Synthesis of Thieno[2,3-*d*]pyrimidines from 4,6-Dichloropyrimidine-5-carbaldehydes

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Several thieno[2,3-*d*]pyrimidines have been prepared by intramolecular cyclisation of 6-(substituted methylthio)-5-pyrimidinecarbaldehyde and carbonitrile intermediates derived from 6-chloropyrimidine-5-carbaldehydes and 5-carbonitriles and methyl thioglycolate or 5-formylpyrimidine-4-(3*H*)-thiones and appropriate α-halogeno compounds. Thienopyrimidines **18** and **5c** were nitrated to the corresponding nitro compounds **23** and **24**. Hydrolysis at position 4 of compound **18** also occurred during nitration. The ester **5g** was hydrolysed in base to the acid **25**.

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The majority of thieno[2,3-*d*]pyrimidines have been synthesised from thiophenes. Synthesis from pyrimidines includes cyclisation of intermediate 4-substituted methylthio-5-cyanopyrimidines [1-10], ethyl 4-substituted methylthiopyrimidine-5-carboxylates [11-13], 5-alkylhalo-4-mercapto- [14,15] and 4-mercapto-5-(phenylethynyl or trimethylsilylethynyl)pyrimidines [16-17], and, cyclodehydration of 4-acylmethylthio- [18,19], (5-acetyl or acetylmethyl-4-ethoxycarbonylmethylthio or mercapto- [20-22] and 4-hydroxy-5-ethylmercaptopyrimidines [23].

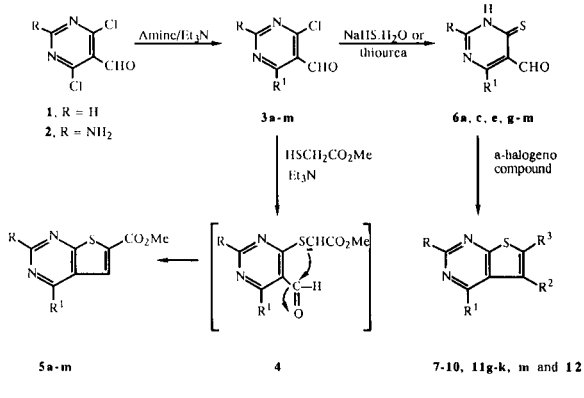
Our interest in thieno[2,3-*d*]pyrimidine synthesis emerges from the numerous reports on their diverse biological activities. We have converted several thieno[2,3-*d*]-pyrimidines into thieno[2,3-*d*:4,5-*d'*]dipyrimidines [24] and also studied their interaction with metals [25]. We now wish to elaborate on the synthesis of this ring system.

In a general strategy thieno[2,3-*d*]pyrimidines were prepared by building a thiophene ring around positions 5 and 6 of a suitably substituted pyrimidine by a Dieckmann type intramolecular process. 4,6-Dichloropyrimidine-5-carbaldehyde **1** [26] and 2-amino-4,6-dichloropyrimidine-5-carbaldehyde **2** [27] were used as starting materials for all thienopyrimidines synthesised. These starting materials were converted into five different types of pyrimidine precursors **3, 6, 13, 15** and **17** for cyclisation to thienopyrimidines as explained below.

Treatment of pyrimidines **1** and **2** with one molecular equivalent each of the appropriate amine and triethylamine resulted in the replacement of one of the two equivalent chlorine atoms to give the 4-substituted derivatives **3b-f, h-m** in high yields. Compound **3a** [30] was prepared by bubbling ammonia through a solution of **1** in dry benzene at 0° and compound **3g** [28] by treating **2** with a saturated solution of ethanolic ammonia at 0°. The remaining chlorine atom in each of the pyrimidines **3a-m** was replaced by a methoxycarbonylmethylthio group by reaction with one molecular equivalent of methyl thioglycolate and two of triethylamine in refluxing methanol. The reaction proceeded *via* a postulated intermediate **4** to give, after loss of water, the corresponding methyl thieno[2,3-*d*]pyrimidine-6-carboxylates **5a-m.**

Mercapto compounds of the general formula $HSCH_2R$ where R is electron withdrawing are rare. In order to vary

Scheme I

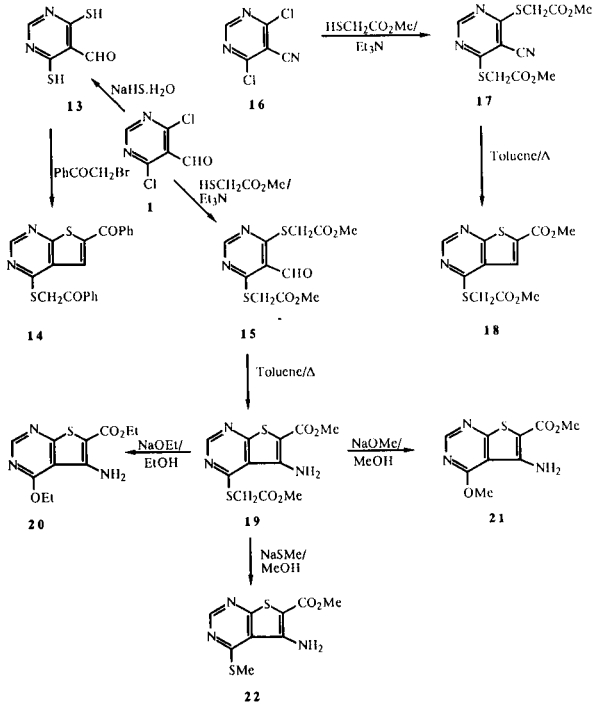


3a, 5a or 6a	R=H, R^1= NH_2	**7**	R=H, R^1=NH_2, R^2= H, R^3= CO_2Et
3b or 5b	R=H, R^1=NHMe	**8**	R=H, R^1= NHEt, R^2= H, R^3= COPh
3c, 5c or 6c	R=H, R^1=NMe_2	**9**	R=H, R^1= NMe_2, R^2= H, R^3= COPh
3d or 5d	R=H, R^1=NEtPh	**10**	R=R^1= $N(CH_2)_4$, R^2= H, R^3= COPh
3e, 5e or 6e	R=H, R^1=$N(CH_2)_4$	**11g**	R=R^1= NH_2, R^2= H, R^3= CN
3f or 5f	R=H, R^1=morpholino	**11h**	R=NH_2, R^1=NHEt, R^2=H, R^3=CN
3g, 5g or 6g	R=R^1= NH_2	**11i**	R=NH_2, R^1= NEt_2, R^2= H, R^3= CN
3h, 5h or 6h	R=NH_2, R^1=NHEt	**11j**	R=NH_2, R^1= NHPh, R^2= H, R^3= CN
3i, 5i or 6i	R=NH_2, R^1= NEt_2	**11k**	R=NH_2, R^1= NEtPh, R^2= H, R^3= C
3j, 5j or 6j	R=NH_2, R^1= NHPh	**11m**	R= NH_2, R^1= morpholino, R^2= H, R^3= CN
3k, 5k or 6k	R=NH_2, R^1= NEtPh	**12**	R = R^1= NH_2, R^2= H, R^3= $CONH_2$
3l or 5l	R=NH_2, R^1= $N(CH_2)_4$		
3m, 5m or 6m	R=NH_2, R^1= morpholino		

the 6-substituent of the thienopyrimidines synthesised so far, we used an alternative route which utilized the more readily available α-halogeno analogues (chloroacetamide, chloroacetonitrile, ethyl bromoacetate and phenacyl bromide) in the cyclisation step. Thus the pyrimidines **3a, c, e** and **g-m** were smoothly converted into the corresponding pyrimidine-4(3*H*)-thiones **6a, c, e** and **g-m** by stirring in a methanolic solution of sodium hydrogen sulphide or by treatment with thiourea. In a following step the thiones **6a, c, e,** and **g-k** and **m** were condensed and cyclised with the appropriate α-halogeno compound by warming for a few minutes is an aqueous solution of sodium carbonate. The resulting thienopyrimidines **7-10, 11g-k,m** and **12** were obtained in 60-81% yields (Scheme I).

The two routes to thieno[2,3-*d*]pyrimidines employed so far have a common initial step involving replacement of one of two identical chlorine atoms by another group. This works fairly well when the substituent introduced is an amino, alkylamino, or saturated cyclic amino group but it is difficult to introduce other groups such as single arylamino, hydroxy or methoxy group cleanly and in good yield. To overcome this both chlorine atoms of a dichloropyrimidine were replaced by methoxycarbonylmethylthio groups. After that one group was used to form a thiophen ring and the other used as a leaving group in nucleophilic substitution. In practice, the bis(methoxycarbonylmethylthio)aldehyde **15** was isolated by stirring at room temperature the dichloropyrimidine **1** with two molecular equivalents each of methyl thioglycolate and triethylamine for 30 minutes. Similarly, but after stirring for 2 days, 4,6-dichloropyrimidine-5-carbonitrile **16** [29] was converted into bis(methoxycarbonylmethylthio)carbonitrile **17**. Refluxing pyrimidines **15** and **17** in toluene containing base produced the cyclised products **18** and **19** respectively. The latter type of cyclisation forming a 5-amino-6-carbalkoxythienopyrimidine was first introduced by Santilli and coworkers [1]. We have extended this chemistry by substituting both chlorine atoms of 4,6-dichloropyrimidine-5-carbonitrile by methoxycarbonylmethylthio groups prior to cyclisation (Scheme II).

Scheme II



In an earlier paper [24] we showed that the methoxycarbonylmethylthio group of compound **19** can be selectively displaced with amines. Here we tested if the same applies for ethoxide, methoxide and methanethiolate anions. Reaction of compound **19** with these nucleophiles gave derivatives **20-22**, respectively. Derivative **22** was obtained by simply stirring compound **19** in a methanolic solution of sodium methanethiolate at room temperature. However, at this temperature, compound **19** did not react with sodium ethoxide/ethanol or sodium methoxide/methanol, but on heating to reflux, the transesterified 4-ethoxy derivative **20** and the 4-methoxy derivative **21** were formed, respectively (Scheme II).

The principle of preparing a pyrimidine ring with two substituted methylthio groups and using one to provide a thiophene ring and the other as a leaving group was further investigated. Dichloropyrimidine **1** was converted into the dimercaptopyrimidine **13** which was condensed and cyclised with phenacyl bromide to yield the thienopyrimidine **14**. To our surprise compound **14** was inert to nitrogen, oxygen and sulfur nucleophiles under conditions where displacement of the methoxycarbonylmethylthio group of compound **19** occurred. It is possible that the bulky phenacylthio group causes steric hinderance to nucleophilic substitution.

Thienopyrimidine **18** was nitrated to the 5-nitro-4(3*H*)-one derivative **23** whereas under similar conditions thieno-

Scheme III

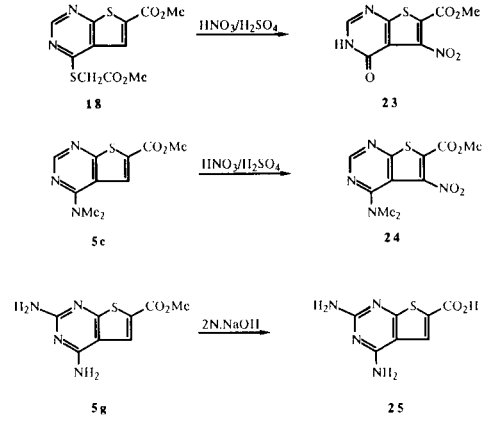
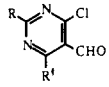


Table I

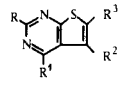
4-(Amino or substituted amino)-6-chloropyrimidine-5-carbaldehydes



R	R^1	Compound	Yield %	Mp °C	Recrystallisation Solvent	Molecular Formula	Analyses % Calcd./Found		
							C	H	N
H	NHMe	**3b**	75	158-159	propan-2-ol	$C_6H_6ClN_3O$	42.00 41.93	3.52 3.41	24.49 24.38
H	NMe_2	**3c**	80	139-141	propan-2-ol	$C_7H_8ClN_3O$	45.30 45.01	4.34 4.28	22.36 22.64
H	NEtPh	**3d**	80	117-119	propan-2-ol	$C_{13}H_{12}ClN_3O$	59.66 59.49	4.62 4.51	16.06 15.91
H	$N(CH_2)_4$	**3e**	80	116-117	propan-2-ol	$C_9H_{10}ClN_3O$	51.10 51.07	4.76 4.83	19.86 19.81
H	morpholino	**3f**	95	93-94	ethanol	$C_9H_{10}ClN_3O_2$	47.48 47.53	4.43 4.48	18.46 18.28
NH_2	NHEt	**3h**	70	174-176	propan-2-ol	$C_7H_9ClN_4O$	41.91 42.08	4.52 4.68	27.97 27.95
NH_2	NEt_2	**3i**	70	134-137	toluene	$C_9H_{13}ClN_4O$	47.27 47.67	5.73 5.75	24.50 24.60
NH_2	NHPh	**3j**	60	205-207	propan-2-ol	$C_{11}H_9ClN_4O$	53.14 53.01	3.65 3.61	22.53 22.48
NH_2	NEtPh	**3k**	70	166-169	toluene	$C_{13}H_{13}ClN_4O$	56.42 56.75	4.73 4.90	20.25 19.92
NH_2	$N(CH_2)_4$	**3l**	75	181-184	toluene	$C_9H_{11}ClN_4O$	47.69 47.66	4.89 4.86	24.72 24.92
NH_2	morpholino	**3m**	80	173-174	propan-2-ol	$C_9H_{11}ClN_4O_2$	44.45 44.44	4.57 4.67	23.09 23.01

Table II

Thieno[2,3-d]pyrimidines from 6-chloropyrimidine-5-carbaldehydes



Compound	R	R^1	R^2	R^3	Yield %	Mp °C	Recrystallisation Solvent	Method/ reflux time (hours)	Molecular Formula	Analyses % Calcd./Found		
										C	H	N
5a	H	NH_2	H	CO_2Me	30	250-253	dimethylformamide	A/10	$C_8H_7N_3O_2S$	45.92 45.59	3.37 3.41	20.08 20.13
5b	H	NHMe	H	CO_2Me	80	240-241	methanol	A/10	$C_9H_9N_3O_2S$	48.42 48.18	4.06 4.13	18.82 19.11
5c	H	NMe_2	H	CO_2Me	78	206-208	petroleum ether (b.p. 100-120°)	A/10	$C_{10}H_{11}N_3O_2S$	50.32 50.62	4.61 4.67	18.02 17.71
5d	H	NEtPh	H	CO_2Me	89	179-180	petroleum ether (b.p. 100-120°)	A/10	$C_{16}H_{15}N_3O_2S$	61.56 61.32	4.97 4.82	13.48 13.41
5e	H	$N(CH_2)_4$	H	CO_2Me	90	195-197	petroleum ether (b.p. 100-120°)	A/10	$C_{12}H_{13}N_3O_2S$	54.71 54.74	5.03 4.98	16.08 15.96
5f	H	morpholino	H	CO_2Me	70	150-151	petroleum ether (b.p. 100-120°)	A/10	$C_{12}H_{13}N_3O_3S$	51.54 51.60	4.73 4.69	14.81 15.04
5g	NH_2	NH_2	H	CO_2Me	68	270(dec)	dimethyl sulfoxide-water	A/10	$C_8H_8N_4O_2S$	51.41 42.81	3.60 3.69	25.00 25.08
5h	NH_2	NHEt	H	CO_2Me	71	228-229	methanol	A/24	$C_{10}H_{12}N_4O_2S$	47.61 47.58	4.80 4.44	22.21 22.45
5i	NH_2	NEt_2	H	CO_2Me	70	170-173	propan-2-ol	A/24	$C_{12}H_{16}N_4O_2S$	45.92 51.47	5.75 5.89	19.98 19.98
5j	NH_2	NHPh	H	CO_2Me	65	177(dec)	dimethyl sulfoxide-water	B/10	$C_{14}H_{12}N_4O_2S$	55.99 56.02	4.03 4.00	18.65 18.67
5k	NH_2	NEtPh	H	CO_2Me	60	206-208	toluene	B/10	$C_{16}H_{16}N_4O_2S$	58.52 58.58	4.91 4.76	17.06 16.91
5l	NH_2	$N(CH_2)_4$	H	CO_2Me	40	273(dec)	dimethyl sulfoxide	B/10	$C_{12}H_{14}N_4O_2S$	51.78 51.36	5.07 5.14	20.13 20.09
5m	NH_2	morpholino	H	CO_2Me	83	210-213	toluene	B/10	$C_{12}H_{14}N_4O_2S$	48.97 48.93	4.79 4.53	19.03 19.09

pyrimidine **5c** gave the expected 5-nitro derivative **24**. Methyl 2,4-diaminothieno[2,3-*d*]pyrimidine-6-carboxylate **5g** was hydrolysed in base to the corresponding acid **25** (Scheme III).

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The ir spectra were recorded as Nujol mulls between sodium chloride discs on a Perkin-Elmer 297 spectrometer. The pmr spectra were measured in deuteriochloroform and/or dimethyl sulfoxide-d_6 solutions on a Perkin-Elmer R32 or a Varian EM 390A instrument, using tetramethylsilane as an internal standard. Mass spectral measurements were recorded on a Kratos MS 30 spectrometer using an ionisation energy of 70 eV and introduction by direct insertion probe. Tlc was performed on Fluka silica gel aluminium cards. Microanalyses were performed by Butterworth Laboratories Ltd, Teddington, Middlesex, England.

General Procedure for the Preparation of 4-(Amino or substituted amino)-6-chloropyrimidine-5-carbaldehydes **3b-f** and **h-m**.

To a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde

[26] **1** (3.46 g, 20 mmoles) in chloroform (250 ml) at 0°, were added dropwise triethylamine (2.02 g, 20 mmoles) and the appropriate amine (20 mmoles). Stirring was continued at room temperature for 8 hours and then the reaction mixture was filtered, washed with brine (3 x 80 ml), dried over anhydrous sodium sulphate, filtered and concentrated to afford a solid. The pyrimidines **3b-f** were purified by recrystallisation (Table I).

In a similar manner, 2-amino-4,6-dichloropyrimidine-5-carbaldehyde [27] **2** (3.84 g, 20 mmoles) in chloroform with triethylamine (2.02 g, 20 mmoles) and the appropriate amine (20 mmoles) was converted into the pyrimidines **3h-m** (Table I).

The pyrimidines **3a** and **3g** were prepared by known procedures [30,28].

General Procedures A and B for the Preparation of 4-(Amino or substituted amino)thieno[2,3-*d*]pyrimidine-6-carboxylates **5a-m**.

Procedure A.

Methyl thioglycolate (0.74 g, 7 mmoles) and triethylamine (1.41 g, 14 mmoles) were added dropwise to a suspension of the appropriate 4-(amino or substituted amino)-6-chloropyrimidine-5-carbaldehyde **3** (7 mmoles) in methanol (50 ml). The mixture was refluxed to give a clear solution within 15 minutes, then refluxing was continued for 10 or 24 hours. The solvent was evaporated under reduced pressure to near dryness and the residue stirred with cold water (20 ml) for a few minutes. The product was filtered off, washed with water, dried and recrystallised from a suitable solvent (Table II).

Procedure B.

As in Procedure A except that the precipitated product was filtered off, washed with water, dried, and recrystallised from a suitable solvent (Table II).

General Procedures C and D for the Preparation of Pyrimidine-4(3*H*)-thiones **6a,c,e,g-k** and **m**.

Procedure C.

To a stirred suspension of the appropriate 4-(amino or substituted amino)-6-chloropyrimidine-5-carbaldehyde **3** (5 mmoles) in methanol (30 ml) at room temperature was added dropwise a solution of sodium hydrogen sulphide monohydrate (0.74 g, 10 mmoles) in methanol (40 ml). The temperature of the mixture was raised to the boiling point and kept there with stirring for 1 hour. The solvent was evaporated *in vacuo* and the residue dissolved in water (25 ml) and filtered. The clear solution was acidified with 4*N*-acetic acid to give the free thione, which was left to stand overnight, filtered off, washed with water, and dried. The product was purified by dissolving it in 2*N*-sodium hydroxide, filtering, then acidifying with 4*N*-acetic acid (Table III).

Procedure D.

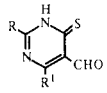
The appropriate 4-(amino or substituted amino)-6-chloropyrimidine-5-carbaldehyde **3** (5 mmoles) and thiourea (10 mmoles) were heated under reflux in 80% aqueous ethanol (100 ml) for 3 hours. The reaction mixture was left to stand at room temperature overnight, the solid filtered off, washed with ethanol and then added portionwise to a stirred solution of sodium hydroxide (0.8 g, 20 mmoles) in water (20 ml). The resulting mixture was heated at 60° for 1 hour, cooled, and the clear solution acidified with 4*N*-acetic acid. The free thione was filtered off, washed with water, and dried. The product was purified as in Procedure C (Table III).

General Procedure for Reaction of Pyrimidine-4(3*H*)-thiones **6a,c,e,g-k** and **m** with α-Halogeno Compounds.

The appropriate 5-formylpyrimidine-4(3*H*)-thione **6** (3 mmoles) was dissolved in a solution of anhydrous sodium carbonate (1 g, 9 mmoles) in water (25 ml). The mixture was warmed to 50°, then while stirring, the appropriate α-halogeno compound (chloroacetamide, chloroacetonitrile, ethyl bromoacetate or phenacyl bromide) (3 mmoles) was added dropwise. Precipitation occurred within a few minutes and the reaction mixture was left to stir at room temperature for 10 minutes before filtering. The collected solid was washed with water, cold ethanol, diethyl ether and dried. It was then recrystallised from a suitable solvent. Thienopyrimidines **7-10**, **11g-k,m** and **12** were prepared in this manner (Table IV).

Table III

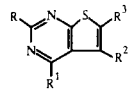
6-(Amino or substituted amino)-5-formylpyrimidine-4(3H)-thiones



Compound	R	R^1	Procedure	Yield %	Mp °C	Molecular Formula	Analyses % Calcd. / Found		
							C	H	N
6a	H	NH_2	C	80	240(dec)	$C_5H_5N_3OS$	38.70 38.52	3.25 3.38	27.08 26.83
6c	H	NMe_2	D	63	230-233	$C_7H_9N_3OS$	45.89 45.56	4.95 5.23	22.93 22.68
6e	H	$N(CH_2)_4$	D	77	200-202	$C_9H_{11}N_3OS$	51.66 51.52	5.30 5.46	20.08 19.91
6g	NH_2	NH_2	C	65	173-176	$C_5H_6N_4OS$	35.29 35.04	3.55 3.67	35.91 35.75
6h	NH_2	NHEt	C	75	265(dec)	$C_7H_{10}N_4OS$	42.41 42.57	5.08 5.35	28.26 28.51
6i	NH_2	NEt_2	C	60	167(dec)	$C_9H_{14}N_4OS$	47.77 47.84	6.23 6.32	24.76 24.50
6j	NH_2	NHPh	C	65	227-229	$C_{11}H_{10}N_4OS$	53.64 53.46	4.09 4.30	22.75 22.93
10k	NH_2	NEtPh	C	85	112(dec)	$C_{13}H_{14}N_4OS$	56.91 56.77	5.14 5.18	20.42 20.56
6l	NH_2	$N(CH_2)_4$	C	65	198(dec)	$C_9H_{12}N_4OS$	48.20 48.27	5.39 5.55	24.98 24.90
6m	NH_2	morpholino	C	95	157(sub)	$C_9H_{12}N_4O_2S.1/2H_2O$	43.18 42.97	5.23 5.35	22.39 22.43

Table IV

Thieno[2,3-d]pyrimidines from 5-formylpyrimidine-4(3H)-thiones



Compound	R	R^1	R^2	R^3	Yield %	Mp °C	Recrystallisation Solvent	Molecular Formula	Analyses % Calcd./Found		
									C	H	N
7	H	NH_2	H	CO_2Et	40	260 (dec)	ethanol	$C_9H_9N_3O_2S$	48.43 48.35	4.04 4.24	18.84 18.71
8	H	NHEt	H	COPh	80	180-181	ethanol	$C_{15}H_{13}N_3OS$	63.58 63.42	4.62 4.73	14.83 15.06
9	H	NMe_2	H	COPh	78	175-176	ethanol	$C_{15}H_{13}N_3OS$	63.58 63.82	4.62 4.51	14.83 15.02
10	H	$N(CH_2)_4$	H	COPh	90	190-192	ethanol	$C_{17}H_{15}N_3OS$	66.00 65.81	4.89 4.73	13.58 13.66
11g	NH_2	NH_2	H	CN	70	273-274	dimethyl sulfoxide water	$C_7H_5N_5S$	43.97 44.14	2.64 2.70	36.62 36.48
11h	NH_2	NHEt	H	CN	60	222-227	toluene	$C_9H_9N_5S$	49.30 49.40	4.14 4.13	31.94 31.73
11i	NH_2	NEt_2	H	CN	65	162.5-164	methanol	$C_{11}H_{13}N_5S$	53.42 53.42	5.30 5.23	28.32 28.24
11j	NH_2	NHPh	H	CN	75	281-284	methanol	$C_{13}H_9N_5S$	58.41 58.50	3.39 3.44	26.20 26.43
11k	NH_2	NEtPh	H	CN	70	288-289	propan-1-ol	$C_{11}H_{11}N_5S$	53.86 53.86	4.52 4.42	28.55 28.49
11m	NH_2	morpholino	H	CN	75	280-282	methanol	$C_{11}H_{11}N_5OS$	50.56 50.69	4.24 4.36	26.80 26.87
16	NH_2	NH_2	H	$CONH_2$	81	350(dec)	dimethyl sulfoxide water	$C_7H_7N_5OS$	40.18 40.13	3.37 3.21	33.47 33.43

Table V

IR and PMR of selected Pyrimidines

Compound	IR (cm-1)	PMR (δ)
3h	3200, 3350 (NH), 1680 (CO)	1.15 (t, 3H, Me, J = 8 Hz), 3.28-3.65 (m, 2H, CH_2), 7.40-7.80 (bs, 2H, NH_2), 8.95-9.25 (s, 1H, NH), 9.89 (s, 1H, CHO)
3i	3380, 3340, 3200 (NH), 1640 (CO)	1.13 (t, 6H, 2 x Me, J = 8 Hz), 3.45 (q, 4H, 2 x CH_2, J = 8 Hz), 7.00-7.80 (bs, 2H, NH_2), 9.90 (s, 1H, CHO)
3j	3450, 3300, 3150 (NH), 1640 (CO)	7.00-7.90 (m, 5H, Ph), 7.70-8.20 (bs, 2H, NH_2), 9.95 (s, 1H, CHO), 11.10-11.30 (bs, 1H, NH)
3m	3360, 3200 (NH), 1640 (CO)	3.35-3.58 (m, 4H, CH_2NCH_2), 3.58-3.80 (m, 4H, CH_2OCH_2), 7.20-7.80 (bs, 2H, NH_2), 9.86 (s, 1H, CHO)
6c	3150 (NH), 1670 (CO)	3.10 (s, 6H, 2 x Me), 7.95 (d, 1H, H-2, J = 4 Hz), 10.40 (s, 1H, CHO), 13.65-14.00 (bs, 1H, NH)
6g	3450, 3250 (NH), 1710 (CO)	7.50-8.20 (bs, 2H, NH_2), 8.70-9.20 (bs, 2H, NH_2), 10.33 (s, 1H, CHO), 10.95-11.60 (bs, 1H, NH)
6h	3300, 3240, 3100 (NH), 1660 (CO)	1.12 (t, 3H, Me), 3.20-3.65 (m, 2H, CH_2), 6.50-8.20 (bs, 2H, NH_2), 9.50-9.90 (bs, 1H, NH), 10.30 (s, 1H, CHO), 11.10-11.40 (bs, 1H, NH).
6j	3400, 3150 (NH), 1660 (CO)	7.00-7.90 (m, 5H, Ph), 7.35-8.70 (bs, 2H, NH_2), 10.39 (s, 1H, CHO), 11.40-11.80 (bs, 1H, NH), 11.60-11.98 (bs, 1H, NH)
6l	3350, 3200 (NH), 1660 (CO)	1.70-2.00 (m, 4H, CH_2CH_2), 3.00-3.80 (m, 4H, CH_2NCH_2), 6.50-6.70 (bs, 2H, NH_2), 10.33 (s, 1H, CHO), 11.05-11.35 (bs, 1H, NH)
6m	3350, 3200 (NH), 1640 (CO)	3.40-3.80 (m, 8H, morpholino), 6.80-7.60 (bs, 2H, NH_2), 10.20 (s, 1H, CHO), 11.00-11.60 (bs, 1H, NH)

[a] Spectra of all above compounds measured in dimethyl sulfoxide-d_6 [b] All signals intergrated for the correct number of protons.

4,6-Dimercaptopyrimidine-5-carbaldehyde (**13**).

4,6-Dichloropyrimidine-5-carbaldehyde **1** (6.01 g, 34 mmoles) in methanol (40 ml) was treated with a solution of sodium hydrogen sulfide monohydrate (10.10 g, 136 mmoles) in methanol (200 ml) as described in Procedure C. The product was purified further by reprecipitation from an *N,N*-dimethylformamide solution (10 ml) by addition of water (5 ml) to give 6.04 g (43%) of **13** as pale yellow powder, mp >215° dec; ir: 1680 cm^{-1} (CO).

Anal. Calcd. for $C_5H_4N_2OS_2$: C, 34.87; H, 2.34; N, 16.26. Found: C, 34.73; H, 2.27; N, 15.92.

6-Benzoyl-4-phenacylthiothieno[2,3-*d*]pyridine (**14**).

To a stirred solution of 4,6-dimercaptopyrimidine-5-carbaldehyde **13** (3.90 g, 10 mmoles) in methanol (40 ml) and triethylamine (5.0 g, 50 mmoles) at room temperature, was added dropwise a solution of phenacyl bromide (9.95 g, 50 mmoles) in methanol (10 ml). The mixture was stirred for 2 hours and the precipitated solid filtered off washed with water, methanol and dried. Recrystallisation from methanol gave 7.23 g (82%) of **14** as yellow needles, mp 160-161°; ir: 1730 cm^{-1} (CO) broad; pmr (dimethyl sulfoxide-d_6): δ 3.93 (s, 2H, CH_2), 5.63 (s, 1H, H-5), 6.67 (s, 1H, H-2), 7.13-7.82 (m, 10H, 2 x Ph); ms: m/z 390 (M^+).

Anal. Calcd. for $C_{21}H_{14}N_2O_2S_2$: C, 64.59; H, 3.61; N, 7.17. Found: C, 64.74; H, 3.43; N, 7.35.

4,6-Bis(methoxycarbonylmethylthio)pyrimidine-5-carbaldehyde (**15**).

To a solution of 4,6-dichloropyrimidine-5-carbaldehyde **1** (4 g, 22 mmoles) in dioxane (25 ml), were added triethylamine (2.53 g, 25 mmoles) and methyl thioglycolate (2.33 g, 22 mmoles). The reaction mixture was stirred at room temperature for 30 minutes, and then treated with cold water. The precipitated solid was filtered off, washed with water, dried, and recrystallised from petroleum ether (bp 100-120°) to give 6.32 g (88%) of **15** as off white needles, mp 120-121°; ir: 1745 (ester CO); 1690 cm^{-1} (formyl CO); pmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ 3.75 (s, 6H, 2 x

Table VI

IR and PMR of selected Thieno[2,3-d]pyrimidines

Compound	IR (cm-1)	PMR (δ)
5b	3180 (NH), 1735 (CO)	3.00 (s, 3H, OMe), 3.08 (d, 3H, NMe, J = 6 Hz), 7.80-8.00 (bs, 1H, NH), 8.35 (s, 1H, H-5), 8.45 (s, 1H, H-2)
5c	1725 (CO)	3.20 (s, 3H, NMe), 3.42 (s, 3H, NMe), 3.85 (s, 3H, OMe), 7.96 (s, 1H, H-5), 8.10 (s, 1H, H-2)
5d	1715 (CO)	1.30 (t, 3H, Me, J = 7 Hz), 3.70 (s, 3H, OMe), 4.03 (q, 2H, CH_2, J = 7 Hz), 6.00 (s, 1H, H-5), 7.10-7.51 (m,5H, Ph), 8.50 (s, 1H, H-2)
5g	3450, 3400, 3300, 3100 (NH),	3.84 (s, 3H, OMe), 6.30-6.65 (bs, 2H, NH_2-2), 7.10-7.55 (bs, 2H, NH_2-4), 8.25 (s, 1H, H-5) 1680 (CO)
5i	3490, 3380, 3280, 3150 (NH),	1.18 (t, 3H, Me, J = 8 Hz), 3.25-3.65 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 6.40-6.65 (bs, 2H, NH_2), 7.70-1680 (CO)7.95 (bs, 1H, NH), 8.25 (s, 1H, H-5)
5k	3425, 3325, 3225 (NH),	1.18 (t, 3H, Me, J = 8 Hz), 3.65 (s, 3H, OMe), 4.04 (q, 2H, CH_2, J = 8 Hz), 5.90 (s, 1H, H-5), 6.50-6.90 (bs, 1720 (CO)2H, NH_2), 7.25-7.70 (m, 5H, Ph)
5l	3450, 3300, 3160 (NH),	2.15-2.58 (m, 4H, CH_2CH_2), 3.90-4.41 (m, 4H, CH_2NCH_2), 4.11 (s, 3H, OMe), 8.48 (s, 1H, H-5), 1690 (CO) 11.00-12.50 (bs, 2H, NH_2)
5m	3450, 3375, 3340 (NH),	3.60-3.90 (m, 8H, morpholino), 3.82 (s, 3H, OMe), 6.55-6.70 (bs, 2H, NH_2), 8.02 (s, 1H, H-5) 1720 (CO)
7	3420, 3340 (NH), 1700 (CO)	1.45 (t, 3H, Me, J = 7 Hz), 4.35(q, 2H, CH_2, J = 7 Hz), 7.88 (s, 1H, H-5), 8.35 (s, 1H, H-2), 4.08 (bs, 2H, NH_2)
8	1680 (CO)	1.28 (t, 3H, Me, J = 7 Hz), 3.10 (s, 1H, NH), 3.45-3.65 (m, 2H, CH_2), 7.45-7.95 (m, 5H, Ph), 8.28 (s, 1H, H-5), 8.40 (s, 1H, H-2)
9	1685 (CO)	3.35 (s, 6H, 2 x Me), 7.20-7.80 (m, 5H, Ph), 7.95 (s, 1H, H-5), 8.40 (s, 1H, H-2)
10	1680 (CO)	1.95-2.18 (m, 4H, CH_2CH_2), 3.65-3.85 (m, 4H, CH_2NCH_2), 7.48-7.75 (m, 5H, Ph), 7.93 (s, 1H, H-5), 8.42 (s, 1H, H-2)
11g	3450, 3340, 3150, 3080,	6.20-6.90 (bs, 2H, NH_2-2), 7.05-7.80 (bs, 2H, NH_2-4) 8.14 (s, 1H, H-5)(NH), 2200 (CN)
11h	3500, 3350, 3280, 3125 (NH),	1.19 (t, 3H, Me, J = 8 Hz), 3.47 (q, 2H, CH_2, J = 8 Hz), 6.40-7.00 (bs, 2H, NH_2), 7.70-8.00 (bs, 1H, 2200 (CN) NH), 8.14 (s, 1H, H-5)
11j	3640, 3350, 3275, 3150 (NH),	6.77-7.20 (bs, 2H, NH_2), 7.05-8.00 (m, 5H, Ph), 8.45 (s, 1H, H-5), 9.35-9.60 (bs, 1H, NH) 2200 (CN)
11l	3400, 3300, 3180 (NH),	1.80-2.10 (m, 4H, CH_2CH_2), 3.51-3.85 (m, 4H, CH_2NCH_2), 6.40-6.82 (bs, 2H, NH_2), 8.25 (s, 1H, H-5) 2200 (CN)
11m	3430, 3300, 3160 (NH),	3.60-3.90 (m, 8H, morpholino), 6.65-6.85 (bs, 2H, NH_2), 8.33 (s, 1H, H-5) 2200 (CN)
12	3475, 3450, 3425, 3340,	6.05-6.65 (bs, 2H, NH_2-2), 6.85-7.40 (bs, 2H, NH_2-4), 7.20-7.80 (bs, 2H, $CONH_2$), 7.88 (s, 1H, H-5) 3140 (NH), 1660 (CO)

[a] Pmr spectra of compounds **5d** and **7-10** measured in deuteriochloroform, spectra of **5c, g, k** and **m,11g, h, j, l** and **m** and **12** measured in dimethyl sulfoxide-d_6. spectrum **5b** measured in deuteriochloroform with few drops of dimethyl sulfoxide-d_6 and spectrum **5l** measured in deuteriotrifluoroacetic acid.

OMe), 4.05 (s, 4H, 2 x SCH_2), 8.70 (s, 1H, H-2), 10.62 (s, 1H, CHO); ms: m/z 316 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S_2$: C, 41.76; H, 3.82; N, 8.86. Found: C, 41.92; H, 3.76; N, 8.82.

4,6-Bis(methoxycarbonylmethylthio)pyrimidine-5-carbonitrile (**17**).

To a solution of 4,6-dichloropyrimidine-5-carbonitrile **16** [29] (3.20 g, 10 mmoles) was added methyl thioglycolate (2.12 g, 20 mmoles). The reaction mixture was stirred at room temperature for 2 days and then evaporated to dryness. The residue was treated with water (50 ml) and stirred for a few minutes. The insoluble material was filtered, dried, and recrystallised from toluene to give 2.5 g (43%) of **17** as off white needles, mp 158-160°; ir: 2215 (CN), 1740 cm^{-1} (CO); pmr (deuteriochloroform): δ 3.80 (s, 6H, 2 x OMe), 4.10 (s, 4H, 2 x CH_2), 8.73 (s, 1H, H-2); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S_2$: C, 42.16; H, 3.54; N, 13.41. Found: C, 42.21; H, 3.58; N, 13.47.

General Procedure for Cyclisation of Pyrimidines **15** and **17**.

The pyrimidines **15** and **17** (5 mmoles) and triethylamine (0.5 g, 5 mmoles) in dry toluene (30 ml) were heated under reflux for 4 hours. After cooling the insoluble material was filtered off, dried, and then suspended in water (30 ml), stirred for a few minutes, filtered, and dried to give **18** or **19** in 67 and 78% yields, respectively.

4-Carboxymethylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, 4,6-Dimethyl Ester (**18**).

This compound was obtained as off white needles (toluene), mp 143-144°; ir: 1745 cm^{-1} (CO); pmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ 3.75 (s, 3H, OMe), 3.98 (s, 3H, OMe-4), 4.15 (s, 2H, SCH_2), 7.95 (s, 1H, H-5), 8.75 (s, 1H, H-2); ms: m/z 298 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S_2$: C, 44.29; H, 3.54; N, 9.39. Found: C, 44.41; H, 3.43; N, 9.52.

5-Amino-4-carboxymethylthiothieno[2,3-*d*]pyrimidine-6-carboxylic Acid, 4,6-Dimethyl Ester (**19**).

This compound was obtained as pale yellow needles (toluene), mp 171-173°; ir: 3460, 3350 (NH), 1750, 1690 cm^{-1} (CO); pmr (dimethyl sulfoxide-d_6): δ 3.67 (s, 3H, OMe-4), 3.78 (s, 3H, Me-4), 3.87 (s, 2H, SCH_2), 6.70-6.91 (bs, 1H, NH_2), 8.75 (s, 1H, H-2); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O_4S_2$: C, 42.16; H, 3.54; N, 13.41. Found: C, 42.23; H, 3.51; N, 13.49.

Reaction of Methyl 5-Amino-4-methoxycarbonylmethylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (**19**) with Sodium Ethoxide, Sodium Methoxide and Sodium Methanethiolate.

Ethyl 5-amino-4-ethoxythieno[2,3-*d*]pyrimidine-6-carboxylate (**20**).

A solution of compound **19** (1.25 g, 4 mmoles) and sodium (0.28 g, 12 mmoles) in dry ethanol (25 ml) was heated under reflux for 10 minutes. Upon cooling the precipitated solid was filtered off, washed with water and crystallised from ethanol to give 0.95 g (89%) of **20** as off white needles, mp 127-128°; ir: 3440, 3335 (NH), 1680 cm^{-1} (CO); pmr (dimethyl sulfoxide-d_6): δ 1.25 (t, 3H, ester Me, J = 7 Hz), 1.30 (t, 3H, ether Me, J = 7 Hz), 3.96 (q, 2H,

ether CH_2, J = 7 Hz), 4.20 (q, 2H, ester CH_2, J = 7 Hz), 6.46-6.60 (bs, 2H, NH_2), 8.55 (s, 1H, H-2); ms: m/z 267 (M^+).

Anal. Calcd. for $C_{11}H_{13}N_3O_3S$: C, 49.43; H, 4.90; N, 15.72. Found: C, 48.98; H, 4.94; N, 15.63.

Methyl 5-Amino-4-methoxythieno[2,3-*d*]pyrimidine-6-carboxylate (**21**).

A solution of compound **19** (0.94 g, 3 mmoles) and sodium (0.21 g, 9 mmoles) in dry methanol (20 ml) was heated under reflux for 10 minutes. The precipitated solid was filtered off, washed with methanol and crystallised from methanol to give 0.65 g (94%) of **21** as off white needles, mp 183-184°; ir: 3440, 3340 (NH), 1685 cm^{-1} (CO); pmr (dimethyl sulfoxide-d_6): δ 3.90 (s, 3H, ether OMe), 4.20 (s, 3H, ester OMe), 6.40-6.60 (bs, 2H, NH_2), 8.60 (s, 1H, H-2); ms: m/z 227 (M^+).

Anal. Calcd. for $C_8H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56. Found: C, 45.02; H, 3.70; N, 17.78.

Methyl 5-Amino-4-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylate (**22**).

A solution of compound **19** (1.56 g, 5 mmoles) and sodium methanethiolate (1.05 g, 15 mmoles) in dry methanol (30 ml), was stirred for 1 hour at room temperature. The precipitated solid from the reaction solution was filtered off, washed with water and crystallised from methanol to give 1.12 g (88%) of **22** as off white needles, mp 219-220°; ir: 3435, 3325 (NH), 1685 cm^{-1} (CO); pmr (dimethyl sulfoxide-d_6): δ 2.65 (s, 3H, SMe), 4.05 (s, 3H, OMe), 6.42-6.55 (bs, 2H, NH_2), 7.85 (s, 1H, H-2); ms: m/z 255 (M^+).

Anal. Calcd. for $C_9H_9N_3O_2S_2$: C, 42.34; H, 3.55; N, 16.46. Found: C, 42.21; H, 3.50; N, 16.68.

6-Methoxycarbonyl-5-nitrothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**23**).

The thienopyrimidine **18** (4.0 g, 13 mmoles) was added portionwise to a stirred mixture of fuming nitric acid (20 ml) and concentrated sulfuric acid (20 ml) at 0°. The resulting solution was stirred at room temperature for 2 hours before ice-water (50 g) was added. The precipitated solid was filtered off, washed with water and purified by precipitation with 4*N*-acetic acid from a 2*N*-sodium hydroxide solution to give 2.5 g (73%) of **23** as an amorphous yellow solid, mp 240° dec; ir: 3150 (NH), 1765 (CO) 1520, 1340 cm^{-1} (NO_2); pmr (dimethyl sulfoxide-d_6): δ 3.85 (s, 3H, Me), 5.84 (bs, 1H, NH), 8.25 (s, 1H, H-2); ms: m/z 255 (M^+).

Anal. Calcd. for $C_8H_5N_3O_5S \cdot H_2O$: C, 35.17; H, 2.58; N, 15.39. Found: C, 35.46; H, 2.36; N, 15.18.

Methyl 4-Dimethylamino-5-nitrothieno[2,3-*d*]pyrimidine-6-carboxylate (**24**).

The thienopyrimidine **5c** (0.9 g, 3.8 mmoles) was added portionwise to a stirred mixture of fuming nitric acid (5 ml) and concentrated sulfuric acid (5 ml) at 0°. The resulting solution was stirred at room temperature for 3 hours before ice-water (25 g) was added. The precipitated solid was filtered off, washed with water and recrystallised from ethanol-water to give 0.46 g (43%) of **24** as yellow needles, mp 158-159°; ir: 1765 (CO) 1525, 1345 cm^{-1} (NO_2); pmr (dimethyl sulfoxide-d_6): δ 3.45 (s, 6H, 2 x Me), 3.83 (s, 3H, OMe), 8.15 (s, 1H, H-2); ms: m/z 282 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_4O_4S \cdot H_2O$: C, 40.00; H, 4.03; N, 18.66. Found: C, 40.18; H, 3.78; N, 18.78.

2,4-Diaminothieno[2,3-*d*]pyrimidine-6-carboxylic Acid (**25**).

To thienopyrimidine **5g** (0.90 g, 4 mmoles) 2*N*-sodium hydroxide (10 ml) was added, and the suspension heated at 100°, for 15 minutes. The resulting solution was cooled, acidified with 4*N*-acetic acid to *p*H 5, and the precipitated solid filtered off, washed with water, methanol and dried. Recrystallisation from dimethyl sulfoxide-water gave 0.71 g (75%) of **25** as a colourless powder, mp 270° dec; ir: 3300, 3100 (NH), 1690 cm^{-1} (CO); pmr (dimethyl sulfoxide-d_6): δ 6.05-6.85 (bs, 2H, NH_2-2), 6.90-7.70 (bs, 2H, NH_2-4), 8.11 (s, 1H, H-5); ms: m/z 211 ($M^+ + 1$).

Anal. Calcd. for $C_7H_6N_4O_2S$: C, 40.00; H, 2.88; N, 26.65. Found: C, 39.79; H, 3.27; N, 26.27.

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