Synthesis of Novel Polyfunctionally Substituted Thieno[2,3-c]pyridazines

Abd El-Aal M. Gaber,[a] Mohamed S. A. El-Gaby,[b]* Adel M. Kamal El-Dean,[a]
Hassan A. Eyada[c] and Ahmed S. N. Al-Kamali[a]
[a]*Department of Chemistry, Faculty of Science, Assiut University, Assiut 71516, Egypt*
[b]*Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt*
[c]*Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt*

4-Cyano-5,6-dimethylpyridazin-3-(2*H*)-thione **3b** was used as a key intermediate for the synthesis of novel polysubstituted thieno[2,3-c]pyridazines.

Keywords: Pyridazine; Thieno[2,3-c]pyridazine and pyrrole derivatives.

INTRODUCTION

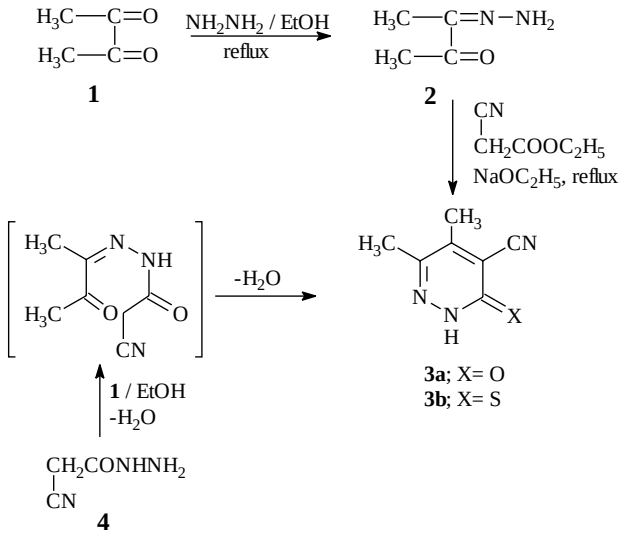
Derivatives of thienopyridazines are important compounds due to their broad range of biological and pharmacological effects.[1-3] Also, it is observed from the literature that the pyrrole nucleus plays a vital role in many biological activities.[4-8] On the basis of these reports and in continuation of our work on pyridazine chemistry,[9-11] we report in this contribution a novel synthesis of functionalized thieno[2,3-c]pyridazines starting from the readily accessible 4-cyano-5,6-dimethylpyridazin-3(2*H*)-thione **3b**.

RESULTS AND DISCUSSION

Druey et al.[12] reported the synthesis of 4-cyano-5,6-dimethylpyridazin-3(2*H*)-one **3a** by treatment of diacetyl **1** with hydrazine hydrate in refluxing ethanol to yield monohydrazone **2** followed by cyclocondensation with ethyl cyanoacetate in the presence of sodium ethoxide, Scheme (I). Our investigation describes the synthesis of pyridazinone **3a** through a one-pot reaction of diacetyl **1** and cyanoacetic acid hydrazide **4** in ethanol at room temperature in good yield (94%). Thiation of compound **3a** with phosphorus pentasulfide under reflux in pyridine afforded the pyridazinethione **3b**. The latter compound was used as a key intermediate for the synthesis of polysubstituted thieno[2,3-c]pyridazine.

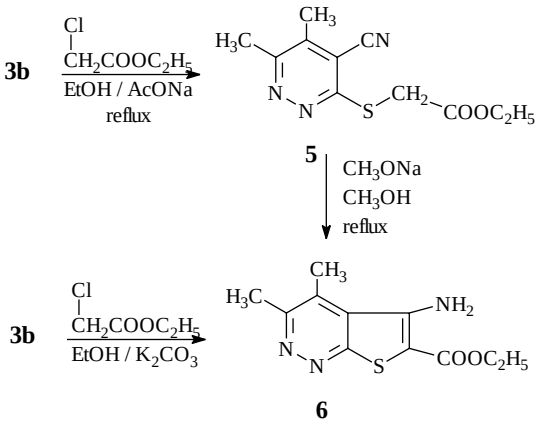
Cyclocondensation of compound **3b** with ethyl chloroacetate was performed in ethanol in the presence of a catalytic amount of potassium carbonate under reflux and yielded the novel thieno[2,3-c]pyridazine derivative **6** in quantitative yield (87%), Scheme (II). The structure of compound **6** was supported by its analytical and spectral data. The infrared spectrum of compound **6** displayed absorption at 3440, 3330 cm^{-1} for NH_2 stretching at 1665 cm^{-1} for C=O stretching with lack of the characteristic absorption due to the C≡N stretching. In the ^{1}H-NMR spectrum ($CDCl_3$) of compound **6** triplet at δ = 1.4 ppm, quartet at δ = 4.4 ppm assigned for ethoxycarbonyl moiety in addition to amino and $2CH_3$ protons. The formation of thienopyridazine **6** is assumed to proceed through initial alkylation of compound **3b** to form the intermediate **5** which readily undergoes intramolecular cyclization under the reaction condition to yield **6**. The intermediate compound **5** was isolated by refluxing of compound **3b** with ethyl chlo-

Scheme I



* Corresponding author. E-mail: m_elgaby@hotmail.com

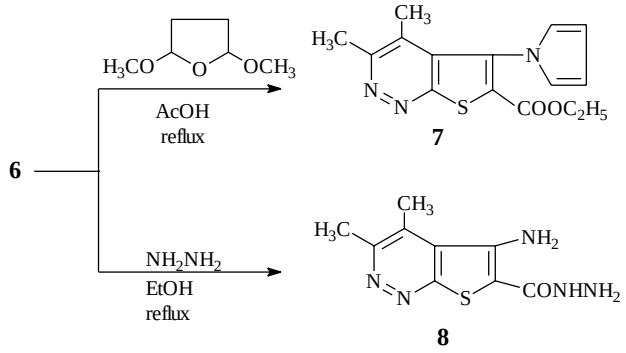
Scheme II



roacetate in refluxing ethanol in the presence of sodium acetate. Also, compound **6** was independently synthesized via another pathway by the refluxing of compound **5** with sodium methoxide in methanol.

The amino group in compound **6** readily reacted with 2,5-dimethoxytetrahydrofuran in acetic acid[13] to give the pyrrolyl derivative **7**. Its infrared spectrum showed the presence of an absorption band at 1720 cm^{-1} (C=O) with absence of NH_2 absorption. The acid hydrazide **8** was prepared by the refluxing of the corresponding ester **6** with hydrazine hydrate in ethanol, Scheme (III).

Scheme III



The ester **7** was reacted with hydrazine hydrate under reflux in ethanol to yield the carbohydrazide **9**. The latter compound was used as a precursor for the synthesis of 1,3,4-oxadiazole, 1,2,4-triazole, pyrazole and carbonylazide derivatives. Thus, treatment of compound **9** with carbon disulfide[11] in refluxing pyridine gave 1,3,4-oxadiazole derivative **10**. Reaction of compound **10** with *p*-bromophenacyl bromide in the presence of sodium acetate under reflux in ethanol yielded the mercapto derivative **11**. The 1,2,4-triazole derivative **13** was obtained by reaction of compound **9** with phenyl isothiocyanate in refluxing pyridine, via the formation of thiourea intermediate **12** followed by elimination of the water molecule, Scheme (IV). Cyclocondensation of compound **9** with acetylacetone in ethanol under reflux furnished the novel pyrazole derivative **14**. Treatment of compound **9** with sodium nitrite in glacial acetic acid at room temperature yielded the carbonylazide derivative **15**.

Our investigation was extended to study the reactivity of carbonylazide **15** towards some nucleophilic reagents. Thus, the carbamate derivatives **17a,b** were obtained by interaction of compound **15** with alcohols in benzene under reflux, via the formation of isocyanate **16** by Curtius rearrangement reaction.[13] Also, treatment of compound **15** with cyclic secondary amine in refluxing benzene led to the formation of the urea derivatives **18a,b**. Compound **15** was converted into pyrrolo[1″,2″:1′,6′]-pyrazino[2′,3′:4,5]thieno[2,3-c]pyridazine derivative **19** by refluxing in *m*-xylene. The formation of **19** is assumed to proceed through Curtius rearrangement of compound **15** into isocyanate **16** followed by intramolecular ring closure[13] to form **19**, Scheme (V).

The reaction of compound **8** with carbon disulfide in pyridine furnished the 1,3,4-oxadiazole derivative **20** which was reacted with phenacyl bromide to give compound **21**. Finally, the pyrrolyl derivative **10** was obtained by treatment of compound **20** with 2,5-dimethoxytetrahydrofuran in boiling acetic acid, Scheme (VI).

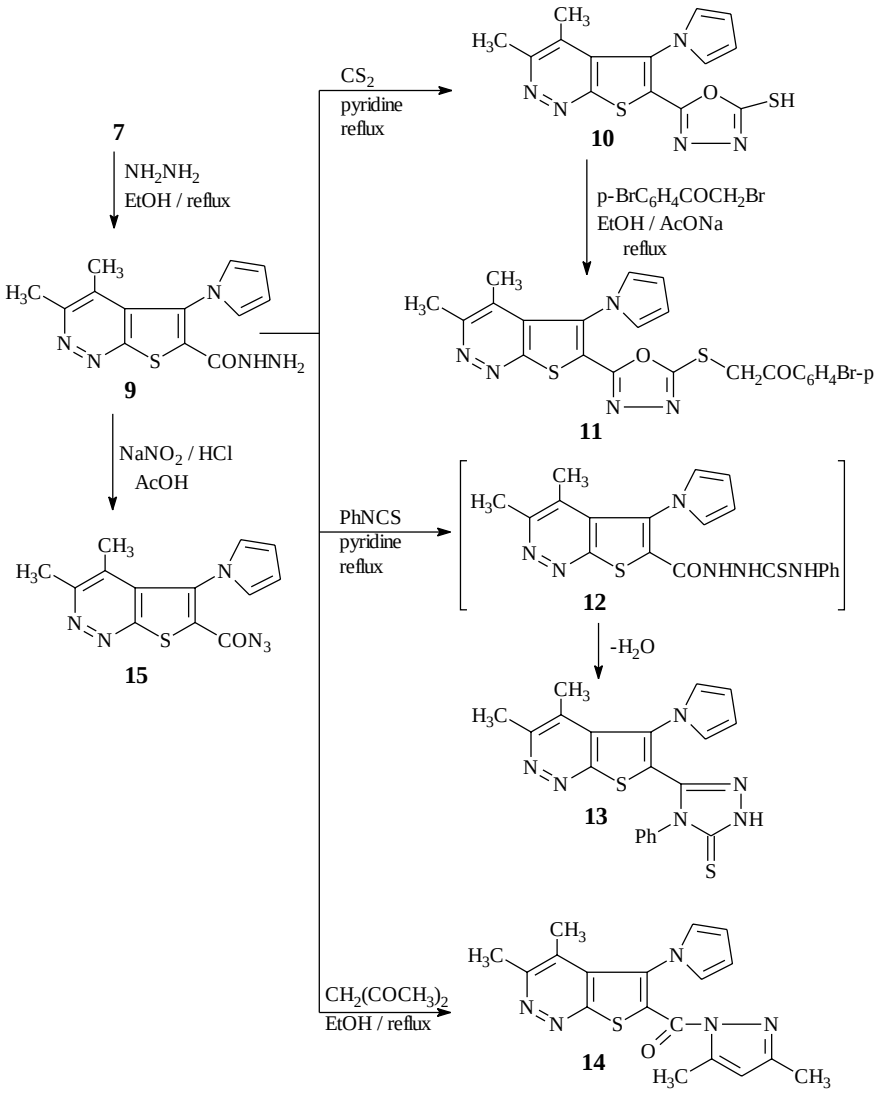
EXPERIMENTAL

Melting points are recorded on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were measured on a Varian 390-90 MHz NMR spectrometer using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C micro-analyzer. The physical and spectral data are collected in Tables 1 and 2, respectively.

4-Cyano-5,6-dimethylpyridazin-3(2*H*)-one (3a)

A mixture of diacetyl **1** (86 mg) and cyanoacetic acid hydrazide **4** (99 mg) in ethanol (20 mL) was stirred at room temperature for 3 h. The solid separated was filtered off and recrystallized to give **3a** (Lit.[12] m.p 211-2).

Scheme IV



4-Cyano-5,6-dimethylpyridazin-3(2*H*)-thione (3b)

A mixture of compound **3a** (149 mg) and phosphorus pentasulfide (266 mg) in pyridine (10 mL) was refluxed for 2 h, then allowed to cool and poured into cold water (10 mL) and neutralized with HCl. The solid product was collected and recrystallized to give **3b**.

4-Cyano-3-ethoxycarbonylmethylthio-5,6-dimethyl pyridazine (5)

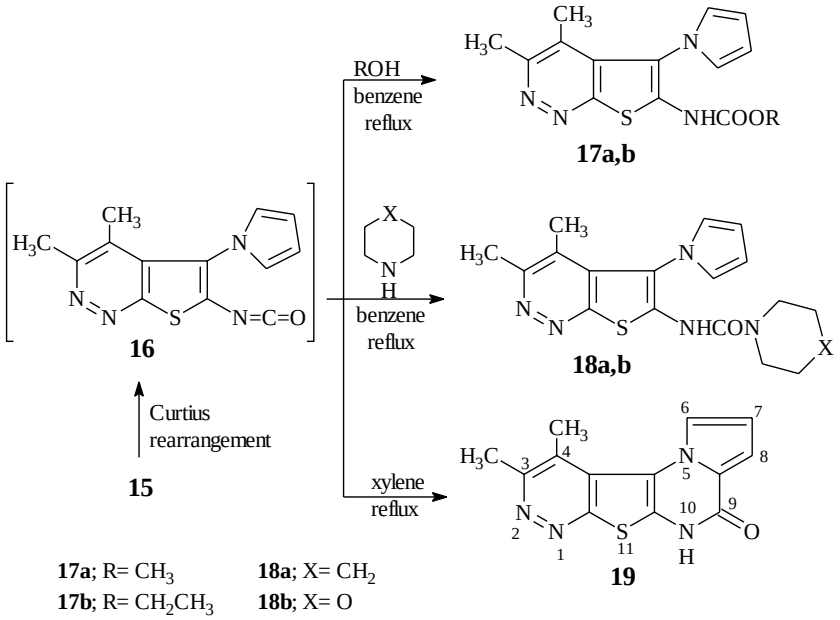
A mixture of compound **3b** (165 mg), fused sodium acetate (98 mg) and ethyl chloroacetate (122 mg) in ethanol (30 mL) was heated under reflux for 2 h, then allowed to cool, then poured into water (10 mL). The solid product was collected and recrystallized to give **5**.

5-Amino-3,4-dimethyl-6-ethoxycarbonylthieno[2,3-c]pyridazine (6)

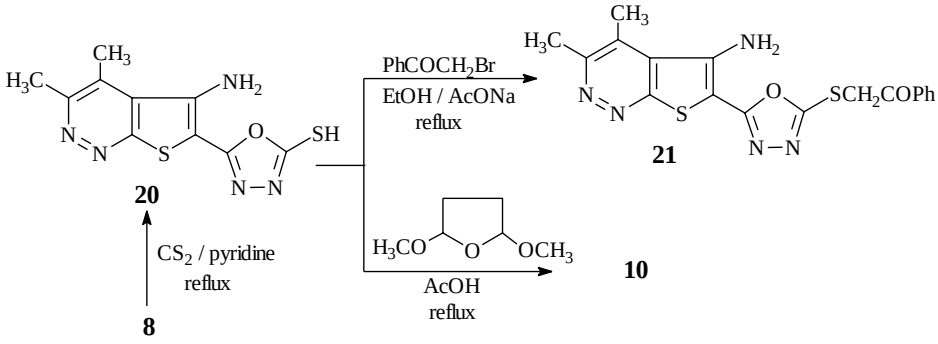
Method A: A mixture of compound **3b** (165 mg), ethyl chloroacetate (122 mg) and anhydrous potassium carbonate (166 mg) in ethanol (30 mL) was heated under reflux for 3 h, then allowed to cool and acidified with HCl. The solid product was collected and recrystallized to give **6**.

Method B: A sample of compound **5** (351 mg) in sodium methoxide (23 mg Na/30 mL methanol) was heated under reflux for 2 h, then allowed to cool and poured into cold water (20 mL) and acidified with HCl. The solid product was

Scheme V



Scheme VI



collected by filtration, washed with water and recrystallized to give **6**.

3,4-Dimethyl-6-ethoxycarbonyl-5-(pyrrol-1-yl)thieno[2,3-c]pyridazine (7)

A solution of compound **6** (251 mg) and 2,3-dimethoxytetrahydrofuran (132 mg) in acetic acid (1 mL) was heated under reflux for one h, then allowed to cool and poured into cold water (20 mL). The solid product was collected and recrystallized to give **7**.

5-Amino-3,4-dimethylthieno[2,3-c]pyridazine-6-carbohydrazide (8) and 3,4-dimethyl-5-(pyrrol-1-yl)-thieno[2,3-c]pyridazine-6-carbohydrazide (9): General procedure

A mixture of ester **6** or **7** (251 mg or 301 mg) and hydrazine hydrate (99%; 51 mg) in ethanol (30 mL) was heated under reflux for 5 h, then allowed to cool. The solid product was collected and recrystallized to give **8** or **9**.

The mass spectrum of compound **8** exhibited a molecular ion peak at *m/z* = 237.17 (13.4%) with base peak at *m/z* = 79.05.

3,4-Dimethyl-6-(2-mercapto-1,3,4-oxadiazol-5-yl)-5-(pyrrol-1-yl)-thieno[2,3-c]pyridazine (10) and 5-amino-3,4-dimethyl-6-(2-mercapto-1,3,4-oxadiazol-5-yl)-thieno[2,3-c]-pyridazine (20): General procedure

A mixture of carbohydrazide **9** or **8** (287 mg or 237 mg) and carbon disulfide (2 mL) in pyridine (5 mL) was heated under reflux for 12 h, then allowed to cool and poured into cold water (30 mL) and acidified with HCl. The solid product

Table 1. Physical data of the synthesized compounds

Compd. No.	M.p. (°C)	Yield (%)	Solvent Cryst (Color)	Molecular formula (Mol. Wt.)	Elemental analyses			
					C%	H%	N%	S%
3a	210-2	94	Ethanol	$C_7H_7N_3O$	56.37	4.73	28.17	
			(White)	(149.15)	56.20	4.80	28.20	
3b	213-5	90	Ethanol	$C_7H_7N_3S$	50.89	4.27	25.44	19.41
			(Yellow)	(165.21)	50.80	4.10	25.50	19.30
5	120-1	66	Ethanol	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72	12.76
			(Brown)	(251.31)	52.37	5.25	16.60	12.80
6	240-2	87	Ethanol	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16.72	12.76
			(Yellow)	(251.31)	52.60	5.01	16.80	12.80
7	170-1	82	Ethanol	$C_{15}H_{15}N_3O_2S$	59.78	5.02	13.94	10.64
			(Brown)	(301.37)	59.70	5.10	13.80	10.70
8	> 300	75	Ethanol	$C_9H_{11}N_5OS$	45.55	4.67	29.51	13.51
			(Yellow)	(237.28)	45.60	4.68	29.33	13.62
9	286-7	94	Ethanol	$C_{13}H_{13}N_5OS$	54.34	4.56	24.37	11.16
			(Yellow)	(287.35)	54.20	4.50	24.40	11.70
10	> 340	81	Ethanol	$C_{14}H_{11}N_5OS_2$	51.05	3.37	21.26	19.47
			(Yellow)	(329.40)	51.10	3.30	21.30	19.50
11	280-2	83	Ethanol	$C_{22}H_{16}BrN_5O_2S_2$	50.19	3.06	13.30	12.18
			(White)	(526.44)	50.20	3.00	13.40	12.20
13	240-1	80	DMF	$C_{20}H_{16}N_6S_2$	59.38	3.99	20.78	15.85
			(Yellow)	(404.52)	59.30	3.80	20.80	15.80
14	194-5	90	Ethanol	$C_{18}H_{17}N_5OS$	61.52	4.88	19.93	9.12
			(White)	(351.43)	61.50	4.90	19.80	9.13
15	140-1	90	$CHCl_3$	$C_{13}H_{10}N_6OS$	52.34	3.38	28.17	10.75
			(Yellow)	(298.33)	52.30	3.40	28.20	10.40
17a	232-3	92	Ethanol	$C_{14}H_{14}N_4O_2S$	55.62	4.67	18.53	10.60
			(White)	(302.36)	55.70	4.50	18.50	10.60
17b	280-1	85	Ethanol	$C_{15}H_{16}N_4O_2S$	56.94	5.10	17.71	10.13
			(White)	(316.38)	56.80	5.00	17.70	10.10
18a	170-3	81	Ethanol	$C_{18}H_{21}N_5OS$	60.82	5.95	19.70	9.02
			(White)	(355.46)	60.80	5.80	19.80	9.10
18b	180-1	71	Ethanol	$C_{17}H_{19}N_5O_2S$	57.13	5.36	19.59	8.97
			(White)	(357.44)	57.20	5.30	19.50	8.90
19	> 300	95	DMF	$C_{13}H_{10}N_4OS$	57.77	3.73	20.73	11.86
			(Yellow)	(270.31)	57.80	3.70	20.80	11.80
20	> 300	68	Ethanol	$C_{10}H_9N_5OS_2$	43.00	3.25	25.07	22.96
			(Yellow)	(279.34)	43.00	3.50	25.10	22.90
21	220-2	82	Ethanol	$C_{18}H_{15}N_5O_2S_2$	54.39	3.80	17.62	16.13
			(Yellow)	(397.48)	54.39	3.80	17.60	16.20

was collected and recrystallized to give **10** or **20**, respectively.

3,4-Dimethyl-5-(pyrrol-1-yl)-6-[5-(4-bromobenzoylmethylthio)-1,3,4-oxadiazol-2-yl]-thieno[2,3-c]pyridazine (11) and 5-amino-3,4-dimethyl-6-(5-benzoylmethylthio-1,3,4-oxadiazol-2-yl)-thieno[2,3-c]pyridazine (21): General procedure

A mixture of compound **10** or **20** (329 mg or 279 mg), *p*-bromophenacyl bromide or phenacyl bromide (278 mg or 199 mg) and fused sodium acetate (98 mg) in ethanol (30 mL) was heated under reflux for 3 h. On cooling, the precipitated solid was collected and recrystallized to give **11** or **21**, respectively.

3,4-Dimethyl-5-(pyrrol-1-yl)-6-(4-phenyl-3-thioxo-1,2,4-triazolin-3-yl)-thieno[2,3-c]pyridazine (13)

A mixture of compound **9** (287 mg) and phenyl isothiocyanate (135 mg) in dry pyridine (10 mL) was heated under reflux for 24 h, then allowed to cool and poured into cold water (10 mL) and acidified with HCl. The solid product was collected and recrystallized to give **13**.

Table 2. Spectral data of the synthesized compounds

Compd No.	IR/ν_{max} (cm^{-1})	^{1}H NMR (δ/ppm)
3a	3400 (NH), 2200 (C≡N), 1660 (C=O).	DMSO-d_6: 2.3, 2.4 (2s, 6H, $2CH_3$), 10.8 (hump, 1H, NH).
3b	3300 (NH), 2200 (C≡N).	
5	2220 (C≡N), 1730 (C=O).	$CDCl_3$: 1.35 (t, 3H, CH_3), 2.55, 2.77 (2s, 6H, $2CH_3$), 4.1-4.4 (m, 4H, $2CH_2$).
6	3440, 3330 (NH_2), 1665 (C=O).	$CDCl_3$: 1.4 (t, 3H, CH_3), 2.7, 3.3 (2s, 6H, $2CH_3$), 4.4 (q, 2H, CH_2), 6.8 (s, 2H, NH_2).
7	1720 (C=O)	$CDCl_3$: 1.1 (t, 3H, CH_3), 1.73, 2.65 (2s, 6H, $2CH_3$), 4.2 (q, 2H, CH_2), 6.3, 6.7 (2m, 4H, pyrrole ring).
8	3420, 3300, 3200 (NH_2, NH), 1670 (C=O).	
9	3300, 3210, 3100 (NH, NH_2), 1640 (C=O).	DMSO-d_6: 1.9, 2.7 (2s, 6H, $2CH_3$), 4.7 (hump, 3H, NH + NH_2), 6.4, 7.1 (2m, 4H, pyrrole ring).
10	2930-2730 (SH).	CF_3COOD: 2.3, 3.15 (2s, 6H, $2CH_3$), 6.7, 7.05 (m, 4H, pyrrole ring).
11	1670 (C=O).	CF_3COOD: 2.2, 3.1 (2s, 6H, $2CH_3$), 4.8 (s, 2H, SCH_2), 6.5, 6.9 (2m, 4H, pyrrole ring), 7.8-8.2 (m, 4H, Ar-H).
13	3140 (NH).	DMSO-d_6: 1.7, 2.7 (2s, 6H, $2CH_3$), 6.4, 7.2 (2s, 4H, pyrrole ring), 7.3-7.5 (m, 5H, Ar-H), 10.30 (s, 1H, NH).
14	1690 (C=O).	$CDCl_3$: 1.8, 1.95, 2.08, 2.7 (4s, 12H, $4CH_3$), 6.3, 6.8 (2s, 4H, pyrrole ring), 7.3 (s, 1H, pyrazole-H).
15	2180 (N_3), 1650 (C=O).	$CDCl_3$: 1.85, 2.88 (2s, 6H, $2CH_3$), 6.5, 6.8 (2s, 4H, pyrrole ring).
17a	3240 (NH), 1685 (C=O).	$CDCl_3$: 1.7, 2.72 (2s, 6H, $2CH_3$), 3.8 (s, 3H, OCH_3), 6.6, 6.8 (2s, 4H, pyrrole ring), 7.2 (hump, 1H, NH).
17b	3250 (NH), 1685 (C=O).	
18a	3390 (NH), 1660 (C=O).	
18b	3400 (NH), 1680 (C=O).	$CDCl_3$: 1.9, 2.8 (2s, 6H, $2CH_3$), 3.2-3.6 (m, 8H, morpholine ring), 6.5, 6.8 (2s, 4H, pyrrole ring), 7.4 (s, 1H, NH).
19	3100 (NH), 1670 (C=O).	CF_3COOD: 1.9, 2.8 (2s, 6H, $2CH_3$), 6.6, 6.8 (2s, 3H, pyrrole ring).
20	3450, 3320 (NH_2), 2920-2800 (SH).	
21	3340, 3240 (NH_2), 1690 (C=O).	CF_3COOD: 3.3, 3.6 (2s, 6H, $2CH_3$), 5.3 (s, 2H, SCH_2), 7.8-8.2 (m, 5H, Ar-H).

(3,4-Dimethyl-5-(pyrrol-1-yl)-thieno[2,3-c]pyridazin-6-yl)-(3,5-dimethylpyrazol-1-yl)-ketone (14)

A mixture of carbohydrazide **9** (287 mg) and acetylacetone (100 mg) in ethanol (30 mL) was heated under reflux for 6 h, then allowed to cool. The solid product was collected and recrystallized to give **14**.

3,4-Dimethyl-5-(pyrrol-1-yl)-thieno[2,3-c]pyridazine-6-carbonylazide (15)

To an ice cooled solution of compound **9** (287 mg) in acetic acid (5 mL), sodium nitrite solution (69 mg in 3 mL H_2O) was added dropwise during ten minutes. The stirring was continued after that addition 1 h, then allowed to stand for 2 h. The solid product was collected to give **15**.

3,4-Dimethyl-5-(pyrrol-1-yl)-6-(alkyloxycarbonylamino)-thieno-[2,3-c]pyridazines (17a,b) and 3,4-dimethyl-5-(pyrrol-1-yl)-6-(1-piperidino or 4-morpholino carbonyl-amino)-thieno[2,3-c]pyridazines (18a,b): General procedure

A mixture of compound **15** (298 mg) and alcohol or cyclic secondary amine (33 mg, 47 mg or 85 mg, 87 mg) in dry benzene (10 mL) was refluxed for 1 h, then allowed to cool. The solid product was collected and recrystallized to give **17a,b** or **18a,b**, respectively.

3,4-Dimethylpyrrolo[1″,2″:1′,6′]pyrazino[2′,3′:4,5]thieno-[2,3-c]pyridazin-9(10*H*)-one (19)

A sample of compound **15** (298 mg) in dry *m*-xylene (5

mL) was heated under reflux for 1 h, then allowed to cool. The solid product was collected and recrystallized to give **19**.

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