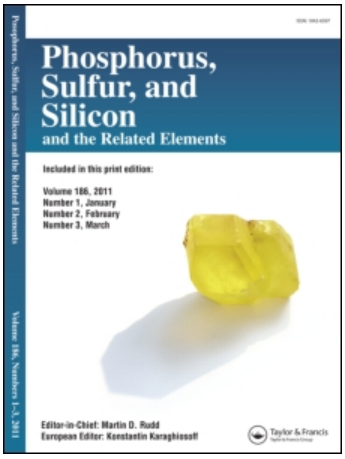

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Synthesis and Reactions of Some New Thieno[2,3-C]pyridazine Derivatives

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Synthesis and Reactions of Some New Thieno[2,3-C]pyridazine Derivatives

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The alkylation of 4-cyano-5,6-dimethylpyridazin-3(2H)-thione ***3*** *with some halo compounds gave the S-alkylated products* ***4a–c****, which upon treatment with ethanolic sodium ethoxide afforded the cyclized thienopyridazines* ***5a–c*** *as products. Pyridazothienotriazines* ***6a–c*** *were prepared by the treatment of compounds* ***5a–c*** *with nitrous acid, while their reaction with triethyl orthoformate and with carbon disulfide gave the corresponding pyrimidothienopyridazines* ***7a–c,*** *and* ***8a–c****, respectively. S-alkylated products* ***9a–o*** *were obtained by the reaction of* ***8a–c*** *with some halo compounds.*

Keywords Pyridazine; pyridazothienotriazine; pyrimidothienopyridazine; thieno[2,3-c]pyridazine

INTRODUCTION

The pyridazine moiety is found in many pharmaceuticals, herbicides, insecticides, and fungicides.[1,2] In addition, a considerable number of pyridazine derivatives were found to have antibacterial,[3] analgesic,[4] anti-inflammatory,[5] and acetyl-cholinesterase inhibitor properties,[6] and act as aldose reductase inhibitors and antioxidants.[7] Moreover, thienopyridazine derivatives are also important compounds because of their broad range of biological and pharmacological effects.[8–13]

In view of the above and in continuation of the work on pyridazine chemistry,[14–16] we report here the synthesis of some new pyridazine, thieno[2,3-c]pyridazine, pyridazothienotriazine, and pyrimidothienopyridazine derivatives starting from the readily accessible 4-cyano-5,6-dimetheylpyridazin-3(2*H*)-thione **3**.

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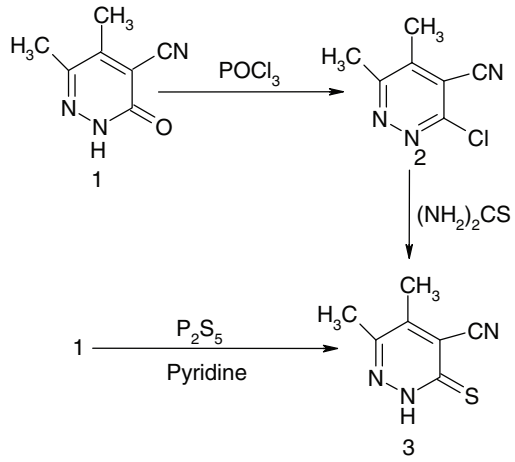
RESULTS AND DISCUSSION

The starting compound 4-cyano-5,6-dimethylpyridazin-3(2*H*)-one **1** was prepared by the reaction of diacetyl and cyanoacetic acid hydrazide in ethanol at room temperature in a good yield (94%). When compound **1** was refluxed with phosphorus oxychloride, it gave the 3-chloropyridazine derivative **2** in 90% yield. Compound **2** was subjected to an addition–elimination reaction with thiourea in ethanol under reflux to afford 4-cyano-5,6-dimethylpyridazin-3(2*H*)-thione **3**.

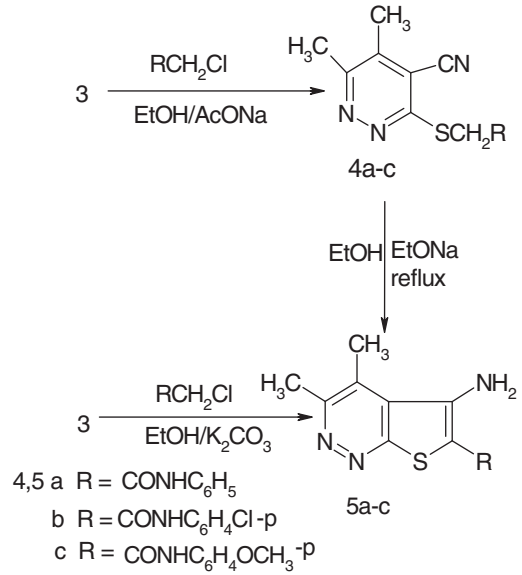
Also, the structure of compound **3** was established by another synthetic route, via thionation of compound **1** with phosphorus pentasulfide under reflux in pyridine as shown in Scheme 1.



SCHEME 1

The thione derivative **3** was used as a versatile compound for building fused heterocyclic systems condensed with the pyridazine moiety. Thus, reaction with N-substituted chloroacetamide in refluxing ethanol in the presence of fused sodium acetate furnished the *s*-alkylated products **4a–c**, which underwent a Thorpe–Ziegler type of cyclization in the presence of sodium ethoxide to produce the novel thieno[2,3-c]pyridazines **5a–c**. An alternative one-step synthesis of **5a–c** was achieved by the reaction of **3** with the alkylating agents in the presence of potassium carbonate in boiling ethanol (Scheme 2).

The chemical structures of **4a–c** and **5a–c** were determined by their IR and ^{1}H-NMR spectra. The IR spectra of **4a–c** showed the characteristic bands at 1670–1680 cm^{-1} due to a carbonyl group and the



SCHEME 2

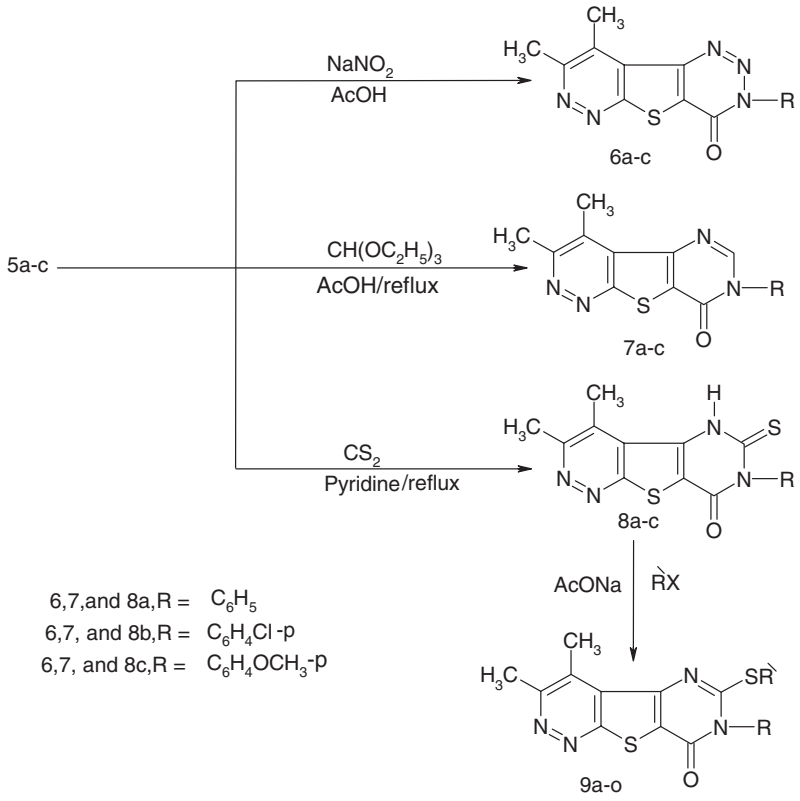
disappearance of the band at about 3300 cm^{-1} due to the -NH group of compound **3**.

The ^{1}H-NMR spectrum (DMSO-d_6) of **4a** showed two singlets at $\delta =$ 2.35 ppm and $\delta =$2.6 ppm due to methyl groups, and a singlet at $\delta =$ 4.2 ppm due to the methylene protons. The IR spectra of compounds **5a–c** showed the absence of bands for the carbonitrile group and the appearance of bands at 3440–3280 cm^{-1} for (NH_2) 3300–3280 cm^{-1} and at 1600–1585 cm^{-1} for carbonyl groups; the lowering of the frequency is due to intermolecular hydrogen bonding. The ^{1}H-NMR spectra of compounds **5a–c** exhibited the absence of the signal for the methylene protons and the appearance of a new signal at $\delta = 7.2$–7.05 ppm due to the amino groups.

Pyridazo[′4,′3:4,5] thieno[3,2-d][1,2,3]triazine derivatives **6a–c** were obtained by diazotization of **5a–c** with sodium nitrite in glacial acetic acid at 0°C. The structures of **6a–c** were confirmed by elemental analysis and spectral data. The IR spectra of **6a–c** showed the absence of any absorption bands attributed to NH_2 and NH functional groups. Moreover, the ^{1}H-NMR spectra of compounds **6a–c** revealed the disappearance of the signals due to -NH_2 and -NH protons. Cyclization of compounds **5a–c** with triethyl orthoformate in the presence of catalytic amounts of glacial acetic acid produced the pyrimidothienopyridazine derivatives**7a–c**. Refluxing of compounds **5a–c** with carbon disulfide in

pyridine afforded the corresponding pyrimidothienopyridazinethione derivatives **8a–c**.

S-substituted pyrimidothienopyridazines **9a–o** were achieved by the reaction of compounds **8a–c** with some halo compounds in ethanol containing sodium acetate (Scheme 3).



9	R	R′	**9**	R	R′
a	Ph	CH_2COCH_3	**i**	C_6H_4Cl-*p*	$CH(Me)CO_2Me$
b	Ph	CH_2COPh	**j**	C_6H_4Cl-*p*	CH_2COPh
c	Ph	$CH_2COC_6H_4Cl$-*p*	**k**	C_6H_4Cl-*p*	$CH_2COC_6H_4Cl$-*p*
d	Ph	$CH_2COC_6H_4Br$-*p*	**l**	C_6H_4OMe-*p*	CH_2COPh
e	Ph	CH_2COOEt	**m**	C_6H_4OMe-*p*	$CH_2CONHC_6H_4OMe$-*p*
f	Ph	$CH(Me)CO_2Me$	**n**	C_6H_4OMe-*p*	CH_2CO_2Et
g	Ph	CH_2CN	**o**	C_6H_4OMe-*p*	$CH_2CONHC_6H_4Cl$-*p*
h	C_6H_4Cl-*p*	CH_2CO_2Et			

SCHEME 3

EXPERIMENTAL

Melting points were determined 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. Elemental analyses were performed on a Perkin Elmer 240 C microanalyzer. The mass spectra were recorded on a Jeol JMS 600 apparatus. Physical and spectral data are shown in Table I, together with suitable solvents for recrystallization.

4-Cyano-5,6-dimethylpyridazin-3(2*H*)-one (1)

This compound was prepared according to the reported method.[14]

3-Chloro-5,6-dimethylpyidazin-4-carbonitrile (2)

Compound **1** (10 mmol) was refluxed with phosphorus oxychloride (15 mL) for 3 h. The cooled reaction mixture was slowly added into crushed ice water (100 mL). The resulting solid was collected by filtration and recrystallized from the proper solvent to give **2**.

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

Method A

A mixture of compound **2** (10 mmol) and thiourea (13 mmol) in dry ethanol (50 mL) was heated under reflux for 4 h. The obtained solid product was collected by filtration and recrystallized from the proper solvent to give **3**.

Method B

A mixture of compound **1** (10 mmol) and phosphorus pentasulfide (13 mmol) in dry pyridine (20 mL) was refluxed for 4 h, then allowed to cool, and was poured into cold water (100 mL). The solid product was collected by filtration and recrystallized from the proper solvent to give **3**.

Alkylation of 4-Cyano-5,6-dimethylpyridazin-3(2H)-thione: Formation of (4a–c)

A mixture of compound **3** (10 mmol), α-halo carbonyl compound (10 mmol), and fused sodium acetate (14 mmol) in ethanol (30 mL) was heated under reflux for 2 h, then allowed to cool. The solid product was collected by filtration and recrystallized from the proper solvent to give **4a–c**.

TABLE I Physical and Spectral Data of the Synthesized Compounds 1–9

Compd. No.	M.P. (°C) Solvent	Yield % (Color)	Molecular formula (M.wt.)	Elemental analyses [Calcd./Found] C%	H%	N%	S%	IR/υ_{max} (cm^{-1})	^{1}H-NMR (δ/ppm)
1	210 Ethanol	94 (White)	$C_7H_7N_3O$ (149.15)	56.37 56.20	4.73 4.80	28.17 28.20		3400(NH), 2200 (C ≡N),1660(C=O).	DMSO-d_6; 2.3, 2.4(2s,6H, $2CH_3$),10.8 (hump, 1 H, NH).
2	80 Pet.ether	90 (White)	$C_7H_6ClN_3$ (167.60)	50.16 50.30	3.16 3.70	25.07 25.15		2210(C ≡N).	DMSO-d_6; 2.4, 2.7(2s, 6H, $2CH_3$).
3	213 Ethanol	90 (Yellow)	$C_7H_7N_3S$ (165.12)	50.89 50.80	4.27 4.10	25.44 25.50	19.41 19.30	3300(NH), 2200 (C ≡N).	DMSO-d_6; 2.33, 2.4,(2 s,6H , $2CH_3$), 12.24(hump, 1 H, NH).
4a	180 Ethanol	80 (White)	$C_{15}H_{14}N_4OS$ (298.35)	60.38 60.20	4.73 4.81	18.78 18.90	10.75 10.82	3300(NH), 2220 (C ≡N), 1680 (C=O).	DMSO-d_6; 2.35, 2.6 (2s, 6H, $2CH_3$),4.2 (s, 2H, CH_2) 7.0–7.6 (m, 5H , Ar-H), 9.3 (s, 1 H, NH).
4b	165 Ethanol	87 (White)	$C_{15}H_{13}ClN_4OS$ (332.80)	54.13 53.85	3.94 4.01	16.83 16.88	9.63 9.53	3280 (NH),2220 (C ≡N), 1670 (C=O).	$CDCl_3$; 2.60, 2.8, (2s, 6H, $2CH_3$),4.3 (s, 2H, CH_2), 7.2,7. 5(2d, 4H, Ar-H), 9.2 (s, 1 H, NH).
4c	174 Ethanol	64 (White)	$C_{16}H_{16}N_4O_2S$ (328.38)	58.52 58.72	4.91 5.19	17.06 16.88	9.76 10.00	3290(NH), 2220 (C ≡N), 1670 (C=O).	$CDCl_3$; 2.34,2.6(2s, 6H, $2CH_3$), 3.62 (s,3H,OCH_3), 4.05(s,2H, CH_2), 6.6, 7.3 (2d, 4H, Ar-H), 9.2(s, 1H, NH).

(Continued on next page)

TABLE I Physical and Spectral Data of the Synthesized Compounds 1–9 *(Continued)*

Compd. No.	M.P. (°C) Solvent	Yield % (Color)	Molecular formula (M.wt.)	Elemental analyses [Calcd./Found] C%	H%	N%	S%	IR/υ_{max} (cm^{-1})	^{1}H-NMR (δ/ppm)
5a	322 Ethanol	68 (Orange)	$C_{15}H_{14}N_4OS$ (298.35)	60.38 60.42	4.73 4.62	18.78 18.88	10.75 10.92	3400, 3300 (NH_2), 1600 (C=O).	DMSO-d_6; 2.77, 3.4 (2s, 6H, $2CH_3$), 7.1 (s, 2H, NH_2), 7.25–7.4 (m, 5H, Ar-H), 8.86 (s, 1H, NH).
5b	340 Ethanol	70 (Yellow)	$C_{15}H_{13}ClN_4OS$ (332.80)	54.13 54.30	3.94 4.02	16.83 17.10	9.63 9.55	3440, 3300, 3180 (NH_2, NH), 1585 (C=O).	DMSO-d_6; 2.8, 3.5 (2s, 6H, $2CH_3$), 7.2–7.7(m, 6H, Ar-H and NH_2), 8.70 (s, 1H , NH).
5c	318 Ethanol	89 (Yellow)	$C_{16}H_{16}N_4O_2S$ (328.38)	58.52 58.71	4.91 5.01	17.06 17.01	9.76 9.80	3390, 3280, 3120 (NH_2, NH), 1600 (C=O).	$CDCl_3$; 2.7, 3.3 (2s, 6H, $2CH_3$), 3.90 (s, 3H, OCH_3), 7.05–7.7 (m, 6H , Ar-H and NH_2), 8.7 (s, 1H, NH).
6a	210 Acetic acid	85 (Yellow)	$C_{15}H_{11}N_5OS$ (309.34)	58.24 58.19	3.58 3.61	22.64 22.70	10.36 10.40	1670 (C =O).	CF_3 COOD; 2.6, 3.3 (2s, 6H ,$2CH_3$) 7.5–7.85 (m, 5H ,Ar-H).
6b	200 Acetic acid	80 (Yellow)	$C_{15}H_{10}ClN_5OS$ (343.79)	52.40 52.31	2.93 3.00	20.37 20.42	9.33 9.50	1685 (C =O).	CF_3 COOD; 2.7, 3.4 (2s, 6H ,$2CH_3$) 7.4–7.9 (m, 5H ,Ar-H).
6c	262 Ethanol	90 (Yellow)	$C_{16}H_{13}N_5O_2S$ (339.36)	56.62 56.72	3.86 3.71	20.64 20.58	9.45 9.50	1665 (C=O).	CF_3COOD; 2.5, 3.3 (2s, 6H, $2CH_3$), 4 (s, 3H, OCH_3),7.2–7. 6 (m, 4H , Ar-H).

7a	320 Acetic acid	75 (White)	$C_{16}H_{12}N_4OS$ (308.35)	62.32 62.22	3.92 3.88	18.17 18.15	10.40 10.30	1680 (C=O).	DMSO-d_6; 2.7, 3.5 (2s, 6H, $2CH_3$), 7.1–7.5 (m, 5H, Ar-H), 8.6 (s, 1H, Pyrimidine-H).
7b	344 Acetic acid	81 (White)	$C_{16}H_{11}ClN_4OS$ (342.80)	56.06 56.10	3.23 3.61	16.34 16.38	9.35 9.28	1680 (C=O).	CF_3COOD; 3.2, 3.5(2s, 6H, $2CH_3$), 7.2, 7.6 (2d, 4H, Ar-H), 8.7 (s, 1H, Pyrimidine-H).
7c	328 Acetic acid	81 (White)	$C_{17}H_{14}N_4O_2S$ (338.37)	60.34 60.22	4.17 4.21	16.56 16.70	9.48 9.61	1670(C=O).	CF_3COOD; 3.2, 3.4(2s, 6H, $2CH_3$), 4.1 (s, 3H,OCH_3), 7.3, 7.5(2d, 4H, Ar-H), 8.6 (s, 1H, Pyrimidine-H).
8a	300 Pyridine	83 (Yellow)	$C_{16}H_{12}N_4OS_2$ (340.42)	56.45 56.33	3.55 3.42	16.46 16.61	18.84 19.00	3350 (NH), 1670 (C=O).	DMSO-d_6; 2.8, 3.5 (2s, 6H, $2CH_3$), 7.3-7.6 (m, 5H , Ar-H), 11 (s, 1H, NH).
8b	360< Pyridine	90 (Yellow)	$C_{16}H_{11}ClN_4OS_2$ (374.85)	51.26 51.30	2.96 3.01	14.95 15.10	17.11 17.22	3320(NH), 1680 (C=O).	DMSO-d_6; 2.8, 3.5 (2s, 6H, $2CH_3$), 7.6-8 (dd, 4H, Ar-H), 10.5 (s, 1H, NH).

(Continued on next page)

TABLE I Physical and Spectral Data of the Synthesized Compounds 1–9 *(Continued)*

Compd. No.	M.P. (°C) Solvent	Yield % (Color)	Molecular formula (M.wt.)	Elemental analyses [Calcd./Found] C%	H%	N%	S%	IR/υ_{max} (cm^{-1})	^{1}H-NMR (δ/ppm)
8c	350 Pyridine	90 (Yellow)	$C_{17}H_{14}N_4O_2S_2$ (370.43)	55.12 55.21	3.81 3.77	15.12 15.18	17.31 17.40	3400 (NH), 1675 (C=O).	CF_3COOD; 3.2, 3.4 (2s, 6H, $2CH_3$), 4.1 (s,3H, OCH_3), 7.3, 7.6 (2d, 4H, Ar-H).
9a	284 Ethanol	62 (White)	$C_{19}H_{16}N_4O_2S_2$ (396.42)	57.55 57.59	4.07 4.11	14.13 14.21	16.17 16.30	1730 (C=O), 1680 (C=O).	CF_3COOD; 2.6, 3.3, 3.6 (3 s, 9H, $3CH_3$), 4.5 (s,2H , CH_2) , 7.5–7.9 (m, 5H, Ar-H).
9b	270 Ethanol	77 (White)	$C_{24}H_{18}N_4O_2S_2$ (458.53)	62.86 63.01	3.96 3.92	12.22 12.30	13.98 13.89	1680 (2C=O).	$CDCl_3$; 2.7, 2.9(2s, 6H, $2CH_3$) , 4.8 (s, 2H, CH_2), 7.2–8.2 (m ,10H , Ar –H).
9c	280 Ethanol	69 (White)	$C_{24}H_{17}ClN_4O_2S_2$ (492.98)	58.47 58.61	3.48 3.38	11.36 11.43	13.01 13.12	1675 (C=O).	CF_3COOD; 2.7, 3.1, (2 s, 6H, $2CH_3$), 4.9 (s,2H, CH_2), 7.4-8(m, 9H, Ar-H).
9d	210 Ethanol	87 (White)	$C_{24}H_{17}BrN_4O_2S_2$ (537.44)	53.63 53.53	3.19 3.12	10.42 10.31	11.93 12.02	1670 (C=O).	CF_3COOD; 2.9, 3.2, (2 s, 6H, $2CH_3$), 5.2 (s,2H , CH_2), 7.6–8.5(m, 9H, Ar-H).
9e	220 Ethanol	68 (White)	$C_{20}H_{18}N_4O_3S_2$ (426.49)	56.32 56.41	4.25 3.02	13.14 13.24	15.03 15.10	1735 (C=O), 1680 (C=O).	$CDCl_3$; 1.3 (t, 3H, CH_3) 2.9, 3.1(2s, 6H, $2CH_3$), 4.1 (s, 2H, CH_2), 4.3 (q, 2H,OCH_2), 7.1–7.5 (m,5H, Ar –H).

9f	308	69	$C_{20}H_{18}N_4O_3S_2$	56.32	4.25	13.14	15.03	1700 (C=O) 1670 (C=O).	CF_3COOD; 1.4 (d, 3H, CH_3), 2.6, 3.2 (2s, 6H, $2CH_3$),3.5(s,3H,CH_3,of ester), 4.5 (q,1H, CH), 7.2-8 (m, 5H, Ar-H).
	Ethanol	(White)	(426.49)	56.38	3.11	13.22	15.20		
9g	352	69	$C_{18}H_{13}N_5OS_2$	56.97	3.45	18.46	16.90	2220 (C ≡N), 1670 (C=O).	CF_3COOD; 2.8, 3.1, (2 s, 6H, $2CH_3$),4.5 (s,2H , CH_2), 7.5-8(m, 5H, Ar-H).
	Ethanol	(White)	(379.44)	56.87	3.33	18.61	17.02		
9h	224	87	$C_{20}H_{17}ClN_4O_3S_2$	52.11	3.72	12.15	13.91	1730 (C=O), 1675 (C=O).	$CDCl_3$; 1.4 (t, 3H, CH_3), 3, 3.2 (2s, 6H, $2CH_3$), 4.2 (s, 2H, CH_2), 4.33(q, 2H, OCH_2), 7.6, 7.8 (2d,4H, Ar –H).
	Ethanol	(White)	(460.94)	52.09	3.68	12.11	13.86		
9i	246	83	$C_{20}H_{17}ClN_4O_3S_2$	52.11	3.72	12.15	13.91	1730(C=O), 1670 (C=O).	$CDCl_3$; 1.5(d, 3H, CH_3), 2.6, 2.7 (2s, 6H, $2CH_3$), 3.7(s, 3H, CH_3 of ester),4.4 (q, 1H, CH), 7.4, 7.5 (2d, 4H, Ar-H).
	Ethanol	(White)	(460.94)	52.06	3.81	12.10	13.88		
9j	234	62	$C_{24}H_{17}ClN_4O_2S_2$	58.47	3.48	11.36	13.01	1675 (2C=O).	$CDCl_3$; 2.7, 3 (2s, 6H, $2CH_3$),4.9(s,2H, CH_2), 7.5-8.1(m, 9H, Ar-H).
	Ethanol	(White)	(492.98)	58.32	3.38	11.24	13.12		

(Continued on next page)

TABLE I Physical and Spectral Data of the Synthesized Compounds 1–9 *(Continued)*

Compd. No.	M.P. (°C) Solvent	Yield % (Color)	Molecular formula (M.wt.)	Elemental analyses [Calcd./Found] C%	H%	N%	S%	IR/υ_{max} (cm^{-1})	^{1}H-NMR (δ/ppm)
9k	286 Ethanol	71 (White)	$C_{24}H_{16}Cl_2N_4O_2S_2$ (527.42)	54.65 54.62	3.06 3.18	10.62 10.48	12.16 12.07	1680 (2C=O).	CF_3COOD; 2.8, 3.1 (2s, 6H,2CH_3), 5.1 (s, 2H, CH_2), 7.6, 7.7, 8.2, 8.4 (4d, 8H, Ar-H).
9l	238 Ethanol	85 (White)	$C_{25}H_{20}N_4O_3S_2$ (488.56)	61.46 61.37	4.13 4.16	11.47 11. 53	13.12 13.21	1675(C=O).	$CDCl_3$; 2.7, 2.8 (2s, 6H, 2CH_3),3.8(s,3H, OCH_3), 4.7(s, 2H, CH_2), 7.1-7.8 (m, 9H, Ar-H).
9m	284 Ethanol	90 (White)	$C_{26}H_{23}N_5O_4S_2$ (533.60)	58.52 58.64	4.34 4.39	13.13 13.35	12.02 12.27	3230 (NH), 1685-1670 (br, 2C=O).	CF_3COOD; 3.2 , 3.4 (2s, 6H,2CH_3), 4, 4.1 (2s, 6H ,2OCH_3), 4.4 (s, 2H, CH_2), 7.1–7.5 (m, 8H, Ar-H).
9n	200 Ethanol	71 (White)	$C_{21}H_{20}N_4O_4S_2$ (456.52)	55.25 54.35	4.42 4.22	12.27 12.10	14.04 13.90	1740 (C=O).	$CDCl_3$; 1.4 (t, 3H, CH_3), 2.9, 3 (2s, 6H, 2CH_3), 3.9(s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 4.3 (q, 2H, OCH_2), 7.2, 7.4 (2d,4H, Ar –H).
9o	256 Ethanol	92 (White)	$C_{25}H_{20}ClN_5O_3S_2$ (538.02)	55.81 56.01	3.75 3.66	13.02 13.22	11.92 12.00	3225 (NH), 1690-1640 (br, 2C=O).	CF_3COOD; 3.3, 3.5 (2s, 6H, 2CH_3), 4 (s, 3H, OCH_3), 4.3 (s, 2H, CH_2), 7-7.5 (m, 8H, Ar-H).

3-Amino-4,5-dimethyl-2-substitutedthieno[2,3-c]pyridazines (5a–c): General Procedure

Method A

A sample of compound **4a–c** (10 mmol) in sodium ethoxide (10 mmol Na/30 mL ethanol) was heated under reflux for 3 h, then allowed to cool. The solid product was collected by filtration, washed with water, and recrystallized from the proper solvent to give **5a–c**.

Method B

A mixture of compound **3** (10 mmol), α-halocarbonyl compound (10 mmol), and potassium carbonate (12 mmol) in ethanol (40 mL) was heated under reflux for 3 h. The separated product was collected when cooled, washed with water, and recrystallized from the proper solvent to give **5a–c**.

3,4-Dimethyl-7-substitutedpyridazo[′4,′3:4,5]thieno[3,2-d][1,2,3]triazine-8-ones (6a–c): General Procedure

To an ice cold solution of compound **5a–c** (10 mmol) in acetic acid (20 mL), sodium nitrite solution (0.5 g/2 mL H_2O) was added dropwise with stirring during 30 min. After the addition was finished, stirring was continued for additional 1 h. The solid product was collected by filtration and recrystallized from the proper solvent to give **6a–c**.

3,4-Dimethyl-7-substitutedpyrimido[′4,′5:4,5]thieno[2,3-c]pyridazine-8-ones (7a–c)

To mixture of **5a–c** (10 mmol) and triethyl orthoformate (5 mL), drops of acetic acid were added. The reaction mixture was heated for 2 h. The solid product **7a–c** was collected by filtration and recrystallized from the proper solvent.

3,4-Dimethyl-7-substituted -8-oxo–5,6,7,8–tetrahydropyrimido-[′4,′5:4,5]thieno[2,3-c]pyridazine-6-thiones (8a–c): General Procedure

A mixture of **5a–c** (10 mmol) and carbon disulfide (10 mL) in dry pyridine (30 mL) was heated on a water bath for 15 h. The solid product was collected by filtration and recrystallized from the proper solvent to give **8a–c**.

Reaction of Pyrimidothienopyridazinethiones (8a–c) with Halo Compounds: Formation of Compounds (9a–o)

A mixture of **8a–c** (10 mmol) and sodium acetate (12 mmol) in ethanol (30 mL) was refluxed for 2 h, then the respective halo compound (10 mmol) was added and refluxed for an additional 1 h. The solid product that separated upon cooling was collected by filtration, washed with water, and recrystallized from the proper solvent to give **9a–o**.

MS (**9h**) 460 (M^+; 42.70%) 462 (M+2, 0.02%), 415 (0.2%), 387 (11.7%), 341 (19.6%), 313 (0.9%), 249 (5.1%), 197 (9.3%), 149 (6.2%),125 (14.6%), and 92 (9.1%).

MS (**9n**) 517 (M^+; 62.7%), 483 (7.5%), 460 (15.9%), 443 (base peak; 100%), 411 (48.6%), 337 (52%), 254 (47.8%), and 121 (66.3%).

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