Analytical data of compounds 2–13

Compound No.	*M.P(0 C) Yield(%)*	*Formula (M.W)*	*Calculated/Found*			
			C	*H*	*N*	*S*
2	300	$C_{13}H_{11}N_5S$	57.99	4.08	26.02	11.89
	90	269	57.82	4.00	25.92	11.78
3	220	$C_{13}H_8N_6S$	55.71	2.85	30.00	11.42
	80	280	55.63	2.78	29.84	11.32
4	340	$C_{14}H_9N_5S$	60.21	3.27	25.08	11.46
	75	279	60.14	3.16	24.96	11.35
5	>360	$C_{15}H_{11}N_5S$	61.43	3.75	23.89	10.92
	67	293	61.34	3.62	23.76	10.81
6	280	$C_{14}H_9N_5S_2$	54.01	2.89	22.50	20.57
	82	311	53.91	2.72	22.41	20.45
7a	210	$C_{18}H_{15}N_5O_2S_2$	54.40	3.97	17.63	16.12
	72	397	54.30	4.00	17.51	15.98
7b	200	$C_{22}H_{15}N_5OS_2$	61.53	3.49	16.31	14.91
	86	429	61.50	3.35	16.23	14.78
8	285	$C_{16}H_{13}N_7OS_2$	50.13	3.39	25.58	16.71
	95	383	50.21	3.34	25.37	16.60
9	120(decomp.)	$C_{16}H_{10}N_8O\,S_2$	48.73	2.53	28.42	16.24
	69	394	48.61	2.41	28.35	16.13
10a	310	$C_{23}H_{17}N_7OS_2$	58.59	3.60	20.80	13.58
	84	471	58.44	3.62	20.72	13.40
10b	325	$C_{24}H_{19}N_7O_2S_2$	57.48	3.79	19.56	12.77
	78	501	57.40	3.57	19.37	12.67
11	220	$C_{14}H_7N_5S$	60.64	2.52	25.27	11.55
	67	277	60.54	2.41	25.13	11.48
12	320	$C_{14}H_8N_6S$	57.53	2.73	28.76	10.95
	72	292	57.43	2.62	28.63	10.81
13a	>360	$C_{20}H_{11}N_5S$	67.98	3.11	19.83	9.06
	84	353	67.87	3.00	19.73	9.00
13b	> 360	$C_{21}H_{13}N_5OS$	65.79	3.39	18.27	8.35
	77	383	65.52	3.27	18.10	8.24

TABLE II Spectral data of compounds 2–13

Compound No.	*IR(λ Cm^{-1})/^{1}H-NMR(δ ppm)*
2	3400,3300,3200(NH_2,NH)and 1600(C=N). (DMSO-d_6): δ 3.3(m,4H,2CH_2), δ 7.4–7.8(m,4H,ArH), δ 8.3(s,1H,NH)and δ 8.9(s,2H,NH_2).
3	2980(CH,aliph.) and 1600(C=N). (DMSO-d_6): δ 3.1(m,4H,2CH_2) and δ 7.2–7.9(m,4H,ArH).
4	1610(C=N). (DMSO-d_6): δ 3.2(m,4H,2CH $_2$), δ 7.4–7.8(m,4H,ArH) and δ 9.2(s,1H,CH pyrim.).
5	3050 (CH.arom), 2960(CH,aliph.) and 1600(C=N). (DMSO-d_6): δ 2.7(s,3H,CH_3), δ 3.5(m,4H,2CH_2) and δ 7.6–8.1(m,4H,ArH).
6	3220(NH), 1600(C=N) and 1210(C=S). (DMSO-d_6): δ 3.4(m,4H,2CH_2), δ 7.5–8.0(m,4H,ArH) and δ 8.4(s,1H,NH).
7a	3040 (CH.arom), 2950(CH,aliph), 1740(C=O,ester). ($CDCl_3$): δ 1.2(t,3H,CH_3), δ 3.8(q,2H,CH_2), δ 3.2(m,4H,2CH_2) and δ 7.6–8.1- (m,4H,ArH).
7b	1670(C=O) and 1600(C=N). ($CDCl_3$): δ 3.2(m,4H,2CH_2), δ 4.2(s,2H,S-CH_2) and δ 7.6–8.3(m,9H,ArH).
8	3400,3180(NH_2,NH), 1660(C=O) and 1620(C=N). (CF_3COOD) δ 3.4(m,4H,2CH_2), δ 4.4(s,2H,S-CH_2) and δ 7.5–8.3(m,4H,ArH).
9	2210(azide: N_3), 1700(C=O) and 1610(C=N). (DMSO-d_6): δ 3.5(m,4H,2CH_2), δ 4.2(s,2H,S-CH_2) and δ 7.4–8.1(m,4H,ArH).
10a	3220(NH), 1660(C=O) and 1590(C=N). (DMSO-d_6): δ 3.4(m,4H,2CH_2), δ 4.5(s,2H,S-CH_2), δ 7.4–8.1(m,9H,ArH), δ 9.4(s,1H,CH) and δ 10.3(s,1H,NH).
10b	3200(NH), 2950(CH,aliph.), 1670(C=O) and 1600(C=N). ——
11	3420,3200(NH_2),2220(C≡N) and 1610(C=N). (DMSO-d_6) δ 7.4–7.9(m,4H,ArH), δ 8.7(s,2H,NH_2) and δ 9.2(s,1H,CH).
12	3400,3300(NH_2),2230(C≡N) and 1620(C=N). (CF_3COOD): δ 7.8–8.2(m,9H,ArH).
13a	3300(NH_2),2210(C≡N) and 1610(C=N). (DMSO-d_6) δ 7.8–8.2(m,9H,ArH) and δ 8.7(s,2H,NH_2).
13b	3380(NH_2),2220(C≡N) and 1600(C=N) ——

2,3-Dihydro-imidazo[1″,2″:1′,6′]1,2,3-triazino[4′,5′:5,4]thieno[2,3-b] quinoxaline (3)

To a mixture of compound **2** (0.01mol) in acetic acid (15 ml), sodium nitrite solution (1.4g in 4 ml water) was added dropwise with stirring. The reaction mixture was left to stand for 3 hr. The solid was collected and recrystallized from ethanol as yellow crystals.

2,3-Dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoxaline (4)

A sample of compound **2** (0.5g) in triethyl orthoformate (10 ml) in presence of (1ml) acetic acid was refluxed for 3 hr, the solid product which formed on heating was seperated and recrystallized from acetic acid as orange crystals.

5-Methyl-2,3-dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno [2,3-b] quinoxaline (5)

A sample of compound **2** (0.5g) in acetic anhydride (12 ml) was refluxed for 4 hr, then allowed to cool. The solid product was collected and recrystallized from acetic acid as pale yellow crystals.

2,3-Dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoxalin-5(6H)thione (6)

To a mixture of compound **2** (2.0 g) and carbon disulfide (5 ml) in alcoholic potassium hydroxide solution (10 ml, 10 %) was heated under reflux on a water bath for 5 hr, and the excess of carbon disulfide was eliminated. After acidifaction with hydrochloric acid, the solid product was collected and recrystallized from ethanol as yellow crystals.

Alkylation of 6 : prepration of S-alkylated derivatives (7a,b)

To a mixture of equimolar (0.01 mol) amounts of the thione **6** and the haloderivative in ethanol (30 ml) sodium acetate (0.015 mol) was added, the reaction mixture was refluxed for 2 hr, then allowed to cool. The solid product was collected washed with water and recrystallized from ethanol.

(2,3-Dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoxalin-5-yl-thio) acetichydrazide (8)

A mixture of 7a (0.01mol) and hydrazine hydrate (0.01mol) in ethanol (30 ml) was refluxed for 3 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol as yellowish crystals.

(2,3-Dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoxalin-5-yl-thio) aceticazide (9)

To a solution of **8** (1.0g) in acetic acid (15 ml) was added dropwise with stirring sodium nitrite solution (1.5 g in 5 ml water). The reaction mixture was then allowed to stand for 2 hr. The sold product was filtered washed with water and recrystallized from ethanol as yellow crystals.

Arylidene(2,3-dihydro-imidazo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno [2,3-b]-quinoxalin-5-ylthio) acetichydrazide (10a,b)

General procedure: A mixture of an equimolar ratio of **8** (0.002 mol) and each of the aromatic aldehydes (benzaldehyde, *p*-anisaldehyde) in ethanol (15 ml) and piperidine was refluxed for 4 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol.

4-Amino-3-cyano-(2H)-pyrido[2′,3′:4,5]thieno[2,3-b]quinoxaline (11)

A mixture of **1** (0.01mol) and acrylonitrile (0.01 mol) in pyridine was refluxed for 4 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol as red crystals.

2,4-Diamino-3-cyano-pyrido[2′,3′:4,5]thieno[2,3-b]quinoxaline (12)

A mixture of **1** (0.01mol) and malononitrile (0.01mol) in pyridine (20 ml) was refluxed for 2 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol as yellowish crystals.

2-Aryl-3-carbonitrile-4-Amino-pyrido[2′,3′:5,4]thieno[2,3-b]-quinoxalines (13a, b)

A mixture of **1** (0.01mol) and arylidine malononitrile (0.01mol) in pyridine (25 ml) was refluxed for 3 hr, then allowed to cool. The solid product was collected and recrystallized from ethanol.

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