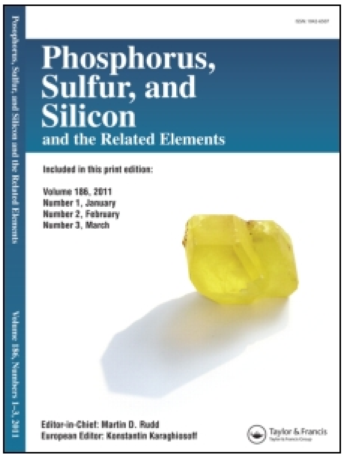

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS, A NEW ROUTE TO SYNTHESIS OF THIOPYRANO[3,2-C]PYRIDINE, THIOPYRANO[4,3-B]PYRIDINE, AND BIPYRIDYL DERIVATIVES

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS, A NEW ROUTE TO SYNTHESIS OF THIOPYRANO[3,2-C]PYRIDINE, THIOPYRANO[4,3-B]PYRIDINE, AND BIPYRIDYL DERIVATIVES

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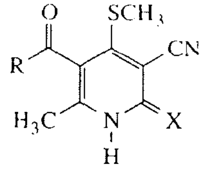
Pyridine derivatives (**4a, d, e**) were reacted with carbon disulfide in dry tetrahydrofurane (THF) in the presence of potassium *tert*-butoxide under Argon to yield thiopyanopyridine derivatives (**7, 10**). Also (**2a, 4c**) were reacted with carbon disulfide under the same condition producing the dithioacetal derivatives (**13**) which were converted to bipyridyl derivatives (**14**) *via* reaction with cyanothioacetamide in isopropyl alcohol and sodium isopropoxide.

Keywords: Thiopyrano[3,2-c]pyridine; Thiopyrano[4,3-b]pyridine; Bipyridines; Accurate mass

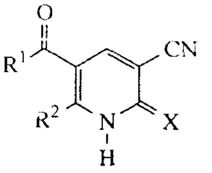
Polyfunctionally substituted condensed pyridines are interesting as potential pharmaceuticals[1] and agrochemicals.[2] Thienopyridines and thiopyranopyridines are of special importance due to reported biological activities.[3] Recently we have developed a synthesis of the pyridinethiones **1–3** and could utilise these thiones for the synthesis of thieno[2,3-b]pyidines.[4–6] In the present paper we report on the utility of **1–3** for synthesis of thiopyanopyridines.

*Corresponding author.



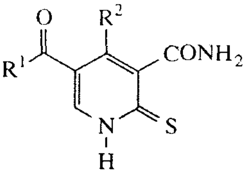
(1)

a, $R=CH_3$, X=S
b, $R=OCH_3$, X=S
c, $R=CH_3$, X=O



(2)

a, $R^1=R^2=CH_3$, X=S
b, $R^1=OC_2H_5$, $R^2=CH_3$, X=S
c, $R^1=OC_2H_5$, $R^2=CH_2CO_2C_2H_5$, X=S
d, $R^1=OC_2H_5$, $R^2=CH_2CH_3$, X=S
e, $R^1=OCH_3$, $R^2=CH_3$, X=S
f, $R^1= R^2= -(CH_2)_3-$, X=S
g, $R^1=R^2=CH_3$, X=O



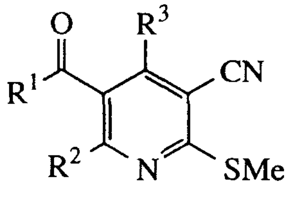
(3)

a, $R^1=R^2=CH_3$
b, $R^1=OC_2H_5$, $R^2=CH_3$
c, $R^1=OCH_3$, $R^2=CH_3$

It was found that methylation of (**1a,b**) and (**2a–c**) with methyl iodide in ethanolic sodium hydroxide afforded the corresponding methyl thioether (**4a–e**) in a good yield.

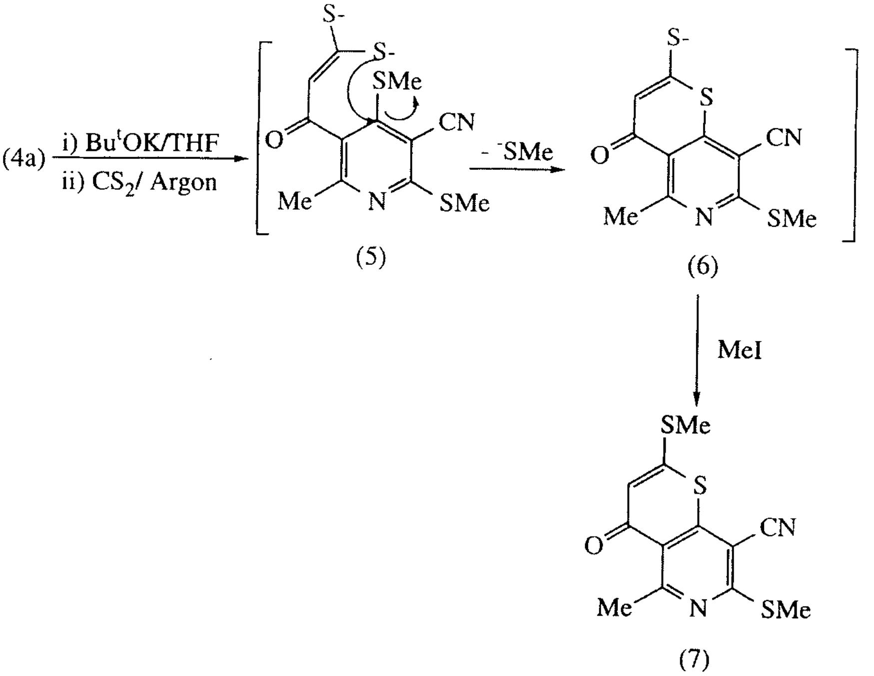
Reaction of (**4a**) with carbon disulfide in dry tetrahydrofuran under argon using potassium tert-butoxide as a base followed by methylation with methyl iodide afforded thiopyrano[3,2-c]pyridine derivative (**7**) in good yield. It is believed that **7** is formed via the intermediates **5** and **6** (*cf.* scheme 1).

Similarly reacting (**4e**) with carbon disulfide under the same condition afforded the thiopyrano[4,2-b]pyridine derivative (**10**). This compound was also



(4)

a, $R^1=R^2=CH_3$, $R^3=SCH_3$
b, $R^1=OCH_3$, $R^2=CH_3$, $R^3=SCH_3$
c, $R^1=R^2=CH_3$, $R^3=H$
d, $R^1=OC_2H_5$, $R^2=CH_3$, $R^3=H$
e, $R^1=OC_2H_5$, $R^2=CH_2CO_2C_2H_5$, $R^3=H$



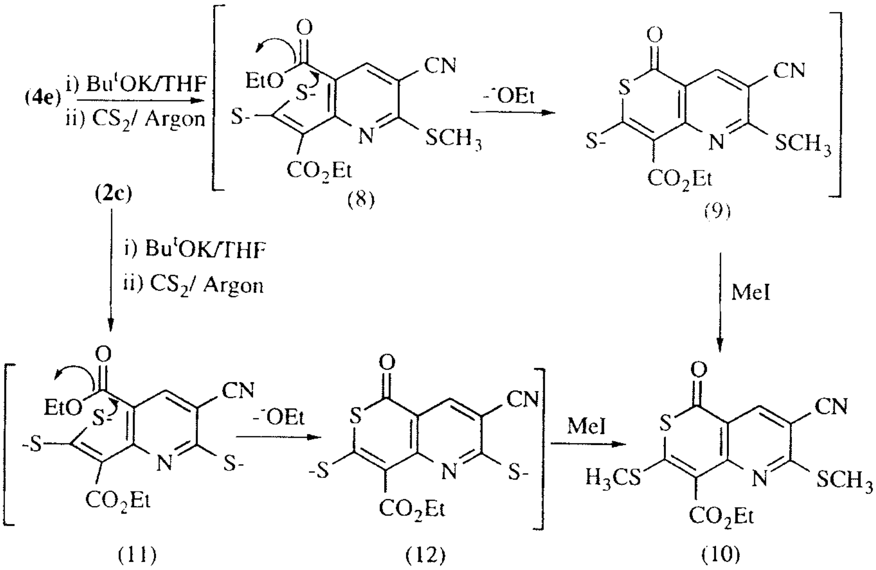
SCHEME 1

obtained by reacting (**2c**) with carbon disulfide under the same condition used to react **4e** with the same reagent (*cf* scheme 2). It is believed that (**10**) is formed from (**4e**), carbon disulfide and methyl iodide through intermediates (**8**) and (**9**), while (**11**) and (**12**) are the intermediates for formation of (**10**) from (**2c**), carbon disulfide and methyl iodide.

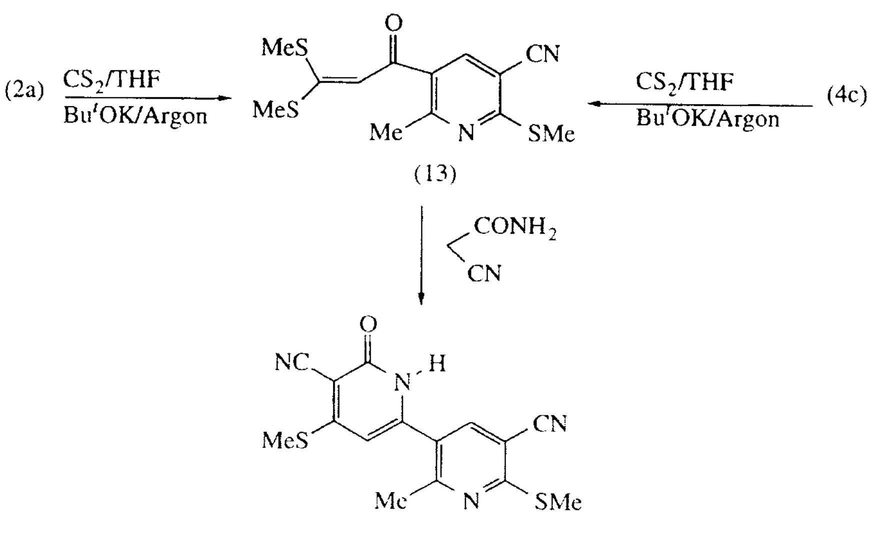
The reaction of (**2a**) with carbon disulfide and methyl iodide afforded the corresponding dithioacetal derivative (**13**), which is also obtained by treatment of (**4c**) with carbon disulfide and methyl iodide under the same condition. The bipyridyl derivative **14** could be also prepared *via* reacting **13** with cyano-acetamide (*cf* Scheme 3).

5-Acetyl-3-cyano-6-methylpyridine-2(1H)-one (**2g**) afforded the pyridone (**15**) on treatment with carbon disulfide followed by methylation with methyl iodide in THF and potassium tert-butoxide. The ^{1}HNMR spectrum of (**15**) showed singlet signal at δ_H 5.53 corresponding to the vinyl proton in addition to methyl signal at δ_H 2.63, S methyl signal at δ_H 1.56, NH signal at δ_H 11.9 and pyri-dinone H-4 at δ_H 7.57 ppm.

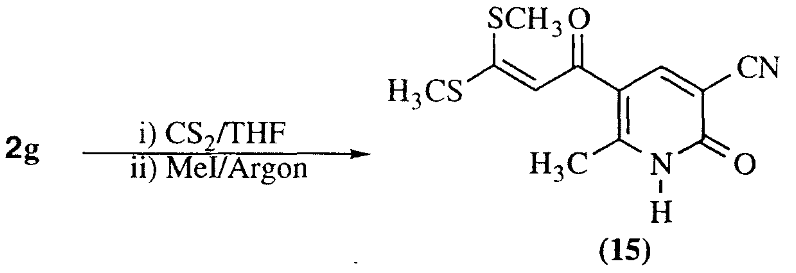
Finally *5-acetyl-3-cyano-6-methyl-4-methylthiopyridin-2(1H)-one* (**1c**) reacted with carbon disulphide and methyl iodide in THF in the presence of potassium



SCHEME 2



SCHEME 3



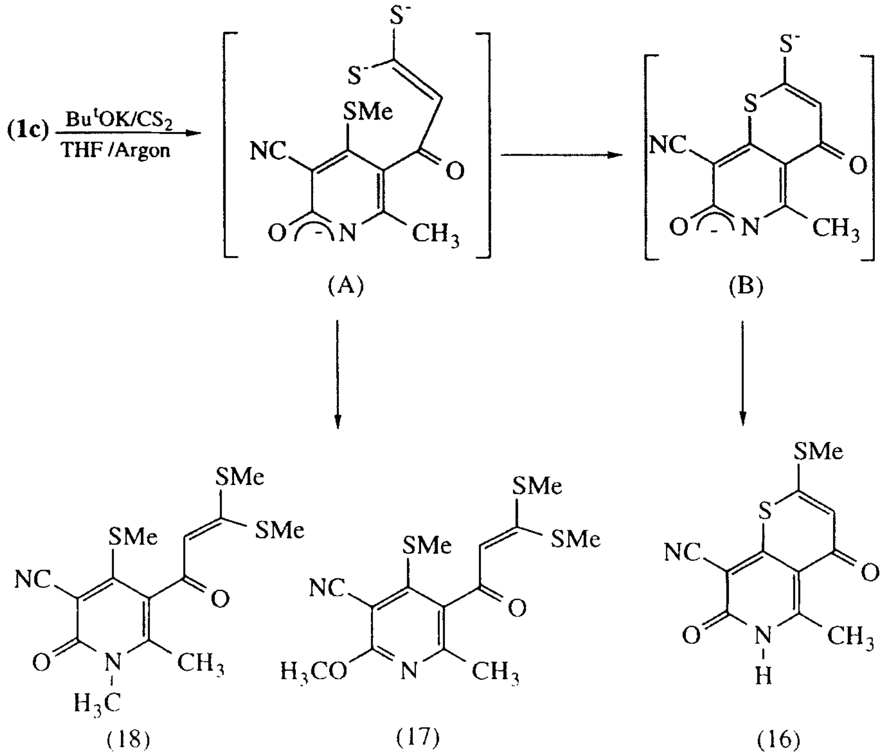
tert-butoxide as a base under argon to yield a mixture of products. This mixture was boiled in ethanol and the ethanol insoluble part was isolated by filteration and identified as *8-cyano-4,7-dioxo-5-methyl-2-methylthiothiopyrano[3,2-c] pyridine* (**16**). The structure of this product was confirmed from spectral data. The ethanol soluble part is believed to be a mixture of **17** and **18** in the ratio 2:1. This mixture could not be separated into its consituents but its ^{1}HNMR shows that it is a mixture of **17** as a major product and **18** as minor one. These products are believed to be formed *via* the mechanism in scheme 4 which include intermediates formation of (**A, B**). Trials to control this reaction to yield only one product failed.

EXPERIMENTAL

M.P.s are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer for Nujol mulls NMR spectra were recorded on a Bruker AC300 spectrometer at 300 MHz for solutions of $CDCl_3$ and [$^2H_6$]dimethyl sulfoxide with tetramethylsilane (TMS) as internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) and Kratos Concept (high resolution) spectrometers using electron impact (EI) or chemical ionization with ammonia (CI). Microanalysis were carried out at the microanalytical laboratory in Chemistry Department, Manchester University.

General Method for Preparation of 4a-e

A solution of the pyridinethione (4 mmol) in a mixture of ethanol (10 mL) and aqueous sodium hydroxide (5 mL, 10%) was stirred at room temperature for one hour then treated with an excess of methyliodide, stirring was continued for 2h. Water was then added, and the solid product, so formed, was recovered by filtration and was recrystallized from ethanol to give (**4a–e**).



SCHEME 4

5-Acetyl-3-cyano-6-methyl-2,4-bis(methylthio)pyridine (4a)

Yield (1g, 95%), m.p. 102–104°C. .IR, shows ν_{max} 2219 (CN), and 1699 cm^{-1} (C=O). ^{1}HNMR, [$CDCl_3$], shows δ_H 2.57 (3H, s, CH_3CO), 2.54 (3H, s, SCH_3), 2.53 (3H, s, SCH_3) and 2.42 ppm (3H, s,CH_3), ^{13}CNMR,[$CDCl_3$], shows δ_C at 202.26, 164.22, 156.13, 146.907, 135.699, 114.363, 108.106, 32.026, 22.94, 19.266, and 13.413 ppm. Mass (EI), shows M^+ at m/z 252, (M^+-CH_3) at m/z 237 and at m/z 221 which is the base peak. Elemental analysis, requires ($C_{11}H_{12}N_2OS_2$), C 52.37, H 4.80, N 11.11%, found, C 52.17, H 4.55, N 10.85%.

Methyl-2,4-bis(methylthio)-3-cyano-6-methylpyridine-5-carboxylate (4b)

The product extracted by ether, dried and evaporated to give yellowish green semisolid yield (1g, 95%). IR, shows ν_{max} 2930 (C-H), 2220 (CN), and 1733 cm^{-1} (C=O, ester). ^{1}HNMR,[$CDCl_3$], shows δ_H 3.9 (3H, s, OCH_3), 2.56 (3H, s, SCH_3), 2.54 (3H, s, SCH_3), and 2.47 ppm (3H, s, CH_3). Mass(CI), shows

($M^+ + 1$) at m/z 269 which is the base peak. Accurate mass (CI), requires ($M^+ + 1$) ($C_{11}H_{12}N_2O_2S_2$), 269.0418, found, 269.0415.

5-Acetyl-3-cyano-6-methyl-2-methylthiopyridine (4c)

Yield (0.9g, 83%), m.p. 155–156°C. IR, shows ν_{max} at 2227 (CN) and 1685 cm^{-1} (CO). ^{1}HNMR [$CDCl_3$], shows δ_H at 8.07 (1H, s, ring-H), 2.77 (3H, s, COCH_3), 2.63 (3H, s, SCH_3), and 2.54 ppm (3H, s, ring-CH_3). ^{13}CNMR [$CDCl_3$], shows δ_C at 197.2, 165.34, 162.58, 141.27, 126.95, 115.06, 28.95, 25.79, and 13.18 ppm. Mass (EI), shows M^+ at m/z 206 and (M^+-CH_3) at m/z 191. Accurate mass (EI), requires M^+ ($C_{10}H_{10}N_2OS$), 206.0514. found, 206.0508.

Ethyl-3-cyano-6-methyl-2-methylthiopyridine-5-carboxylate (4d)

Yield (2g, 97%), m.p. 135–137°C. IR, shows ν_{max} at 2230 (CN), and 1716 cm − 1 (C=O). ^{1}HNMR [$CDCl_3$], shows δ_H at 8.28 (1H, s, ring-H), 4.33 (2H, q, O$CH_2$$CH_3$), 2.84 (3H, s, S$CH_3$), 2.63 ppm (3H, s, ring-CH_3) and 1.37 ppm (3H, t, $OCH_2$$CH_3$). Mass (EI), shows M^+ at m/z 236 which is the base peak, (M^+-C_2H_4) at m/z 208 (95%) and (M^+-OC_2H_5) at m/z 191. Elemental Analysis, requires ($C_{11}H_{12}N_2O_2S$), C 55.92, H 5.12, N 11.86%. found, C 55.87, H 5.09, N 11.93%.

Ethyl-3-cyano-6-(ethoxycarbonylmethyl)-2-methylthiopyridine-5-carboxylate (4e)

The reaction mixture was poured onto ice-water, and the oily material was extracted by $CHCl_3$ and dried using $MgSO_4$. The solvent was evaporated to afford a red oily substance solidified to a crystalline plates in yield (2.8g, 99%). m.p. 120–122°C IR, shows ν_{max} at 3080 (C-H), 2223 (CN), and 1720 cm^{-1} (C=O). ^{1}H NMR [$CDCl_3$], shows δ_H at 8.35 (1H, s, ring-H), 4.35 (2H, q, $CH_3$$CH_2$O), 4.26 (2H, s, -$CH_2$$CO_2$-), 4.14 (2H, q, -$CH_2$$CO_2$-), 2.61 (3H, s, S$CH_3$), 1.34 (3H, t, $CH_3$$CH_2$O), and 1.23 ppm (3H, t, $CH_3$$CH_2$O). Mass (EI), shows M^+ at m/z 308. Accurate mass (EI), requires M^+ ($C_{14}H_{16}N_2O_4S$), 308.0831, found, 308.0829.

General Method for the Reaction of 4a,c,e 2a,c,g and 1c with Carbon Disulfied and Methyl Iodide

To a solution of potassium *tert*-butoxide (0.224g, 2mmol) in dry THF (50ml), (4a or 4c or 4e or 2a or 2c or 2g or 1c) (1mmol) in dry THF was added dropwise. The reaction mixture was stirred at room temperature under argon for about 15 minutes. An excess of carbon disulfide (1ml) was then added dropwise. Stirring was continued for 30 minutes at room temperature. Then an excess of methyl iodide (1 mL) was added. The reaction mixture was left stirring at room temperature for about 2h. Then poured onto ice/coled water, the solid obtained was collected by filtration, and recrystallised from the proper solvent.

8-Cyano-2,7-dimethylthio-5-methyl-4-H-thiopyrano{3,2-c]pyridine-4-one (7)

Crystallization from chloroform, yield (0.24g, 81.7 %) m.p.243–245°C. IR, shows ν_{max} at 2216 (CN), 1661 (C=O), and 1622 cm^{-1} (C=C). ^{1}HNMR [$CDCl_3$] shows δ_H at 6.72 (1H, s, H-3), 3.02 (3H, s, CH_3), 2.80 (3H, s, SCH_3) and 2.60 ppm (3H, s, SCH_3). Mass (EI), shows M^+ at *m/z* 294 which is the base peak and (M^+-CH_3) at *m/z* 279. Accurate mass (EI), requires M^+ ($C_{12}H_{10}N_2OS_3$), 293.9955, found, 293.9950.

Ethyl-3-Cyano-2,7-bis(methylthio)-5-oxo-5H-thiopyrano[4,3-b]pyridine-8-carboxylate (10)

Crystallization from ethanol, yield (0.3g, 84%), m.p. 202–203°C. IR, shows ν_{max} at 2226 (CN), 1722 (C=O), and 1649 cm^{-1} (C=C, C=N). ^{1}HNMR [$CDCl_3$], shows δ_H at 8.41 (1H, s, ring-H), 4.34 (2H, q, CH_3CH_2O), 2.58 (3H, s, SCH_3), 2.53 (3H, s, SCH_3), and 1.33 ppm (3H, t, CH_3CH_2O). Mass (EI), shows M^+ at *m/z* 352 which is the base peak. Accurate mass (EI), requires M^+ ($C_{14}H_{12}N_2O_3S_3$), 352.0010, found, 352.00030.

5-Cyano-3-(3,3-bismethylthiopropenoyl)-2-methyl-6-methylthiopyridine (13)

Crystallisation from ethanol, yield (0.23g, 76%), m.p. 177–179°C. IR, shows ν_{max} 2226 (CN), 1667 (C=O), and 1625 cm^{-1} (C=C). ^{1}HNMR [$CDCl_3$], shows δ_H at 7.82 (1H, s, ring-H), 6.27 (1H, s, vinyl-H), 2.72 (3H, s, ring-CH_3), 2.63 (3H, s, SCH_3), and 2.53 (6H, s, SCH_3). Mass (EI), shows M^+ at *m/z* 310, and (M^+-CH_3) at 295 which is the base peak. Accurate mass (EI), requires M^+ ($C_{13}H_{14}N_2OS_3$), 310.0268, found 310.0262.

5-Cyano-3-(3,3-bismethylthiopropenoyl)-2-methylpyridine-6(1H)-one (15)

Crystallization from ethanol, yield (0.2, 72%) m.p. >300°C. IR, shows ν_{max} at 2228 (CN), 1678 (C=O), and 1629 (C=C). ^{1}HNMR [DMSO-d_6 + $CDCl_3$], shows δ_H at 11.9 (1H, br, exch., NH), 7.57 (1H, s, ring-H), 5.53 (1H, s, vinyl-H), 2.63 ppm (3H, s, ring-CH_3), and 1.56 (6H, s, SCH_3). Mass (EI), shows M^+ at *m/z* 280. Accurate mass (EI), requires ($C_{12}H_{12}N_2O_2S_2$), 280.0340, found, 280.0343.

8-Cyano-5-methyl-2-methylthio-6,7-dihydro-4H-thiopyrano[3,2-c]pyridine-4,7-dione (16)

Crystallization from acetic acid, yield (0.3g, 63%) m.p. 295–300°C decomp. IR, shows ν_{max} at 2219 (CN), 1670 (C=O), and 1625 cm^{-1} (C=C). ^{1}HNMR, [DMSO-d_6] shows δ_H at 12.70 (1H, br.,exch., NH), 6.05 (1H, s, H-3), 2.44 (3H, s, SCH_3), and 2.20 ppm (3H, s, CH_3). Mass (EI), shows M^+ at *m/z* 264 which is the base peak. Accurate mass, requires ($C_{11}H_8N_2O_2S_2$), 264.0027, found, 264.0012

Evaporation of filterate afforded other solid product which was shown to be a mixture of 17, and 18, crystallisation from ethanol, (0.22g, 35.6%), m.p. 250–252°C. IR, shows ν_{max} at 2217 cm^{-1} (CN), 1641 cm^{-1} (C=O). ^{1}HNMR, [DMSO-d_6+$CDCl_3$] shows δ_H at 6.29 (1H, s, vinyl-H), 5.96 (1H, s, vinyl-H), 3.37 (3H, s, OCH_3), 2.69 (3H, s, NCH_3), 2.46 (3H, s, SCH_3), 2.42 (6H, s, SCH_3), 2.37 (6H, s, SCH_3), 2.31 (6H, s, SCH_3), 2.16 ppm (3H, s, CH_3). Mass (CI), shows (M^+ + 1) at *m/z* 341, and (EI), shows M^+ at *m/z* 340. Accurate mass (EI), requires M^+ ($C_{14}H_{16}N_2O_2S_3$), 340.0374, found, 340.0375.

3-Cyano-6-(3-cyano-6-methyl-2-methylthiopyridin-3-yl)-4-methylthio-pyridine-2(1H)-one (14)

To a solution of sodium isopropoxide prepared from sodium (0.05g, 2 mmol) and isopropanol (30 mL) was added ketene dimethylthioacetal (13) (0.31 g, 1 mmol), and cyanoacetamide (0.08g, 1 mmol). The reaction mixture was heated under reflux for one hour. After cooling it was acidified to pH 4 by conc. HCl, and the solid obtained was recovered by filtration in yield (0.26g, 79%), and recrystallised from acetone, m.p. >300°. IR, shows ν_{max} at 3469 (NH), 2220 (CN), and 1652 cm-1 (C=O). ^{1}HNMR [DMSO-d_6 + $CDCl_3$], shows δ_H at 12.45 (1H, br. exch., NH), 8.12 (1H, s, ring-H), 6.40 (1H, s, ring-H), 2.62 (3H, s, ring-CH_3), 2.58 (3H, s, SCH_3), and 2.56 ppm (3H, s, SCH_3). Mass (EI), shows M^+ at *m/z* 328. Accurate mass (EI), requires M^+ ($C_{15}H_{12}N_4OS_2$), 328.0452, found 328.0448.

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