The Dimroth rearrangement: synthesis and interconversion of isomeric triazolothienopyrimidines

Atef A. Hamed[a*], El-Sayed H. El-Ashry[b], Ibrahim F. Zeid[a] and Hesham F. Badr[a]

[a]*Chemistry Department, Faculty of Science, Menoufia University, Egypt*

[b]*Chemistry Department, Faculty of Science, Alexandria University, Egypt*

Triazolo-thieno[3,2-*e*]pyrimidines obtained by cyclisation of 4-hydrazino-2-(methylthio)thieno[2,3-*d*]pyrimidine with formic acid, acetic acid, cyanogen bromide and carbon disulfide, and by oxidation of the derived aldehyde hydrazones, are found to be the triazolo[4,3-*c*] isomers. These [4,3-*c*] compounds resist isomerisation in acid, but they undergo Dimroth rearrangement to the [1,5-*c*] isomers under basic conditions. The crystal structure of one such rearranged product, 5-methoxy-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (**13b**) was confirmed by X-ray analysis.

Keywords: dimroth rearrangement; hydrazines; fused pyrimidines, thiophenes, 1,2,4-triazoles; crystal structures

Fused pyrimidines attract considerable attention because of their wide spectrum of biological activities. Thienopyrimidines occupy a special position: some of them exhibit antiallergic,[1,2] antihistaminic,[3,4] antihypertensive,[5,6] antiinflamatory,[7,8] antimicrobial,[9,10] antiviral,[11] antitumor[12,13] activities. Heterocycles containing the 1,2,4-triazole nucleus also show biological activity; several have been used as bactericidal,[14] insecticidal,[15] antitumor,[16] and antiinflammatory[17] agents. The introduction of a triazole ring into the thienopyrimidine system is expected to influence the biological activities significantly. In fact, some of them have been reported to display pronounced antibacterial[18] and anticonvulsant[19] activities.

Rearrangements in heterocyclic chemistry are of potential value for the synthesis of heterocyclic compounds which may otherwise require more elaborate routes, particularly in the pyrimidine series. One of the most interesting of these is the Dimroth rearrangement.[20] Isomerisation of triazolothienopyrimidines has been reported by a number of workers. Several factors may influence this rearrangement, such as the reaction conditions and the type and position of the substituents. In continuation of our interest in the synthesis and structural elucidation of thienopyrimidines,[21,22] we report herein the synthesis, structure and reactivity of some compounds of this class which possess a methylthio or methoxy group on the pyrimidine ring.

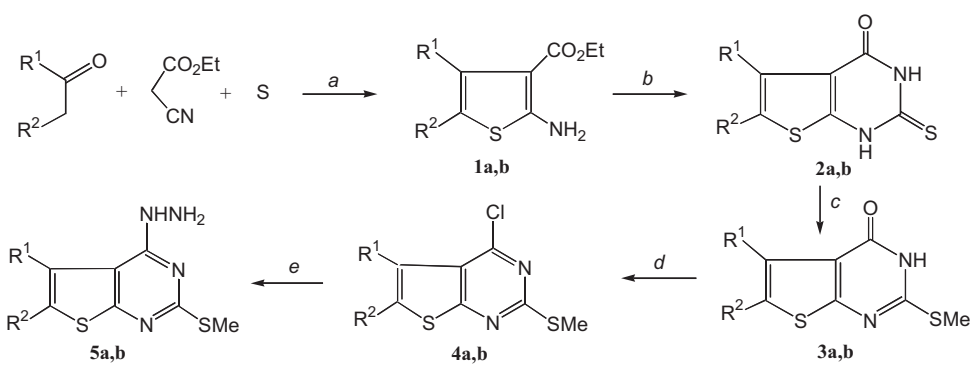
Results and discussion

The reaction of enamino esters **1a,b**, prepared by Gewald's method,[23] with thiourea or potassium thiocyanate gave the corresponding thienopyrimidines **2a,b**. Subsequent reaction with dimethyl sulfate, phosphorus oxychloride and then hydrazine hydrate afforded the hydrazines **5a,b**.[24] (Scheme 1)

A series of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines was synthesised by condensation of the 4-hydrazino-2-(methylthio)thienopyrimidines (**5a**,**b**) with various one-carbon donors. For instance, with formic acid the thienotriazolopyrimidines **6a**,**b**, were prepared, while with acetic acid the hydrazide **7b** was obtained, which underwent dehydrative cyclisation upon heating in DMF to furnish the 3-methyl analogue **8b**. The 3-thioxo derivative **10b** was obtained by the reaction of **5b** with carbon disulfide in pyridine. Reaction of **5a**,**b** with cyanogen bromide in presence of HCl resulted in the formation of the 3-amino derivatives **9a**,**b.** Condensation of **5a**,**b** with aromatic aldehydes gave the hydrazones **11a–e**, and oxidative cyclisation of these last compounds by ethanolic $FeCl_3$ gave the 3-aryl-5-(methylthio)thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **12a–c** (Scheme 2).

The structure proposals of these compounds were consistent with their analytical and spectral data (^{1}H and ^{13}C NMR, IR, mass spectra and elemental analyses). The ^{1}H NMR spectrum of **6a** showed singlets at 2.45, 2.56 and 2.78 ppm for three methyl groups. The triazole proton absorbed at δ 9.35 ppm. The methylene groups of **6b** resonated at 1.88, 2.83 and 3.02 ppm, besides a singlet signal at 2.78 ppm due to the methylthio group. The triazole proton gave a peak at 9.38 ppm.

When thienotriazolopyrimidines **6a,b** were allowed to react with $NaOCH_3$, new compounds were obtained. The products were 5-methoxythieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]

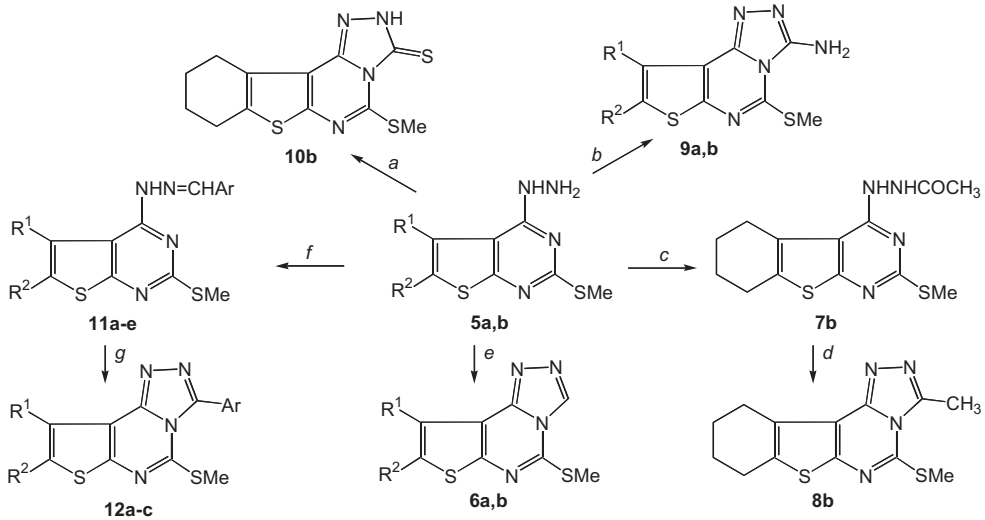


1-5: a, $R^1 = R^2 = CH_3$, **b**, $R^1R^2 = (CH_2)_4$

Reagents and conditions: *a*, morpholine, EtOH; *b*, KSCN, dioxan/ EtOH; *c*, aq. NaOH, Me_2SO_4; *d*, $POCl_3$; *e*, $N_2H_4.H_2O$ / EtOH

Scheme 1 Formation of the hydrazines **5a,b**.

* Correspondent. E-mail: atef2000_99@yahoo.com



Compd	R^1	R^2	Ar
5a	CH_3	CH_3	
5b	$(CH_2)_4$		
6a	CH_3	CH_3	
6b	$(CH_2)_4$		
9a	CH_3	CH_3	
9b	$(CH_2)_4$		
11a	CH_3	CH_3	Ph
11b	CH_3	CH_3	4-BrC_6H_4
11c	CH_3	CH_3	4-FC_6H_4
11d	$(CH_2)_4$		4-BrC_6H_4
11e	$(CH_2)_4$		4-FC_6H_4
12a	CH_3	CH_3	Ph
12b	CH_3	CH_3	4-FC_6H_4
12c	$(CH_2)_4$		4-BrC_6H_4

Reagents and conditions: *a*, CS_2, pyridine; *b*, BrCN/HCl; *c*, CH_3CO_2H, heat; *d*, DMF, heat; *e*, HCO_2H; *f*, ArCHO; *g*, $FeCl_3$/EtOH

Scheme 2 Synthesis of the thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **6, 8–10, 12.**

pyrimidines (**13a,b**) as indicated by their physical and spectral characteristics.

The ^{1}H NMR spectrum of **13a** showed bands at 2.41 and 2.49 ppm for two methyl groups beside resonance at 4.22 ppm due to a methoxy group, with disappearance of the methylthio group. The triazole proton of **13a** and **13b** appeared at δ 8.52 and 8.34 ppm respectively. The ^{13}C NMR spectrum of **13b** displayed signals at 22.5, 23.4, 25.25 and 25.4 ppm for the methylene carbons and a signal at 57.0 ppm from the methoxy group. Additionally, seven *sp*^{2} carbon peaks are found, attributed to the thiophene ring and C=N groups. The ^{1}H NMR showed a marked contrast in the absorption of the triazole protons. While compounds **6a,b** showed the peak at around 9.4 ppm, the triazole proton in **13a,b** appeared more shielded, showing as a singlet around 8.4 ppm. This is in accordance with the observation of Shishoo *et al.*[25-27] that the triazole protons of triazolo[4,3-*c*] isomers are more deshielded than those of [1,5-*c*] isomers. The structural proposal of 5-methoxy-8,9,10,11-tetramethylenethieno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidine (**13b**) was further confirmed by X-ray crystallographic analysis. (Fig. 1 and Table 1)

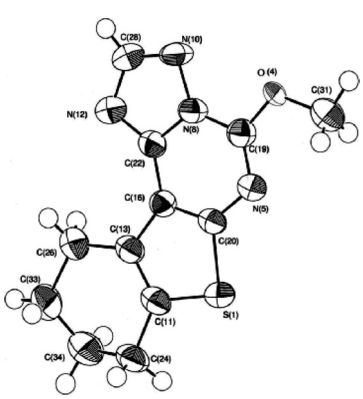
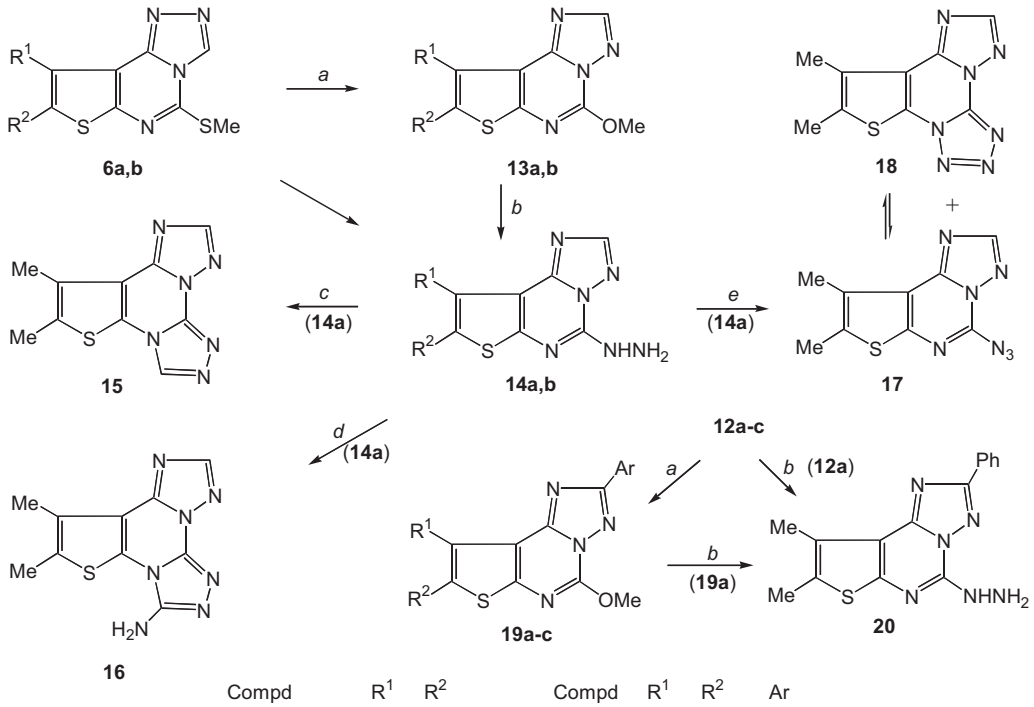


Fig. 1 Crystal structure of compound **13b**.

Table 1 Selected bond lengths(Å) and angles(°) of compound **13b**

Atoms	Distance	Atoms	Angle
C11–C13	1.359(4)	C11–S1–C20	90.97(14)
C11–C24	1.513(4)	S1–C11–C24	121.4(2)
C24–C34	1.534(5)	C13–C11–C24	125.1(3)
C34–C33	1.490(5)	C22–N12–C28	102.5(3)
C33–C26	1.527(5)	C11–C13–C16	110.6(3)
C26–C13	1.501(4)	C11–C13–C26	123.0(3)
C13–C16	1.433(4)	C19–N4–C31	115.7(2)
C16–C20	1.374(4)	C16–C13–C26	126.4(3)
C20–S1	1.727(3)	C19–N5–C20	116.7(3)
S1–C11	1.736(3)	C13–C16–C20	114.0(3)
C20–N5	1.368(4)	C13–C16–C22	130.6(3)
N5–C19	1.287(4)	C20–C16–C22	115.4(3)
C19–N8	1.380(4)	O4–C19–N5	125.2(3)
N8–C22	1.386(4)	O4–C19–N8	113.2(3)
C22–C16	1.419(4)	N5–C19–N8	121.5(3)
N8–N10	1.372(3)	S1–C20–N5	122.1(2)
N10–C28	1.316(4)	S1–C20–C16	111.0(2)
C28–N12	1.367(4)	N5–C20–C16	126.9(3)
N12–C22	1.332(4)	N10–N8–C19	127.0(3)
C19–O4	1.323(4)	N10–N8–C22	109.9(2)
O4–C31	1.439(4)	C19–N8–C22	123.1(2)
		N12–C22–C16	134.6(3)
Atoms	Angle	C11–C24–C34	108.7(3)
N8–C22–N12	109.0(3)	C13–C26–C33	111.0(3)
N8–C22–C16	116.4(2)	N10–C28–N12	117.1(3)
N8–N10–C28	101.4(2)	C26–C33–C34	114.0(3)
S1–C11–C13	113.4(2)	C24–C34–C33	112.6(3)

The reaction of **13a,b** with hydrazine hydrate afforded the hydrazino derivatives **14a,b**. Furthermore, when the triazolothienopyrimidines **6a,b** reacted with hydrazine hydrate they produced compounds identical with **14a,b** in all respects (NMR, IR, mass spectrum, elemental analysis and mixed m.p). The ^{1}H NMR spectrum (DMSO-d_6) of **14a** showed two signals at 2.47 and 2.62 ppm for methyl groups and two broad signals at 4.18 and 8.91 ppm for the $NHNH_2$ group. The triazole proton signal appeared at 8.29 ppm. Evidently isomerisation has occurred during the course of nucleophilic replacement of the methylthio group by hydrazine. A rare



Compd	R^1	R^2	Compd	R^1	R^2	Ar
13a, 14a	CH_3	CH_3	**19a**	CH_3	CH_3	Ph
13b, 14b	$(CH_2)_4$		**19b**	CH_3	CH_3	4-FC_6H_4
			19c	$(CH_2)_4$		4-BrC_6H_4

Reagents and conditions: *a*, NaOMe / MeOH; *b*, $N_2H_4.H_2O$; *c*, HCO_2H, heat; *d*, BrCN / HCl; *e*, $NaNO_2$ / HCl

Scheme 3 Synthesis of the thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines **13–20**.

example of the Dimroth rearrangement catalysed by hydrazine hydrate has been reported before.[28]

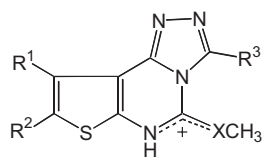
Boiling **14a** under reflux in formic acid resulted in the formation of the corresponding bis-triazolothienopyrimidine **15**. Its ^{1}H NMR spectrum showed two signals at δ 2.50 and 2.56 ppm for the two methyl groups and two triazole protons at 8.68 and 9.65 ppm. The reaction of **14a** with cyanogen bromide in presence of HCl afforded the 7-amino–bis-triazolothienopyrimidine derivative **16**. Its ^{1}H NMR spectrum showed two methyl signals at 2.38 and 2.45 ppm and a broad peak at δ 3.44 due to NH_2 group. The triazole proton appeared at δ 8 49 ppm.

The reaction of **14a** with nitrous acid at 0°C led to the formation of the tetracyclic compound **18**, as a minor product which was found in equilibrium in DMSO with the 5-azido derivative **17**. The ^{1}H NMR spectrum of **17** and **18** (in DMSO-d_6) showed signals at 2.43, 2.44 (major), 2.55, 2.56 (minor) corresponding to the four methyl groups of the two tautomers, beside two peaks at 8.57 (major) and 8.86 ppm (minor), characteristic for the triazole protons. The relatively downfield region of the methyl groups as well as the triazole proton of **18** is probably attributable to the deshielding effect of the tetrazole ring. Its ^{13}C NMR exhibit resonances at 13.14, 13.88 (major) and 13.29, 13.78 (minor) for the methyl groups. Thiophene carbons appeared at δ 118.9, 127.0, 133.8 and 140.8 ppm, in addition to four signals characteristic of C=N groups. The IR spectrum (KBr) of **17** showed a strong absorption band at 2162 cm^{-1} due to the azido group.

Treatment of 3-arylthieno[3,2-*e*][1,2,4]triazolo[4,3-*c*] pyrimidines (**12a–c)** with $NaOCH_3$ furnished the isomeric products 2-arylthieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines (**19a–c**). Compound **19a** underwent hydrazinolysis to afford the hydrazine derivative **20** (Scheme 3). Reaction of **12a** with hydrazine hydrate gave a product identical with **20** in all respects (^{1}H NMR, IR, mixed m.p.).

Isomerisation of the fused triazole system can be assumed to proceed through a sequence of ring opening and ring closure reactions of the pyrimidine ring as shown in Scheme 4.

Apparently, a methylthio or methoxy group at the 5-position in the triazolo[4,3-c]thienopyrimidines renders them resistant towards acid-catalysed isomerisation. This failure to isomerise under acidic conditions could be due to the stabilisation through delocalisation of the positive charge on the pyrimidine ring (**21**), thereby rendering the nucleophilic ring opening of the pyrimidine system more difficult. It has been observed that 5-unsubstituted, 5-alkyl- and 5-aralkyl-thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines undergo isomerisation to [1,5-c] isomers under both acidic and basic conditions, whereas the systems with 5-phenyl and 5-styryl substituents resist isomerisation under acidic conditions.[25,27]

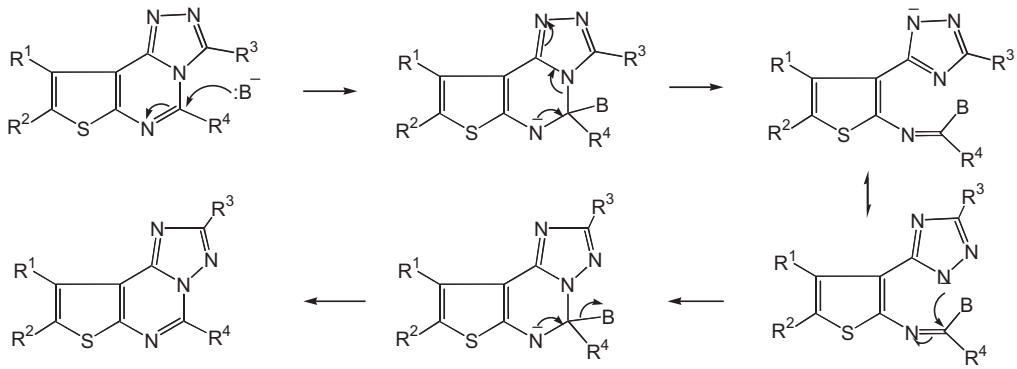


21

Experimental

IR spectra were recorded with Perkin–Elmer model 1720 FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were determined with Varian EM390 and Bruker AC–250 spectrometers. The chemical shifts in ppm are expressed in the δ scale using TMS as internal standard. Coupling constants are given in Hz. Mass spectra were recorded on an AEI MS 30 spectrometer. TLC was performed on Merck silica gel 60-F254 precoated plastic plates. Microanalyses were performed in the microanalysis units of the Universities of Cairo (Egypt) and Odense (Denmark).

4-Hydrazino-5,6-dimethyl-2-(methylthio)thieno[2,3-d]pyrimidine (**5a**): The chloro-compound **4a**[24] (0.24 g, 1 mmol) and $N_2H_4.H_2O$ (5 ml) were boiled under reflux in ethanol (10 ml) for 1 h. The colourless product that separated on cooling was filtered off and



Scheme 4 The Dimroth rearrangement of thieno[3,2-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines.

recrystallised from ethanol as colourless crystals (0.18 g, 75%), m.p. 220–221°C (lit.[24] m.p. 222°C). NMR (DMSO-d_6): δ_H 2.33 (s, 3H, Me), 2.36(s, 3H, Me), 2.50 (s, 3H, SMe), 4.66 (bs, 2H, NH) 8.09, (bs, 1H, NH); δ_C 13.42 (SMe), 14.08 (Me), 14.35 (Me), 113.34 (C5), 125.02 (C4a), 126.61 (C6),158.18 (C7a), 164.53 (C2), 165.00 (C4).

4-Hydrazino-2-(methylthio)-5,6,7,8-tetrahydro[1]benzothieno [2,3-d]pyrimidine (**5b**): Compound **5b** was prepared from **4b**[24] by the procedure described above for **5a**, as colourless crystals (0.19 g, 71%), m.p. 180–182°C. NMR (DMSO-d_6): δ_H 1.77 (bm, 4H, $2CH_2$), 2.50 (s, 3H, Me), 2.71 (bm, 2H, CH_2), 2.86 (bm, 2H, CH_2), 4.63 (bs, 2H, NH), 7.93 (bs, 1H, NH); δ_C 14.49 (SMe), 22.95 (CH_2), 23.14 (CH_2), 25.68 (CH_2), 26.26 (CH_2), 112.59 (C5), 127.57 (C4a), 130.16 (C6), 158.52 (C7a), 165.55 (C2), 165.60 (C4). Anal. calcd for $C_{11}H_{14}N_4S_2$ (266.36): C, 49.60; H, 5.29; N, 21.03. Found: C, 49.83; H, 5.54; N, 21.23%.

8,9-Dimethyl-5-(methylthio)thieno[3,2-e][1,2,4]triazolo[4,3-c] pyrimidine (**6a**)

The hydrazine **5a** (2.40 g, 10 mmol) was boiled under reflux in formic acid (10 ml) for 8 h. The reaction mixture was allowed to cool and poured onto ice-cold water (100 ml). The product that separated was filtered off, washed with water, dried and crystallised from ethanol as colourless crystals (1.75 g, 70%), m.p. 238-240°C (lit.[24] m.p. 242°C). NMR (DMSO-d_6): δ_H 2.45 (s, 3H, Me), 2.56 (s, 3H, Me), 2.77 (s, 3H, SMe), 9.35 (s, 1H, N=CH). MS: *m/z* 250 (M^+).

5-(Methylthio)-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine (**6b**): From **5b** (2.66 g, 10 mmol) and formic acid as described above, the product was obtained as colourless crystals (2.04 g, 74%), m.p. 208–210°C. NMR (DMSO-d_6): δ_H 1.88 (bs, 4H, $2CH_2$), 2.78 (s, 3H, SMe), 2.83 (bm, 2H, CH_2), 3.02 (bm, 2H, CH_2), 9.38 (s, 1H, N=CH). Anal. calcd for $C_{12}H_{12}N_4S_2$ (276.34): C, 52.15; H, 4.37; N, 20.27. Found: C, 52.3; H, 4.46; N, 20.17%.

4-(2-Acetylhydrazino)-2-(methylthio)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine (**7b**): The hydrazine **5b** (2.66 g, 10 mmol) was boiled under reflux in glacial acetic acid for 6 h. The reaction mixture was allowed to cool and poured into water (100 ml). The solid that separated was filtered off, dried and crystallised from ethanol as a yellow powder (2.18 g, 71%), m.p. 258-260°C. IR (KBr): ν_{max} 1622 (C=N and C=C), 1674 cm^{-1} (C=O). NMR ($CDCl_3$): δ_H 1.93 (bm, 4H, $2CH_2$), 2.73 (s, 3H, Me), 2.85 (bm, 2H, CH_2), 3.11 (s, 3H, Me), 3.15 (bm, 2H, CH_2), 4.81 (s, 1H, NH). Anal. calcd for $C_{13}H_{16}N_4OS_2$ (308.40): C, 50.62; H, 5.22; N, 18.16. Found: C, 50.93; H, 5.16; N, 18.43%.

3-Methyl-5-(methylthio)-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**8b**): The acetylhydrazine **7b** (3.08 g, 10 mmol) was boiled under reflux in DMF (15 ml) for 4 h and then allow to cool. The solid product was collected and recrystallised from DMF as yellow crystals (1.65 g, 57%), m.p.255–258°C. Anal. calcd for $C_{13}H_{14}N_4S_2$ (290.24): C, 53.79; H, 4.86; N, 19.30. Found: C, 53.52; H, 4.92; N, 19.51

3-Amino-8,9-dimethyl-5-(methylthio)thieno[3,2-e][1,2,4]triazolo-[4,3-c]pyrimidine (**9a**): The hydrazine **5a** (2.4 g, 10 mmol) and cyanogen bromide (1.06 g, 10 mmol) were stirred in 2N hydrochloric acid (30 ml) at room temperature for 24 h. The solid that separated was filtered off, washed with water, and dried *in vacuo*. Recrystallisation from ethanol afforded yellow crystals (1.4 g, 52%), m.p. 178–180°C. NMR (DMSO-d_6): δ_H 2.40 (s, 3H, Me), 2.44 (s, 3H, Me), 2.68 (s, 3H, Me), 4.12 (bs, 2H, NH); δ_C 12.67 (Me), 12.75 (Me), 14.13 (SMe), 115.31 (C9), 126.59 (C9a), 132.17 (C8), 142.51 (C6a), 146.89 (C10), 147.03 (C3) and 148.30 (C5). Anal. calcd for $C_{10}H_{11}N_5S_2$ (265.33): C, 45.26; H, 4.17; N, 26.39. Found: C, 45.52; H, 4.33; N, 26.27%.

3-Amino-5-(methylthio)-8,9,10,11-tetrahydro[1]benzothieno[3,2-e] [1,2,4]triazolo[4,3-c]pyrimidine (**9b**): From **5b** and cyanogen bromide as described for **9a**: yellow crystals (1.9 g, 65%), m.p. 188–191°C (lit.[29] m.p. 252°C). MS: *m/z* 291(M^+).

5-(Methylthio)-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine-3(2H)-thione (**10b**): The hydrazine **5b** (2.66 g, 10 mmol) and CS_2 (5 ml) in pyridine (15 ml) were slowly brought to the boil, heated under reflux for 8 h, and then allowed to cool. The solid product was collected and recrystallised from ethanol to give a yellow powder (2.06 g, 67%), m.p. 268–270°C. NMR (DMSO-d_6): δ_H 1.83 (bm, 4H, $2CH_2$), 2.50 (s, 3H, SMe), 2.80 (bm, 2H, CH_2), 3.19 (bm, 2H, CH_2), 14.33 (bs, 1H, NH). Anal. calcd for $C_{12}H_{12}N_4S_3$ (308.44): C, 46.73; H, 3.91; N, 18.16. Found: C, 46.80; H, 3.83; N, 18.28%.

The hydrazones **11a–e**: *general procedure*

The hydrazines **5a**,**b** (10 mmol) and the appropriate aromatic aldehyde (10 mmol) in ethanol (30 ml) containing a few drops of glacial acetic acid, were boiled under reflux for 2 h. The product that separated on cooling was filtered off, dried, and crystallised from ethanol.

Benzaldehyde [5,6-dimethyl-2-(methylthio)thieno[2,3d]pyrimidin-4-yl]hydrazone (**11a**): From **5a** and benzaldehyde (1.06 g, 10 mmol); colourless crystals (2.46 g, 75%), m.p. 208–211°C (lit.[24] m.p. 182°C). NMR (DMSO-d_6): δ_H 2.39 (s, 3H, Me), 2.49 (s, 3H, Me), 2.56 (s, 3H, SMe), 7.44 – 7.73 (m, 5H, Ph), 8.39 (s, 1H, N=CH), 10.21 (s, 1H, NH); δ_C 14.1 (Me), 14.45 (Me), 15.3 (Me), 114.5 (C5), 125.4 (C4a), 127.7 (C6), 128.5, 129.75, 130.5, 135.5 (Ph), 146.9 (C7a), 154.9 (C2), 165.4 (C4), 167.7 (N=CH).

4-bromobenzaldehyde [5,6-dimethyl-2-(methylthio)thieno[2,3-d] pyrimidin-4-yl]hydrazone (**11b**): From **5a** and 4-bromobenzaldehyde(1.85 g, 10 mmol); yellow crystals (2.80, 69%), m.p. 200–203°C. NMR (DMSO-d_6): δ_H 2.40 (s, 3H, Me), 2.48 (s, 3H, Me), 2.55 (s, 3H, SMe), 7.66 (s, 4H, ArH), 8.35 (s, 1H, N=CH), 10.30 (s, 1H, NH); δ_C 13.77 (Me), 14.1 (Me), 14.9 (Me), 114.05 (C5), 123.3 (C4a), 128.2 (C-6), 124.95, 130.1, 132.4, 134.3 (Ar), 145.2 (C7a), 154.25 (C2), 165.0 (C4), 167.2 (N=CH). Anal. calcd for $C_{16}H_{15}BrN_4S_2$ (407.30): C, 47.18; H, 3.70; N, 13.75. Found: C, 47.43; H, 3.95; N, 13.59%.

4-Fluorobenzaldehyde [5,6-dimethyl-2-(methylthio)thieno[2,3-d] pyrimidin-4-yl]hydrazone (**11c**): From **5a** (1.24 g, 10 mmol) and 4-fluorobenzaldehyde; colourless crystals (2.46 g, 71%), m.p.188–190°C. NMR (DMSO-d_6): δ_H 2.40 (s, 3H, Me), 2.49 (s, 3H, Me), 2.55 (s, 3H, SMe), 7.28-7.34 (m, 2H, Ar), 7.75–7.80 (m, 2H, ArH), 8.38 (s, 1H, N=CH), 10.24 (s, 1H, NH); δ_C 13.8 (Me), 14.1 (Me), 14.9 (SMe), 114.0 (C5), 125,0 (C4a), 128.1 (C6), 116.6, 129.35, 129.5, 131.5, 131.7, 161.7 (Ar), 145.4 (C7a), 154.35 (C2), 165.0 (C4), 167.1 (N=CH). Anal. calcd for $C_{16}H_{15}FN_4S_2$ (346.40): C, 55.49; H, 4.37; N, 16.20. Found: C, 55.88; H, 4.29; N, 16.46%.

4-Bromobenzaldehyde [2-(methylthio)-5,6,7,8-tetrahydro[1] benzothieno[2,3-d]pyrimidin-4-yl]hydrazone (**11d**): From **5b** (2.66 g, 10 mmol) and 4-bromobenzaldehyde (1.85 g, 10 mmol); pale yellow crystals (2.68, 62%), m.p. 141–143°C. NMR (DMSO-d_6): δ_H 1.82 (bs, 4H, $2CH_2$), 2.55 (s, 3H, SMe), 2.78 (bm, 2H, CH_2), 3.00 (bm, 2H, CH_2), 7.66 (s, 4H, ArH), 8.34 (s, 1H, N=CH), 10.17 (s, 1H, NH); δ_C 14.47 (Me), 23.0, 23.1, 25.9, 26.9 ($4CH_2$), 113.6 (C5), 123.65 (C4a), 127.5 (C6), 129.5, 131.1, 131.7, 132.8, 132.9, 134.7 (Ar), 145.6 (C7a), 154.6 (C2), 165.5 (C4), 168.3 (N=CH). Anal. calcd for $C_{18}H_{17}BrN_4S_2$ (433.34): C, 49.88; H, 3.95; N, 12.92. Found: C, 49.56 H, 3.68; N, 12.77%.

4-Fluorobenzaldehyde[2-(methylthio)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yl]hydrazone (**11e**): From **5b** (2.66 g, 10 mmol) and 4-fluorobenzaldehyde (1.24 g, 10 mmol); orange crystals (2.65 g, 71%), m.p. 200–201°C. NMR (DMSO-d_6): δ_H 1.82 (bm, 4H, $2CH_2$), 2.55 (s, 3H, SMe), 2.76 (bm, 2H, CH_2), 3.00 (bm, 2H, CH_2), 7.27–7.33 (m, 2H, ArH), 7.74–7.78 (m, 2H, ArH), 8.37 (s, 1H, N=CH), 10.08 (s, 1H, NH); δ_C 14.50 (Me), 23.0, 23.1, 25.9, 26.9 ($4CH_2$), 113.2 (C-5), 124.9 (C4a), 127.5 (C6), 116.7, 129.7, 131.6, 132.0, 132.1, 162.1 (Ar), 145.75 (C7a), 165.4 (C2), 165.5 (C4), 168.2 (N=CH). Anal. calcd for $C_{18}H_{17}FN_4S_2$ (372.34): C, 58.05; H, 4.59; N, 15.04. Found: C, 58.29; H, 4.89; N, 15.32%.

Synthesis of 3-aryl compounds **12a–c**: *general procedure*
Ferric chloride (0.4 g) in ethanol (5 ml) was added dropwise into a boiling solution of the aldehyde hydrazone **11** (2 mmol) in ethanol (50 ml). Heating was continued for 30 min and the mixture was then kept overnight at room temperature. Evaporation of the solvent under reduced pressure, washing the residue rapidly with water, and drying, afforded a solid product which could be recrystallised from ethanol.

8,9-Dimethyl-5-(methylthio)-3-phenylthieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**12a**): From **11a** (0.65 g, 2 mmol); colourless crystals (0.40 g, 62%), m.p. 215–217°C. NMR (DMSO-d_6): δ_H 2.48 (s, 3H, Me), 2.51 (s, 3H, Me), 2.61 (s, 3H, SMe), 7.53-7.71 (m, 5H, Ph); δ_C 12.9 (Me), 12.95 (SMe), 14.8 (Me), 116.3 (C9), 126.8 (C9a), 127.3 (C8), 127.6, 130.7, 131.5, 132.1 (Ph), 145.75 (C6a), 146.2 (C5), 146.7 (C10), 148.65 (C3). MS: *m/z* 326 (M^+). Anal. Calcd for $C_{16}H_{14}N_4S_2$ (326.40): C, 58.87; H, 4.32; N, 17.16; Found: C, 58.57; H, 4.65; N, 17.44%.

8,9-Dimethyl-3-(4-fluorophenyl)-5-(methylthio)thieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**12b**): From **11c** (0.67 g, 2 mmol); pale yellow crystals (0.42 g, 63%), m.p. 259–260°C. NMR (DMSO-d_6): δ_H 2.51 (s, 3H, Me), 2.64 (s, 3H, Me), 2.65 (s, 3H, SMe), 7.39 (m, 2H, ArH), 7.74 (m, 2H, ArH). Anal. Calcd for $C_{16}H_{13}FN_4S_2$ (344.28): C, 55.81; H, 3.81; N, 16.29; Found: C, 55.50; H, 4.11; N, 16.54%.

3-(4-Bromophenyl)-5-(methylthio)-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (**12c**): From **11d** (0.87 g, 2 mmol); pale yellow crystals (0.48 g, 55%), m.p. 187–190°C. NMR (DMSO-d_6): δ_H 1.91 (bm, 4H, $2CH_2$), 2.55 (s, 3H, SMe), 2.86 (bm, 2H, CH_2), 3.05 (bs, 2H, CH_2), 7.67 (d, 2H, ArH), 7.77 (d, 2H, ArH); δ_C 15.6 (Me), 22.4, 23.2, 25.3, 25.7 ($4CH_2$), 115.5 (C9), 125.2 (C9a), 127.2 (C8), 129.4, 131.3, 134.1, 135.5 (Ar), 145.3 (C6a), 146.7 (C5), 147.2 (C10), 150.2 (C3). Anal. Calcd for $C_{18}H_{15}BrN_4S_2$ (431.38): C, 50.12; H, 3.51; N, 13.01; Found: C, 50.43; H, 3.77; N, 13.29%.

5-Methoxy-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**13a**): Sodium metal (0.04 g, 1 mg-atom) was dissolved in absolute methanol (10 ml). The methylthio compound **6a** (0.25 g, 1 mmol) was added and the solution heated under reflux for 1 h and then allowed to stand 12 h at room temperature. The solid product obtained was filtered off, dried, and crystallised from ethanol as colourless crystals (0.16 g, 68%), m.p. 190–192°C. NMR (DMSO-d_6): δ_H 2.41 (s, 3H, Me), 2.50 (s, 3H, Me) 4.22, (s, 3H, OMe), 8.52 (s, 1H, N=CH). Anal. Calcd for $C_{10}H_{10}N_4OS$ (234.24): C, 51.27; H, 4.29; N, 23.92; Found: C, 51.49; H, 4.63; N, 23.81%.

5-Methoxy-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**13b**): Prepared from **6b** (0.28 g, 1 mmol) as described for **13a**; colourless crystals (0.18 g, 69%), m.p. 188–190°C. NMR (DMSO-d_6): δ_H 1.96 (bm, 4H, $2CH_2$), 2.87 (bm, 2H, CH_2), 3.13 (bm, 2H, CH_2), 4.34 (s, 3H, OMe), 8.34 (s, 1H, N=CH); δ_C 22.5, 23.4, 25.3, 25.4 ($4CH_2$), 57.1 (OMe), 116.0 (C9), 128.8 (C9a), 134.0 (C8), 147.3 (C6a), 150.7 (C5), 153.1 (C10), 154.65 (C2). MS: *m/z* 260 (M^+). Anal. calcd for $C_{12}H_{12}N_4OS$ (260.27): C, 55.37; H, 4.64; N, 21.52; Found: C, 55.56; H, 4.79; N, 21.77%.

5-Hydrazino-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**14a**): *Method A*: A mixture of **6a** (0.25 g, 1 mmol) and hydrazine hydrate (10 ml) was heated under reflux for 4 hours. The solid product that separated after cooling was filtered, dried and crystallised from ethanol to furnish colourless crystals (0.16 g, 68%), m.p. 258–260°C. NMR (DMSO-d_6): δ_H 2.48 (s, 3H, Me), 2.59 (s, 3H, Me), 4.67 (s, 2H, NH_2), 8.27 (s, 1H, N=CH), 8.88 (s, 1H, NH); δ_C 12.4 (Me), 12.5 (Me), 112.0 (C9), 125.4 (C9a), 126.2 (C8), 145.4 (C6a), 148.8 (C5), 153.2 (C10), 154.6 (C2). MS: *m/z* 234 (M^+). Anal. Calcd for $C_9H_{10}N_6S$ (234.26): C, 46.14; H, 4.30; N, 35.87; Found: C, 46.43; H, 4.49; N, 36.11%.

Method B: From the methoxy compound **13a** (0.23 g, 1 mmol) and hydrazine hydrate as described above: yield (0.17 g, 72%).
5-Hydrazino-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**14b**): From **6b** (0.28 g, 1 mmol) and hydrazine hydrate as described for **14a**; the product formed white leaflets (0.16 g, 62%), m.p. 244–247°C. NMR (DMSO-d_6): δ_H 1.86 (bm, 4H, $2CH_2$), 2.77 (bm, 2H, CH_2), 2.96 (bm, 2H, CH_2), 4.62 (s, 2H, NH_2), 8.49 (s, 1H, N=CH), 9.12 (s, 1H, NH). Anal. Calcd for $C_{11}H_{12}N_6S$ (260.28): C, 50.75; H, 4.64; N, 32.28; Found: C, 50.90; H, 4.37; N, 32.51%.

10,11-Dimethylthieno[3,2-e]bis[1,2,4]triazolo[4,3-a:1',5'-c]pyrimidine (**15**): Compound **14a** (0.23 g, 1 mmol) was heated in formic acid or triethyl orthoformate (10 ml)under reflux for 4 h. After cooling, the reaction mixture was poured into ice-water. The solid product that separated was collected and isolated by column chromatography, using 10% CH_2Cl_2/MeOH) as eluent to give colourless crystals (0.14 g, 57%), m.p. 297–300°C. NMR (DMSO-d_6): δ_H 2.50 (s, 3H, Me),2.56 (s, 3H, Me), 8.68 (s, 1H, N=CH), 9.64 (s, 1H, N=CH); δ_C 13.5 (Me), 13.6 (Me), 116.5 (C11), 128.8 (C11a), 130.8 (C10), 137.6 (C8a), 143.7 (C4a), 148.1 (C12), 154.9 (C2 + C7). MS: *m/z* 244 (M^+). Anal. Calcd for $C_{10}H_8N_6S$ (244.25): C, 49.17; H, 3.30; N, 34.40; Found: C, 49.43; H, 3.64; N, 34.16%.

7-Amino-10,11-dimethylthieno[3,2-e]bis[1,2,4]triazolo[4,3-a:1',5'-c]pyrimidine (**16**): The hydrazine **14a** (2.3 g, 10 mmol) and cyanogen bromide (1.06 g, 10 mmol) in 2N HCl (30 ml) were stirred at room temperature for 24 h. The solid product that separated was filtered off, washed with water, dried and crystallised from ethanol to furnish fine yellow crystals (1.97 g, 76%), m.p. 220–222°C. NMR (DMSO-d_6): δ_H 2.39 (s, 3H, Me), 2.49 (s, 3H, Me), 3.28 (bs, 2H, NH_2), 8.49 (s, 1H, N=CH). Anal. Calcd for $C_{10}H_9N_7S$ (259.26): C, 46.32; H, 3.49; N, 37.81; Found: C, 46.11; H, 3.13; N, 37.67%.

5-Azido-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**17**) *and 8,9-dimethyltetrazolo[1,5-a]thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine* (**18**): $NaNO_2$ (0.52 g) in water (3 ml) was added dropwise with stirring to an ice-cold solution of **14a** (1.15 g. 5 mmol) in conc. HCl (35%, 10 ml). Stirring was continued for 48 h at room temperature and then the mixture was poured into cold water. The solid formed was collected by filtration, dried and crystallised from ethanol as yellow fine crystals (0.16 g, 65%), m.p. 150–153°C. IR (KBr): ν_{max} 2162 (N_3), 1615 cm^{-1} (C=N and C=C). (**17**): NMR (DMSO-d_6): δ_H 2.43 (s, 3H, Me), 2.44 (s, 3H, Me), 8.57(s, 1H, N=CH); δ_C 13.1 (Me), 13.9 (Me), 118.9 (C9), 127.0 (C9a), 133.8 (C8), 140.8 (C6a), 150.2 (C5), 151.0 (C10), 155.1 (C2). (**18**): NMR (DMSO-d_6): δ_H 2.55 (s, 3H, Me), 2.56 (s, 3H, Me), 8.86 (s, 1H, N=CH); δ_C 13.3 (Me), 13.8 (Me), 118.9 (C11), 127.0 (C11a), 133.8 (C10), 140.8 (C8a), 150.2 (C4a), 151.0 (C12), 156.1 (C-). MS: *m/z* 245 (M^+). Anal. Calcd for $C_9H_7N_7S$ (245.24): C, 44.07; H, 2.87; N, 39.98; Found: C, 44.42; H, 2.57; N, 39.67%.

5-Methoxy-8,9-dimethyl-2-phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**19a**): This was prepared from **12a** (0.34 g, 1 mmol) as described in the formation of **13a**; colourless crystals (0.22 g, 71%), m.p. 200–202°C. NMR (DMSO-d_6): δ_H 2.42 (s, 3H, Me), 2.57 (s, 3H, Me), 4.22 (s, 3H, OMe),7.55 (m, 3H, Ph), 8.22 (m, 2H, Ph). Anal. Calcd for $C_{16}H_{14}N_4OS$ (310.33): C, 61.92; H, 4.54; N, 18.05; Found: C, 61.67; H, 4.84; N, 18.29%.

2-(4-Fluorophenyl)-5-methoxy-8,9-dimethylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**19b**): From **12b** (0.32 g, 1 mmol) as described for **13a**: colourless crystals (0.24 g, 73%), m.p. 190–192°C. NMR (DMSO-d_6): δ_H 2.42 (s, 3H, Me), 2.56 (s, 3H, Me), 4.22 (s, 3H, OMe), 7.35 (m, 2H, ArH), 8.23 (m, 2H, ArH). Anal. Calcd for $C_{16}H_{13}FN_4OS$ (328.22): C, 58.54; H, 3.98; N, 17.06; Found: C, 58.79; H, 3.70; N, 17.32%.

2-(4-Bromophenyl)-5-methoxy-8,9,10,11-tetrahydro[1]benzothieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**19c**): From **12c** (0.43 g, 1 mmol) as described for **19a**.; colourless crystals (0.29 g, 70%), m.p. 212–215°C. NMR (DMSO-d_6): δ_H 1.97 (bm, 4H, $2CH_2$), 2.87 (bm, 2H, CH_2), 3.19 (bm, 2H, CH_2), 4.35 (s, 3H, OMe), 7.62 (bd, 2H, ArH), 8.25 (bd, 2H, Ar-H). Anal. calcd for $C_{18}H_{15}BrN_4OS$ (415.26): C, 52.05; H, 3.63; N, 13.49; Found: C, 52.42; H, 3.37; N, 13.68%.

5-Hydrazino-8,9-dimethyl-2-phenylthieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**20**): Compound **12a** (0.32 g, 1 mmol) or **19a** (0.33 g, 1 mmol) was heated under reflux in ethanol (15 ml) containing hydrazine hydrate (2 ml) for 4 h. The solid product that separated on cooling was collected and recrystallised from ethanol as white leaflets (0.16 g, 52%), m.p. 245–248°C. NMR (DMSO-d_6): δ_H 2.41 (s, 3H, Me), 2.55 (s, 3H, Me), 4.65 (bs, 2H, NH_2), 7.57 (m, 3H, Ph), 8.28 (m, 2H, Ph), 9.09 (s, 1H, NH). Anal. Calcd for $C_{15}H_{14}N_6S$ (310.33): C, 58.05; H, 4.54; N, 27.07; Found: C, 57.85; H, 4.24; N, 27.42%.

Crystal structure determination
Compound **13b**, $C_{12}H_{12}N_4OS$, formed triclinic crystals which were examined at the X-ray Crystallography Unit of the N.R.C., Cairo. The data were handled, and all diagrams and calculations were performed, using maXus (Bruker Nonius, Delt & MacScience, Japan). One

molecule of the unit cell is shown in Fig. 1, and the bond lengths and angles are listed in Table 1. Fuller details can be obtained from the corresponding author.

The Danish International Development Agency (DANIDA) is gratefully acknowledged for financial support.

Received 16 February 2008; accepted 16 May 2008
Paper 08/5099 *doi:10.3184/030823408X327875*

References

1 E. Gillespie, K.W. Dungan, A.W. Gomol and R.J. Seidehamel, *Int. J. Immunopharmacol*., 1985, **7**, 655.
2 A.W. Gomol and D.L. Temple, *Drug Dev. Res*., 1987, **10**, 57.
3 C.J. Shishoo, V.S. Shirsath, I.S. Rathod and V.D. Yande, *Eur. J. Med. Chem*., 2000, **35**, 351.
4 C.J. Shishoo, V.S. Shirsath, I.S. Rathod, M.J. Patil and S.S. Bhargava, *Arzneim. Forsch*., 2001, **51**, 221.
5 K. Unverferth, *Pharmazie*, 1990, **45**, 545.
6 P.K. Russel, J.B. Press, R.A. Rampulla, J.J. McNally, R. Falotico, J.A. Keiser, D.A. Bright and A. Tobia, *J. Med. Chem*., 1988, **31**, 1786.
7 A. Cannito, M. Perrssin, C. Luu Duc, F. Huguet, C. Gaultier and G. Narcisse, *Eur. J. Med. Chem*., 1990, **25**, 635.
8 A. Santagati, M. Modica, M. Santagati, A. Caruso and V. Cutuli, *Pharmazie*, 1994, **49**, 64.
9 C.D. Patil, G.S. Sadana and K.D. Deadhar, *J. Indian Chem. Soc*., 1991, **68**, 169.
10 S. El-Bahaie and M.G. Assy, *Pharmazie*, 1990, **45**, 216.
11 M.N. Nasr and M.M. Gineinnah, *Arch. Pharm*., 2002, **335**, 289.
12 S. Sasaki, N. Cho, Y. Nara, M. Harada, S. Endo, N. Suzuki, S. Furuya and M. Fujino, *J. Med. Chem*., 2003, **46**, 113.
13 V.D. Patil, D.S. Vise, L.L. Worting, R.C. Bloomer and L.B. Townsend, *J. Med. Chem*., 1985, **28**, 423.
14 V.J. Ram, H.K. Pandey and A.J. Vietinek, *J. Heterocycl. Chem*., 1981, **18**, 1277.
15 R.P. Dickinson, A.W. Bell, C.A. Hitchcock, S. Narayana-Swami, S.J. Ray, K. Richardson and P.F. Troke, *Bioorg. Med. Chem. Lett*., 1996, **6**, 2031.
16 N. Ulusoy, A. Gursoy and G. Otuk, *Farmaco*, 2001, **56**, 947.
17 E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu and G. Altinok, *Farmaco*, 2002, **57**,101.
18 M.A. El-Sherbeny, M.B. El-Ashmawy, H.I. El-Subbagh, A.A. El-Emam and F.A. Badria, *Eur. J. Med. Chem*., 1995, **30**, 445.
19 M. Santagati, M. Modica, A. Santagati, F. Russo and S. Spampinato, *Pharmazie*, 1996, **51**, 7.
20 D.J. Brown and J.S. Harper, *J. Chem. Soc*., 1963, 1276.
21 A.A. Hamed, H.F. Badr and E.H. El-Ashry, *Z. Naturforsch*., 2001, **56B**, 826.
22 A.A. Hamed, I.F. Zeid, H.H. El-Ganzory and M.T. Abdel Aal, *Monatsh. Chem*., 2008, in press.
23 K. Gewald, E. Schinke and H. Bottcher, *Chem. Ber.,* 1966, **99**, 94.
24 A.M. Abdel-Fatah, A.S. Aly, F.A. Gad, N.A. Hassan and A.B.A. El-Gazzar, *Phosphorus, Sulfur, Silicon*, 1991, **60**, 223.
25 C.J. Shishoo, M.B. Devani, G.V. Ullas, S. Ananthar,and V.S. Bhadti, *J. Heterocycl. Chem.*, 1985, **22**, 83
26 C.J. Shishoo, M.B. Devani, G.V. Ullas, S. Ananthar and V.S. Bhadti, *J. Heterocycl. Chem.*, 1981, **18**, 43.
27 C.J. Shishoo, M.B. Devani, G.V. Ullas, S. Ananthar and V.S. Bhadti, *J. Heterocycl. Chem.*, 1985, **22**, 825.
28 N.V. Volkova, V.N. Konyukhov, T.G. Koksharova, L.G. Dianova and Z.V. Pushkareva, *Khim. Geterotsikl. Soedin*., 1979, 262.
29 M.H.B. Khandker, M. Rahman, K.H. Abdur Rahim, M.I. Hossain and M. Abu Nasser, *Acta Pharm*., 2006, **56**, 441.