Synthesis of Polysubstituted Benzene, Pyridine, Pyran, and Polyfunctionally Condensed Pyridine Derivatives

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การสังเคราะห์สารที่ถูกเกณฑ์หลายแห่งจากเบนซิน พิริดีน พิราน และอนุพันธ์ของพิริดีนที่เกิดจากการกลืนตัวของสารที่มีหมู่ฟังก์ชั่นหลายหมู่

ฟาทิ เอ. อาบู-ชานาบ, โมฮาเม็ด อาร์. ซาลิม, บาซิล เจ. เวดฟีลด์ และ โมฮาเม็ด เอช. เอลนากดี (2541)
วารสารวิจัยวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย **23 (2)**

รายงานนี้เป็นวิธีวิเคราะห์เบนซินและพิรานที่ถูกแทนที่หลายแห่ง และสังเคราะห์อนุพันธ์ของ พิริดีนที่เกิดจากการกลืนตัวของสารที่มีหมู่ฟังก์ชั่นหลายหมู่ โดยให้ทำปฏิกิริยาผ่านเมทิลีนไนไตรล์ที่มีหมู่เอนเอมีนที่ว่องไว

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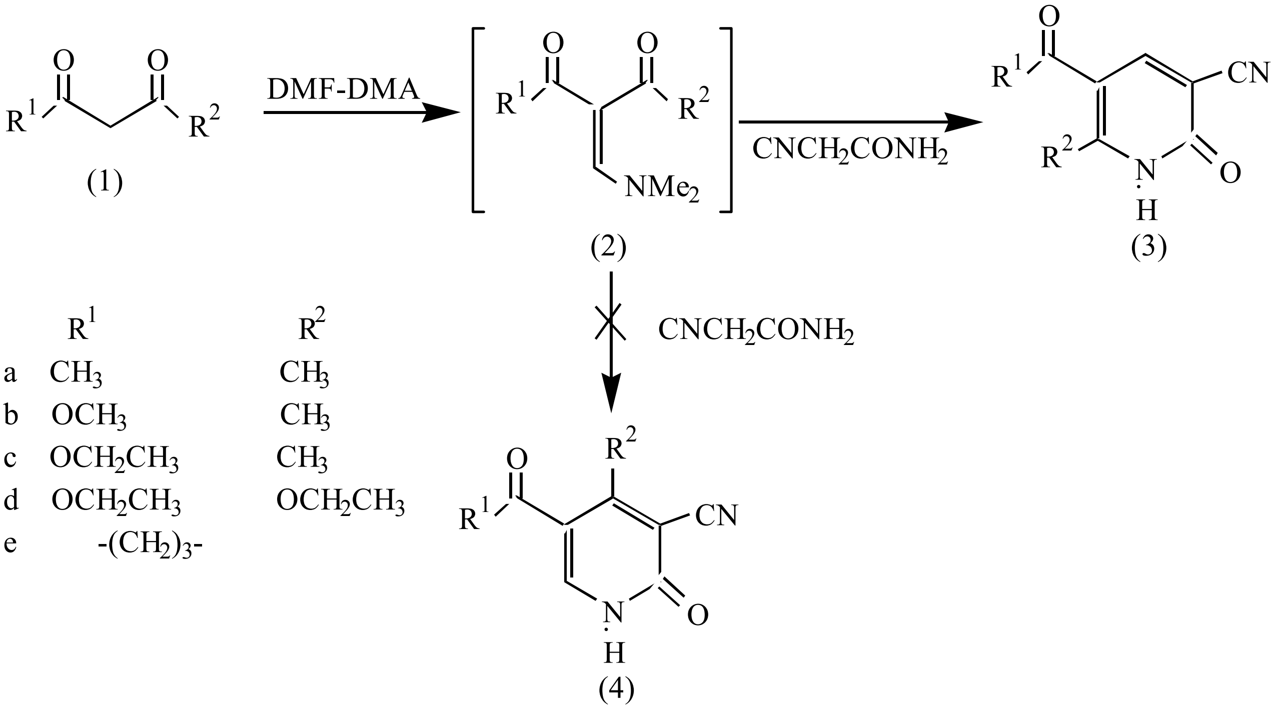
INTRODUCTION

The considerable biological and medicinal activities of polyfunctionally substituted pyridines(1-3) and condensed pyridine(4-8) have stimulated considerable recent research aimed at developing syntheses of these compounds. Recently we have shown(9,10) that the reaction of enamines (**2**) derived from the dicarbonyl compounds (**1a-e**) with cyanoacetamide gives 2, 3, 5, 6-tetrasubstituted pyridine derivatives (**3**), although the reaction of **2** with cyanoacetamide has been claimed(11) to afford **4**, (*cf.* Scheme 1).



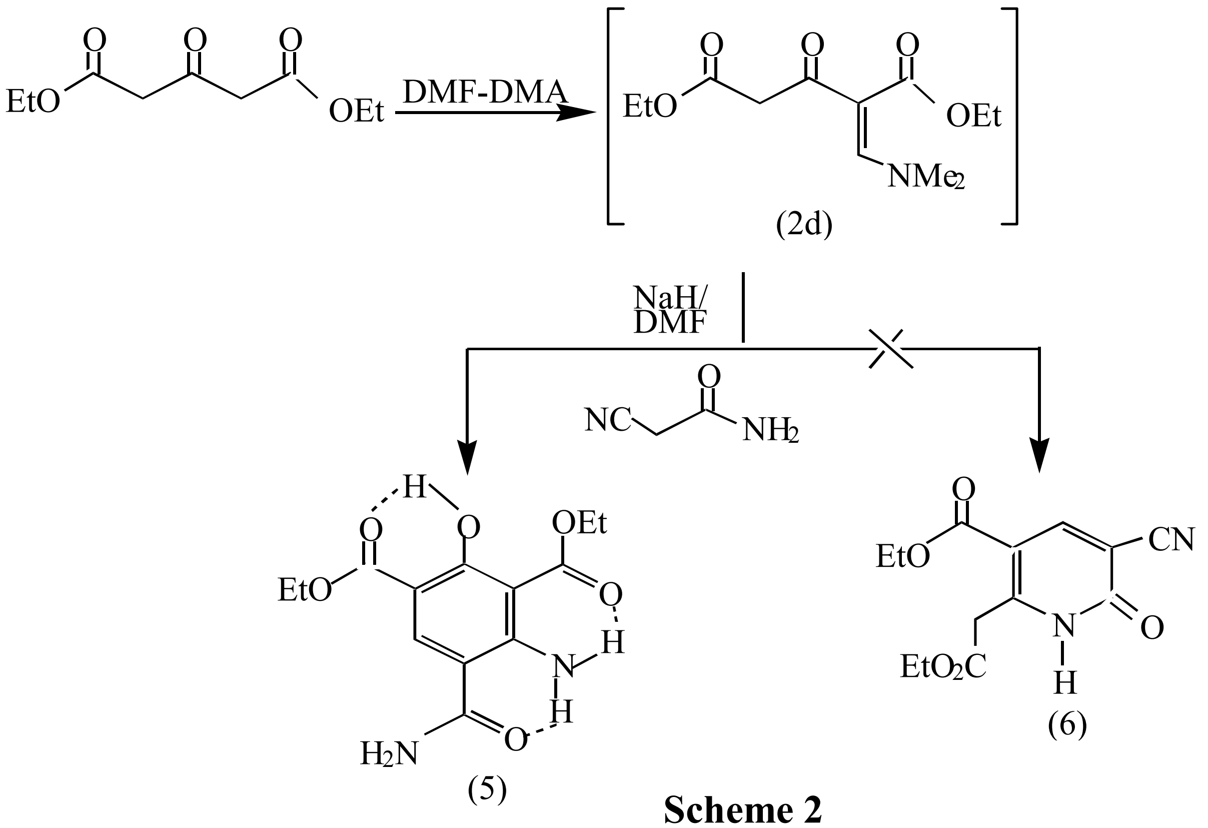
Scheme 1

RESULTS AND DISCUSSION

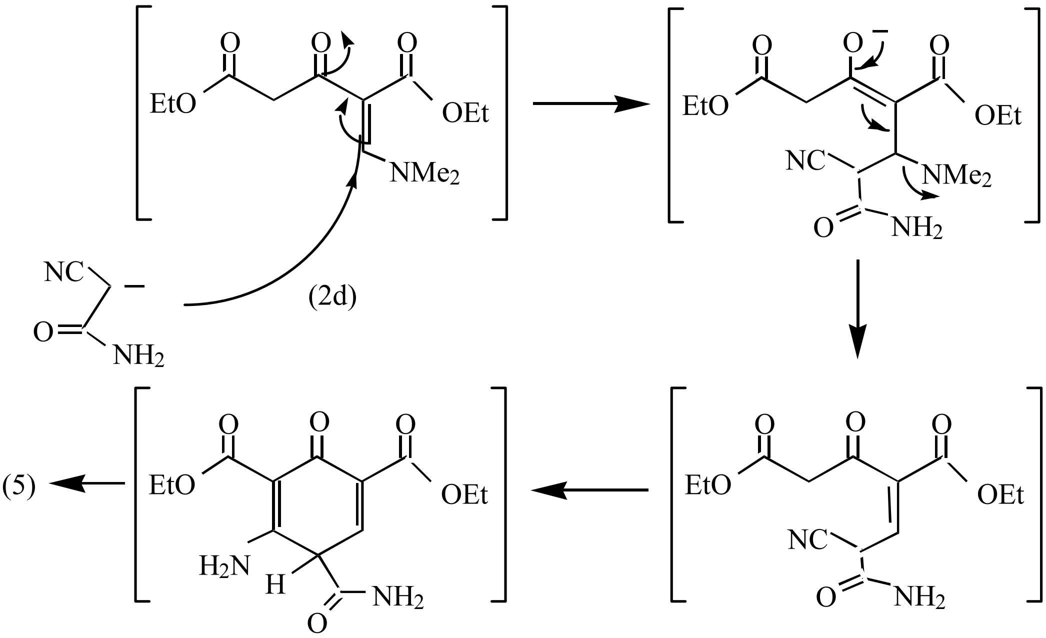
In continuation of this work we investigated the reaction of **2d** (prepared *via* condensation of diethy l, 3-acetonedicarboxylate with dimethylformamide dimethyl acetal, DMF-DMA) towards cyanoacetamide. This reaction afforded the pentasubstituted benzene **(5)** rather than the expected pyridone derivative **(6)** (Scheme 2).

The structure of compound **5** was confirmed by its ^1H NMR spectrum which shows an exchangeable signal for one proton at δ 12.27 ppm for the intramolecular hydrogen bonded OH, a broad exchangeable signal at δ 8.22 ppm for two protons of the amide NH_2 group, a singlet at δ 8.19 ppm for the ring proton and two broad exchangeable signals at δ 7.82 and 7.02 ppm for two protons of the amino group. It is believed that **5** is formed *via* a sequence such as that outlined in (Scheme 3).

In contrast, the reaction of enamine **(2d)** with malononitrile and sodium hydride in DMF produced the pyridone derivative (**7a**) rather than pentasubstituted benzene derivative (**8a**) (Scheme 4). The reaction was repeated using piperidine and ethanol and compound **7b** was separated. The ^1H NMR spectrum for compound **7a** shows the methylene group (a) at δ 4.03 ppm as a singlet, and the IR spectrum for **7b** shows the disappearance of the cyano group. The most likely route to the formation of pyridone

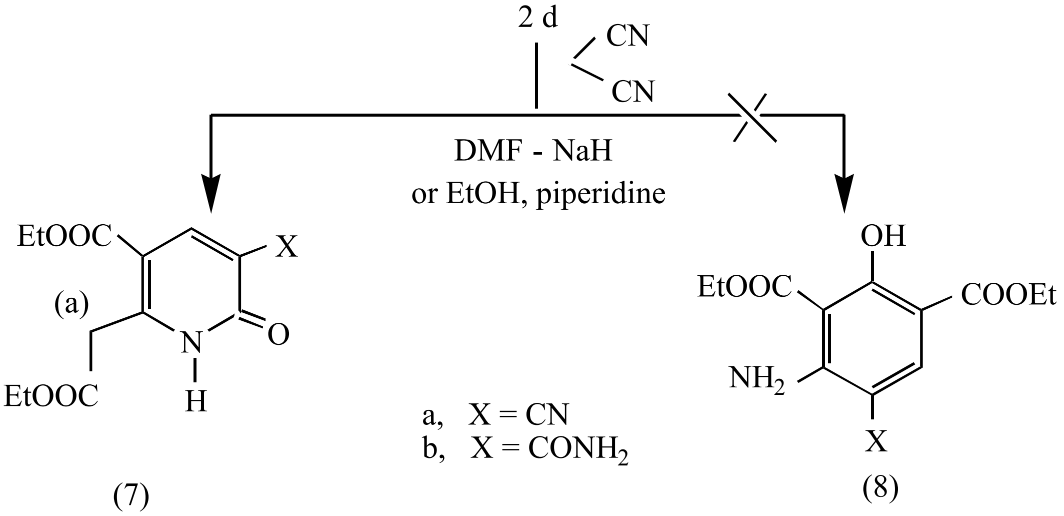


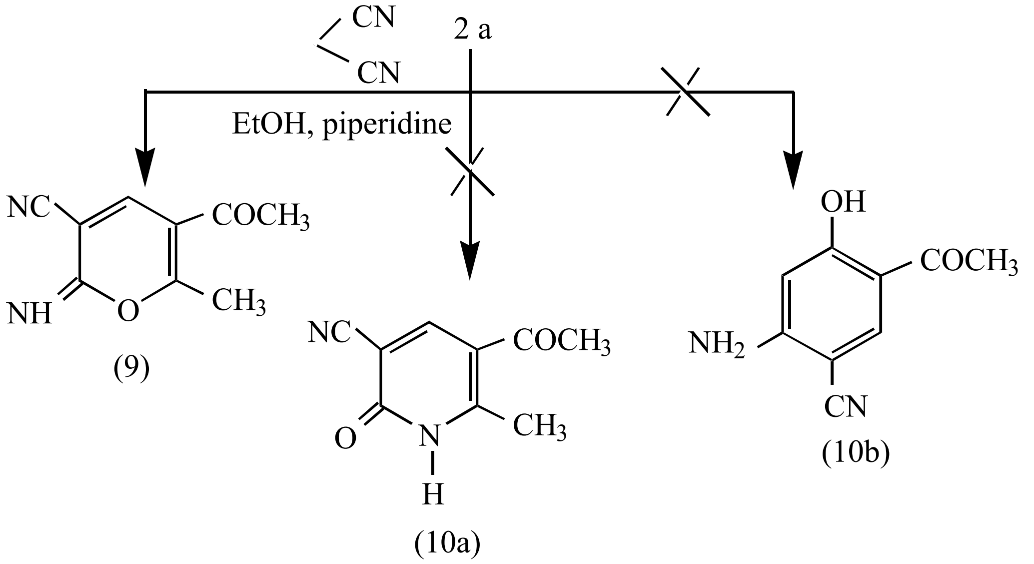
Scheme 2



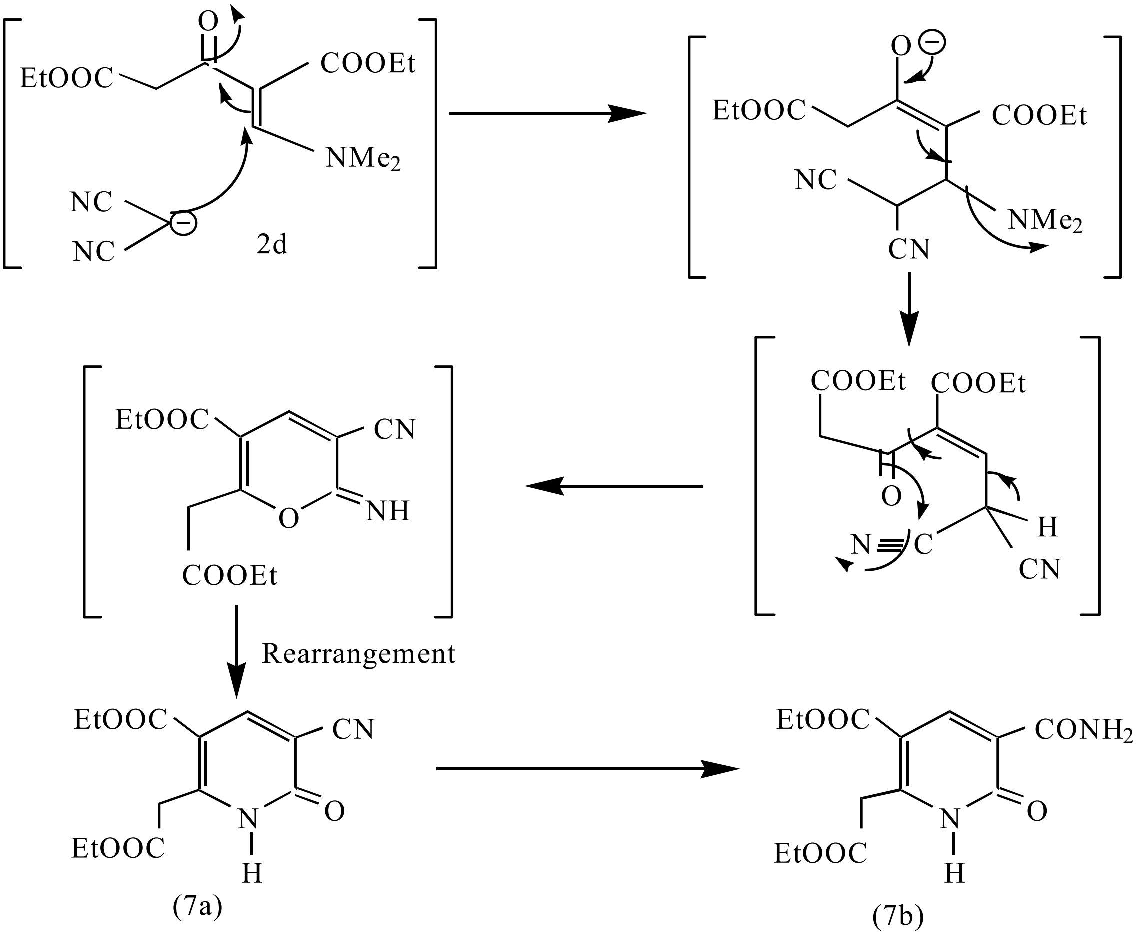
Scheme 3

derivatives (**7a&b**) is outlined in Scheme 5. While the reaction of enamine (**2a**) with malononitrile and piperidine in ethanol furnished the pyran derivative (**9**) but not the pyridone derivative **(10a)** or tetrasubstituted benzene derivative (**10b**) (Scheme 4) its ^{1}H NMR spectrum shows two singlets at δ 2.55 and 2.37 for the two methyl groups in structure **9,** and NH of pyridone (**10a**) would normally appear at over 12 ppm in ^{1}H NMR.



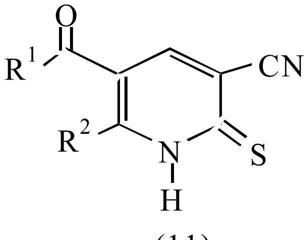


Scheme 4



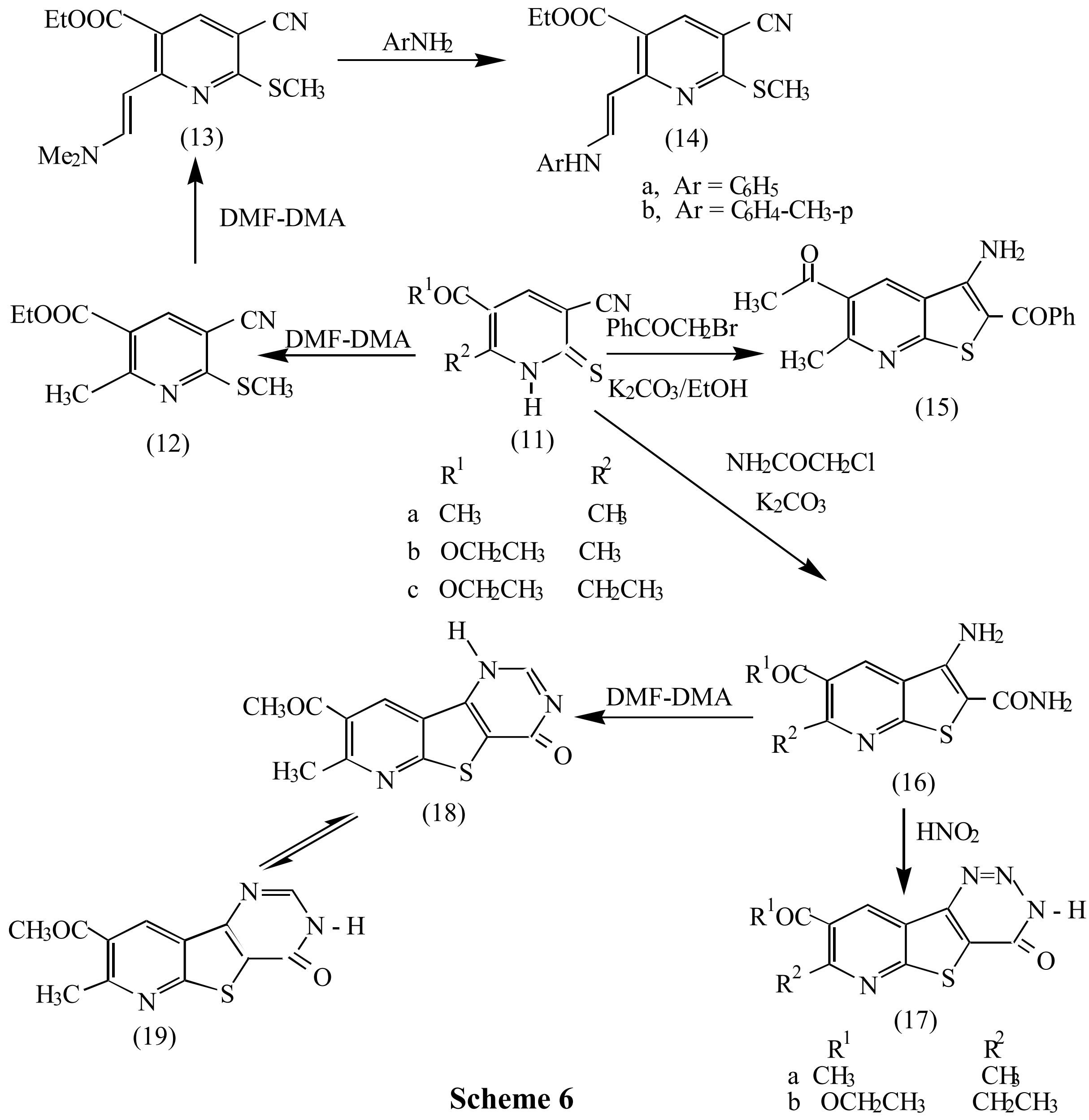
Scheme 5

We have recently reported(9) efficient synthesis of **11a-c** *via* the reaction of **2a,c,d** with cyanothioacetamide. In this article we report on the utility of these compounds for the synthesis of polyfunctionally condensed pyridines such as **12-19** (Scheme 6).



(11)

	R^1	R^2
a	CH_3	CH_3
b	OCH_2CH_3	CH_3
c	OCH_2CH_3	CH_2CH_3



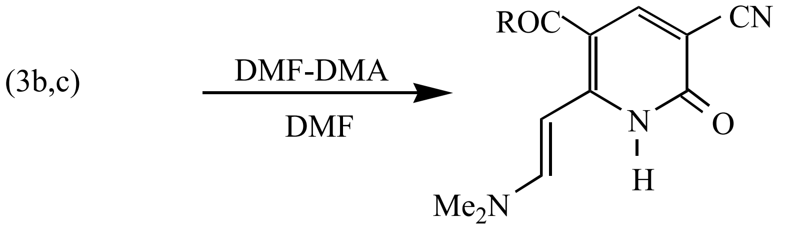
Scheme 6

Thus methylation of 3-cyano-5-carbethoxy-6-methylpyridine-2(1*H*)-thione (**11b**) with DMF-DMA afforded the corresponding methylthioether (**12**). Treatment of **12** with DMF-DMA in anhydrous DMF afforded the corresponding *N,N*-dimethylenamine (**13**) which is assigned the configuration based on the presence of two doublets at δ 8.10 and 6.47 ppm corresponding to the two *trans* vinyl protons with coupling constant 12.4 Hz. Treatment of (**13**) with aromatic amines(12) in glacial acetic acid gave the corresponding *N*-arylenamines (**14a,b**) without cyclization (Scheme 6), and ^{1}H NMR of **14a** shows a triplet at δ 1.38, quartet at δ 4.32 for the ethyl group and doublet at δ 10.97 ppm, exchangeable for the NH group.

The pyridine-2(1*H*)-thione (**11a**) reacted with phenacyl bromide in the presence of K_2CO_3 under reflux in ethanol to give the thieno[2,3-b]pyridine derivative (**15**). Also, pyridine-2(1*H*)-thione derivatives (**11a-c**) reacted with chloroacetamide in the presence of K_2CO_3 under reflux in ethanol to give thieno

[2,3-b]pyridine derivatives (**16a-c**) (Scheme 6). Treatment of (**16a,c**) with nitrous acid afforded the pyrido[2,3-b]thieno[3,2-b]-1,2,3-triazine derivatives (**17a,b**) with a good yield. Also, compound (**16a**) on treatment with DMF-DMA afforded a product that is formulated as pyrido [2,3-b]thieno[3,2-d]pyrimidin-4(3*H*)-one (**18**) and its tautomer (**19**) (Scheme 6). Tautomer (**18**) is believed to be the major one as ^{1}H NMR shows two singlets at δ 8.93 and 8.43 ppm corresponding to the two ring protons and a broad exchangeable signal at 10.75 ppm for the NH of structure (**18**), whereas the NH of structure (**19**) would normally appear at over 12 ppm.

Finally, pyridine-2(1*H*)-one derivatives (**3b,c**) reacted with DMF-DMA in hot anhydrous DMF to afford enamines (**20**) with a good yield.



(20)

a, R = OCH_3
b, R = OCH_2CH_3

EXPERIMENTAL

M.p.'s are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer for Nujol mulls. The ^{1}H and ^{13}C 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 an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) and Kratos Concept (high resolution, HRMS) spectrometers using electron impact (EI) or chemical ionization with ammonia (CI). Microanalysis was carried out in the micro-analytical laboratory at the Department of Chemistry, Manchester University, U.K.

3-Amino-2,6-bis(carbethoxy)-4-carbamoylphenol (5)

A mixture of diethyl 1,3-acetone dicarboxylate (2.02 g, 10 mmol) and (DMF-DMA) (1.19 g, 10 mmol) in anhydrous *N,N*-dimethylformamide (DMF) in a dry flask under argon (10 mL) was stirred at room temperature for 24 h. In a second flask, a mixture of sodium hydride (0.48 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) in anhydrous DMF (10 mL) was stirred under argon at room temperature for 10 min. The contents of the second flask were transferred by syringe into the first flask, and the resulting mixture was stirred for 24 h. A mixture of ethanol (25 mL) and water (25 mL) was added, then the reaction mixture was acidified with concentrated HCl to pH 4, and stirring was continued for 24 h. The product so formed was recovered by filtration and purified by recrystallisation from methanol, yielding 1 g (35%) solid, m.p. 221-223°C. **IR,** shows ν_{max} at 3447, 3367 (OH), 3200, 1687 (CO) and 1642 cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d$_6$- CDCl$_3$),** δ = 12.27 (s, 1H, exch., OH), 8.22 (br., 2H, exch. amide), 8.19 (s, 1H, ring-H), 7.82 (br. 1H, exch., NH), 7.02 (br., 1H, exch., NH), 4.37-4.27 (2q, 7Hz, 4H, $2CH_3\underline{CH_2}O$), 1.36-1.28 ppm (2t, 7Hz, 6H, 2<u>CH</u>$_3$CH$_2$O). **Mass (EI),** ($C_{13}H_{16}N_2O_6$), (M^+), *m/z* = 296, (M^+-C_2H_5OH), *m/z* = 250. **HRMS (EI),** requires **M**$^+$ 296.1008, found 296.1007.

Calcd. C 52.70; H 5.40; N 9.45 %

Found. C 52.90; H 5.25; N 9.61 %

Ethyl-3-cyano-6-(carbethoxymethyl)pyridine-2 (1H)-one-5-carboxylate (7a)

The reaction was carried out as described above using diethyl 1,3-acetonedicarboxylate (2.0 g, 10 mmol), DMF-DMA (1.19 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and sodium hydride (0.48 g, 10 mmol) in anhydrous DMF (30 mL) solvent: ethanol, yield 1.4 g (67%) solid, m.p. 240°C. **IR,** shows ν_{max} at 3341 (NH), 2231 (CN), 1749, 1710 (CO), 1667 (CO) cm^{-1}. **^{1}H NMR, (300 MHz, DMSO-d$_6$-CDCl$_3$),** δ = 12.75 (br., 1H, exch., NH), 8.30 (s, 1H, ring-H), 4.32 (q., 7Hz, 2H, O<u>CH</u>$_2$CH$_3$), 4.23 (q, 7Hz, 2H, <u>OCH</u>$_2$CH$_3$), 4.26 (s, 2H, CH$_2$), 1.36 (t, 7Hz, 3H, OCH$_2$<u>CH</u>$_3$), 1.29 ppm (t, 7Hz, 3H, OCH$_2$<u>CH</u>$_3$), **^{13}C NMR, (75 MHz, DMSO-d$_6$-CDCl$_3$),** δ = 179.44, 167.68, 162.23, 152.14, 144.19, 124.63, 115.22, 114.69, 77.43, 76.99, 76.58, 62.57, 62.32, 36.75, 14.07, 14.02. **Mass (EI),** ($C_{13}H_{14}N_2O_5$), (M^+), *m/z* = 278 which is the base peak.

Calcd. C 56.11; H 5.03; N 10.07 %

Found. C 56.01; H 5.15; N 10.25 %

Ethyl-3-carbamoyl-6-(carbethoxymethyl) pyridine-2(1H)-one-5-carboxylate (7b)

The reaction was carried out as described above using diethyl-1,3-acetone dicarboxylate (2.0 gm, 10 mmol), DMF-DMA (1.19 g, 10 mmol) malononitrile (0.66 g, 10 mmol), piperidine (1 mL) in absolute ethanol (30 mL), solvent, ethanol, yield 1.2 g, (59%), m.p. 217°C solid. **IR,** shows ν_{max} at 3385, 3190 (NH), 1730, 1705, 1660 (CO) cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d$_6$-CDCl$_3$),** δ = 12.76 (br., 1H, exch. NH), 8.9 (d, 1H, exch., *J* = 3.5 Hz, NH), 8.84 (s, 1H, ring-H), 7.06 (br., 1H, exch., *J* = 3.5 Hz, NH), 4.19 (q, 7Hz, 2H, <u>OCH</u>$_2$CH$_3$), 4.08 (q, 6Hz, 2H, <u>OCH</u>$_2$CH$_3$), 4.03 (s, 2H, CH$_2$), 1.25 (t, 7Hz, 3H, OCH$_2$<u>CH</u>$_3$), 1.17 ppm (t, 6Hz, 3H, OCH$_2$<u>CH</u>$_3$). **Mass (EI),** ($C_{13}H_{16}N_2O_6$), (M^+), *m/z* = 296, (M^+-C_2H_5OH), *m/z* = 250, and (M^+-74) at *m/z* = 222 which is the base peak.

Calcd. C 52.70; H 5.40; N 9.45 %

Found. C 52.96; H 5.80; N 9.20 %

5-Acetyl-3-cyano-6-methyl-2-imino pyran (9)

The reaction was carried out as described above using acetylacetone (1 g, 10 mmol), DMF-DMA (1.19 g, 10 mmol), malononitrile (0.66 g, 10 mmol), piperidine (1 mL) in absolute ethanol (30 mL), solvent, ethanol, yield 0.6 g, (60%), m.p. 250°C, solid. **IR,** shows ν_{max} at 3330 (NH), 2210 (CN), 1670 (CO) cm^{-1}. **^{1}H NMR, (300 MHz-DMSO-d$_6$),** δ = 8.23 (s, 1H, ring-H), 6.04-6.12 (br., 1H, exch. NH), 2.55 (s, 3H, COCH$_3$), 2.37 ppm (s, 3H, CH$_3$). **Mass (EI),** ($C_9H_8N_2O_2$), (M^+), *m/z* = 176 (42), 161 (100), 133 (14), 105 (8), 78 (22), 64 (15).

Calcd. C 61.36; H 4.54; N 15.90 %

Found. C 61.45; H 4.35; N 15.75 %

Ethyl-5-cyano-2-methyl-6-methylthiopyridine -3-carboxylate (12)

Equimolecular amounts of **11b** (1.92 g, 10 mmol), and DMF-DMA (1.19 g, 10 mmol) in anhydrous DMF (10 mL) were stirred overnight at room temperature. The reaction mixture was poured onto ice water, and the solid obtained was recrystallized from ethanol, yield 2 g (97%), solid, m.p. 135-137°C. **IR,** shows ν_{max} at 2230 (CN), 1716 (CO) cm^{-1}. **^{1}H NMR (300 MHz, CDCl$_3$),** δ = 8.28 (s, 1H, ring-H), 4.33 (q, 6Hz, 2H, O<u>CH</u>$_2$CH$_3$), 2.84 (s, 3H, S<u>CH</u>$_3$), 2.63 (s, 3H, ring-<u>CH</u>$_3$), 1.37 ppm (t, 6Hz, 3H, OCH$_2$<u>CH</u>$_3$). **Mass (EI),** ($C_{11}H_{12}N_2O_2S$), (M^+), *m/z* = 236 which is the base peak, (M^+-C_2H_4), *m/z* = 208 and (M^+-OC_2H_5) *m/z* = 191.

Calcd. C 55.93; H 5.02; N 11.86 %

Found. C 55.87; H 5.09; N 11.93 %

Ethyl-5-cyano-2-[2(N,N-dimethylamino) ethenyl]-6-methylthiopyridine-3-carboxylate (13)

A mixture of (**12**) (2.36 g, 10 mmol) and DMF-DMA (1.19 g, 10 mmol) in anhydrous DMF (10 mL) was stirred overnight at room temperature. Then the reaction was heated at 120-125°C for about 0.5 h. The reaction mixture was poured onto ice-cold water, and the solid obtained was recovered by filtration and purified by recrystallisation from ethanol, yield 2 g (79%), solid, m.p. 172-174°C. **IR,** shows ν_{max} at. 2215 (CN), 1702 (CO), 1643 cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$),** δ= 8.12 (s, 1H, ring-H), 8.10 (d, 1H, vinyl-H, *J*=12.39 Hz), 6.47 (d, 1H, vinyl-H, *J*=12.45 Hz), 4.27 (q, 7Hz, 2H, $O\underline{CH_2}CH_3$), 3.03 (s, 6H, br., $\underline{Me_2}N$), 2.57 (s, 3H, $S\underline{CH_3}$), 1.34 ppm (t, 7Hz, 3H, $OCH_2\underline{CH_3}$). **Mass (EI),** ($C_{14}H_{17}N_3O_2S$), (M^+), *m/z* = 291 which is the base peak.

Calcd. C 57.73; H 5.84; N 14.43 %

Found. C 57.69; H 6.11; N 13.96 %

General Method for the reaction of (13) with aniline derivatives

Equimolar amounts of (**13**) (0.3 g, 1 mmol) and aromatic amine (1 mmol) were dissolved in acetic acid (15 mL). The reaction mixture was stirred at room temperature overnight. The solid was recovered by filtration and purified by recrystallisation from the proper solvent.

Ethyl-5-cyano-2-[2(N-phenylamino)ethenyl]-6-methylthiopyridine-3-carboxylate (14a)

Crystallisation from ethanol, yield 0.3 g, (94%), solid, m.p. 210-211°C. **IR,** shows ν_{max} at 3667, 2214 (CN), 1700 (CO) cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$),** δ = 10.97 (d, 1H, br., exch., NH, *J*=12.35 Hz), 8.22 (s, 1H, ring-H), 7.35-7.23 (m, 3H, ArH), 7.07-7.02 (m, 3H, ArH), 7.00 (d, 1H, vinyl-H), 4.32 (q, 6Hz, 2H, $O\underline{CH_2}CH_3$), 2.79 (s, 3H, $S\underline{CH_3}$), 1.38 ppm (t, 6Hz, 3H, $OCH_2\underline{CH_3}$). **Mass (EI),** ($C_{18}H_{17}N_3O_2S$), (M^+) *m/z* = 339.

Calcd. C 63.71; H 5.01; N 12.38 %

Found. C 63.17; H 5.05; N 12.06 %

Ethyl-5-cyano-2-[2(N-p-tolylamino)ethenyl]-6-methylthiopyridine-3-carboxylate (14b)

Crystallisation from ethanol, yield 0.33 g, (96%), solid, m.p. 210-211°C. **IR,** shows ν_{max} at 3650, 2212 (CN), 1702 (CO) cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$),** δ = 10.98 (d, 1H, br., exch., NH, *J*=12.25 Hz), 8.21 (s, 1H, ring-H), 7.25 (dd, 12,3Hz , 1H, vinyl-H), 7.13 (d, 2H, ArH, *J*=8.2 Hz), 6.89 (d, 2H, ArH, *J*=8.38 Hz), 6.60 (d, 12Hz , 1H, vinyl-H), 4.32 (q, 7Hz, 2H, $O\underline{CH_2}CH_3$), 2.77 (s, 3H, $S\underline{CH_3}$), 2.30 (s, 3H, $\underline{CH_3}$), 1.37 ppm (t, 7Hz, 3H, $OCH_2\underline{CH_3}$). **Mass (EI),** ($C_{19}H_{19}N_3O_2S$), (M^+), *m/z* = 353.

Calcd. C 64.58; H 5.38; N 11.90 %

Found. C 64.77; H 5.59; N 11.62 %

5-Acetyl-3-amino-2-benzyl-6-methylthieno[2,3-b]pyridine (15)

Equimolar amounts of (**11a**) (1.92 g, 10 mmol) and phenacyl bromide (1.99 g, 10 mmol) as well as anhydrous potassium carbonate (2 g, 15 mmol) in absolute ethanol (30 mL) were heated under reflux for 3 hours. The reaction mixture was diluted with water, and the product was collected by filtration and recrystallisation from acetic acid, yield 2.7 g (86%), solid, m.p. 185-186°C. **IR,** shows ν_{max} at 3425, 3326 (NH_2), 1695 (CO) cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$),** δ = 8.26 (s, 1H, ring-H), 7.91-7.82 (m, 2H, ArH), 7.60-7.43 (m, 3H, ArH), 7.21 (s, 2H, exch., NH_2), 2.83 (s, 3H, $CO\underline{CH_3}$), 2.62 ppm (s, 3H, $\underline{CH_3}$). **Mass (CI),** ($C_{17}H_{14}N_2O_2S$), (M^++1), *m/z* = 311 which is the base peak. **HRMS (CI),** requires (M^++1), 311.0854, found, 311.0849.

Calcd. C 65.80; H 4.51; N 9.03 %

Found. C 65.75; H 4.40; N 9.25 %

General method for the reaction of pyridine-2 (1H)-thione derivatives (11a-c) with chloroacetamide

Equimolar amounts of *pyridine*-2(1*H*)-*thione* (**11a-c**) (10 mmol) and chloroacetamide (0.66 g, 10 mmol) as well as anhydrous potassium carbonate (2 g, 15 mmol) in absolute ethanol (30 mL), were heated under reflux for 3 hours. The reaction mixture was diluted by water, and the product was collected by filtration.

5-Acetyl-3-amino-6-methylthieno[2,3-b] pyridine-2-carboxamide (16a)

Crystallisation from acetic acid, yield 2.3 g, (93%), solid, m.p. 270-271°C. **IR,** shows ν_{max} at 3400, 3325 (NH_2), 1715, 1685 (CO), 1652 cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6- $CDCl_3$),** δ = 8.92 (s, 1H, ring-H), 7.21 (br. 2H, exch., NH_2), 6.94 (br. 2H, exch., NH_2), 2.71 (s, 3H, $COCH_3$), 2.62 ppm (s, 3H, ring-CH_3). **Mass (EI),** ($C_{11}H_{11}N_3O_2S$), (M^+), *m/z* = 249 which is the base peak. **HRMS (EI),** requires (M^{+}), 249.0572, found, 249.0567.

Calcd. C 53.01; H 4.41; N 16.86 %

Found. C 53.25; H 4.48; N 16.70 %

3-Amino-5-carbethoxy-6-methylthieno[2,3-b] pyridine-2-carboxamide (16b)

Crystallisation from acetic acid, yield 2.6 g, (95%) solid, m.p. 245-247°C. **IR,** shows ν_{max} at 3477, 3302, 3185 (NH_2), 1709 (CO), 1643 (CO) cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6-$CDCl_3$),** δ= 8.79 (s, 1H, ring-H), 7.01 (br. 2H, exch., NH_2), 6.37 (br. 2H, exch., NH_2), 4.32 (q, 7Hz ,2H, $CH_3\underline{CH_2}O$), 2.79 (s, 3H, ring-$\underline{CH_3}$), 1.36 ppm (t, 7Hz, 3H, $\underline{CH_3}CH_2O$). **Mass (EI),** ($C_{12}H_{13}N_3O_3S$), (M^{+}), *m/z* = 279, and (M^+-NH_3), *m/z* = 262. **HRMS (EI),** requires M^+, 279.0677, found, 279.0680.

Calcd. C 51.61; H 4.65; N 15.05 %

Found. C 51.80; H 4.80; N 15.16 %

3-Amino-5-carbethoxy-6-ethylthieno[2,3-b] pyridine -2-carboxamide (16c)

Crystallisation from acetic acid, yield 2.7 g, (92.5%), solid, m.p. 210-212°C. **IR,** shows ν_{max} at 3443, 3347, 3172 (NH_2), 1710 (CO), 1686 (CO) cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6-$CDCl_3$),** δ = 8.84 (s, 1H, ring-H), 7.22 (br. 2H, exch., NH_2), 6.93 (2H, br. exch., NH_2), 4.34 (q,6Hz, 2H, $CH_3\underline{CH_2}O$), 3.14 (q, 7Hz , 2H, $CH_3\underline{CH_2}$-ring), 1.37 (t, 6Hz , 3H, $\underline{CH_3}CH_2O$), and 1.24 ppm (t, 7Hz, 3H, $\underline{CH_3}CH_2$-ring). **Mass (EI),** ($C_{13}H_{15}N_3O_3S$), (M^+), *m/z* = 293 which is the base peak.

Calcd. C 53.24; H 5.12; N 14.33 %

Found. C 53.10; H 5.16; N 14.31 %

General method for the reaction of 3-aminothieno[2,3-b]pyridine-2-carboxamide derivatives (16a,c) with nitrous acid

A solution of (**16a, or c**) (1 mmol) in acetic acid (25 ml) was treated with sodium nitrite (0.14 g, 2 mmol) portionwise with stirring at room temperature for 1 hour. The solid was collected and purified by recrystallisation from the proper solvent.

8-Acetyl-7-methyl-3,4-dihydropyrido [2,3:5,4] thieno[3,2-d]triazine-4-one (17a)

Crystallisation from acetic acid, yield 0.22 g, (83%) solid, m.p. 210°C. **IR,** shows ν_{max} at 3286 (NH), 1695 (CO) cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6-$CDCl_3$),** δ = 15.55 (br. 1H, exch., NH), 9.02 (d, 1H, *J* = 0.96 Hz, changed to singlet on deuteration, ring-H), 2.77 (s, 3H, $CO\underline{CH_3}$), 2.7 ppm (s, 3H, ring-$\underline{CH_3}$). **Mass (EI),** ($C_{11}H_8N_4O_2S$), (M^+), *m/z* = 260 which is the base peak, and (M^+-CH_3), *m/z* = 245.

Calcd. C 50.77; H 3.07; N 21.54 %

Found. C 50.69; H 2.91; N 21.25 %

Ethyl-7-ethyl-3,4-dihydropyrido [2,3:5,4]thieno [3,2-d]-triazine-4-one-8-carboxylate (17b)

Crystallisation from acetic acid, yield 0.32 g, (82%) solid, m.p. 178-180°C. **IR,** shows ν_{max} at 3305 (NH), 1715 (CO) cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6-$CDCl_3$),** δ = 13.56 (br. 1H, exch., NH), 9.26 (s, 1H, ring-H), 4.46 (q, 7Hz, 2H, $CH_3\underline{CH_2}O$), 3.38 (q, 6Hz ,2H, $CH_3\underline{CH_2}$-ring), and 1.45 (t, 7Hz, 3H, $\underline{CH_3}CH_2O$), and 1.39 ppm (t, 6Hz ,3H, $\underline{CH_3}CH_2$-ring). **Mass (EI),** ($C_{13}H_{12}N_4O_3S$), (M^+), *m/z* = 304, (M^+-CH_3CH_2), *m/z* = 275 which is the base peak. **HRMS (EI),** requires M^+ 304.0630, found, 304.0627.

Calcd. C 51.13; H 3.94; N 18.42 %

Found. C 51.39; H 3.85; N 18.27 %

8-Acetyl-7-methylpyrido[2,3-b]thieno[3,2-d] pyrimidine-4(3H)-one (18)

A solution of (**16a**) (0.30 g, 1 mmol) in dry DMF (10 mL) was treated with DMF-DMA (0.12 g, 1 mmol) portionwise with stirring at room temperature, and stirred for a further 12 h. The solid was collected and purified by recrystallisation from acetic acid, yield 0.21 g, (82%), solid, m.p. 317-319°C. **IR,** shows ν_{max} at 3354 (NH), 1725, 1690 (CO), 1664 cm^{-1}. **^{1}H NMR (300 MHz, DMSO-d_6-$CDCl_3$),** δ = 10.75 (br. 1H, exch., NH), 8.93 (s, 1H, ring-H), 8.43 (s, 1H, CH), 2.87 (s, 3H, $CO\underline{CH_3}$), 2.08 ppm (s, 3H, CH_3). **Mass (EI),** ($C_{12}H_9N_3O_2S$), (M^+), *m/z* = 259, and (M^+-CH_3), *m/z* = 244 which is the base peak. **HRMS (EI),** requires, 259.0415, found, 259.0414.

Calcd. C 55.59; H 3.47; N 16.21 %

Found. C 55.38; H 3.42; N 16.42 %

3-Cyano-5-carbomethoxy-6-[2(N,N-dimethylamino) vinyl]pyridine-2(1H)-one (20a)

The reaction was carried out as above using (**3b**) (1.92 g, 10 mmol), and the reaction mixture was heated at 120°C for about 0.5 h. The solid obtained was purified by recrystallisation from ethanol; yield 1.9 g (78%), solid, m.p. >300°C. **IR,** shows ν_{max} at 2206 (CN), 1704 (CO), 1627 cm^{-1}. **^{1}H NMR (300 MHz, CDCl$_3$),** δ = 11.45 (br. 1H, exch., NH), 8.18 (d, 1H, vinyl-H, *J* = 13.21 Hz), 8.17 (s, 1H, ring-H), 6.35 (s, 1H, vinyl-H, *J*=13.24 Hz), 3.69 (s, 3H, O$\underline{CH_3}$), 3.16 (s, 3H, br., $\underline{Me}$N), 2.91 ppm (s, 3H, br., $\underline{Me}$N). **Mass (EI),** ($C_{12}H_{13}N_3O_3$), (M^+), *m/z* = 247 which is the base peak.

Calcd. C 58.29; H 5.26; N 17.00 %

Found. C 58.36; H 4.95; N 16.70 %

3-Cyano-5-carbethoxy-6-[2(N,N-dimethylamino)ethenyl]pyridine-2(1H)-one (20)

The reaction was carried out as above using (**3c**)(2 g, 10 mmol), and the solid obtained was purified by recrystallisation from ethanol, yield 2.00 g (79%) solid, m.p. >300°C. **IR,** shows ν_{max} at 2211 (CN), 1706 (CO), 1632 cm^{-1}. **^{1}H NMR (300 MHz, CDCl$_3$),** δ = 11.41 (br. 1H, exch., NH), 8.16 (d, 1H, vinyl-H, *J*=13.21 Hz), 8.16 (s, 1H, ring-H), 6.35 (d, 1H, vinyl-H, *J*=13.24 Hz), 4.15 (q, 7Hz,3H, O$\underline{CH_2}$CH$_3$). 3.16 (s, 3H, br., $\underline{Me}$N), 2.91 (s, 3H, br., $\underline{Me}$N), 1.27 ppm (t, 7Hz, 3H, OCH$_2\underline{CH_3}$). **Mass (EI),** ($C_{13}H_{15}N_3O_3$), (M^+), *m/z* = 261 which is the base peak. **HRMS (EI),** requires M^+, 261.1113, found, 261.1112.

Calcd. C 59.77; H 5.74; N 16.09 %

Found. C 60.09; H 5.81; N 15.80 %

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