Nucleophilic Displacements in Pyridine Rings

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The reactions of halopyridines containing an electron withdrawing group (-CN, -CO_2R, -COMe, -NO_2) with sulphur nucleophiles is reported.

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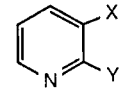
Halogen atoms in the 2(6) and 4 positions of pyridine rings can easily be replaced by nucleophiles [1]. It has long been established in the benzene series that halogen atoms are made more labile when electron withdrawing groups are present in the *ortho* and *para* positions to the halogen atom. We wish now to report the results of our study into the reactions of pyridines containing a halogen atom *ortho* to an electron withdrawing group. When 2-chloro-3-cyanopyridine **1** and 2-chloro-3-nitropyridine **2** were treated with methyl 3-mercaptopropionate in the presence of base, rapid substitution of the halogen atom occurred to yield the thioesters **3** and **4** respectively. The thioether groups in both **3** and **4** underwent a retro Michael addition when treated with strong bases under reflux conditions. Thus, when **3** was heated in dry THF with sodium hydride loss of methyl acrylate was observed and 3-cyano-2(1*H*)-pyridinthione **5** was obtained in 68% yield. Reduction of **4** with iron powder and acetic acid gave the amine **6** which was converted into its benzoyl derivative **7** with benzoyl chloride in pyridine. Treatment of **7** with sodium methoxide in methanol followed by reaction of the intermediate thione with phenacyl bromide gave the ketone **8** in 57% yield. This reaction offers a new route for the preparation of pyridinethiones. Halogen atoms in the 4-position of pyridine rings are much more reactive than halogen atoms in 2-positions. When 4-chloro-3-nitropyridine **9** was treated with methyl 3-mercaptopropionate in the presence of sodium methoxide a complex reaction occurred. It did not prove possible to isolate any pure compounds from the reaction. However the crude reaction product was reduced with iron powder and acetic acid and the intermediate amine benzoylated to yield the thioester **10** in 5% yield. It is likely that the low yield results from attack of the base on the thioester function in the manner described above. Reaction between **1** and 2-mercaptoethylamine in the presence of base gave the amine **11** which was isolated as its acetyl derivative **12**. Although thiirane is known to polymerise in the presence of base, we attempted to rapidly generate an anion from thiirane and react it with **1**. Unfortunately polymerisation was too rapid and the only pyridine product which could be isolated from the reaction mixture was 3-cyano-2-methoxypyridine **13** produced by attack of the base (sodium methoxide) on **1**. Halogen atoms in the 3 position are much less labile than 2 or 4 halogen atoms, and we have noted that even in the presence of electron withdrawing groups nucleophilic displacement of such halogen atoms is slow. For example 3-chloro-2-cyanopyridine **14** reacted slowly with methyl 3-mercaptopropionate in the presence of sodium methoxide to yield only the disulphide **15**.



1 X = CN, Y = Cl

2 X = NO_2, Y = Cl

3 X = CN, Y = 3-tpme

4 X = NO_2, Y = 3-tpme

6 X = NH_2, Y = 3-tpme

7 X = NHCOPh, Y = 3-tpme

8 X = NHCOPh, Y = S-CH_2-COPh

11 X = CN, Y = S-CH_2-CH_2-NH_2

12 X = CN, Y = S-CH_2CH_2NHAc

13 X = CN, Y = OCH_3

14 X = Cl, Y = CN

29 X = Br, Y = CO_2Me

34 X = CO_2Me, Y = Cl

35 X = CO_2Me, Y = SCH_2CO_2Me

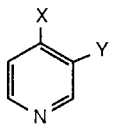
39 X = CO_2Me Y = $SCH_2CONHNHH_2$

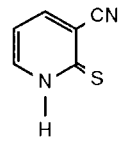
41 X = COMe, Y = Cl

45 X = Br, Y = COMe

(3-tpme = S-CH_2CH_2-CO_2Me)

Several groups [2-5] have reported that reaction of **1** with anions generated from thioglycolic acid derivatives to yield thieno[2,3-*b*]pyridines by intramolecular cyclisation of the intermediate thioethers. We have studied the reaction of *all* four pyridines with a chlorine atom adjacent





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9 X = Cl, Y = NO_2

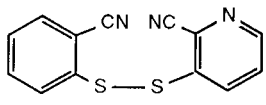
10 X = 3-tpme, Y = NHCOPh

16 X = CN, Y = Cl

17 X = Cl, Y = CN

28 X = CO_2Me, Y = Br

42 X = COMe, Y = Br



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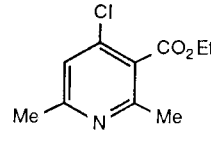

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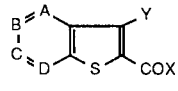
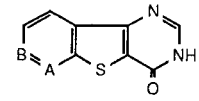
to cyano group **1**, **14**, **16** and **17** with methyl thioglycolate. In all cases no intermediate thioethers could be isolated and the thienopyridines **18-21** were formed in good yield. Similarly **1**, **14** and **16** reacted with thioglycolamide in the presence of base to yield the 3-amino-2-carboxamidothienopyridines **22-24**. When **22** and **24** were heated with triethylorthoformate the tricycles **25** and **26** were obtained whilst **23** gave only the imidate **27** under the same reaction conditions.



	A	B	C	D	X	Y
18	CH	CH	CH	N	OMe	NH_2
19	N	CH	CH	CH	OMe	NH_2
20	CH	CH	N	CH	OMe	NH_2
21	CH	N	CH	CH	OMe	NH_2
22	CH	CH	CH	N	NH_2	NH_2
23	N	CH	CH	CH	NH_2	NH_2
24	CH	CH	N	CH	NH_2	NH_2
27	N	CH	CH	CH	NH_2	N=CHOEt
31	CN	CH	N	CH	OMe	OH
32	N	CH	CH	CH	OMe	OH
33	CMe	N	CMe	CH	OMe	OH
36	CH	CH	CH	N	OMe	OH
37	CMe	N	CMe	CH	OMe	$O^-N_2H_5^+$
38	CH	CH	CH	N	OMe	$O^-N_2H_5^+$
40	CH	CH	CH	N	OMe	$O^-NH_4^+$
43	N	CH	CH	CH	OMe	Me
44	CH	CH	N	CH	OMe	Me



25 A = N, B = CH

26 A = CH, B = N

Thienopyridines were also obtained from the reaction between halopyridine esters and methyl thioglycolate. Thus methyl 3-bromopyridine-4-carboxylate **28**, methyl 3-bromopyridine-2-carboxylate **29** and ethyl 4-chloro-2,6-dimethylpyridine-3-carboxylate **30** reacted with methyl thioglycolate to yield the thienopyridines **31**, **32** and **33**, respectively. Reaction between methyl 2-chloropyridine-3-carboxylate **34** and methyl thioglycolate gave a mixture of the thioether **35** and the thienopyridine **36**. Treatment of **35** with sodium methoxide also gave **36**. All four 3-hydroxythienopyridines were acidic. Both **33** and **36** gave salts **37** and **38** respectively with hydrazine hydrate. Treatment of **35** with hydrazine hydrate in methanol gave the hydrazide **39** whilst treatment of **35** with methanolic ammonia resulted in cyclisation to the thieno[2,3-*b*]pyridine and conversion to its ammonium salt **40**.

Both 3-acetyl-2-chloropyridine **41** and 4-acetyl-3-bromopyridine **42** reacted with methyl thioglycolate to yield the 3-methylthienopyridines **43** and **44** respectively, however under identical conditions 2-acetyl-3-bromopyridine **45** failed to react.

EXPERIMENTAL

The synthesis of all intermediate disubstituted pyridines will be reported later. For general method see reference [6]. All pmr spectra were recorded in deuteriochloroform unless otherwise stated.

2-(2-Carbomethoxyethylthio)-3-cyanopyridine **3**.

A mixture of dry DMF (30 ml), sodium methoxide (from sodium (0.23 g)), methyl 3-mercaptopropionate (1.20 g) and 2-chloro-3-cyanopyridine (1.38 g) was stirred at room temperature for 1 hour. The mixture was poured into water (200 ml), the product filtered, washed with water and recrystallised from ethyl acetate/light petroleum to yield pure **3** (1.60 g, 76%), mp 101-102° as heavy colourless prisms; ir (potassium bromide): 3080, 3010, 2965, 2230, 1745, 1740, 1575, 1550, 1435, 1400, 1370, 1245, 1235, 1170 cm^{-1}; pmr: δ 2.78 (2H, t), 3.49 (2H, t), 3.68 (3H, s), 7.02 (1H, dd), 7.72 (1H, dd), 8.45 (1H, dd); ms: m/e 222 (22%) M^+.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 53.8; H, 4.4; N, 12.6. Found: C, 54.1; H, 4.5; N, 12.6.

2-(2-Carbomethoxyethylthio)-3-nitropyridine **4**.

A mixture of dry DMF (30 ml), sodium methoxide (from sodium (0.41 g)), 2-chloro-3-nitropyridine (2.78 g) and methyl 3-mercaptopropionate (2.20 g) was stirred at room temperature for 30 minutes. The mixture was poured into water and treated exactly as described for **3** to yield the title compound as yellow crystals (2.91 g, 69%), mp 85-86°; ir (potassium bromide): 3095, 2965, 1740, 1585, 1565, 1515, 1435, 1340, 1230, 760 cm^{-1}; pmr: δ 2.76 (2H, t), 3.46 (2H, t), 3.48 (3H, s), 7.12 (1H, dd), 8.39 (1H,

dd), 8.58 (1H, dd); ms: m/e 242 (1%) M^+.

Anal. Calcd. for $C_9H_{10}N_2O_4S$: C, 44.7; H, 4.2; N, 11.5. Found: C, 44.5; H, 4.0; N, 11.5.

3-Cyano-2(1*H*)-pyridinthione **5**.

A mixture of the ester **3** (1.5 g), sodium hydride (50% oil dispersion, 0.47 g) and THF (30 ml) was heated under reflux for five hours. The excess hydride was destroyed by the addition of ethanol (5 ml), the solvents removed *in vacuo* and the residue treated with water (50 ml). The *p*H was adjusted to 6 and the solids filtered to yield pure **5** (0.64 g, 68%). An analytical sample was prepared by recrystallisation from ethanol, yellow needles mp 243-246° (reported [7] mp 248-250°); ir (potassium bromide): 3250-2600 (broad), 2240, 1580, 1325, 1240 cm^{-1}; pmr δ (hexadeuteriodimethylsulphoxide): 6.86 (1H, dd), 7.94 (1H, dd), 8.12 (1H, dd), 14.30 (1H, broad s, exchangeable); ms: m/e 136 (77%) M^+.

Anal. Calcd. for $C_6H_4N_2S$: C, 53.0; H, 3.0; N, 20.6; S, 23.6. Found: C, 53.1; H, 2.9; N, 20.5; S, 23.2.

3-Amino-2-(2-carbomethoxyethylthio)pyridine **6**.

A mixture of the nitro compound **4** (3.4 g), glacial acetic acid (30 ml) and water (5 ml) was warmed on a steam bath and reduced iron powder (5 g) added in small portions. The mixture was heated at 100° for 30 minutes, diluted with water and the *p*H cautiously adjusted to 6. The mixture was filtered and extracted (×4) with ether. The dried ethereal extracts were concentrated *in vacuo* and distilled (Kugelrohr) to yield the amine **6** bp 175°/0.6 mm Hg (2.50 g) as a colourless oil; ir (sodium chloride): 3455, 3365, 3065, 3010, 2960, 2860, 1735, 1620, 1585, 1455, 1430, 1255, 1230, 1200, 1180, 1120, 800 cm^{-1}; pmr: δ 2.72 (2H, t), 3.42 (2H, t), 3.61 (3H, s), 3.88 (2H, broad s, exchangeable), 6.77 (2H, d), 7.78 (1H, t).

The amine darkened on prolonged exposure to air and was converted into its *N*-benzoyl derivative **7** (55%) mp 133-134° (colourless needles); ir (potassium bromide): 3280, 3030, 2975, 1740, 1640, 1425, 1320, 1210 cm^{-1}; pmr: δ 2.72 (2H t), 3.67 (2H, t), 3.80 (3H, s), 8.5-6.9 (9H, complex becoming 8H, complex on deuterium exchange); ms: m/e 316 (8%) M^+.

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.8; H, 5.1; N, 8.9; S, 10.1. Found: C, 60.4; H, 5.2; N, 8.9; S, 9.8.

3-Benzamido-2-benzoylmethylthiopyridine **8**.

A solution of the ester **7** (400 mg) in methanol (50 ml) containing sodium methoxide (from Na (0.25 g)) was heated under reflux for 1 hour. The intensely red solution was treated with phenacyl bromide (800 mg) and the solution allowed to stand for one hour. The solvents were removed *in vacuo*, the *p*H adjusted to 8 with dilute acid and the mixture extracted with ethyl acetate. The dried extracts were concentrated *in vacuo*, the residue crystallised from ethyl acetate/light petrol to afford crude **8**. Recrystallisation from the same solvent combination gave pure **8** as colourless needles (250 mg, 57%), mp 155-157° dec; ir (potassium bromide): 3260, 3080, 3010, 2980, 2920, 1690, 1655, 1580, 1520, 1455, 1395 cm^{-1}; pmr: δ 4.69 (2H, s), 8.2-6.8 (13H, complex becoming 12H, complex on deuterium exchange), 8.36 (1H, dd); ms: m/e 348 M^+.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 69.0; H, 4.6; N, 8.0, S, 9.2. Found: C, 68.5; H, 4.8; N, 8.1; S, 9.5.

3-Benzamido-4-(2-carbomethoxyethylthio)pyridine **10**.

An ice cold mixture of 4-chloro-3-nitropyridine **9** (5.6 g), dry DMF (60 ml), sodium methoxide (from sodium (0.82 g)) and methyl 3-mercaptopropionate (4.4 g) was stirred at 0° for 30 minutes. The mixture was poured into water, extracted with ethyl acetate and the dried extracts concentrated *in vacuo* to yield a complex (tlc) semi solid mass. The crude product was dissolved in 80% acetic acid and reduced with iron powder. The crude product was isolated as described for **6** and was shown by tlc to be a complex mixture. The mixture of compounds (2 g) was treated with dry pyridine (10 ml) and benzoyl chloride overnight. The solution was poured into water, extracted with dichloromethane to yield after concentration a yellow oil which crystallised from ether (1.25 g). Recrystallisation (and decolourisation) from ethanol gave fine colourless needles (560 mg, 5%) of pure **10**, mp 117°; ir (potassium bromide): 3260, 3045, 3020, 2965, 2940, 1735, 1650, 1575, 1510, 1470, 1290, 1215 cm^{-1}; pmr: δ 2.62 (2H, t), 3.17 (2H, t), 3.59 (3H, s), 7.6-7.1 (4H, complex), 8.1-7.7 (2H, complex), 8.20 (1H, d), 8.64 (1H, broad s, exchangeable), 9.21 (1H, s); ms: m/e 318 (1%) M^+.

Anal. Calcd. for $C_{16}H_{16}N_2O_3S$: C, 60.8; H, 5.1; N, 8.9; S, 10.1. Found: C, 60.4; H, 5.1; N, 8.9; S, 10.0.

2-(2-Acetylaminoethylthio)-3-cyanopyridine **12**.

A mixture of dry DMF (30 ml), sodium methoxide (from sodium (0.25 g)) and 2-mercaptoethylamine hydrochloride (0.6 g) was stirred at room temperature for 10 minutes and 2-chloronicotinonitrile (0.7 g) added. After one hour the mixture was poured into water (100 ml) and extracted (× 2) with ethyl acetate. The dried extracts were concentrated *in vacuo* and the residue treated with dry pyridine (5 ml) and acetic anhydride (2 ml). The solution was heated on a steam bath for a half hour, the mixture poured onto ice/water and the solution extracted with ethyl acetate. The extracts were dried, concentrated *in vacuo* to yield a syrup which crystallised from ether. Recrystallisation from ethyl acetate/light petroleum gave pure **12** (645 mg, 58%) as small colourless needles mp 113°; ir (potassium bromide): 3300, 3090, 2950, 2860, 2230, 1640, 1555, 1390 cm^{-1}; pmr: δ 1.99 (3H, s), 3.0-3.8 (4H, complex), 6.70 (1H, broad s, exchangeable), 7.04 (1H, dd), 7.78 (1H, dd), 8.50 (1H, dd); ms: m/e 221 (7%) M^+.

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 54.3; H, 5.0; N, 19.0. Found: C, 54.1; H, 4.9; N, 19.0.

Reaction of **1** with Sodium Methoxide/Thiirane.

Thiirane (650 mg, freshly distilled) was added to an ice cold solution of sodium methoxide (from sodium (0.23 g)) in dry DMF (50 ml). A white solid (presumably a polymer) was immediately deposited and **1** (1.38 g) was rapidly added. After 10 minutes the mixture was filtered, the filtrate poured into water (250 ml) and the solution allowed to stand overnight at 0°. The precipitated solids were purified by vacuum sublimation to yield 3-cyano-2-methoxypyrimidine (360 mg, 27%) as long colourless needles mp 78° identical in all respects (tlc, mmp, ir and pmr) to an authentic sample.

Bis(2-cyano-3-pyridyl)disuphide **15**.

A solution of **14** (1.0 g), dry DMF (20 ml) and sodium methoxide (from sodium (0.17 g)) was stirred at room temperature for 1 hour. The mixture was poured into water, extracted with ethyl acetate and the dried extracts concentrated *in vacuo*. The resulting solid was shown by tlc to be a mixture of product and unreacted **14**. The solid was washed with cold ether to remove the unreacted starting material to yield almost pure **15**. Recrystallisation from ethyl acetate gave the pure disulphide **15** (110 mg, 11%), mp 227°; ir (potassium bromide): 3080, 2240, 1545, 1420, 790 cm^{-1}: pmr δ (hexadeuteriodimethylsulphoxide): 7.72 (2H, 2dd), 8.34 (1H, dd), 8.85-8.64 (3H, complex); ms: m/e 270 (100%) M^+, 135 (16%).

Anal. Calcd. $C_{12}H_6N_4S_2$: C, 53.3; H, 2.2; N, 20.7; S, 23.7. Found: C, 52.9; H, 2.0; N, 20.7; S, 24.1.

Reaction of Halocyanopyridines, Halopyridine Esters and Halopyridine Ketones with Derivatives of Thioglycolic Acid.

A mixture of the halopyridine (0.01 mole), dry DMF (20 ml), sodium methoxide (0.01 mole) and either methyl thioglycolate or thioglycolamide (0.01 mole) was stirred at room temperature (method A) or warmed on a steam bath (method B) for a period of one to two hours. The mixture was poured into ice water the product filtered, washed with ice cold water and recrystallised from the appropriate solvent.

3-Amino-2-carbomethoxythieno[2,3-*b*]pyridine **18**.

This was prepared from **1** and methyl thioglycolate (method A). The reaction time was one hour. Pure **18** was obtained as bright yellow needles (ethanol), (81%) mp 195-197°; ir (potassium bromide): 3435, 3330, 3295, 3215, 3180, 3150, 3060, 2955, 1680, 1655, 1580, 1560, 1525, 1440, 1295 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.81 (3H, s), 7.25 (2H,

broad s, exchangeable), 7.45 (1H, dd), 8.54 (1H, dd), 8.68 (1H, dd); ms: m/e 208 (100%) M^+.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.9; H, 3.85; N, 13.45. Found: C, 52.0; H, 3.9; N, 13.6.

3-Amino-2-carbomethoxythieno[3,2-*b*]pyridine **19**.

Condensation between methyl thioglycolate and **14** (method A) over a two hour period gave **19**. Recrystallisation from ethyl acetate/light petroleum gave pure **19** as colourless leaflets (35%), mp 122°; ir (potassium bromide): 3460, 3320, 3070, 3030, 3000, 2960, 1675, 1625, 1555, 1525, 1440, 1380, 1325, 1260 cm^{-1}; pmr: δ 3.84 (3H, s), 6.21 (2H, broad s, exchangeable), 7.16 (1H, dd), 7.82 (1H, dd), 8.22 (1H, dd); ms: m/e 208 (100%) M^+.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.9; H, 3.85; N, 13.45; S, 15.4. Found: C, 51.6; H, 3.9; N, 13.3; S, 15.0.

3-Amino-2-carbomethoxythieno[2,3-*c*]pyridine **20**.

Condensation between methyl thioglycolate and **16** (method A) over a 1 hour period gave **10**. Recrystallisation from ethanol gave fine pale yellow needles (63%), mp 178°; ir (potassium bromide): 3500-3100 (complex), 3060, 3020, 2965, 1690, 1675, 1630, 1550, 1320, 1280, 1275 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.80 (3H, s), 7.04 (2H, s, exchangeable), 7.92 (1H, d), 8.35 (1H, d), 8.86 (1H, s); ms: m/e 208 (76%) M^+.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.9; H, 3.85; N, 13.45. Found: C, 52.1; H, 3.6; N, 13.3.

3-Amino-2-carbomethoxythieno[3,2-*c*]pyridine **21**.

Reaction between methyl thioglycolate and **17** (method A) over a 1 hour period gave **21**. Recrystallisation from ethyl acetate gave pure **21** as pale yellow needles (63%), mp 225-227° dec; ir (potassium bromide): 3440, 3295, 3205, 3170, 3040, 3015, 2965, 1685, 1630, 1595, 1435, 1340, 1290 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.82 (3H, s), 7.25 (2H, broad s, exchangeable), 7.84 (1H, dd), 8.50 (1H, d) 9.35 (1H, d); ms: m/e 208 (100%) M^+.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.9; H, 3.85; N, 13.45. Found: C, 51.9; H, 3.9; N, 13.4.

3-Amino-2-carboxamidothieno[2,3-*b*]pyridine **22**.

Condensation between **1** and thioglycolamide (method A) over a one hour period gave **22**. Recrystallisation from ethanol gave pure **22** (80%) as bright yellow needles, mp 270-272° dec, (reported [8] mp 249-252°); ir (potassium bromide): 3460, 3350, 3290, 3190, 1660, 1515, 1430, 1370, 755 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 7.18 (4H, broad s, exchangeable), 7.44 (1H, dd), 8.45 (1H, dd), 8.64 (1H, dd); ms: m/e 193 (96%) M^+.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.8; H, 3.7; N, 21.8; S, 16.6. Found: C, 49.4; H, 3.5; N, 21.4; S, 16.4.

3-Amino-2-carboxamidothieno[3,2-*b*]pyridine **23**.

Condensation between **14** and thioglycolamide (method A) as described for **22** gave crude **23**. Recrystallisation from aqueous ethanol gave pure **23** as a pale yellow microcrystalline powder (43%), mp 209-211°; ir (potassium bromide): 3340, 3180, 3050, 2995, 1660, 1620, 1585, 1430, 1390, 1240, 805 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): 7.00 (4H, broad s, exchangeable), 7.49 (1H, dd), 8.37 (1H, dd), 8.65 (1H, dd); ms: m/e 193 (100%) M^+.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.8; H, 3.7; N, 21.8; S, 16.6. Found: C, 50.0; H, 3.7; N, 21.4; S, 16.6.

3-Amino-2-carboxamidothieno[2,3-*c*]pyridine **24**.

Reaction between **17** and thioglycolamide (method A) gave the title compound. Recrystallisation from ethanol gave small pale yellow needles (74%), mp 281-284° dec; ir (potassium bromide): 3440, 3340, 3280, 3180, 1670, 1610, 1555, 1510, 1375 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 7.22 (4H, broad d, exchangeable), 8.00 (1H, d), 8.50 (1H, d), 9.12 (1H, s); ms: m/e 193 (100%) M^+.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.8; H, 3.7; N, 21.8; S, 16.6. Found: C, 49.8; H, 3.7; N, 21.6; S, 16.6.

2-Carbomethoxy-3-hydroxythieno[2,3-*c*]pyridine **31**.

Condensation between methyl thioglycolate and methyl 3-bromopyridine-4-carboxylate **28** (method B) for 1½ hours gave **31**. Recrystallisation and decolourisation from ethanol gave pure **31** (20%), mp 157-159° dec; ir (potassium bromide): 3290 (broad), 1675, 1570, 1520, 1340, 1260 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.99 (3H, s), 7.81 (1H, d), 8.56 (1H, d), 9.09 (1H, s), 10.40 (1H, broad s, exchangeable); ms: m/e 209 (38%) M^+.

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.7; H, 3.4; N, 6.7. Found: C, 51.7; H, 3.4; N, 6.8.

2-Carbomethoxy-3-hydroxythieno[3,2-*b*]pyridine **32**.

Methyl thioglycolate and methyl 3-bromopyridine-2-carboxylate **29** (method B) for one hour gave **32**. Recrystallisation from ethyl acetate gave fine needles of pure **32** (25%), mp 185.5-187.5°; ir (potassium bromide): 1675 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.99 (3H, s), 7.41 (1H, dd), 8.11 (1H, dd), 8.77 (1H, dd), 10.00 (1H, broad s, exchangeable); ms: m/e 209 (54%) M^+.

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.7; H, 3.4; N, 6.7; S, 15.3. Found: C, 51.8; H, 3.3; N, 6.5; S, 15.5.

2-Carbomethoxy-3-hydroxy-4,6-dimethylthieno[3,2-*c*]pyridine **33**.

Ethyl 4-chloro-2,6-dimethylpyridine-3-carboxylate **30** and methyl thioglycolate were reacted (method B) for 20 minutes. Recrystallisation from ethyl acetate gave fine colourless needles (21%), mp 168-169°; ir (potassium bromide): 3290, 1680, 1595, 1565, 1200 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 2.51 (3H, s), 2.82 (3H, s), 3.87 (3H, s), 7.63 (1H, s), 10.20 (1H, broad s, exchangeable); ms: m/e 237 (42%) M^+.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9; S, 13.50. Found: C, 55.8; H, 4.7; N, 6.2; S, 13.5.

The hydrazine salt of **33** was prepared from **33** (700 mg), ethanol (15 ml) and hydrazine hydrate (1 ml) by warming the reactants for a few minutes. The salt **37** crystallised on cooling and was recrystallised from hot ethanol to yield pure **37** as fine pale yellow needles (650 mg, 82%), mp 169-170°; ir (potassium bromide): 3350, 3230, 3150-1800 (broad), 1660, 1590, 1440, 1360, 1230 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 2.41 (3H, s), 2.50 (3H, s), 3.61 (3H, s), 6.28 (5H, broad s, exchangeable), 7.24 (1H, s); ms: m/e 237 (51%) (salt-N_2H_4).

Anal. Calcd. for $C_{11}H_{11}NO_3S{\cdot}N_2H_4$: C, 49.0; H, 5.6; N, 15.6; S, 11.9. Found: C, 49.3; H, 5.7; N, 15.2; S, 11.7.

Treatment of **37** with dilute aqueous sulphuric acid regenerated **33**.

Methyl 2-Carbomethoxymethylthiopyridine-3-carboxylate **35** and 2-Carbomethoxy-3-hydroxythieno[2,3-*b*]pyridine **36**.

Methyl thioglycolate and methyl 2-chloropyridine-3-carboxylate **34** were reacted together (method A) for one hour. When the reaction mixture was poured into water **35** was obtained. Recrystallisation from ether/light petroleum gave pure **35** as long, heavy, colourless needles (29%), mp 102.5-103.5; ir (potassium bromide): 3095, 3070, 3015, 2995, 1740, 1720, 1570, 1545, 1295, 1280 cm^{-1}; pmr: δ 3.68 (3H, s), 3.89 (5H, s), 6.90 (1H, dd), 8.12 (1H, dd), 8.38 (1H, dd); ms: m/e 241 (22%) M^+.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8; S, 13.3. Found: C, 50.1; H, 4.6; N, 6.1; S, 13.0.

Acidification (acetic acid) of the aqueous filtrate gave **36**. Recrystallisation from ethanol gave pure **36** as pale yellow needles (13%), mp 159-161°; ir (potassium bromide): 3000 (broad), 1685, 1590, 1570, 1520, 1310, 100 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.87 (3H, s), 7.51 (1H, dd), 8.36 (1H, dd), 8.75 (1H, dd). The HO proton was not observed; ms: m/e 209 (40) M^+.

Anal. Calcd. for $C_9H_7NO_3S$: C, 51.7; H, 3.4; N, 6.7; S, 15.3. Found: C, 51.9; H, 3.3; N, 6.9; S, 15.2.

The hydrazine salt **38** was prepared as described for **37**. Recrystallisation from ethanol gave pure **38** (61%) as fine yellow needles mp 152.5-154°; ir (potassium bromide): 3300-2000 (broad), 1675, 1580, 1570, 1475, 1445, 1280, 1230 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.67 (3H, s), 6.01 (5H, broad s, exchangeable), 7.26 (1H, dd), 8.04 (1H, dd), 8.50 (1H, dd); ms: m/e 209 (37%) (salt-N_2H_4).

Anal. Calcd. for $C_9H_7NO_3S \cdot N_2H_4$: C, 44.8; H, 4.6; N, 17.4; S, 13.2. Found: C, 44.8; H, 4.6; N, 16.8; S, 13.1.

2-Carbomethoxy-3-hydroxythieno[2,3-*b*]pyridine **36**.

Diester **35** (1 g) was added to a solution of sodium methoxide (from sodium (0.25 g) and methanol (25 ml)) and the mixture stirred overnight. The solution was poured into water, acidified with acetic acid and the product filtered. Recrystallisation from dilute ethanol gave pure **36** (780 mg, 90%) identical in all respects (tlc, mp, mmp and ir) to the material reported above.

2-Carbomethoxy-3-methylthieno[2,3-*b*]pyridine **43**.

A mixture of methyl thioglycolate and 3-acetyl-2-chloropyridine **41** was condensed (method A) for 2 hours. The crude product was recrystallised from aqueous ethanol to yield colourless needles of pure **43** (16%), mp 122-122.5°; ir (potassium bromide): 1710 cm^{-1}; pmr: δ 2.75 (3H, s), 3.95 (3H, s), 7.35 (1H, dd), 8.10 (1H, dd), 8.68 (1H, dd); ms: m/e 207 (100%) M^+.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 58.0; H, 4.4; N, 6.8; S, 15.5. Found: C, 57.6; H, 4.3; N, 6.5; S, 15.3.

2-Carbomethoxy-3-methylthieno[2,3-*c*]pyridine **44**.

A mixture of 4-acetyl-3-bromopyridine **42** and methyl thioglycolate was reacted for 1 hour (method A). The crude product was recrystallised from ethanol to yield fine, colourless needles of pure **44** (66%), mp 128-129°; ir (potassium bromide): 1720 cm^{-1}; pmr: δ 2.76 (3H, s), 3.96 (3H, s), 7.68 (1H, dd), 8.57 (1H, d), 9.14 (1H, dd); ms: m/e 207 (22%) M^+.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 58.0; H, 4.4; N, 6.8; S, 15.5. Found: C, 57.6; H, 4.3; N, 6.5; S, 15.4.

Methyl 2-(Carboxyhydrazidomethylthio)pyridine-3-carboxylate **39**.

A solution of the diester **35** (1.0 g), absolute ethanol (35 ml) and hydrazine hydrate (0.4 g) was stirred at room temperature for 24 hours. The solution was filtered, the product washed with cold ethanol and recrystallised from hot ethanol to yield pure **39** as lustrous needles (400 mg, 40%), mp 158.5-159.5°; ir (potassium bromide): 3305, 3250, 3050, 2960, 1715, 1675, 1610, 1285 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 3.83 (2H, s), 3.88 (3H, s), 4.16 (2H, broad s, exchangeable), 7.25 (1H, dd), 8.21 (1H, dd), 8.61 (1H, dd), 9.06 (1H, broad s, exchangeable); ms: m/e 210 (100%) M^+, 166 (5%) $(M\text{-}CH_2CONHNH_2)^+$.

Anal. Calcd. for $C_9H_{11}N_3OS$: C, 44.8; H, 4.6; N, 17.4; S, 13.3. Found: C, 44.4; H, 4.6; N, 17.0; S, 13.2.

Pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one **25**.

A mixture of the amide **22** (1.22 g) and triethylorthoformate (150 ml) was heated under reflux for 2 hours. The solution was cooled, solvents removed *in vacuo* and the crystalline residue recrystallised from acetic acid to yield pure **25** (630 mg, 49%) as a white solid, mp 347-349° (dec.); (reported [5], [9] mp 340°); ir (potassium bromide): 3160 (broad), 1670, 1590, 1555, 1380 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 7.64 (1H, dd), 8.37 (1H, s), 8.72 (1H, d), 8.85 (1H, d), 12.90 (1H, broad s, exchangeable); ms: m/e 203 (58%) M^+.

Anal. Calcd. for $C_9H_5N_3OS$: C, 53.2; H, 2.5; N, 20.7; S, 15.8. Found: C, 53.6; H, 2.6; N, 20.3; S, 15.7.

Pyrido[4',3':4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-one **26**.

A mixture of the amide **24** (1.3 g) and triethylorthoformate (150 ml) was heated under reflux for 2 hours. The mixture was filtered, cooled overnight and the product removed by filtration. Recrystallisation from boiling DMF gave pure **26** (1.03 g, 75%) as a microcrystalline white solid, mp >340° (dec.); ir (potassium bromide): 3050, 2900-2100 (broad), 1680, 1590, 1430, 1405 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 8.13 (1H, dd), 8.32 (1H, s), 8.69 (1H, d), 9.40 (1H, d), 10.4-13.8 (1H, very broad s, exchangeable); ms: m/e 203 (100%) M^+.

Anal. Calcd. for $C_9H_5N_3OS$: C, 53.2; H, 2.5; N, 20.7; S, 15.8. Found: C, 53.0; H, 2.6; N, 20.4; S, 15.6.

2-Carboxamide-3-ethoxymethyleneaminothieno[3,2-*b*]pyridine **27**.

A mixture of the amide **23** (0.5 g) and triethylorthoformate (20 ml) was heated under reflux for 2 hours. The hot mixture was filtered to yield crude **27** (395 mg, 61%). The solid was recrystallised from triethylorthoformate to yield pure **27** (325 mg) as small almost colourless needles, mp >350°; ir (potassium bromide): 3490, 3380, 3330, 3100, 1670, 1600, 1565, 1520, 1440, 1385 cm^{-1}; pmr (hexadeuteriodimethylsulphoxide): δ 1.39 (3H, t), 4.40 (2H, q), 7.46 (1H, dd), 7.94 (2H, broad s, exchangeable), 8.44 (1H, dd), 8.70 (1H, dd), 9.29 (1H, s); ms: m/e 249 (15%) M^+.

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.1; H, 4.3; N, 17.0. Found: C, 53.0; H, 4.4; N, 16.9.

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