Synthesis of new thieno- and pyrazolo- pyridazine derivatives

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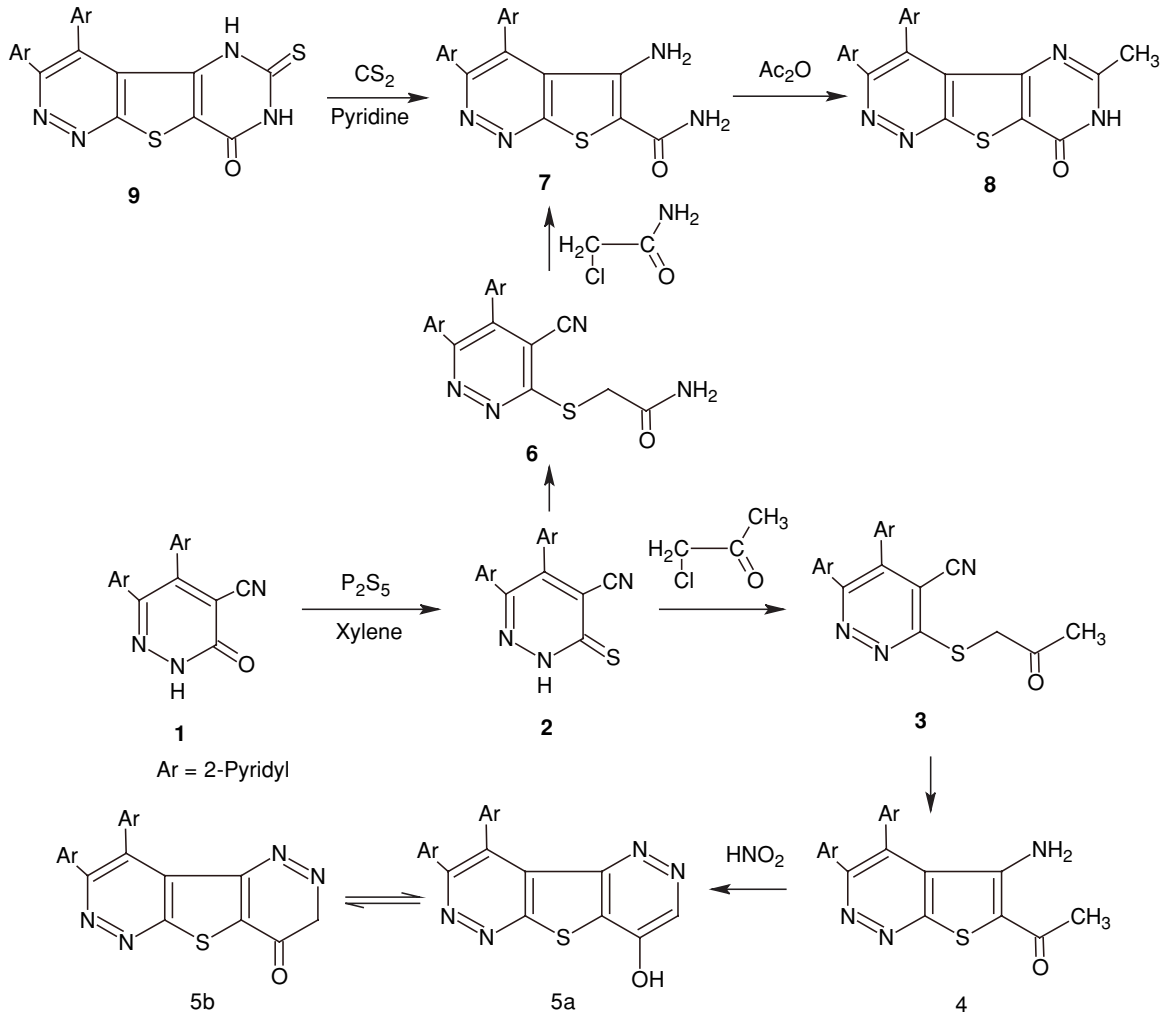
5,6-Di(pyridin-2-yl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile **2** has been reacted with ahalocompounds, such as chloroacetone, chloroacetamide, ethyl chloroacetate and chloroacetic acid gave the corresponding 2-S-alkylated pyridazine derivatives **3**, **6**, **10** and **13** which have been cyclised to give the corresponding thienopyridazine derivatives **4**, **7**, **11**, and **14** respectively. Reaction of **15** with hydrazine hydrate gave the corresponding pyrazolopyridazine **16**.

Keywords: pyridazines, theno-pyrazolo derivatives

In continuation of our studies[1-6] directed towards synthesis of new pyridazines annelated with various five and six membered heterocycles, we report here the synthesis of thieno- and pyrazolo-pyridazines likely to possess biologically active compounds. The starting material 3-oxo-5,6-di(pyridin-2-yl)-2,3-dihydropyridazine-4-carbonitrile **1** has been prepared via the reaction of 2,2'-pyridil monohydrazone with ethyl cyanoacetate in refluxing sodium ethoxide.

5,6-Di(pyridin-2-yl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile **2** has been prepared via the reaction of 3-oxo-5, 6-di(pyridin-2-yl)-2,3-dihydropyridazine-4-carbonitrile **1** with P_2O_5 in dry xylene.[7]

Alkylation of the pyridazinethione **2** with chloroacetone in sodium ethoxide[8] gave 2-*S*-acetonylpyridazine **3** which on cyclisation by boiling in 10% ethanolic potassium hydroxide afforded thieno[2,3-*c*]pyridazine **4**. The structures of both **3** and **4** were established from their correct analytical data, and IR spectra which showed the absence of CN group while a newly born NH_2 group was detected. Also, ^{1}H NMR of each **3** and **4** revealed the signals of NH_2 protons while the signals of S-CH_2 was absent. In view of the above data, the reaction proceeded via addition of the anion of S-CH_2 on CN group. The position of NH_2 and $COCH_3$ groups in compound **4** was confirmed via its reaction with nitrous acid which probably proceeded through the diazotisation of NH_2 group then,



Scheme 1

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coupled with the advanced active CH_3 group to give 8,9-di(pyridin-2-yl)-pyridazino[3',4':4,5]thieno[2,3-c]pyridazin-4-ol **5a** or 8,9-dipyridin-2-yl-pyridazino [3',4':4,5]thieno [2,3-*c*]pyridazin-4(3*H*)-one **5b**. Both IR and ^{1}H NMR spectra of **5** showed the presence of an enolic OH group.

In a similar route, the pyridazinothione **2** reacted with chloroacetamide in refluxing sodium ethoxide[9] to give the corresponding derivative **6** which on cyclisation in 10% ethanolic KOH gave the corresponding thieno[2,3-*c*] pyridazine **7** via loss of HCl molecule. The structures of **6** and **7** were supported from its elemental analysis, IR and ^{1}H NMR spectra.

The reactivity and position of NH_2 and $CONH_2$ groups in compound **7** was used for building a third ring through its reaction with acetic anhydride to give 3,4-di(pyridin-2-yl)-primido[4',5':4,5]thieno[2,3-*c*]-pyridazin-8(7*H*)-one **8**, while, reaction of **6** with CS_2 in refluxing pyridine afforded 6, 7-dihydrothiopyrimido[4',5':4,5thieno[2,3-*c*]-pyridazin-8 (5*H*)-one **9**.

The structures of **8** and **9** were established based on their elemental analysis, IR and ^{1}H NMR spectra.

Furthermore, the pyridazinothione **2** reacted with ethyl chloroacetate in sodium ethoxide to give 2-*S*-ethoxy-carbonylmethoxypyridazine **10** via the loss of HCl molecule. The IR spectrum of **10** showed CO, CN groups and the ^{1}H NMR revealed the signals of $COOCH_2CH_3$ protons. The compound **10** was cyclised in 10% ethanolic KOH solution to give thieno[2,3-*c*]pyridazine-2-carboxylate **11** via the addition of *S*-CH_2COOEt anion to CN group. The structure of **11** was confirmed from its analytical data, IR and ^{1}H NMR spectra and chemically through reaction of **11** with hydrazine hydrate in boiling ethanol to give the 5-amino-3, 4-di(pyridin-2-yl)thieno[2,3-*c*]pyridazin-6-carbohydrazide **12**. The structure of **12** was established based on IR and ^{1}H NMR spectral data and elemental analysis.

Alkylation of pyridazinethione **2** with chloroacetic acid in boiling sodium ethoxide[10] afforded 2-*S*-carboxymethylpyridazine **13** which on cyclisation in boiling ethanolic KOH gave 3-aminothieno[2,3-b]-pyridazin **14**. The structure of **14** was established from IR and ^{1}H NMR spectra which showed the absence of the carboxylic group and newly porn of NH_2 group as evidence that decarboxylation accure by the effect of heat.

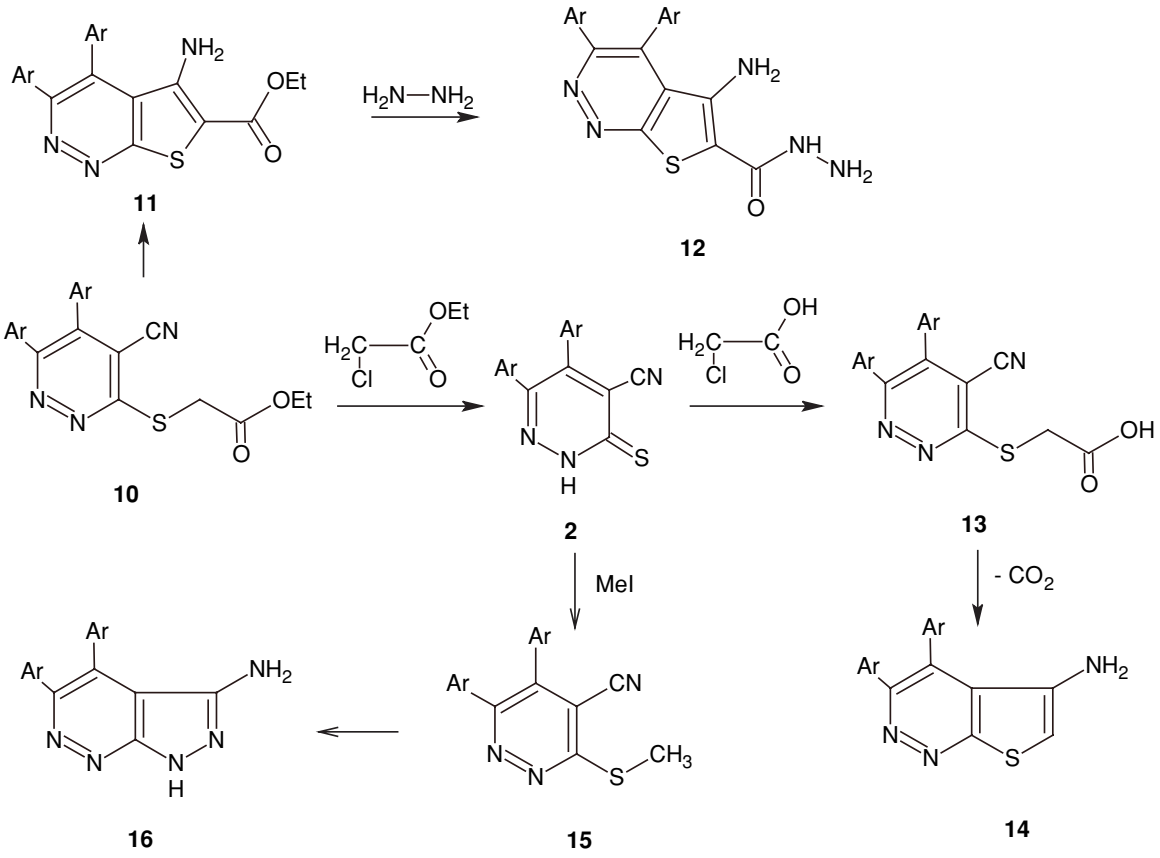
Also, it has been found that the pyridazinethione **2** reacted with methyl iodide in sodium ethoxide to give 2-*S*-methyl-pyridazin **15** via loss of hydrogen iodide. The structure of **15** was established based on IR and ^{1}H NMR spectra and elemental analysis.

A good structure proof of **15** was given via its reaction with hydrazine derivative in refluxing ethanol to give 3-amino-4, 5-di(pyridin-2-yl)-1*H*-pyrazolo[3,4-*c*]pyridazine **16**. The reaction product was sulfur free and in its IR spectrum, the CN group was absent and replaced by the NH_2 group. Its ^{1}H NMR has

Table 1 Characterisation and physical data of compounds **1–16**

Found %/ Calcd%				Mol.formula (mol. mass)	Solvent yield/%	M.p./°C	Comp no.
S	N	H	C				
	25.44 25.22	3.27 3.11	65.45 65.32	$C_{15}H_9N_5O$	T 65	278	**1**
10.99 10.91	24.04 24.00	3.09 3.07	61.84 61.65	$C_{15}H_9N_5S$	B 65	220	**2**
9.22 9.18	20.16 20.09	3.74 3.65	62.23 62.11	$C_{18}H_{13}N_5SO$	E 63	235	**3**
9.22 9.19	20.16 20.09	3.74 3.60	62.23 62.15	$C_{18}H_{13}N_5SO$	DMF 75	295	**4**
8.93 8.77	23.45 23.36	2.79 2.72	60.33 60.13	$C_{18}H_{10}N_6SO$	T 85	146	**5**
8.10 8.00	24.12 24.01	3.44 3.40	58.61 58.55	$C_{17}H_{12}N_6SO$	E 73	282	**6**
8.10 8.02	24.12 24.06	3.44 3.40	58.61 58.52	$C_{17}H_{12}N_6SO$	E 77	185	**7**
8.61 8.55	22.57 22.51	3.22 3.16	61.61 61.44	$C_{19}H_{12}N_6SO$	B 65	275	**8**
16.41 16.35	21.53 21.47	2.56 2.50	55.38 55.23	$C_{18}H_{10}N_6S_2O$	A 73	300	**9**
8.50 8.44	18.56 18.50	3.97 3.72	60.46 60.39	$C_{19}H_{15}N_5SO_2$	E 66	135	**10**
8.24 8.12	14.43 14.35	3.09 3.01	62	$C_{19}H_{15}N_2SO_2$	E 77	164	**11**
8.81 8.71	26.99 26.88	3.58 3.52	56.19 56.06	$C_{17}H_{13}N_7SO$	E 70	230	**12**
9.16 9.10	20.05 20.00	3.15 3.14	58.44 58.40	$C_{17}H_{11}N_5SO_2$	E 62	274	**13**
10.49 10.40	22.95 22.88	3.63 3.60	62.93 62.88	$C_{16}H_{11}N_5S$	E 75	222	**14**
10.49 10.37	22.95 22.88	3.63 3.59	62.94 62..85	$C_{16}H_{11}N_5S$	M 66	115	**15**
	33.89 33.81	3.83 3.78	62.28 62.20	$C_{15}H_{11}N_5S$	A 60	285	**16**

A= Acetic acid, B = Benzene, E = Ethanol, T = Toluene, M = Methanol.



Scheme 2

no signals of –S–CH_3 protons while signals of NH and NH_2 protons were detected.

Characterisation and physical data are listed in Table 1, and the spectral data are listed in Table 2.

Experimental

Melting points are uncorrected. IR spectra were recorded on Unicam SP-1200 infrared spectrophotometer using KBr. ^{1}H NMR spectra were recorded on Varian EM300 spectrometer at 60 MHz in DMSO-d_6 (chemical shifts in ppm).

3-oxo-5,6-di(pyridin-2-yl)-2,3-dihydropyridazine-4-carbonitrile (**1**): To a solution of sodium ethoxide (10 g) of sodium metal in 100 ml ethanol), ethyl cyanoacetate (0.01 mol) was added dropwise, then 2,2'-pyridil monohydrazone was added as solid. the reaction mixture was refluxed for 3 h on water bath, then poured up on ice/HCl. The solid separated was filtered, dried and crystallised from toluene to give **1**.

5,6-Di(pyridin-2-yl)-3-thioxo-2,3-dihydropyridazine-4-carbonitrile (**2**): A solution of pyridazinone **1** (0.01 mole) and P_2S_5 (0.03 mol) was refluxed in dry xylene for 2h. The reaction mixture was filtered on hot and the exess solvent was evaporated under reduced pressure.

Table 2 Spectral data

Compd. No.	IR (cm^{-1})	^{1}H NMR (ppm)
3	1610(C=N),1710 (CO) of acetonyl and 2230 (CN).	2.2 (*s*, 3H, $COCH_3$), 3.0 (*s*, 2H, S–CH_2) and 6.7–7.7 (*m*, 8H, aromatic protons)
4	1620(C=N),1710 (acetyl CO)and 3330 (NH_2).	2.2 (*s*, 3H, $COCH_3$), 4.5 (*s*, br, 2H, NH_2) and 6.2–7.3 (*m*, 8H, aromatic protons)
5	1610(C=N),1630(N=N),1680 (CO) and 3220 (OH).	2.9 (*s*, 1H pyridazine H_3), 7.0–7.8 (*m*, 8H, aromatic protons), 12.2 (*s*, br, 1H, OH enolic)
6	1620(C=N), 1665 (CO amidic), 2220 (CN), 3420 (NH_2).	4.5 (*s*, 2H, S–CH_2), 5.6 (*s*, br, 2H, NH_2), 7.2–7.9 (*m*, 8H, aromatic protons)
7	1615(C=N),1660 (CO amidic), 3460-3300 (two NH_2 groups).	4.8 (*s*, br, 2H, NH_2), 5.9 (*s*, br, 2H, $CONH_2$) and 6.8–7.9 (*m*, 8H, aromatic protons)
8	1615(C=N),1690 (CO), 2960(aliphatic protons) and 3170 (NH).	1.6 (*s*, 3H, CH_3), 6.2–7.8 (*m*, 8H, aromatic and NH protons)
9	1620(C=N),1690 (CO) and 3280, 3150 (two NH).	–
10	1620(C=N),1730 (CO ester), 2220 (CN).	1.3 (*t*, 3H, CH_2–CH_3), 3.4 (*q*, 2H, CH_2 –CH_3) and 6.9–7.7 (*m*, 8H, aromatic protons)
11	1620(C=N),1735 (CO ester) and 3350 (NH_2).	1.5 (*t*, 3H, CH_2–CH_3), 4.8 (*q*, 2H, CH_2CH_3), 5.9 (*s*, br, 2H, NH_2) and 7.2–7.9 (*m*, 8H, aromatic protons)
12	1615(C=N),1630 (CO hydrazide), 3470-3150 (two NH_2 and NH).	–
13	1620(C=N),1670 (CO acid) and 2218 (CN).	6.8–7.7(*m*, 8H,aromatic protons) and 9.2 (*s*, br, 1H, OH)
14	!620(C=N)and 3220(NH_2).	–
15	1360(C-S)and1615(C=N).	2.5(*s*, 3H, CH_3) and 6.3–7.2 (*m*.8H, aromatic protons)
16	1625(C=N)and3470-3160 (NH_2,NH).	3.9 (*s*, br, NH_2),6.2 (*s*,br,1H,NH) and 7.1–8.2 (*m*, 8H, aromatic protons)

The solid separated was filtered and crystallised from benzene to give **2** as orange crystals.

2-S-(Alkylated)pyridazine derivatives **3**, **6**, **10**, **13** and **15**: (general procedure): A solution of each **2** (0.01 mole) and each of chloroacetone, chloroacetamide, ethyl chloroacetate, chloroacetic acid and methyl iodide (0.01 mole) was heated under reflux in methanolic sodium methoxide (prepared from 0.01 mole of sodium metal in 30 ml methanol) for 6 h. The reaction products were filtered off and recrystallised from the proper solvents to yield compounds **3**, **6, 10**, **13** and **15** respectively.

5-Amino[3,4-c]pyridazine derivatives **4**, **7**, **11** and **14**: (general procedure) : A solution of each **3**, **6**, **10** and **13** (0.01 mole) in 30 ml ethanol was heated under reflux for 8 h with potassium hydroxide (0.02 mole). The reaction mixture was then cooled and acidified with dilute HCl. The products obtained were filtered off, washed with water and recrystallised from proper solvents to give **4**, **7**, **11** and **14** respectively.

8,9-di(pyridin-2-yl)-pyridazino[3',4':4,5]thieno[2,3-c]pyridazin-4-ol **5**: A cold solution of **4** (0.01 mole) in concentrated HCl (1 ml) was treated with a cold solution of sodium nitrite in ice bath for 2 h. The solid product obtained was filtered off, washed with water and recrystallised from toluene to give compound **5**.

6-Methyl-3,4-di(pyridin-2-yl)-pyrimido[4',5':4,5]pyridazin-8(7H)-one **8**: A solution of the thienopyridazine **7** (0.01 mole) in acetic anhydride (30 ml) was heated under reflux for 7 h. The solid separated after cooling was filtered and recrystallised from benzene to give **8**.

6,7-Dihydrothiopyrimido[4',5':4,5]thieno[2,3-c]pyridazine 8(5H)-one **9**: A solution of the thienopyridazine **7** (0.01 mole) in pyridine (30 ml) was heated with carbon disulfide (0.02 mole) under reflux for 5 h. The reaction mixture was cooled, poured onto ice cold water and acidified with dilute HCl. The solid obtained was filtered off and then recrystallised from ethanol to give **9**.

3-Amino-4,5-di(2-pyridyl)-1H-pyrazolo[3,4-c]pyridazine **16**: A solution of **2** (0.01 mole) in ethanol (30 ml) was treated with hydrazine hydrate (10 ml) and then heated under reflux for 8 h. The solid obtained after cooling was filtered off and recrystallised from acetic acid to give **16**.

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References

1 F.A. Yassin, *Egypt. J. Chem*., 2004, **47**, 427.
2 F.A. Yassin, *Bull, Fac. Pharm. Cairo Unives*., 1991, **29**, 45.
3 F.A. Yassin, *J. Chem. Soc. Pak*., 1991, **13**, 267.
4 A. Deep, B. Baumy, F.A. Yassin and R. Fikry, *Z. Naturforch*, 1992, **47B**, 418.
5 A. Deep, P.N. Essawy, F.A. Yassin and R. Fikry, *Z. Naturforch*, 1991, **46B**, 835.
6 A. Deep, S.A. Aid, M.M. Hamad and F.A. Yassin, *J. Chin. Chem. Soc.,* 1990, **37**, 287.
7 M.F. Ismail, N.A. Shams, O.M. Elsawy, *Synthesis*, 1980, 410.
8 F.A. Attaby and S.M. Eldin, Egypt. *J. Pharm. Sci*., 1998, **39**, 347.
9 F.A. Attaby *Arch. Pharm.Res.,* 1990, **13**, 274.
10 F.A. Attaby, S.M. Eldin and M.A.A.Elneairy *J. Chem. Res*., 1998, (M) **10**, 2754(S), 632.