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A SYNTHESIS OF SOME PYRIDINYLPYRIMIDINES FROM KETENEDITHIOACETALS

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Abstract: Some studies are reported on the preparation of a new class of substituted 5-(2-pyridinyl)pyrimidines, starting with cyano(2-pyridinyl)ketenedithioacetal. This has been reacted with amidines under base-catalysed conditions, giving a variety of different products, the structures of which have been determined. Synthesis of two novel tricyclic systems, (29) and (30), have also been developed.

In the course of some recent work to identify novel inhibitors of gastric acid secretion, a series of pyridinylpyrimidines was required. Although a few pyridinylpyrimidines of general structure (1) were known[1,2], none of the reported syntheses allowed for introduction of the required substituents. However, pyrimidines with phenyl in place of the pyridine ring have been prepared.[3-7] Of interest was the preparation of pyrimidine (2) from the ketenedithioacetal[8] (3) (Scheme 1). The preparation of the cyanopyrimidine (4) from dicyanoketenedimethyldithioacetal (5) has also been reported (Scheme 2).[9] We required hydrogen or alkyl substituents at C-2 of the pyrimidine and it was noticeable that formamidine, and simple alkyl amidines such as acetamidine had not been used for the conversion of ketenedimethyldithioacetals to pyrimidines. Nevertheless, it appeared that the approach used for the synthesis of these pyrimidines could be extended to the required pyridinylpyrimidines. This paper reports our results.

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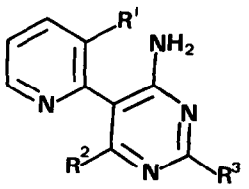
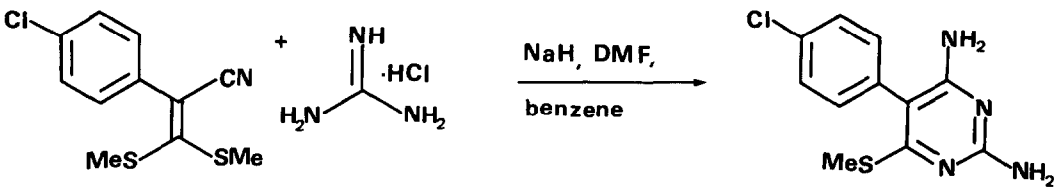


1

The known pyridine ketenedithioacetal (6) [10], available from 2-pyridineacetonitrile was used in our initial attempts to prepare pyridinylpyrimidines.

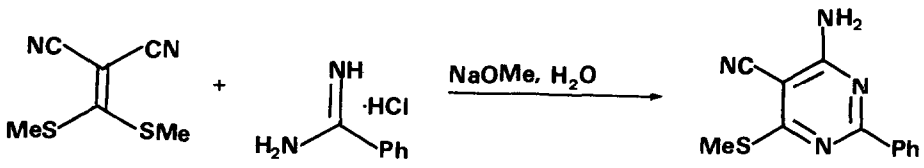
One concern was the geometry of the product arising from displacement of one of the alkylthio groups of (6) by amidines. A cis arrangement of pyridine and nitrogen substituted as in (7), possibly intramolecular hydrogen bonded, could hinder the required cyclisation.

Scheme 1



3 2

Scheme 2

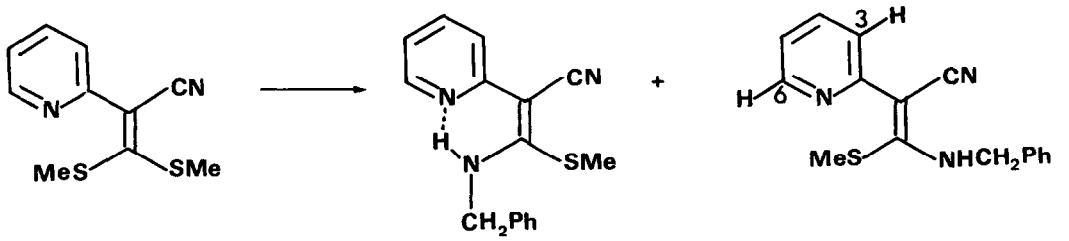


5 4

We therefore investigated the geometry of the product obtained by displacement of the methylthio group with simple nitrogen nucleophiles. The reaction of ketenedithioacetal (6) with aniline, to give a mono substituted product has been reported[10], but no mention was made of the geometry of the product. It was found that ketenedithioacetal (6) with benzylamine gave a single product, in 96% yield, which was shown by n.m.r., using nuclear Overhauser enhancement (n.O.e.) techniques to be the desired isomer (8).

Thus, irradiation of the SCH_3 singlet produced n.O.e.s of 0.2% and 0.3% on 3-H and 6-H respectively on the pyridine ring. Irradiation of the NCH_2 signal produced no measurable n.O.e.s on the pyridine ring.

Scheme 3

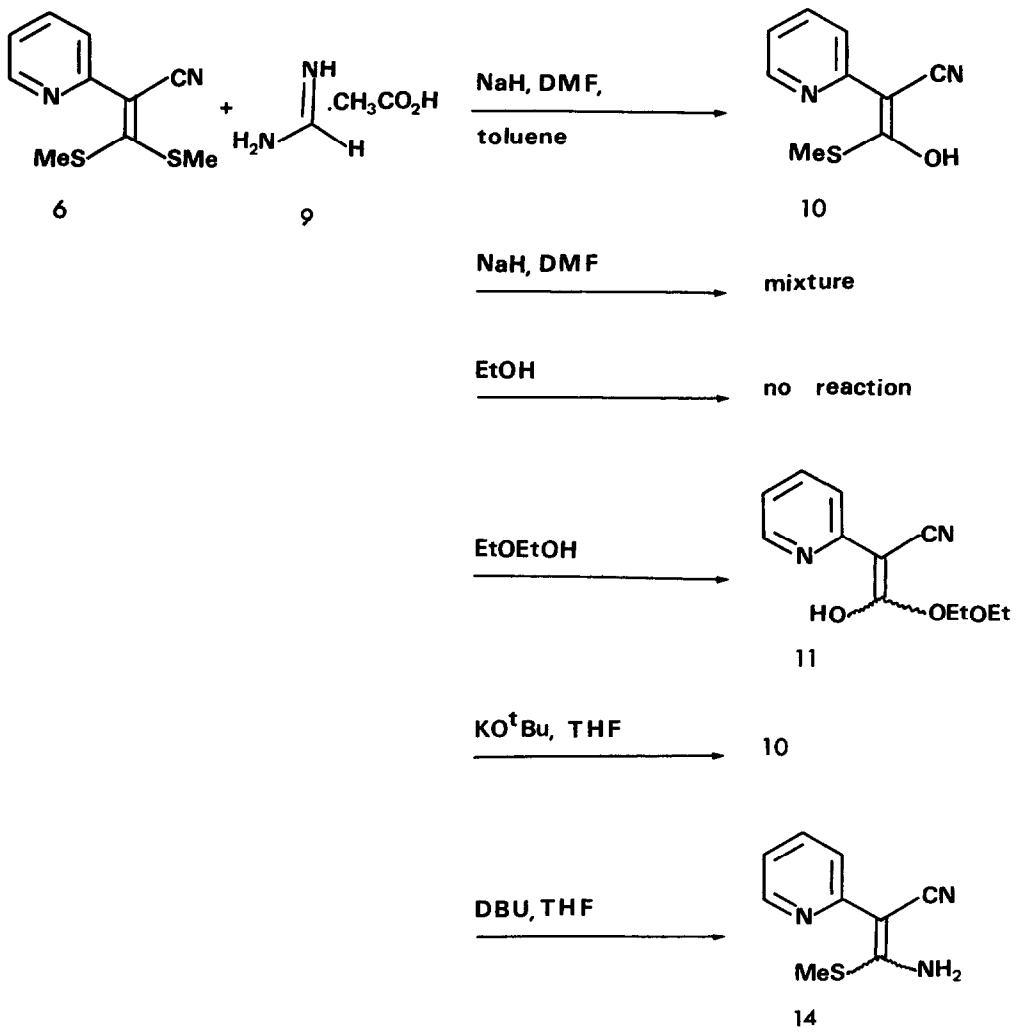


6 7 8

With this result, an investigation of the pyrimidine synthesis was started, beginning with compound (1) (R^1, R^2 = H, R^3 = SMe). Using conditions similar to those reported[8], the ketenedithioacetal (6) was treated with formamidine acetate (9) and sodium hydride in toluene-dimethylformamide (DMF) (20:1). A mixture of products was obtained, the only identifiable compound being the hydroxy substituted (10) (Scheme 4), obtained in 11% yield. The geometry of this compound is as shown: irradiation of the SCH_3 singlet produced n.O.e.s on the pyridine ring (0.6% for 3-H and 6-H), comparable with those previously observed by irradiating the SCH_3 singlet cis to the pyridine ring in the bis-methylthio compound (6). The SCH_3 trans to the pyridine ring in (6) showed no measurable n.O.e.s.

The use of sodium hydride in DMF in this reaction failed. There are examples[11] where pyrimidines have been formed from formamidine acetate without added base but, in this case, no reaction occurred under these conditions. By using ethoxyethanol as solvent, compound (11) was formed. It was concluded that the addition of a base was necessary for the reaction. Using potassium tert-butoxide, in tetrahydrofuran (THF) the only product obtained was the hydroxy-compound (10), in yields of less than 50%. It seemed likely that in compounds (10) and (11) the hydroxyl function present arose from initial substitution by acetate, giving a product which hydrolysed to the hydroxy derivative

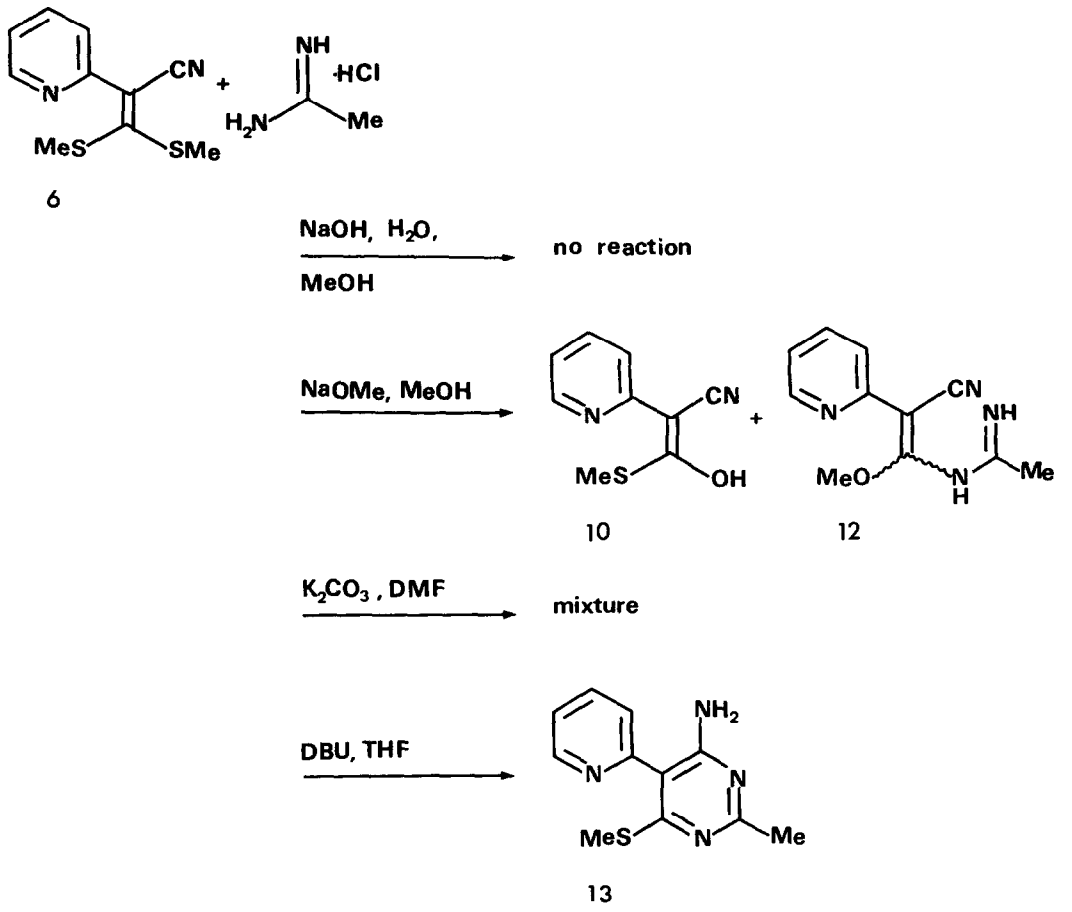
Scheme 4



6 9 10 11 14

during work-up. An amidine salt with a less nucleophilic counterion was therefore employed. In addition, our failure to observe any reaction with the formamidine prompted us to continue our investigation using the more nucleophilic acetamidine which was used as its hydrochloride salt.

Scheme 5



Following the procedure of Middleton and Engelhardt[9], using sodium hydroxide in methanol-water, with acetamidine hydrochloride, it was found that, even after overnight reflux, only starting material was recovered. Using sodium methoxide in methanol, we obtained the hydroxy compound (10) in 39% yield, along with 16% of the methoxy-acetamidine product (12).

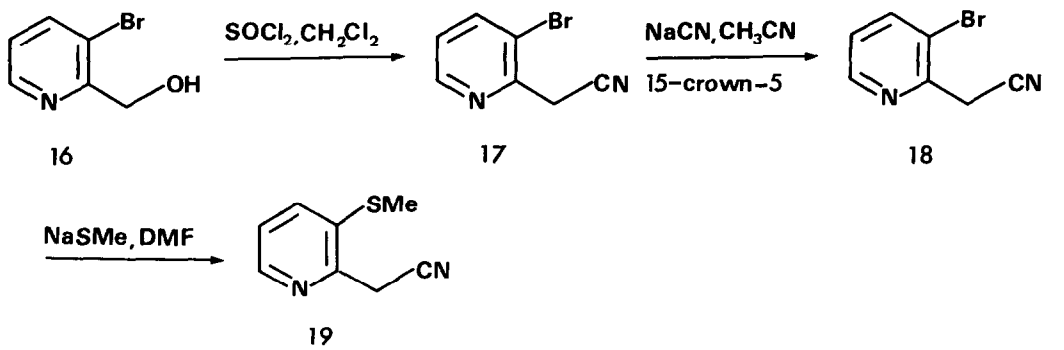
It was now clear to us that it was necessary to use a non-nucleophilic base. An attempt to use potassium carbonate in DMF, gave only a mixture of compounds. However, by using

1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), in THF, under reflux, overnight, the desired pyrimidine (13) was formed in 69% yield.

Having successfully synthesized the pyrimidine (13), variations of R^2 [compound (1)] were investigated. However, with formamidine acetate (9) or its hydrochloride, no pyrimidine was obtained, the only product recovered here, in 13% yield, being the amine (14). With guanidine hydrochloride the amino-pyrimidine (15) was obtained in 56% yield (Table). Urea and thiourea failed to react under these conditions, the starting material being recovered unchanged. S-Methyl thiouronium sulphate gave a mixture of products. The DBU catalysed conditions were also applied to the dicyano compound (5), but only complex mixtures were found.

Attention was next turned to the systems with the required 3-substitutent on the pyridine ring. It was felt that 3-bromo-2-hydroxymethylpyridine[12] (16) could be converted to the desired 3-bromo- (18) and 3-thiomethyl- (19) intermediates. Treatment of hydroxymethylpyridine (16) with thionyl chloride in dichloromethane at gave 3-bromo-2-chloromethylpyridine (17) in 69% yield. Treatment of this with sodium cyanide in acetonitrile with a catalytic amount of 15-crown-5 gave the required pyridineacetonitrile (18) in 74% yield.

Scheme 6

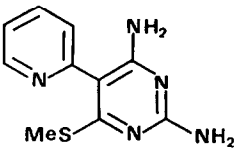
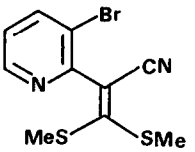
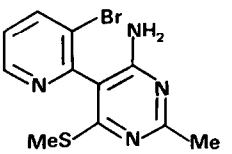
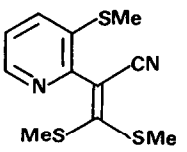
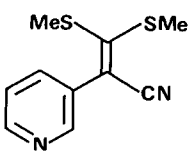
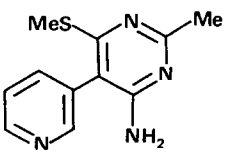
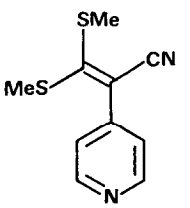
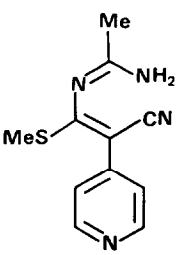


16 17 18 19

The substitution of 3-bromopyridines with sodium methanethiolate in DMF is known[15], but high temperatures (80°C) and/or long reaction times are generally required. In the case of bromopyridine (18) it was found that the reaction proceeded rapidly at room temperature to give 3-thiomethyl-2-pyridylacetonitrile (19) in 74% yield.

Preparation of the 3-bromo- and 3-thiomethyl ketenedithioacetals (20) and (22), from pyridines (18) and (19) respectively, proceeded as expected, in yields of 63% and 73%.

Table Preparation of pyridinylpyrimidines[a]

Reaction Number	Substrate	Product	% Yield
1	6	13	69
2	6	 15	56
3	 20	 21	63
4	 22	 23	85
5	 24	 23	76
6[b]	 26	 27	51

(a) These reactions were carried out using DBU in THF at reflux overnight except for 6; (b) DBU, THF, rt, for 2 hr.

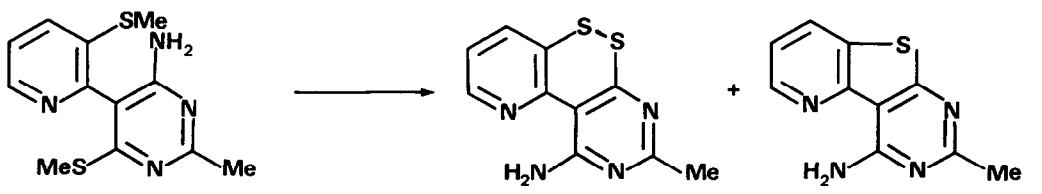
Their reactions with acetamidine hydrochloride in the presence of DBU in THF gave the desired pyrimidines in 63% and 85% yield (Table).

The above methodology has been extended to the preparation of 5-(3-pyridinyl)pyrimidine. Thus, 3-pyridineacetonitrile was converted to the requisite ketenedithioacetal (24) in 80% yield, and hence to the pyrimidine (25) in 76% yield.

An attempt to extend the method to synthesis of the 5-(4-pyridinyl)pyrimidine failed. 4-Pyridineacetonitrile was prepared from 4-chloromethylpyridine hydrochloride by reaction with sodium cyanide in dimethylsulphoxide (DMSO)[14] and conversion to the ketene-dithioacetal (26) proceeded, in 75% yield. However, reaction with acetamidine hydrochloride and DBU in THF gave only the uncyclized product (27), in 51% yield, as a mixture of tautomers. This compound was unstable to heat and could not be cyclized to give the pyrimidine.

We were interested in obtaining the conformationally restricted analogue (28). It was envisaged that demethylation of compound (23) would give a dithiolate dianion which could then be oxidised *in situ* to the disulphide (28) (Scheme 7). Sodium methanethiolate in hot DMF has been used for dealkylations of aryl alkyl sulphides.[15] Using these conditions with compound (23) a tricyclic system was obtained, but this was found to be the thiophene (29) rather than the disulphide (28). This probably arises through the intermediacy of a mono-demethylated product.

Scheme 7



23 28 29

Although the thiophene was an example of a conformationally restricted pyridinylpyrimidine, we were still interested in preparing the disulphide (28). An alternative method for dealkylation of sulphides is to use alkali metals in liquid amines.[16] As this reaction would occur at low temperature, the intramolecular displacement reaction would be disfavoured. This transformation was successfully effected under these conditions but only in 10% maximised yield; the thiophene (29) was still the favoured product, being obtained in 37% yield.

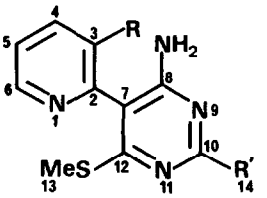
It seems that of the two tricyclic systems, (28) and (29), the thiophene (29) is considerably more stable. Indeed at high temperatures (~200°C), the disulphide (28) spontaneously converts to thiophene (29).

In summary, we have developed a synthesis for a series of pyridinylpyrimidines. One of these, the dithiomethyl compound (23), has been the precursor to two novel tricyclic systems.

Acknowledgement: We wish to thank Professor R. Tsien, University of California, Berkeley, for his original suggestion in this field and for his valuable contributions to the work.

Experimental

Melting points are uncorrected. N.m.r. spectra were recorded on a Bruker AM250 spectrometer relative to tetramethylsilane (internal standard). For the purposes of quoting n.m.r. spectra, the following numbering has been used:



I.r. spectra were recorded on a Perkin-Elmer 1750, or 298 spectrophotometer. Mass spectra were recorded on a Vacuum Generators - 7070F spectrometer. T.l.c. was carried out on glass plates precoated with Merck Kieselgel 60 F_{254}. Column chromatography was carried out with Merck Keiselgel 60 (230-400 mesh). THF was distilled from sodium-benzophenone immediately prior to use. DMF was distilled from CaH_2 and stored over 4A molecular sieves. Dichloromethane was distilled from P_2O_5.

Preparation of 3-benzylamino-3-methylthio-2-(2-pyridyl)propenenitrile (8)

A solution of ketenedithioacetal (6) (222 mg, 1 mmol) and benzylamine (130 µl, 1.2 mmol) in THF (5 ml) was stirred at room temperature for 18 h. The mixture was dried onto silica gel and chromatographed, eluting with hexane-ethyl acetate. 3-benzylamino-3-methylthio-2-(2-pyridyl)propenenitrile (261 mg, 0.93 mmol) was obtained in 93% yield. Found: M^+ 281.101. Calc. for $C_{16}H_{15}N_3S$ 281.0987; δ_H (250 MHz, $CDCl_3$) 2.55 (3 H, s, CH_3), 4.89 (2 H, d, J 8 Hz, CH_2), 6.96-7.20 (1 H, m, 5-H), 7.25-7.41 (5 H, m, PhH), 7.55-7.60 (1 H, m, 3-H), 7.62-7.71 (1 H, m, 4-H), 8.28-8.32 (1 H, m, 6-H), 12.30 (1 H, br s, NH) ν_{max} (KBr) 2180(CN), 1570, 1540 cm^{-1}, m/z 281 (5, M^+), 266 (5 M^+-CH_3), 234 (18 M^+-CH_3S).

General Procedure for Preparation of Ketenedithioacetals

To sodium hydride (12.5 mmol), washed with THF, was added 10 ml THF. The mixture was cooled to 0°C and the pyridineacetonitrile (5 mmol) was added dropwise as a solution in 5 ml THF. After 1 h, carbon disulphide (450 µl, 7.5 mmol) was added, followed by methyl iodide (930 µl, 15 mmol) after a further 1 h. The reaction was stirred at room

temperature overnight, then quenched with water. The THF was evaporated, and the resulting aqueous phase was extracted with dichloromethane. The combined organic phase was dried ($MgSO_4$) and concentrated. Purification was by flash chromatography on silica gel, using ethyl acetate-hexane mixtures as eluant. Yields quoted are chromatographic yields.

Cyano(2-pyridinyl)ketenedimethyldithioacetal (6): (67%) yellow needles (from ethyl acetate) m.p. 64-65°C (lit.[4] 64-65°C); δ_H (250 MHz, $CDCl_3$) 2.41 (3 H, s, CH_3), 2.64 (3 H, s, CH_3), 7.2-7.3 (1 H, m, 5-H), 7.64 (1 H, ddd, J 8,1 and 1 Hz, 3-H), 7.75 (1 H, ddd, J 8,8, and 2 Hz, 4-H), 8.65-8.70 (1 H, m, 6-H).

Cyano(2-(3-bromopyridinyl)ketenedimethyldithioacetal (20): (63%) yellow needles m.p. 33-35°C (from ethyl acetate-hexane). (Found: C, 39.90; H, 2.90; N, 9.30. Calc. for $C_{10}H_9N_2BrS_2$: C 39.87; H, 3.01; N, 9.30%); δ_H (250 MHz, $CDCl_3$). 2.35 (3 H, s, CH_3), 2.65 (3 H, s, CH_3), 7.25 (1 H, dd, J 11, 6 Hz, 5-H), 7.98 (1 H, dd, J 11, 2 Hz, 4-H) 8.64 (1 H, dd, J 6, 2 Hz, 6-H); ν_{max} (KBr) 2191(CN), 1550, 1508, 1463 cm^{-1}; m/z 302, 300 (10, M^+), 285, 287 (100, M^+-CH_3), 221 (70, M^+-Br).

Cyano(2-(3-thiomethylpyridinyl)ketenedimethyldithioacetal (22): (73%) yellow crystals m.p. 80-80.5°C (from ethyl acetate-hexane), (Found: C, 49.45; H, 4.61; N, 10.39. Calc. for $C_{11}H_{12}N_2S_3$: C, 49.22; H, 4.51; N, 10.44%); δ_H (250 MHz, $CDCl_3$) 2.30 (3 H, s, CH_3), 2.48 (3 H, s, CH_3), 2.64 (3 H, s, CH_3), 7.29 (1 H, dd, J 8, 4 Hz, 5-H), 7.60 (1 H, dd, J 8, 2 Hz, 4-H), 8.42 (1 H, dd, J 4, 2 Hz, 6-H); ν_{max} (KBr), 2195(CN), 1555, 1515, 1410 cm^{-1}; m/z 268 (M^+, 25), 253 (100, $M-CH_3$), 221 (50, $M-SCH_3$).

Cyano(3-pyridinyl)ketenedimethyldithioacetal (24): (80%) crystals m.p. 48-48.5°C (from ethyl acetate-hexane) (Found: C, 54.02; H, 4.50; N, 12.64. Calc. for $C_{10}H_{10}N_2S_2$: C, 54.02; H, 4.53; N, 12.60%); δ (250 MHz, $CDCl_3$) 2.38 (3 H, s, CH_3), 2.67 (3 H, s, CH_3), 7.35 (1 H, dd, J 8, 4 Hz, 5-H), 7.84 (1 H, ddd, 8,2, and 2 Hz, 4-H), 8.60 (1 H, dd, 4, 2 Hz, 6-H), 8.80 (1 H, s, 2-H); ν_{max} (KBr) 2208(CN), 1582, 1566, 1505 cm^{-1}; m/z 222 (100, M^+), 207 (25, $M-CH_3$), 175 (25, $M-SCH_3$), 160 (55).

Cyano(4-pyridinyl)ketenedimethyldithioacetal (26) (75%)

Crystals m.p. 59-60°C (from ether) (Found: C, 53.94; H, 4.53; N, 12.53. Calc. for $C_{10}H_{10}N_2S_2$: C, 54.02; H, 4.53; N, 12.60%); δ_H (250 MHz, $CDCl_3$) 2.34 (3 H, s, SCH_3), 2.65 (3 H, s, SCH_3), 7.45 (2 H, d, J 2 Hz, 3-H and 5-H), 8.66 (2 H, d, J 2 Hz, 2-H and 6-H); ν_{max}(KBr) 2204(CN), 1588, 1546, 1505 cm^{-1}; m/z 222 (100, M^+), 207 (35, $M-CH_3$), 175 (45, $M-SCH_3$), 160 (65).

General Procedure for Preparation of 5-Pyridinylpyrimidines:

A mixture of the ketenedithioacetal (0.5 mmol), acetamidine hydrochloride (94.5 mg, 1 mmol) and DBU (149 µl, 1 mmol) in THF (1 ml) was heated under reflux until t.l.c. (ethyl acetate) showed complete disappearance of starting material, accompanied by the appearance of the pyrimidine as a low running spot. In most cases overnight reflux was required. The reaction mixture was partitioned between dichloromethane and water. The organic phase was dried over $MgSO_4$ and concentrated. Purification was by column chromatography, using ethyl acetate-hexane mixtures for elution. An alternative work-up was directly to purify chromatographically the reaction mixture which had been dried onto silica gel.

6-Amino-2-methyl-4-methylthio-5-(2-pyridinyl)pyrimidine (13): (69%) white crystals m.p. 175-176°C (from ethyl acetate-hexane), (Found: C, 57.13; H, 5.32; N, 23.91. Calc. for $C_{11}H_{12}N_4S$: C, 56.88; H, 5.21; N, 24.12%); δ_H (250 MHz, $CDCl_3$) 2.49 (6 H, s, $2xCH_3$), 5.75 (2 H, br s, NH_2) 7.22-7.30 (1 H, m, 5-H), 7.68-7.82 (2 H, m, 3-H and 4-H), 8.68-8.72 (1 H, m, 6-H); δ_C (63 MHz, $CDCl_3$) 13.3 (q, 13-C), 25.7 (q, 14-C),110.4 (s, 7-C), 122.6 (d, 5-C), 126.1 (d, 3-C), 136.7 (d, 4-C), 149.6 (d, 6-C),

153.9 (s, 2-C), 159.9 (s, 8-C), 165.5 (s, 10-C or 12-C), 165.8 (s, 12-C or 10-C); ν_{max} (KBr) 3390, 3280, 1630, 1590, 1560, 1550, cm^{-1}; m/z 232 (25, M^+), 217 (100, $M-CH_3$), 199 (30, M-SH), 185 (15, $M-SCH_3$).

2,6-Diamino-4-methylthio-5-(2-pyridinyl)pyrimidine (15): In this case guanidine hydrochloride (98 mg, 1 mmol) was used in place of acetamidine hydrochloride. The compound was obtained in 56% yield, as pale yellow crystals m.p. 147-147.5°C (from ethyl acetate), (Found: C, 51.57; H, 4.61; N, 30.27. Calc. for $C_{10}H_{11}N_5S$: C, 51.53; H, 4.76; N, 30.05%) δ_H (250 MHz, $CDCl_3$), 2.43 (3 H, s, CH_3), 4.76 (2 H, br s, NH_2), 5.52 (2 H, br s, NH_2) 7.18-7.25 (1 H, m, 5-H), 7.66-7.80 (2 H, m, 3-H and 4-H) 8.61-8.69 (1 H, m, 6-H); ν_{max} (KBr), 3392, 3319, 1661, 1607, 1587, 1566 cm^{-1}; m/z 233 (25, M^+), 218 (100, $M-CH_3$), 186 (10, $M-SCH_3$).

6-Amino-2-methyl-4-methylthio-5-(2-(3-bromopyridinyl)pyrimidine (21): (63%) crystals m.p. 156-156.5°C (from ethyl acetate). (Found: C, 42.40; H, 3.59; N, 18.15. Calc. for $C_{11}H_{11}N_4BrS$; C, 42.45; H, 3.56; N, 18.00%); δ_H (250 MHz, d_6-DMSO) 2.35 and 2.38 (6 H, 2xS, $2xCH_3$), 6.26 (2 H, br s, NH_2), 7.35 (1 H, dd, J 8, 4 Hz, 5-H), 8.15 (1 H, dd, J 8, 1 Hz, 4-H), 8.65 (1 H, dd, J 4, 1 Hz, 6-H); ν_{max} (KBr) 3416, 3300, 1646, 1541, 1450 cm^{-1}; m/z 310, 312 (5, M^+), 295, 297 (s, $M-CH_3$) 263, 265 (5, $M-SCH_3$), 231 (100, M-Br).

6-Amino-2-methyl-4-methylthio-5-(2-(3-methylthiopyridinyl)pyrimidine (23): (85%) white crystals m.p. 194-194.5°C (from $CHCl_3$-methanol) (Found: C, 51.46; H, 5.06; N, 19.97 M^+, 278.066. Calc. for $C_{12}H_{14}N_4S_2$: C, 51.77; H, 5.07; N, 20.13%, M^+, 278.0660;). δ_H (250MHz, $CDCl_3$) 2.43, 2.50 and 2.54 (9 H, 3xs, $3xCH_3$), 4.60 (2 H, br s, NH_2), 7.35 (1 H, dd, J 8, 4 Hz, 5-H), 7.62 (1 H, dd, J 8, 2 Hz, 4-H), 8.52 (1 H, dd, J 4, 2 Hz, 6-H); ν_{max} (KBr) 3484, 3296, 1638, 1558, 1539 cm^{-1}; m/z 278 (15, M^+), 263 (25, $M-CH_3$), 231 (100, $M-SCH_3$).

6-Amino-2-methyl-4-methylthio-5-(3-pyridinyl)pyrimidine (25): (76%). Pale brown powder, m.p. 236-237°C (from methanol) (Found: M^+ 232.0784. Calc. for $C_{11}H_{12}N_4S$: 232.0783) δ_H (250 MHz, d_6-DMSO), 2.34 and 2.37 (6 H, 2xs, $2xCH_3$), 6.28 (2 H, br s, NH_2), 7.50 (1 H, dd, J 7.5, 5 Hz, 5-H), 7.67 (1 H, ddd, J 7.5, 2, 2 Hz, 4-H), 8.40 (1 H, d, J 2 Hz, 2-H), 8.61 (1 H, dd, J 5, 2 Hz, 6-H); ν_{max} (KBr) 3355, 3317, 1654, 1558, 1538, 1419 cm^{-1}; m/z 232 (100, M^+), 231 (75, M^+-H), 217 (20, M^+-CH_3), 199 (65, M^+-SH), 185 (80, M^+-SCH_3).

(2-cyano-1-methylthio-2-(4-pyridinyl)vinyl acetamidine (27)

Using the above procedure except that the reaction was carried out at room temperature, ketenedithioacetal (26) gave (2-cyano-1-methylthio-2-(4-pyridinyl)vinylacetamidine (28) as a mixture of tautomers. Found: M^+ 232.07988. Calc. for $C_{11}H_{12}N_4S$ 232.07988. δ_H (200 MHz, $CDCl_3$) 2.04 (3.9 H, s, CH_3), 2.18 (0.9 H, s, CH_3), 2.30 (0.9 H, s, CH_3), 5.22 (2 H, br s, NH_2), 7.45 (2 H, m, 3-H and 5-H), 7.50 (0.6 H, m, 3-H and 5-H), 8.48 (2 H, m, 2-H and 6-H), 8.53 (0.6 H, m, 2-H and 6-H); ν_{max} (KBr) 3300(NH), 2195(CN), 1660, 1605 cm^{-1}; m/z 232 (100, M^+), 217 (20, M^+-CH_3), 199 (32, M^+-SH), 185 (80, M^+-SCH_3).

3-Bromo-2-chloromethylpyridine (17)

To a solution of the pyridine (16) (5.8 g, 31 mmol) in 50 ml CH_2Cl_2 was added thionyl chloride (11.2 ml, 154 mmol), maintaining the temperature below -5°C. The reaction mixture was warmed to room temperature, and stirred overnight, then cooled to 0°C, and quenched with water. The resultant solution was basified with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and concentrated, giving a black solid which was purified by flash chromatography, eluting with ethyl acetate-hexane. 3-Bromo-2-chloromethylpyridine (17) (4.4 g, 21 mmol) was obtained in 69% yield, as a white crystalline solid, m.p. 46-46.5°C (from hexane-ether) (Found: C, 34.95; H, 2.50; N, 6.78. Calc. for C_6H_5NBrCl: C,

34.90; H, 2.44; N, 6.78%) δ_H (250 MHz, $CDCl_3$) 4.82 (2 H, s, CH_2), 7.17 (1 H, dd, J 8, 4 Hz, 5-H), 7.92 (1 H, dd, J 8, 2 Hz, 4-H), 8.58 (1 H, dd, J 4, 2 Hz, 6-H); ν_{max} (KBr) 3040, 1570, 1420 cm^{-1}. m/z 209 (23, M^+), 207 (100, M^+), 205 (77, M^+), 172 (42, M^+-Cl), 170 (48, M^+-Cl).

3-Bromo-2-cyanomethylpyridine (18)

A mixture of chloromethyl pyridine (17) (413 mg, 2 mmol), NaCN (400 mg, 8 mmol) and 15-crown-5 (20 µl, 0.1 mmol) in acetonitrile (7 ml) was stirred at room temperature for 3 h. The reaction mixture was dried onto silica gel and chromatographed, eluting with dichloromethane. 3-Bromo-2-cyanomethylpyridine (18) (293 mg, 1.5 mmol) was obtained in 74% yield, as a white crystaline solid, m.p. 63-64°C (from ether) (Found: C, 42.84; H, 2.48; N, 14.42. Calc. for $C_7H_5N_2Br$: C, 42.67; H, 2.56; N, 14.22%) δ_H (250 MHz, $CDCl_3$) 4.10 (2 H, s, CH_2), 7.20 (1 H, dd, J 8, 4 Hz, 5-H) 7.91 (1 H, dd, J 8, 1.4 Hz, 4-H), 8.57 (1 H, dd, J 4, 1.4 Hz, 6-H); ν_{max} (KBr), 2260, 2240, 1570, 1425 cm^{-1}; m/z 156, 158 (20, M^+), 196, 198 (100, M^+-CH_2CN), 117 (50, M^+-CH_2CN).

3-methylthio-2-cyanomethylpyridine (19)

A solution of sodium methanethiolate (11 mmol) was prepared by passing methanethiol over sodium hydride in DMF. Once effervescence had ceased the bromopyridine (18) (862 mg, 4.4 mmol) was added dropwise as a solution in DMF. After 1 h the reaction was quenched with ammonium chloride. The mixture was dried onto silica gel and chromatographed, eluting with ethyl acetate-hexane. 3-Methylthio-2-cyanomethylpyridine (19) (537 mg, 3.3 mmol) was obtained as pale brown needles, in 74% yield, m.p. 62.5-63°C (from hexane-ethyl acetate) (Found: C, 58.37; H, 4.92; N, 17.10. Calc. for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06%) δ_H (250 MHz, $CDCl_3$) 2.52 (3 H, s, CH_3), 4.00 (2 H, s, CH_2), 7.28 (1 H, dd, J 9, 6 Hz, 5-H), 7.95 (1 H, dd, J 9, 1.5 Hz, 4-H), 8.41 (1 H, dd, J 6, 1.5 Hz, 6-H), ν_{max} ($CHCl_3$) 3050, 2270(CN), 1570, 1425 cm^{-1}, m/z 164 (100, M^+), 149 (30, M-CH_3), 131 (95, M-SH), 118 (85, M-SCH_2).

4-Amino-2-methyl-9-thia-1,3,5-triazafluorene (29)

A solution of sodium methanethiolate (2.8 mmol) was prepared by passing methanethiol over sodium hydride in DMF. The pyrimidine (23) (111 mg, 0.4 mmol) was added, and the mixture heated at 100°C for 8 h. The DMF was removed and the solid was washed with aqueous HCl (pH~5), filtered, and dried under vacuum. Purification was by column chromatography on silica gel, giving the white crystalline product (sublimes 260°C), (68 mg, 0.3 mmol), in 75% yield (Found: C, 55.28; H, 3.93; N, 25.69. Calc. for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91%) δ_H (250 MHz, d_6-DMSO) 2.51 (3 H, s, CH_3), 7.48 (1 H, dd, J 8, 4 Hz, 5-H), 7.62 (1 H, br s, N-H), 8.20 (1 H, br s, N-H), 8.52 (1 H, dd, J 8, 2 Hz, 4-H), 8.72 (1 H, dd, J 4, 2 Hz, 6-H), ν_{max} (KBr) 3393(NH), 1634, 1574, 1557 cm^{-1}, m/z 216 (100, M^+), 201 (5, M-CH_3) 175 (65, M-$CNCH_3$), 148 (22).

4-Amino-9,10-dihydro-2-methyl-9,10-dithia-1,3,5-triazaphenanthrene (28)

A 100 ml 3-necked flask was charged with pyrimidine (23) (1.11 g, 4 mmol), THF (30 ml) and ammonia (30 ml). A blue solution of lithium (124 mg, 18 mmol) was added slowly to this suspension of (23) in ammonia-THF: An adaptor with a sinter in the centre, on which the lithium was placed, and a bypass tube to allow passage of the ammonia, was positioned between the dry-ice condenser and the reaction flask. Once the addition was complete, the reaction was quenched with NH_4Cl. The ammonia was evaporated, and then a THF solution of iodine was added until a permanent colour was obtained. The resulting mixture was dried onto silica gel and chromatographed, eluting with chloroform. Thiophene (29) (320 mg, 1.5 mmol) was obtained in 37% yield, along with 4-amino-9,10-dihydro-2-methyl-9,10-dithia-1,3,5-triazaphenanthrene (28) (100 mg, 0.4 mmol), in 10% yield, obtained as a yellow solid from methanol, (decomposes to give the thiophene at 200°C). (Found: C,

48.25; H, 3.29; N, 22.44. Calc. for $C_{10}H_8N_4S_2$: C, 48.37; H, 3.25; N, 22.56%). δ_H (250 MHz, d_6-DMSO) 2.36 (3 H, s, CH_3), 7.40 (1 H, dd, J 8, 5 Hz, 5-H), 7.89 (1 H, br s, N-H), 8.04 (1 H, dd, J 8, 1.5 Hz, 4-H), 8.59 (1 H, dd, J 5, 1.5 Hz, 6-H), 8.70 (1 H, br s, N-H) ν_{max} (KBr) 3300 (NH), 1615, 1530 cm^{-1} m/z 248 (M^+, 100), 233 (s, $M-CH_3$), 207 (22, $M-CNCH_3$), 175 (50).

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