# Synthesis of pyrido[2',3':4,5]thieno[2,3-*d*]pyrimidines through Friedländer reactions

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A variety of tri-, tetra- and penta–cyclic pyrido[2',3':4,5]thieno[2,3-*d*]pyrimidines have been synthesised from 5-amino-6-formyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine by Friedländer condensation with aliphatic, alicyclic, and heterocyclic ketones and other active methylene compounds.

**Keywords:** fused thiophenes, pyridines, pyrimidines, amino-aldehydes, Friedländer reactions

Annelation reactions involving suitable aromatic hydrocarbon compounds carrying the aminoaldehyde moiety provide a synthetic entry into heterocyclic systems,[1] and the formation of ring structures from substituted heterocyclic aminoaldehydes is often the method of choice for preparation of polycondensed heterocycles.[2-5]

Thienopyrimidines have been the subject of chemical and biological studies due to their interesting pharmacology,[6] including analgesic,[7] antipyretic,[8] herpes virus inhibitory[9] and anti-inflammatory[10,11] properties. In view of the above activities and in continuation of our work in the synthesis and reactions of various fused thiophenes,[12,13] we report here the preparation of some new fused pyrido-thieno-pyrimidines.

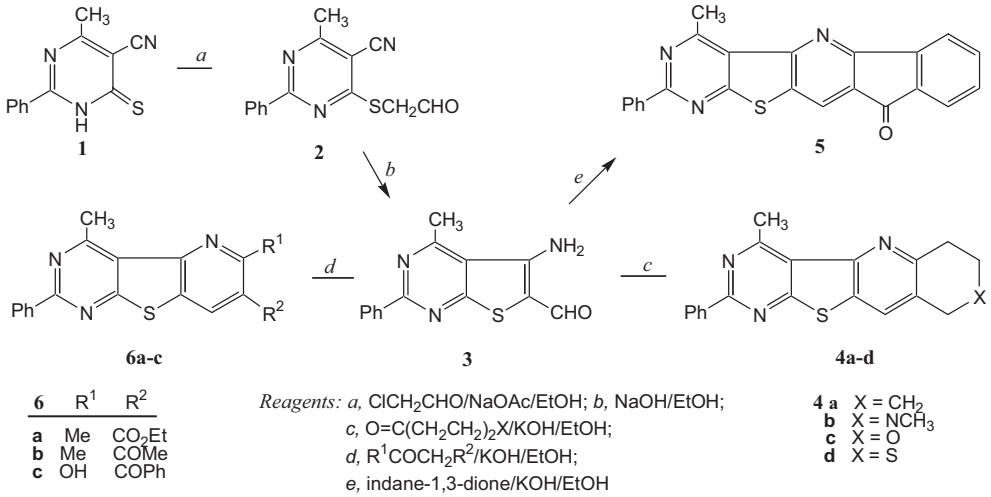
## Results and discussion

The synthesis of the desired compounds started with 5-amino-6-formyl-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine (**3**), which was prepared by the reaction of 6-methyl-4-phenyl-2-thioxo-1,2-dihydropyimidine-5-carbonitrile (**1**) with α-chloroacetaldehyde in ethanol containing sodium acetate to give the intermediate 6-(formylmethylthio) derivative **2**. Upon treatment with ethanolic sodium ethoxide, compound **2** underwent cyclisation to afford the starting compound **3**. The heterocyclic aminoaldehyde **3** opens a direct route to the synthesis of condensed heterocycles of the pyridine series. Thus, Friedländer condensation[14] of **3** with aliphatic cyclic and/or heterocyclic ketones in the presence of ethanolic potassium hydroxide solution leads to the formation of fused tetrahydropyrimidothienoquinoline, pyrimidothienonaphthyridine, pyranopyridothienopyrimidine and thiopyranopyridothienopyrimidine compounds **4a–d**, respectively. The $^1$H NMR spectra of the isolated compounds **4a–d** showed a characteristic singlets at 7.80–8.20 ppm for the H-10 hydrogen. Furthermore, the IR spectra revealed the absence of the characteristic absorption bands at 3450–3300 cm$^{-1}$ for the amino group which indicated the condensation products to be **4a–d**.

Similarly, the aminoaldehyde **3** was allowed to react with indane-1,3-dione under Friedländer condensation conditions to give the indenopyridothienopyrimidine **5.** The IR spectrum of **5** showed a strong absorption band at 1700 cm$^{-1}$ due to C=O. Also the $^1$H NMR spectrum showed a characteristic singlet at 7.95 ppm for the H-11 hydrogen. (Scheme 1).

Annelation reactions of β-diketones with **3** are greatly facilitated by the presence of a doubly activated α-methylene group, and gave different 6,7-disubstituted pyrido-thienopyrimidines according to the direction of ring closure. Thus, treatment of **3** with ethyl acetoacetate and acetylacetone in ethanolic KOH furnished ethyl 3,6-dimethyl-2-phenylpyrido [2',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**6a**) and 7-acetyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*] pyrimidine (**6b**). With ethyl benzoylacetate, compound **3** underwent another route for ring closure, giving 7-benzoyl-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine-6(5*H*)-one (**6c**). The structure of compound **6c** was confirmed by IR which gave characteristic absorption bands at 1700, 1650 cm$^{-1}$ for 2 CO groups and the $^1$H NMR revealed the absence of absorptions for the ester group.

In the case of bifunctional compounds (X-CH$_2$-Y; X, Y = cyano, alkoxycarbonyl, carbamoyl and thiocarbamoyl groups), the amino group in **3** attacked the more electrophilic group to form functionalised pyridothienopyrimidines. Thus,




**Scheme 1**

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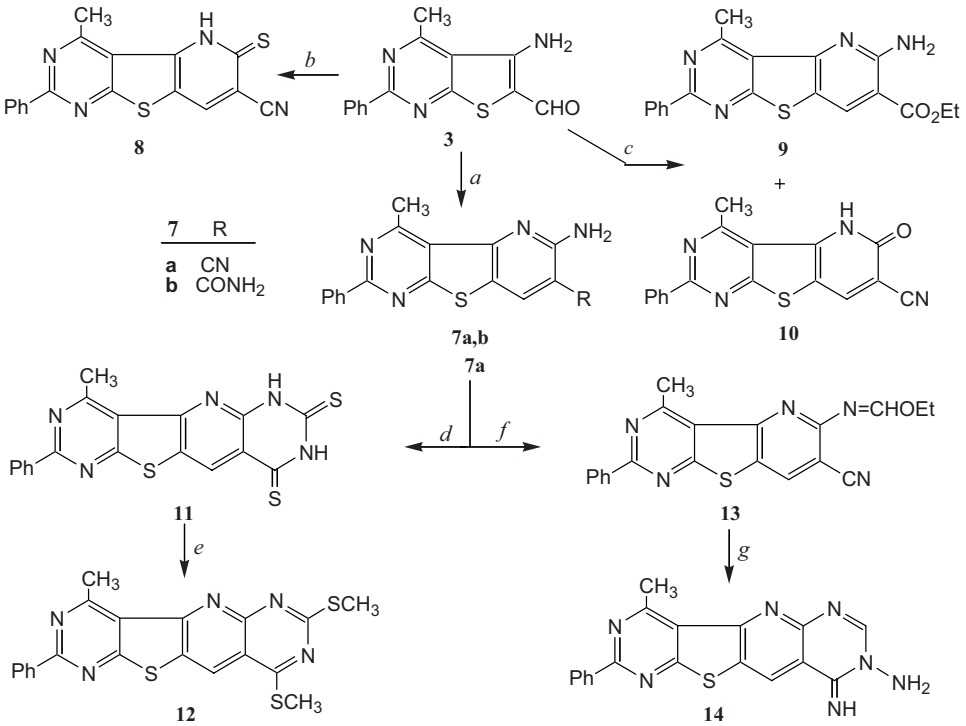


*Reagents: a,* $NCCH_2$-CN/$CONH_2$/piperidine/EtOH; *b*, $NCCH_2$-$CSNH_2$/piperidine/EtOH; *c*, $NCCH_2$-$CO_2Et$/piperidine/EtOH; *d*, $CS_2$/pyridine; *e*, $CH_3I$/acetone/$K_2CO_3$; *f,* $HC(OEt)_3/Ac_2O$; *g*, $N_2H_4$/EtOH

**Scheme 2**

the reaction of **3** with malononitrile and cyanoacetamide in ethanol containing a few drops of piperidine took place via intramolecular addition of the amino group in compound **3** to the cyano function to form the cyclised products 6,7-substituted pyridothienopyrimidines **7a,b**. Unexpectedly, with cyanothioacetamide **3** afforded 7-cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d]pyrimidine-6(5*H*)-thione (**8**), formed by the loss of an ammonia molecule. (Scheme 2)

The structures of compounds **7a,b** and **8** were consistent with their elemental analyses and spectral data. Thus the IR spectrum of **7a** ($R_1 = NH_2$, $R_2 = CN$) reveals characteristic absorption bands at 3450, 3350 $cm^{-1}$ for the $NH_2$ and at 2230 $cm^{-1}$ for the cyano group. Its $^1H$ NMR spectrum presents a characteristic singlet at 6.8 for $NH_2$ and at 8.30 ppm corresponding to H-8 hydrogen. The structure of **8** was confirmed by IR spectrum which revealed the absence of characteristic absorption bands for the $NH_2$ and showed a band at 2230 $cm^{-1}$ due to CN. The reaction of **3** with ethyl cyanoacetate under the same conditions afforded a mixture of ethyl 6-amino-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine-7-carboxylate (**9**) and 7-cyano-6-hydroxy-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine (**10**) which could be separated through fractional crystallisation using acetic acid as a solvent.

The pyridothienopyrimidine derivative **7a** was used as precursor for the synthesis of new pyrimidopyridothienopyrimidines **11, 12** and **14** based on the high reactivity of the β-enaminonitrile moiety. Thus, condensation of **7a** with carbon disulfide in pyridine afforded the corresponding 4-methyl-2-phenylpyrimido[5",4":5',6']pyrido[2',3':4,5]thieno[2,3-*d*]pyrimidine-6,8(7*H*,9*H*)-dithione (**11**), which was easily S-methylated by methyl iodide to give the corresponding 7,9-bismethylthio derivative **12**. Furthermore, treatment of **7a** with triethylorthoformate in refluxing acetic anhydride afforded the intermediate ethoxymethyleneamino derivative **13**. Hydrazinolysis of **13** in ethanol yielded the 8-amino-9-iminopyrimidopyridothienopyrimidine derivative **14** in good yield**.** (Scheme 2). The structure of **14** was established on the basis of IR, which showed the absence of CN absorption at 2220 $cm^{-1}$, while its $^1H$ NMR spectrum showed signals due to the pyrimidine CH at 8.65 ppm.

## Experimental

All melting points were determined on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam spectrophotometer using the KBr wafer technique. $^1H$ NMR spectra were obtained on a Bruker 250 MHz NMR spectrometer. It should be noted that, to enhance the solubility of a number of samples to a level sufficient to provide an adequate spectrum, several drops of TFA-$d_1$ were added to the $CDCl_3$ or DMSO-$d_6$ indicated as the solvent. This probably gave rise to the anomalous deshielding of some of the methyl signals which are reported here. MS were registered on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined using a Perkin-Elmer 240C microanalyser**.**

*6-Methyl-4-phenyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile* (**1**)**:** This compound was synthesised according to a literature procedure; m.p. 228–230°C (lit.[15] m.p. 228–232°C).

*5-Cyano-6-(formylmethylthio)-4-methyl-2-phenylpyrimidine* (**2**): A mixture of the nitrile **1** (2.27 g, 0.01 mol), fused sodium acetate (2 g) and α-chloroacetaldehyde (0.86 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 30 min, cool and then poured into water. The solid product obtained was filtered off and crystallised from ethanol to give white crystals (2.30 g, 84%) of **2,** m.p. 155–156°C. IR: $\nu_{max}$ 2220 (CN), 1710 $cm^{-1}$ (C=O). NMR ($CDCl_3$): $\delta_H$ 2.80 (s, 3H, $CH_3$), 4.30 (s, 2H, $CH_2$), 7.40–7.80 (m, 5H, ArH), 9.60(s, 1H, CHO). Anal. calcd. for $C_{14}H_{11}N_3OS$ (269.32): C, 62.44; H, 4.12; N, 15.6; S, 11.9. Found: C, 62.55; H, 4.08; N, 15.71; S, 11.77%.

*5-Amino-4-methyl-2-phenylthieno[2,3-d]pyrimidine-6-carbaldehyde* (**3**): To compound **2** (2.7 g, 0.001 mol) in absolute ethanol (30 ml) was added a few drops of sodium ethoxide solution, and the mixture was stirred at room temperature for 30 min. The solid product was collected and recrystallised from ethanol to give yellow crystals of **3** (1.90 g 71%), m.p. 200–201°C. IR: $\nu_{max}$ 3450, 3300 ($NH_2$), 1630 $cm^{-1}$ (C=O). NMR (DMSO-$d_6$): $\delta_H$ 2.90 (s, 3H, $CH_3$), 7.20 (s, 2H, $NH_2$), 7.40–7.80 (m, 5H, ArH), 10.20 (s, 1H, CHO). MS: *m/z* (%) 269 (100) [$M^+$]. Anal. calcd. for $C_{14}H_{11}N_3OS$ (269.32):

C, 62.44; H, 4.12; N, 15.60; S, 11.90. Found: C, 62.61; H, 4.18; N, 15.78; S, 12.02%.

*Reaction of aminoaldehyde* **3** *with cyclic and heterocyclic ketones; formation of* **4a–d**, **5** *and* **6a–c.** *General procedure*

A mixture of **3** (1.35 g, 0.005 mol), the appropriate ketone (0.0055 mol) and a few drops of ethanolic KOH (10%) in ethanol (30 ml) was refluxed for 3–6 h. The solid which separated from the hot mixture was filtered off and recrystallised from the indicated solvent**.**

*4-Methyl-2-phenyl-6,7,8,9-tetrahydropyrimido[4',5':5,4]thieno [3,2-b]quinoline* (**4a**): Orange crystals (1.30 g, 79%) from dioxan, m.p. 222–223°C. IR: $\nu_{max}$ 2900 (CH aliphatic), 1540 cm$^{-1}$ (C=N). NMR (DMSOd$_6$): $\delta_H$ 1.80 (m, 4H, 2 $CH_2$), 2.60 (m, 2H, $CH_2$), 2.72(m, 2H, $CH_2$), 2.95 (s, 3H, $CH_3$), 7.20–7.50 (m, 5H, ArH), 7.80 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{17}N_3S$ (331.44): C, 72.48; H, 5.17; N, 12.68; S, 9.67. Found: C, 72.37; H, 5.26; N, 12.80; S, 9.75%.

*4,8-Dimethyl-2-phenyl-6,7,8,9-tetrahydropyrimido[4',5':5,4] thieno[3,2-b][1,6]naphthyridine* (**4b**): Red crystals (1.14 g, 66%) from dioxan, m.p.190–191°C. IR: $\nu_{max}$ 2900 (CH aliphatic), 1550 cm$^{-1}$ (C=N). NMR ($CF_3COOD$): $\delta_H$ 2.80 (s, 3H, $CH_3$), 2.80 (t, 2H, $J$ = 5.2 Hz, $CH_2$), 3.20 (t, 2H, $J$ = 4.8 Hz, $CH_2$), 3.45 (s, 3H, $CH_3$), 4.20 (s, 2H, $CH_2$-N), 7.20–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{18}N_4S$ (346.45): C, 69.34; H, 5.24; N, 16.17; S, 9.25. Found: C, 69.49; H, 5.17; N, 16.31; S, 9.36%.

*4-Methyl-2-phenyl-6,7,8,9-tetrahydropyrano[3'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine* (**4c**): Red crystals (1.08 g, 65%) from acetic acid, m.p. 235–236°C. IR: $\nu_{max}$ 2950 (CH aliphatic), 1530 cm$^{-1}$ (C=N). NMR ($CF_3COOD$): $\delta_H$ 2.75 (t, 2H, $J$ = 5.6 Hz, $CH_2$), 2.95 (s, 3H, $CH_3$), 3.30 (t, 2H, $J$ = 4.8 Hz, $CH_2$), 4.80 (s, 2H, $CH_2$-O), 7.10–7.40 (m, 5H, ArH), 7.65 (s, 1H, H-10). Anal. calcd. for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.61; H, 4.48; N, 12.71; S, 9.53%.

*4-Methyl-2-phenyl-6,7,8,9-tetrahydrothiopyrano[3'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine* (**4d**): Red crystals (1.23 g, 71%) from dioxan, m.p. 227–228°C. IR(KBr) ν = 2950 (CH aliphatic),1540 (C=N) cm$^{-1}$. NMR ($CF_3COOD$): $\delta_H$ 2.55 (t, 2H, $J$ = 4.6 Hz, $CH_2$), 2.80 (t, 2H, $J$ = 5.2 Hz, $CH_2$), 2.90 (s, 3H, $CH_3$), 3.80 (s, 2H, $CH_2$-S), 7.10–7.45 (m, 5H, ArH), 7.61(s, 1H, H-10). Anal. calcd. for $C_{19}H_{15}N_3S_2$ (349.47): C, 65.30; H, 4.33; N, 12.02; S, 18.35. Found: C, 65.43; H, 4.29; N, 12.20; S, 18.48%.

*4-Methyl-2-phenyl-10H-indeno[2'',3'':5',6']pyrido[2',3':4,5]thieno [2,3-d]pyrimidin-10-one* (**5**): Yellow crystals (1.28 g, 68%) from acetic acid, m.p. 301–302°C. IR: $\nu_{max}$ 2950 (CH aliphatic), 1720 cm$^{-1}$ (C=O). NMR (DMSO-d$_6$): $\delta_H$ 2.85 (s, 3H, $CH_3$), 6.90–7.70 (m, 9H, ArH), 7.95 (s, 1H, H-11). Anal. calcd. for $C_{23}H_{13}N_3OS$ (379.44): C, 72.81; H, 3.45; N, 11.07; S, 8.45. Found: C, 73.01; H, 3.47; N, 10.92; S, 8.36%.

*Ethyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylate* (**6a**): Orange crystals (1.47 g, 81%) from dioxan, m.p. 180–181°C. IR: $\nu_{max}$ 2950 (CH aliphatic), 1720 cm$^{-1}$ (C=O). NMR (DMSO-d$_6$): $\delta_H$ 1.50 (t, 3H, $J$ = 7.2 Hz, $CH_3$), 3.20 (s, 3H, $CH_3$), 3.70 (s, 3H, $CH_3$), 4.60 (q, 2H, $J$ = 6.8 Hz, $CH_2$), 7.50–7.90 (m, 5H, ArH), 9.20 (s, 1H, H-8). Anal. calcd. for $C_{20}H_{17}N_3O_2S$ (363.43): C, 66.10; H, 4.71; N, 11.56; S, 8.80. Found: C, 66.26; H, 4.63; N, 11.65; S, 8.68%.

*7-Acetyl-3,6-dimethyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine* (**6b**): Orange crystals (1.20 g, 72%) from ethanol, m.p. 212–213°C. IR: $\nu_{max}$ 2900 (CH aliphatic), 1720 cm$^{-1}$ (C=O). $^1$H NMR ($CDCl_3$): $\delta_H$ 2.45 (s, 3H, $COCH_3$), 2.90 (s, 3H, $CH_3$), 3.30 (s, 3H, $CH_3$), 7.40–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-8). Anal. calcd. for $C_{19}H_{15}N_3OS$ (333.41): C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.58; H, 4.47; N, 12.71; S, 9.56%.

*7-Benzoyl-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-6(5H)-one* (**6c**): Orange crystals (1.63 g, 77%) from acetic acid, m.p. 205–206°C. IR: $\nu_{max}$ 3320 (NH), 2950 (CH aliphatic), 1700 (C=O), 1650 cm$^{-1}$ (C=O). $^1$H NMR ($CF_3COOD$): $\delta_H$ 3.25 (s, 3H, $CH_3$), 7.40–8.50 (m, 10H, ArH), 9.60 (s, 1H, H-8). MS: *m/z* (%) 397 (100) [M$^+$]. Anal. calcd. for $C_{23}H_{15}N_3O_2S$ (397.45): C, 69.51; H, 3.80; N, 10.57; S, 8.07. Found: C, 69.42; H, 3.73; N, 10.63; S, 7.89%.

*Reaction of* **3** *with activated nitriles; preparation of compounds* **7a–d***: General procedure*

A solution containing **3** (1.35 g, 0.005 mol), the appropriate carbonitrile (0.065 mol) and a few drops of piperidine in ethanol (20 ml) was refluxed for 3 h. A solid which separated from the hot mixture was filtered off, washed with ethanol and recrystallised**.**

*6-Amino-7-cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine* (**7a**): From malononitrile, yellow crystals (0.99 g, 62%) from dioxan, m.p. 285–286°C. IR: $\nu_{max}$ 3450, 3350 ($NH_2$), 2220 cm$^{-1}$ (CN). NMR (DMSO-d$_6$): $\delta_H$ 3.40 (s, 3H, $CH_3$), 6.8 (s, 2H, $NH_2$), 7.30–7.70 (m, 5H, ArH), 8.30 (s, 1H, H-8). Anal. calcd. for $C_{17}H_{11}N_5S$ (317.37): C, 64.34; H, 3.49; N, 22.07; S, 10.10. Found: C, 64.41; H, 3.42; N, 22.18; S, 9.97%.

*6-Amino-4-methyl-2-phenylpyrido[2',3'-4,5]thieno[2,3-d] pyrimidine-7-carboxamide* (**7b**): From cyanoacetamide, orange plates (1.37 g, 82%) from acetic acid, m.p. 243–244°C. IR: $\nu_{max}$ 3500, 3450, 3300 ($NH_2$), 1640 cm$^{-1}$ (CO). NMR (DMSO-d$_6$): $\delta_H$ 3.18 (s, 3H, $CH_3$), 5.60 (s, 2H, $NH_2$), 6.80 (s, 2H, $NH_2$), 7.40–7.50 (m, 5H, ArH), 7.85 (s, 1H, H-8). Anal. calcd. for $C_{17}H_{13}N_5OS$ (335.38): C, 60.88; H, 3.91; N, 20.88; S, 9.56. Found: C, 60.69; H, 3.88; N, 20.97; S, 9.64%.

*7-Cyano-4-methyl-2-phenylpyrido[2',3'-4,5]thieno[2,3-d] pyrimidine-6(5H)-thione* (**8**): From cyanothioacetamide, red crystals (1.15 g, 60%) from acetic acid, m.p. 175–176°C. IR: $\nu_{max}$ 3200 (NH), 2230 cm$^{-1}$ (CN). NMR (DMSO-d$_6$): $\delta_H$ 2.95 (s, 3H, $CH_3$), 7.30–7.60 (m, 5H, ArH), 8.20 (s, 1H, H-8), 9.25 (s, 1H, NH). Anal. calcd. for $C_{17}H_{10}N_4S_2$ (334.41): C, 61.06; H, 3.01; N, 16.75; S, 19.17. Found: C, 61.15; H, 2.97; N, 16.65; S, 19.12%.

*Reaction of* **3** *with ethyl cyanoacetate. Preparation and separation of compounds* **9** *and* **10**

A mixture of **3** (1.16 g, 4 mmol), ethyl cyanoacetate (4 mmol) and a few drops of piperidine in ethanol (20 ml) was refluxed for 3 h. A precipitate was collected by filtration. First examination (IR spectra and TLC) showed the product to contain two compounds. This mixture was heated in acetic acid and filtered while hot. The solid compound was collected, washed with ethanol and rerystallised from DMF which was shown to be compound **10**. After cooling, the filtrate gave further solid material which was assigned as compound **9**.

*Ethyl 6-amino-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-7-carboxylate* (**9**): Orange crystals 0.65 g (45%) from acetic acid, m.p. 260–261°C. IR: $\nu_{max}$ 3450, 3300 ($NH_2$), 1700 cm$^{-1}$ (CO). NMR (DMSO-d$_6$): $\delta_H$ 1.30 (t, 3H, $J$ = 7.0 Hz, $CH_3$), 2.85 (s, 3H, $CH_3$), 4.30 (q, 2H, $J$ = 6.8 Hz, $CH_2$), 6.75 (s, 2H, $NH_2$), 7.40–7.50 (m, 5H, ArH), 8.00 (s, 1H, H-8). Anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.71; H, 4.40; N, 15.41; S, 8.74%.

*7-Cyano-4-methyl-2-phenylpyrido[2',3':4,5]thieno[2,3-d] pyrimidine-6(5H)-one* (**10**): Yellow crystals (0.27 g 22%) from DMF, m.p. 280–281°C. IR: $\nu_{max}$ 3250 (NH), 2220 (CN), 1650 cm$^{-1}$ (C=O). NMR ($CF_3COOD$): $\delta_H$ 3.30 (s, 3H, $CH_3$), 7.25–7.55 (m, 5H, ArH), 8.30 (s, 1H, H-8). MS: *m/z* (%) 318 (100) [M$^+$]. Anal. calcd. for $C_{17}H_{10}N_4OS$ (318.35): C, 64.14; H, 3.17; N, 17.60; S, 10.07. Found: C, 64.23; H, 3.09; N, 17.71; S, 10.16%.

*4-Methyl-2-phenylpyrimido[5'',4'':5',6']pyrido[2',3':4,5]thieno[2,3-d] pyrimidine-7,9(6H,8H)-dithione* (**11**): To a solution of **7a** (0.32 g, 0.001 mol) in pyridine (20 ml), carbon disulfide (5 ml) was added. The mixture was refluxed for 24 h. The solid product formed was filtered off, washed several times with ethanol and crystallised from DMF to afford orange crystals (0.35 g (88%), m.p. >300°C. IR: $\nu_{max}$ 3340, 3300 cm$^{-1}$ (2NH). NMR (DMSO-d$_6$): $\delta_H$ 2.95 (s, 3H, $CH_3$), 7.30–7.60 (m, 5H, ArH), 7.70 (s, 1H, H-10), 9.30 (s, 1H, NH), 10.25 (s, 1H, NH). MS: *m/z* (%) 393 (100) [M$^+$]. Anal. calcd. for $C_{18}H_{11}N_5S_3$ (393.50): C, 54.94; H, 2.82; N, 17.80; S, 24.44. Found: C, 55.09; H, 2.79; N, 17.73; S, 24.35%.

*4-Methyl-7,9-bis(methylthio)-2-phenylpyrimido[5'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine* (**12**)**:** A mixture of compound **11** (0.39 g, 0.003 mol), methyl iodide (1.40 g, 0.01 mol) and anhydrous potassium carbonate (0.5 g) in acetone (30 ml) was refluxed 3 h, then allowed to cool, and poured into cold water. The solid product was collected, washed thoroughly with water, dried and recrystallised from ethanol to give yellow crystals, m.p. 270–271°C, yield 0.88 g (70%). IR: $\nu_{max}$ 2980 cm$^{-1}$ (CH-aliphatic). NMR (DMSO-d$_6$): $\delta_H$ 2.78 (s, 6H, 2$CH_3$), 3.10 (s, 3H, $CH_3$), 7.30–7.60 (m, 5H, ArH), 7.90 (s, 1H, H-10). Anal. calcd. for $C_{20}H_{15}N_5S_3$ (421.55): C, 56.98; H, 3.59; N, 16.61; S, 22.82. Found: C, 56.89; H, 3.62; N, 16.49; S, 22.89%.

*7-Cyano-6-(ethoxymethyleneamino)-4-methyl-2-phenylpyrido [2',3'-4,5]thieno[2,3-d]pyrimidine* (**13**): A mixture of *o*-aminonitrile **7a** (0.95 g, 0.003 mol), triethylorthoformate (5 ml) and acetic anhydride (5 ml) was refluxed for 6 h. The solvent was removed under reduced pressure and the resulting solid was recrystallised from dioxan to give white plates (0.89 g, 79%), m.p. 195–196°C. IR: $\nu_{max}$ 2980 (CH-aliphatic), 2220 cm$^{-1}$ (CN). NMR (DMSO-d$_6$): $\delta_H$ 1.25 (t, 3H $J$ = 6.8 Hz, $CH_3$), 3.55 (s, 3H, $CH_3$), 4.20 (q, 2H, $J$ = 7.2 Hz, $CH_2$), 7.30–7.60 (m, 5H, ArH), 8.25 (s, 1H, H-8), 8.75 (s, 1H, N=CH). Anal. calcd. for $C_{20}H_{15}N_5OS$ (373.43): C, 64.33; H, 4.05; N, 18.75;

S, 8.59. Found: C, 64.40; H, 3.98; N, 18.67; S, 8.61%.

*8-Amino-9-imino-4-methyl-2-phenylpyrimido[5'',4'':5',6']pyrido [2',3':4,5]thieno[2,3-d]pyrimidine* (**14**): To a well stirred cold solution of **12** (0.75 g, 0.002 mol) in ethanol (10 ml), 99% hydrazine hydrate (3 ml) was added over 2 h, then the mixture was stirred at room temperature for 6 h and left overnight. The solid that precipitated was filtered off and recrystallised from acetic acid to give yellow crystals (0.55 g, 77%), m.p. 305–306°C. IR: $\nu_{max}$ 3350, 3200 (NH, $NH_2$), 2980 $cm^{-1}$ (CH-aliphatic). NMR (DMSO-$d_6$): $\delta_H$ 3.10 (s, 3H, $CH_3$), 7.45–7.70 (m, 5H, ArH), 8.00 (s, 1H, H-7 pyrimidine), 8.78 (s, 1H, H-10), 9.35 (m, 3H, $NHNH_2$). MS: *m/z* (%) 359 (74) [$M^+$]. Anal. calcd. for $C_{18}H_{13}N_7S$ (359.41): C, 60.15; H, 3.65; N, 27.28; S, 8.92. Found: C, 60.22; H, 3.70; N, 27.34; S, 8.90%.

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## References

1 P. Caluwe, *Tetrahedron*, 1980, **36**, 2359.
2 D.E. Thurston, D.R. Murty, D.R. Langlely and G.B. Jones, *Synthesis*, 1990, 81.
3 D. Tomasik, P. Tomasik and R.A. Abramovitch, *J. Heterocycl. Chem*., 1980, **20**, 1539.
4 B.Y. Riad, S.E. Negm and H.A. Daboun, *Heterocycles*, 1987, **26**, 205.
5 C.T. Alabaster, A.S. Bell, S.F. Campbell, P. Ellis, C.G. Henderson, D.S. Morris, D.A. Roberts, K.S. Ruddock, G.M.R. Samuels and M.H. Stefaniak, *J. Med.Chem*., 1989, **32**, 575.
6 B. Ralf, P. Runland, L. Dieter, L. Gunter and P. Brigitte, Ger. (East) DD, 234, 268; *Chem. Abstr*., 1986**, 105**, 226 631e.
7 C.G. Dave, P.R. Shah, K.C. Dave and V.J. Patel, *J. Indian Chem. Soc*., 1989**, 66**, 48.
8 E. Bousquet, G. Romero, F. Guerrera, A. Caruso and M.A. Roxas, *Farmaco., Ed. Sci.*, 1985**, 40**, 869.
9 N.N. Kaplina, V.L. Shedov, A.N. Fomina, I.S. Nikolaeva, T.V. Pushkina and L.N. Filitis, *U.S.S.R*. 1993, SUI, 389, 23; *Chem. Abstr.,* 1993, **123**, 27 5971w.
10 S. Leistner, G. Wagner, M. Guetscharo and E. Glusa, *Pharmazie*, 1986**, 41**, 54.
11 M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangano and A. Caruso, *Pharmazie*, 2000, **55**, 500.
12 Z.H. Khalil, A.S. Yanni, A.M. Gaber and S.A. Abdel-Mohsen, *Phosphorus, Sulfur Silicon*, 2000, **166**, 57.
13 A.M. Kamal El-Dean, A.A. Geies, H.S. El-Kashef, S. Rault, P. D'Allemagne and J.C. Lancelot, *J. Heterocycl. Chem.,* 2000**, 37***,* 1520.
14 P. Friedländer, *Org. Reactions*, 1982**, 28**, 37.
15 A.M. Kamal El-Dean, *Monash. Chem.,* 1998**, 129**, 523.