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Synthesis of Some Pyrimidothienopyrimidine Derivatives[a]

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Summary. The pyrimidothienopyrimidines **5** and **6** have been synthesized *via* the reaction of compounds **4a**, **b** with CS_2 and were further transformed to related fused heterocyclic systems.

Keywords. Synthesis; Heterocycles; Pyrimidines; Thienopyrimidines; Pyrimidothienopyrimidines.

Synthese einiger Pyrimidothienopyrimidin-Derivate

Zusammenfassung. Die Pyrimidothienopyrimidine **5** und **6** wurden durch Reaktion der Verbindungen **4a**,**b** mit CS_2 hergestellt und weiter zu verwandten kondensierten heterocyclischen Systemen umgesetzt.

Introduction

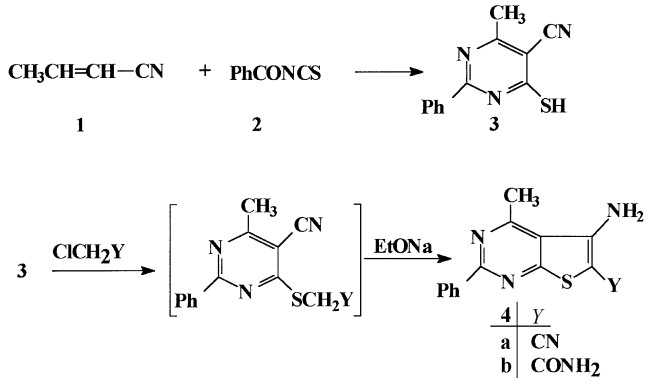
Thienopyrimidines and pyrimidothienopyrimidines have been the subject of chemical and biological studies due to their interesting pharmacology [1] which includes analgesic [2], antipyretic [3], and antiinflammatory [4, 5] properties. In view of the above activities and in continuation of our work in the synthesis of fused heterocycles with thienopyrimidine [6, 7], we report herein the synthesis of some fused pyrimidothienopyrimidines.

Results and Discussion

Recently, *G. Wagner et al.* [9] have reported the synthesis of compound **3** by reaction of dibenzoyldiacetonitrile with cyanothioacetamide. We present its synthesis from crotononitrile (**1**) *via* condensation with benzoylisothiocyanate (**2**). The resulting compound **3** was reacted with chloroacetonitrile and with chloroacetamide in ethanol in the presence of sodium ethoxide to give S-alkylated derivatives as intermediates which upon heating cyclized to the thienopyrimidines **4a**, **b**.

3-Amino-4-methyl-6-phenylthieno[2,3-*d*]pyrimidine-2-carbonitrile (**4a**) and 3-amino-4-methyl-6-phenylthieno[2,3-*d*]pyrimidine-2-carboxamide (**4b**) were

[a] An abstract of this paper was published at the 36th IUPAC congress, Geneva, August 17–22, 1997.

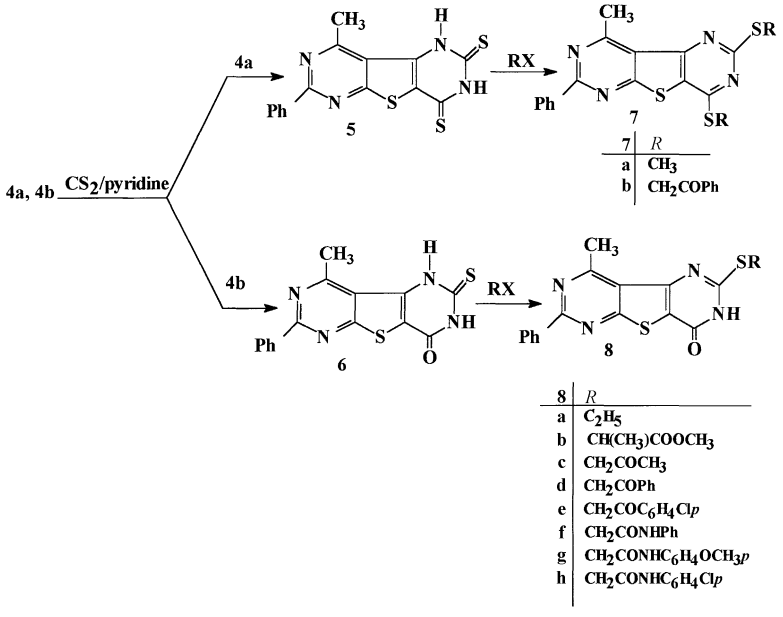


Scheme 1

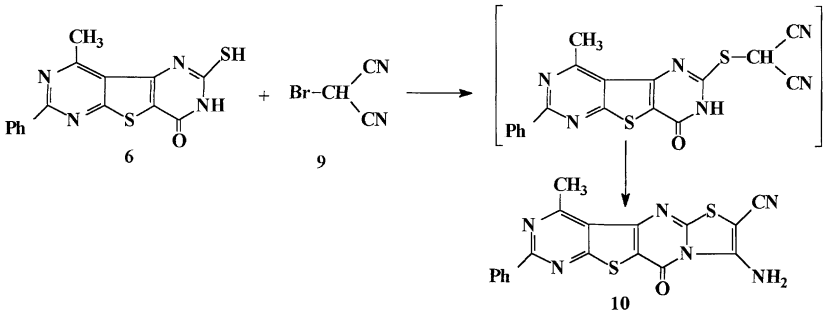
reacted with CS_2 in pyridine to afford pyrimidothienopyrimidines **5** and **6**, respectively.

Reaction of **6** with monobromomalononitrile (**9**) in ethanol in the presence of an equivalent of sodium hydroxide resulted in an S-alkylated derivative which was instable under the reaction condition and cyclized to thiazolopyrimidothienopyrimidine (**10**).

When compound **6** was reacted with hydrazine hydrate in pyridine, 2-hydrazino-9-methyl-7-phenylpyrimido[4′,5′:4,5]thieno[2,3-*d*]pyrimidin-2(3*H*)-one (**11**) was obtained. Compound **11** in turn could be transformed to other fused heterocyclic systems. Condensation with aromatic aldehydes in refluxing ethanol affored the coresponding carbohydrazones **12**. Triazolopyrimidothienopyrimidines **13–15** and tetrazolopyrimidothienopyrimidine **16** were produced from the reaction

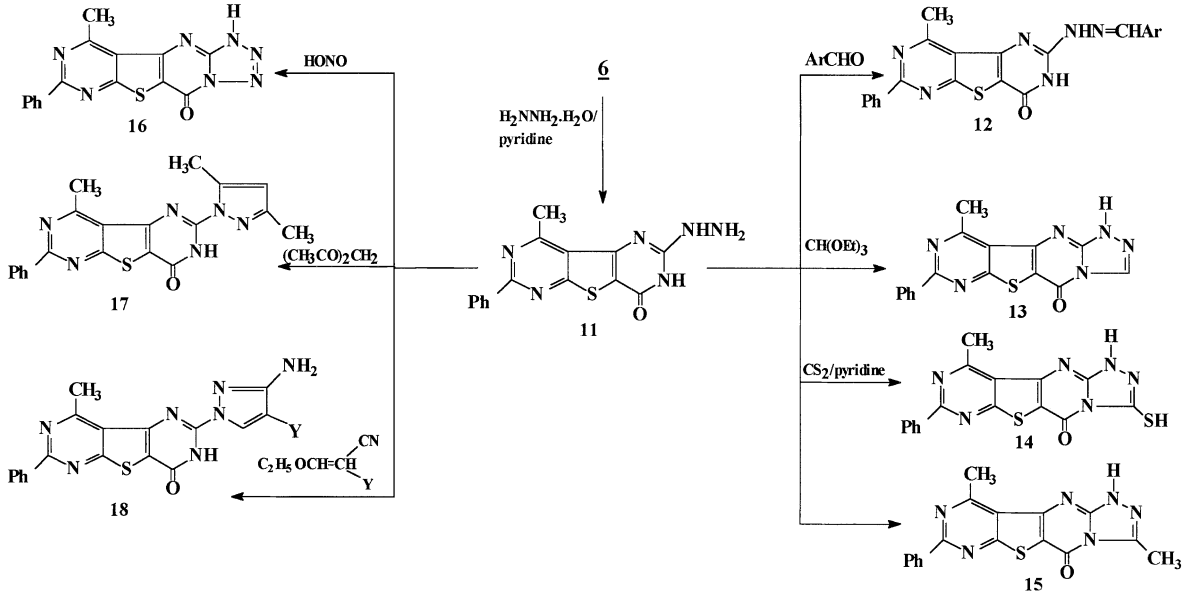


Scheme 2



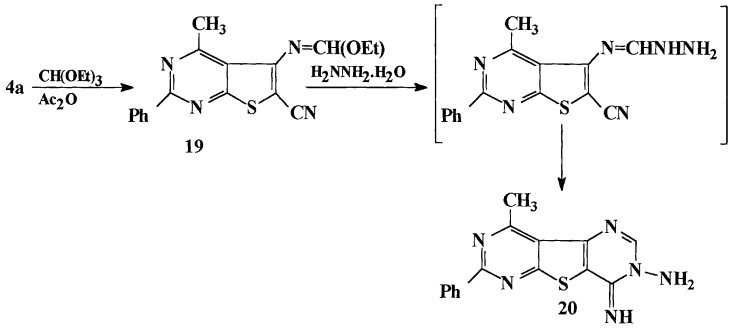
Scheme 3

of **11** with triethyl orthoformate in the presence of catalytic amounts of acetic acid, carbon disulfide in pyridine, acetic anhydride, and nitrous acid. When compound **11** was allowed to react with acetylacetone in ethanol, ethoxymethylene malononitrile, or ethoxymethylene ethylcyanoacetate in ethanol in the presence of acetic acid or with nitrous acid in acetic acid, compounds **17** and **18a**, **b** were obtained.



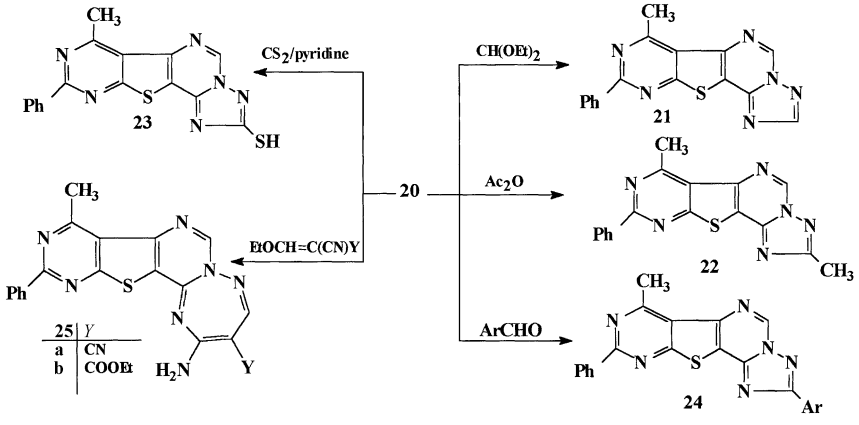
Scheme 4

The o-aminonitrile **4a** was condensed with triethyl orthoformate in acetic anhydride to give 3-ethoxymethyleneamino-4-methyl-6-phenylthieno[2,3-*d*]pyrimidin-2-carbonitrile (**19**). Upon treatment with hydrazine hydrate, **19** afforded the corresponding hydrazone as intermediate which cyclized to pyrimidothienopyrimidine **20** under the reaction conditions.



Scheme 5

Triazolopyrimidothienopyrimidines **21**–**24** were produced when 3-N-amino-4-imino-9-methyl-7-phenylpyrimido[4′,5′;4,5]thieno[2,3-*d*]pyrimidine (**20**) was subjected to a reaction with triethyl orthoformate, acetic anhydride, carbon disulfide in refluxing pyridine, and aromatic aldehydes. Treatment of **20** with ethoxymethlenemalononitrile and ethoxymethylene ethylcyanoacetate in refluxing ethanol in the presence of catalytic amounts of acetic acid resulted in pyrimidothienopyrimidotriazepines **25a**, **b**.



Scheme 6

Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide disks on a Pye Unicam spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were obtained on Varian 390 90 MHz spectrometer in a suitable deuterated solvent. Chemical shifts refer to tetramethylsilane as internal standard. Elemental analyses were obtained on a Perkin Elmer 240 C microanalyzer.

4-Methyl-2-phenyl-6-mercaptopyrimidine-5-carbonitrile (**3**)

To a freshly prepared solution of benzoyl isothiocyanate (0.01 mol) in dry acetone (20 ml), a solution of crotononitrile (8.2 g, 0.01 mol) in acetone (10 ml) was added. The mixture was stirred at room

temperature for 1 h and then refluxed on a steam bath for additional 2 h. The solvent was removed, and the solid product was collected and recrystallized from ethanol as golden yellow crystals.

Yield; 19.13 g (84%); m.p.: 228–230°C (Refs. [8, 9]: m.p.: 228–232°C).

3-Amino-4-methyl-6-phenylthieno[2,3-d]pyrimidin-2-carbonitrile (**4a**):

To a stirred sample of compound **3** (2.3 g, 0.001 mol) in ethanol (20 ml) containing 0.7 g (0.01 mol) sodium ethoxide, chloroacetonitrile (0.01 mol) was added. The mixture was stirred at room temperature for 0.5 h. Then the reaction mixture was heated at 60–70°C for 0.5 h and allowed to cool. The solid product was collected and recrystallized from ethanol as yellow crystals.

Yield: 2.34 g (88%); m.p.: 180°C; $C_{14}H_{10}N_4S$ (266.32); calc.: C 63.14, H 3.78, N 21.04, S, 12.04; found: C 62.94, H 4.00, N 20.88, S 11.90; IR: $\nu = 3300$, 3200 (NH_2), 2220 (CN) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.85$ (s, 3H, CH_3), 6.5 (s, 2H, NH_2), 7.4–8.2 (m, 5H, ArH) ppm.

3-Amino-4-methyl-6-phenylthieno[2,3-d]pyrimidin-2-carbxamide (**4b**)

4b was prepared according to the literature.

Yield: 82%; m.p.: 230°C (Ref. [9]: m.p.: 227–229°C).

7-Phenyl-1,2,3,4-tetrahydro-9-methylpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidin-2,4-dithione (**5**)

A mixture of compound **4a** (2.66 g, 0.01 mol) and CS_2 (2 ml) in pyridine (15 ml) was refluxed for 8 h and then allowed to cool. The solid product was collected and recrystallized from dioxane as orange crystals.

Yield: 2.05 g (76%); m.p.: >320°C; $C_{15}H_{10}N_4S_2$ (310.39); calc.: C 58.04, H 3.25, N 18.05, S 20.66; found: C 57.82, H 3.06, N 17.88, S 20.80; IR: $\nu = 3240$, 3180 (2NH), 3050 (CH Ar), 2250–2220 (2C=S) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.85$ (s, 3H, CH_3), 7.6, 8.5 (2m, 5H, ArH) ppm.

7-Phenyl-1,2,3,4-tetrahydro-4-oxo-9-methylpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidin-2-thione (**6**)

6 was prepared from compound **4b** according to the procedure reported for the preparation of **5**. It was recrystallized from dioxane as orange crystals.

Yield: 2.3 g (78%); m.p.: >320°C; $C_{15}H_{10}N_4OS$ (294.33); calc.: C 61.21, H 3.42, N 19.04, S 10.89; found: C 61.00, H 3.64, N 18.84, S 11.12; IR: $\nu = 3250$, 3180 (2NH), 1680 (C=O), 1250 (C=S) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.9$ (s, 3H, CH_3), 7.65, 8.6 (2m, 5H, ArH) ppm.

2,4-Dialkylmercapto-9-methyl-7-phenylpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidines (**7a**, **b**)

A mixture of compound **5** (1.55 g, 0.005 mol), sodium acetate (980 mg, 0.012 mol), and halo compound (0.005 mol) in ethanol (25 ml) was refluxed for 2 h and then allowed to cool. The solid product was collected, washed with water several times, dried, and recrystallized from ethanol. The physical constants and spectroscopic data of compounds **7a**, **b** are listed in Tables 1 and 2.

2-Alkylmercapto-9-methyl-7-phenlpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidine-4-(3H)-ones (**8a–h**)

Compounds **8a–h** were prepared according to the method reported for the synthesis of **7a**, **b** starting from **6** (1.47 g, 0.005 mol), sodium acetate (490 mg, 0.006 mol), and the appropriate halo compounds (0.005 mol). The physical constants and spectroscopic data of compounds **8a–h** are listed in Tables 1 and 2.

Table 1. Spectroscopic data of compounds **7a**, **b** and **8a–h**

	IR ν (cm^{-1})	^{1}H NMR δ (ppm)
7a	3050 (CH aromatic, 2950 (CH aliphatic), 1600 (C=N)	*DMSO*-d_6; 3.85 (s, 3H, CH_3), 4.0 (s, 6H, $2CH_3$), 7.3–8.3 (m, 5H, ArH)
7b	3050 (CH aromatic), 1690 (2 C=O), 1600 (C=N)	*DMSO*-d_6; 3.8 (s, 3H, CH_3), 4.15 (s, 4H, 2S, CH_2), 7.3–8.4 (m, 15H, Ar-H)
8a	3240 (NH), 1670 (C=O)	*DMSO*-d_6; 3.0 (s, 3H, CH_3), 3.25 (q, 2H, CH_2), 7.45, 8.32 (m, 5H, Ar-H), 12.5 (s, 1H, NH)
8b	3220 (NH), 1710, 1680 (2C=O)	*DMSO*-d_6; 1.85 (d, 1H, CH), 3.35, 3.6, 3.95 (3s, 9H, $3CH_3$), 7.65, 8.3 (2m, 5H, ArH), 12.2 (s, 1H, NH)
8c	3250 (NH), 1700, 1680 (2C=O)	*DMSO*-d_6; 2.95, 3.8 (2s, 6H, $2CH_3$), 4.0 (s, 2H, SCH_2), 7.4–8.3 (m, 5H, ArH), 12.4 (s, 1H, NH)
8d	3240 (NH), 1695, 1670 (2C=O)	*DMSO*-d_6; 3.2 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.4–8.35 (m, 10H, ArH), 12.5 (s, 1H, NH)
8e	3240 (NH), 1700, 1675 (2C=O)	*DMSO*-d_6; 3.25 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.4–8.35 (m, 9H, ArH) 12.5 (s, 1H, NH)
8f	3340, 3240 (2NH), 1680, 1670 (2C=O)	CF_3COOD; 3.2 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.4–8.35 (m, 10H, ArH)
8g	3320, 3180 (2NH), 1685, 1670 (2C=O)	*DMSO*-d_6; 3.0 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2), 6.8–7.6, 8.4 (2m, 9H, Ar-H), 10.2, 12.3 (2s, 2H, 2NH)
8h	3335, 3220 (2NH), 1690, 1670 (2C=O)	CF_3COOD; 3.15 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.4–8.35 (m, 9H, ArH)

3-Amino-10-methyl-8-phenyl-5-oxothiazolo[2″,3″:2′,3′]pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidine-2-carbonitrile (**10**)

To a stirred sample of compound **6** (2.94 g, 0.01 mol) in ethanolic sodium hydroxide solution (4%, 5 ml), bromomalononitrile (1.45 g, 0.01 mol) was added. The mixture was stirred for 15 minutes and then warmed at 50–60°C for another 15 minutes. The solid product was collected and recrystallized from dioxane as yellow crystals.

Yield: 3.05 g (78%); m.p.: >300°C; $C_{18}H_{10}N_6OS_2$ (390.44); calc.: C 55.37, H 2.58, N 21.52, S 16.42; found: C 55.18, H 2.72, N 21.48, S 16.56; IR: $\nu = 3350$, 3250 (NH_2), 1690 (C=O) cm^{-1} ^{1}H NMR (*DMSO*-d_6): $\delta = 2.85$ (s, 3H, CH_3), 6.4 (s, 2H, NH_2), 7.6–8.6 (m, 5H, ArH) ppm.

2-Hydrazino-9-methyl-7-phenylpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidin-4-(3H)-one (**11**)

A mixture of compound **6** (2.94 g, 0.01 mol) and hydrazine hydrate (1 ml, 0.02 mol) in pyridine (20 ml) was refluxed for 10 h or till H_2S evolution ceased. The solid product was collected and recrystallized from *DMF* as yellowish white crystals.

Yield: 74%; m.p.: 300°C; $C_{15}H_{12}N_6OS$ (324.36); calc.: C 55.54, H 3.73, N 25.91, S 9.88; found: C 55.74, H 4.00, N 25.72, 10.12; IR: $\nu = 3400$, 3300, 3250, 3200 (2NH, NH_2), 1660 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.85$ (s, 3H, CH_3), 3.8 (br s, 2H, NH_2), 6.7 (s, 1H, NH), 7.55–8.6 (m, 5H, ArH), 10.8 (s, 1H, NH) ppm.

Table 2. Physical constants of compounds **7a**, **b** and **8a–h**

	m.p. (°C)	Yield (%)	Molecular Formula (Mol.Wt.)	Analytical Data C	H	N	S	Cl
7a	254–255	78	$C_{17}H_{14}N_4S_3$	55.11	3.81	15.12	25.96	
			(370.50)	54.92	4.04	14.94	26.16	
7b	194	82	$C_{31}H_{22}N_4O_2S_3$	64.34	3.83	9.68	16.62	
			(578.72)	64.52	4.06	9.60	16.76	
8a	>300	78	$C_{17}H_{14}N_4OS_2$	57.61	3.98	15.81	18.09	
			(354.44)	57.68	4.08	16.00	17.90	
8b	227–229	82	$C_{19}H_{16}N_4O_3S_2$	55.33	3.91	13.58	15.54	
			(412.48)	55.18	4.12	13.72	15.44	
8c	288	86	$C_{18}H_{14}N_4O_2S_2$	56.53	3.69	14.65	16.77	
			(382.45)	56.66	3.72	14.44	17.00	
8d	298–299	84	$C_{23}H_{16}N_4O_2S_2$	62.15	3.63	12.60	14.42	
			(444.53)	61.94	3.88	12.44	14.68	
8e	304	86	$C_{23}H_{15}ClN_4O_2S_2$	57.68	3.16	11.70	13.39	7.40
			(478.97)	57.44	3.34	11.68	13.53	7.48
8f	>300	82	$C_{23}H_{17}N_5O_2S_2$	60.12	3.73	15.24	13.95	
			(459.54)	60.00	4.01	15.08	14.12	
8g	>320	78	$C_{24}H_{19}N_5O_3S_2$	58.88	3.91	14.31	13.10	
			(489.57)	59.04	4.12	14.23	13.28	
8h	>320	83	$C_{23}H_{16}ClN_5O_2S_2$	55.92	3.26	14.18	12.98	7.18
			(493.99)	56.12	3.06	13.98	13.20	6.96

2-Aryledinehydrazino-9-methyl-7-phenylpyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidin-4(3H)-ones (**12a–d**); *general procedure*

A mixture of compound **11** (1.55 g, 0.005 mol) and the appropriate aldehyde (0.005 mol) in ethanol (30 ml) was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from acetic acid.

12a: Ar = Ph; yellow crystals; Yield: 72%; m.p.: >320°C; $C_{22}H_{16}N_6OS$ (412.47); calc.: C 64.06, H 3.91, N 20.37, S 7.77; found: C 63.88, H 4.10, N 20.14, S 8.00; IR: $\nu = 3360$, 3270 (2NH), 1660 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.80$ (s, 3H, CH_3), 7.35–8.5 (m, 10H, ArH), 9.2 (s, 1H, CH=N) ppm.

12b: Ar = *p*–$C_6H_4OCH_3$; yellow crystals; yield: 80%; m.p.: >320°C; $C_{23}H_{18}N_6O_2S$ (442.49); calc.: C 62.43, H 4.10, N 18.99, S 7.25; found: C 62.32, H 4.00, N 119.12, S 7.08; IR: $\nu = 3340$, 3270 (2NH), 1660 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.85$ (s, 3H, CH_3, 3.3 (s, 3H, OCH_3), 7.55–8.6 (m, 9H, ArH), 8.95 (s, 1H, CH=N) ppm.

12c: Ar = *p*-C_6H_4Cl; yellow crystals; yield: 82%; m.p.: >320°C; $C_{22}H_{15}ClN_6OS$ (446.91); calc.: C 59.13, H 3.38, N 18.80, S 7.17, Cl 7.93; found: C 58.90, H 3.44, N 19.00, S 7. 17, Cl 8.05; IR: $\nu = 3350$, 3270 (2NH), 1670 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.75$ (s, 3H, CH_3), 7.55–8.6 (m, 9H, ArH), 8.9 (s, 1H, CH=N) ppm.

12d: Ar = $C_6H_4NO_2$; yellow crystals; yield: 78%; m.p.: >300°C; $C_{22}H_{15}N_7O_3S$ (457.47); calc.: C 57.76, H 3.30, N 21.43, S 7.01; found: C 58.00, H 3.12, N 21.64, S 6.98; IR: $\nu = 3350$, 3260 (2NH), 1680 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 2.85$ (s, 3H, CH_3), 7.55–8.6 (m, 9H, ArH), 9.0 (s, 1H, CH=N) ppm.

10-Methyl-8-phenyl-1(H)-triazolo[3″,4″:2,3]pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-5-one (**13**)

To a mixture of compound **11** (1.55 g, 0.005 mol) and triethyl orthoformate (0.01 mol) in methanol (20 ml), a few drops of acetic acid were added. The mixture was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from dioxane.

Yellow crystals; m.p.: >300°C; $C_{16}H_{10}N_6OS$ (334.36); calc.: C 57.48, H 3.01, N 25.14, S, 9.59; found: C 57.32, H 3.22, N 24.92, S 9.74; IR: $\nu = 3380$ (NH), 1680 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 3.80$ (s, 3H, CH_3), 7.7–8.3 (m, 5H, ArH), 9.2 (s, H, CH triazole) ppm.

3-Mercapto-10-methyl-8-phenyl-1(H)-triazolo[3″,4″:2,3]pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-5-one (**14**)

A mixture of compound **11** (1.55 g, 0.005 mol) and carbon disulfide (2 ml) in pyridine (15 ml) was refluxed on a steam bath for 10 h and then allowed to cool. The solid product was collected and recrystallized from dioxane.

Orange crystals; yield: 82%; m.p.: >300°C; $C_{1610}N_6OS_2$ (366.42); calc.: C 52.45, H 2.75, N 22.94, S 17.50; found: C 52.18, H 3.00, N 23.14, S 17.74; IR: $\nu = 3050$ (CH aromatic), 3220 (NH), 2850–2720 (SH), 1600 (C=N) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 3.85$ (s, 3H, CH_3), 7.5–8.2 (m, 5H, ArH), 8.6 (s, 1H, CH pyrimidine) ppm.

3,10-Dimethyl-8-phenyl-1(H)-triazolo[3″,4″:2,3]pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-5-one (**15**)

A sample of compound **11** (1.55 g, 0.05 mol) in acetic anhydride (10 ml) was heated under reflux for 3 h, allowed to cool, and poured into cold water. The solid product was collected and recrystallized from acetic acid. Yellow crystals; yield: 78%; m.p.: >300°C; $C_{17}H_{12}N_6OS$ (348.38); calc.: C 58.61, H 3.47, N 24.12, S 9.20; found: C 58.88, H 3.42, N 23.94, S 9.06; IR: $\nu = 3320$ (NH), 1670 (C=O) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 3.0$, 3.80 (2s, 6H, $2CH_3$), 7.6–8.0, 8.3 (2m, 5H, ArH), 9.8 (s, 1H, CH) ppm.

4-Methyl-2-phenyl-6(H)-titrazolo[1″,5″:2,3]pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-10-one (**16**)

To a sample of compound **11** (0.05 mol) dissolved in a mixture of acetic acid/HCl (v/v, 10 ml), sodium nitrite solution (0.01 mol) was added dropwise with stirring during 10 min. The stirring was continued for additional 2 h; then the mixture was allowed to stand for 3 h. The solid product was collected and recrystallized from dioxane.

Orange crystals; yield: 68% m.p.: 280–285°C (decomp); $C_{15}H_9N_7OS$ (307.33); calc.: C 58.62, H 2.95, N 22.79, S 10.43; found: C 58.44, H 3.16, N 23.00, S 10.32; IR: $\nu = 3320$ (NH), 1610 (N=N) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 3.75$ (s, 3H, CH_3), 7.3–8.3 (m, 5H, ArH) ppm.

4-Methyl-2-phenyl-6(3,5-dimethylpyrazol-1-yl)pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-8-one (**17**)

A mixture of compound **11** (0.05 mol), acetyl acetone (0.01 mol), and ethanol (20 ml) was refluxed for 5 h and then allowed to cool. The solid product was collected and recrystallized from acetic acid.

Yellow crystals; yield: 72%; m.p.:>320°C; $C_{20}H_{16}N_6OS$ (388.45); calc.: C 61.84, H 4.15, N 21.63, S 8.25; found: C 62.06, H 3.92, N 21.84, S 8.12; IR: $\nu = 3250$ (NH), 1600 (C=N), no bands characterisitc for NH_2; ^1H NMR (CF_3COOD): $\delta = 2.4$, 2.75, 3.8 (3s, 9H, $3CH_3$), 6.05 (s, 1H, CH pyrazole), 7.4–8.3 (m, 5H, ArH) ppm.

4-Methyl-2-phenyl-6-(3-amino-4-cyanopyrazol-1-yl)pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-8-one (**18a**)

4-Methyl-2-phenyl-6-(3-amino-4-carboethoxy-1-yl)-pyrimido[5′,6′:4,5]thieno[2,3-d]pyrimidin-8-one (**18b**)

To a mixture of compound **11** (0.005 mol) and ethoxymethylenemalononitrile or ethoxymethylene ethylcyanoacetate (0.005 mol) in methanol, a few drops of acetic acid were added as a catalyst. The mixture was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from dioxane.

18a: white crystals; yield: 78%; m.p.: >330°C; $C_{19}H_{12}N_8OS$ (400.42); calc.: C 56.99, H 3.02, N 27.98, S 8.01; found: C 57.19, H 3.26, N 28.08, S 7.77; IR: $\nu = 3330$, 3230, 3150 (NH_2, NH), 2220 (CN), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.80$ (s, 3H, CH_3), 6.8 (s, 2H, NH_2), 7.6–83 (m, 5H, ArH), 8.8 (s, 1H, CH), 12.3 (s, 1H, NH) ppm.

18b: white crystals; yield: 72%; m.p.: >330°C; $C_{21}H_{17}N_7O_3S$ (447.47); calc.: C 56.37, H 3.83, N 21.91, S 7.16; found: C 56.19, H 4.00, N 22.08, S 7.27; IR: $\nu = 3300$, 3200, 3140 (NH_2, NH), 1710 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.5$ (t, 3H, CH_3), 3.5 (q, 2H, CH_2), 3.85 (s, 3H, CH_3), 6.75 (s, 2H, NH_2), 7.6–845 (m, 5H, ArH), 8.8 (s, 1H, CH), 12.5 (s, 1H, NH) ppm.

3-Ethoxymethyleneamino-4-methyl-6-phenylthieno[2,3-d]pyrimidin-2-carbonitrile (**19**)

A mixture of compound **4a** (0.01 mol), triethyl orthoformate (3 ml), and acetic anhydride (10 ml) was heated under reflux for 4 h and then allowed to cool. The solid product was collected and recrystallized from dioxane.

Yellow crystals; yield: 74%; m.p.: 142–143°C; $C_{17}H_{14}N_4OS$ (322.38); calc.: C 63.34, H 4.38, N 17.38, S 9.94; found: C 63.14, H 4.52, N 17.18, S 10.12; IR: $\nu = 3050$ (CH aromatic), 2225 (CN), 1600 (C=N), no band characterestic for NH_2; ^1H NMR (*DMSO*-d_6): $\delta = 1.3$ (t, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.4 (q, 2H, CH_2), 7.5, 8.4 (2m, 6H, ArH, CH=N) ppm.

3-Amino-4-imino-7-phenyl-9-methylpyrimido[4′,5′:4,5]thieno[2,3,-d]pyrimidine (**20**)

A mixture of compound **19** (1.61 g, 0.005 mol) and hydrazine hydrate (0.30 ml, 0.06 mol) in ethanol (20 ml) was refluxed for 2 h and then allowed to cool. The solid product was collected and recrystallized from dioxane.

Yellow crystals; yield: 68%; m.p.: >330°C; $C_{15}H_{12}N_6S$ (308.36); calc.: C 58.43, H 3.92, N 27.25, S 10.40; found: C 58.22, H 4.12, N 27.08, S 10.32; IR: $\nu = 3340$, 3240, 3160 (NH_2, NH), 1580 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.7$ (s, 3H, CH_3), 6.7 (s, 2H, NH_2), 7.35–8.2 (m, 5H, ArH), 8.95 (s, 1H, CH pyrimidine), 10.7 (s, 1H, NH) ppm.

4-Methyl-2-phenyltriazolo[1′′,5′′1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidine (**21**)

To a mixture of compound **20** (1.54 g, 0.005 mol) and triethyl orthoformate (1.7 ml, 0.01 mol) in methanol (20 ml), a few drops of acetic acid were added as a catalyst. The mixture was heated under reflux for 2 h and then allowed to cool. The solid product was filtered off and recrystallized from *DMF*.

Yellow crystals; yield: 72%; m.p.: >333°C; $C_{16}H_{10}N_6S$ (318.36); calc.: C 60.37, H 3.17, N 26.40, S 10.07; found: C 60.22, H 3.32, N 26.48, S 9.92; IR: $\nu = 3050$ (CH aromatic), 1600 (C=N), no bands characteristic for (NH, NH_2); ^1H NMR (CF_3COOD): $\delta = 3.80$ (s, 3H, CH_3), 7.7–8.0, 8.3 (2m, 5H, ArH), 8.45, 9.1 (2s, 2H, 2CH) ppm.

4,8-Dimethyl-2-phenyltriazolo[1″,5″1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidine (**22**)

A sample of compound **20** (1.54 g, 0.005 mol) in acetic anhydride (10 ml) was refluxed for 5 h and then allowed to cool. Under stirring, the reaction mixture was poured into an ice/water mixture (100 ml). The solid product was collected and recrystallized from dioxane.

Yellow crystals; yield: 68%; m.p.: >320°C; $C_{17}H_{12}N_6S$ (332.38); calc.: C 61.43, H 3.64, N 25.28, S 9.65; found: C 61.65, H 3.83, N 25.06, S 9.48; IR: $\nu = 3050$ (CH aromatic), 2950 (CH aliphatic), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): 3.0, 3.80 (2s, 6H, 2 CH_3), 7.6–8.0, 8.3 (2m, 5H, ArH), 9.8 (s, 1H, CH) ppm.

4-Methyl-8-mercapto-2-phenyltriazolo[1″,5″1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidine (**23**)

A mixture of compound **20** (1.54 g, 0.005 mol) and carbon disulfide (2 ml) in pyridine (10 ml) was refluxed on a steam bath for 12 h and then allowed to cool. The excess of CS_2 was removed, and the solid product was collected and recrystallized from *DMF*.

Orange crystals; yield: 75%; m.p.: >330°C; $C_{16}H_{10}N_6S_2$ (350.42); calc.: C 54.84, H 2.88, N 23.98, S 18.30; found: C 55.02, H 3.00, N 23.88, S 18.22; IR: $\nu = 3050$ (CH aromatic), 2900–2750 (SH), 1600 (C=N), no bands characteristic for NH and NH_2; ^1H NMR (CF_3COOD): $\delta = 3.85$ (s, 3H, CH_3), 7.75–8.35 (m, 5H, ArH), 8.9 (s, 1H, CH), 10.5 (s, 1H, SH) ppm.

4-Methyl-8-aryl-2-phenyltriazolo[1″,5″1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-d]pyrimidine (**24**); *general procedure*

A mixture of compound **20** (1.54 g, 0.005 mol) and aromatic aldehyde (0.005 mol) in acetic acid (20 ml) was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from *DMF*.

24a: Ar = Ph; yellow crystals; yield: 74%; m.p.: >320°C; $C_{22}H_{13}N_6S$ (393.45); calc.: C 67.16, H 3.33, N 21.36, S 8.15; found: C 67.02, H 3.12, N 21.38, S 8.22; IR: $\nu = 3050$ (CH aromatic), 1600 (C=N), no bands characteristic for NH and NH_2; ^1H NMR (*DMSO*-d_6); $\delta = 3.80$ (s, 3H, CH_3), 7.6–8.6 (m, 10H, ArH), 9.8 (s, 1H, CH) ppm.

24b: Ar = *p*-$C_6H_4NO_2$; yellow crystals; yield: 74%; m.p.: >320°C; $C_{22}H_{12}N_7O_2S$ (438.44); calc.: C 60.27, H 2.76, N 22.36, S, 7.31; found: C 60.02, H 3.00, N 22.38, S 7.22; IR: $\nu = 3050$ (CH aromatic), 1610 (C=N), no bands characteristic for NH and NH_2; ^1H NMR (*DMSO*-d_6): $\delta = 3.85$ (s, 3H, CH_3), 7.6–8.45 (m, 9H, ArH), 9.8 (s, 1H, CH) ppm.

2-Amino-9-methyl-11-phenylpyrimido[4,5:4′,5′]thieno[2′,3′:4,5]pyrimido[1,6-b]triazebine-3-carbonitrile (**25a**)

Ethyl 2-amino-9-methyl-11-phenylpyrimido[4,5:4′,5′]thieno[2′,3′:4,5]pyrimido[1,6-b]triazebine-3-carboxylate (**25b**)

To a mixture of compound **20** (1.54 g, 0.005 mol) and ethoxymethylenemalononitrile (0.61 g, 0.005 mol) or ethoxymethelene ethylcyanoacetate (0.85 g, 0.005 mol) in methanol (20 ml), a few drops of acetic acid were added. The mixture was refluxed for 3 h and allowed to cool. The solid product was collected and recrystallized from dioxane.

25a: yield: 68%; m.p.: >320°C; $C_{19}H_{12}N_8S$ (384.42); calc.: C 59.36, H 3.15, N 29.15, S 8.34; found: C 59.48, H 3.00, N 28.94, S 8.52; IR: $\nu = 3320$, 3220 (NH_2), 2220 (CN) cm^{-1}; ^1H NMR (CF_3COOD): $\delta = 3.80$ (s, 3H, CH_3), 6.55 (s, 1H, CH triazepine), 7.75–8.35 (m, 5H, ArH), 8.9 (s, 1H, CH pyrimidine) ppm.

25b: yield: 68%; m.p.: >320°C; $C_{21}H_{17}N_7O_2S$ (431.47); calc.: C 58.46, H 3.97, N 22.72, S 7.43; found: C 59.36, H 4.00, N 21.92, S 7.42; IR: $\nu = 3340$, 3240 (NH_2), 1710 (C=O) cm^{-1}; ^1H NMR

(CF_3COOD): $\delta = 1.5$ (t, 3H, CH_3 ester), 3.80 (s, 3H, CH_3), 4.15 (q, 2H, CH_2 ester), 6.50 (s, 1H, CH triazepine), 7.75–8.35 (m, 5H, ArH), 9.0 (s, 1H, CH pyrimidine) ppm.

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