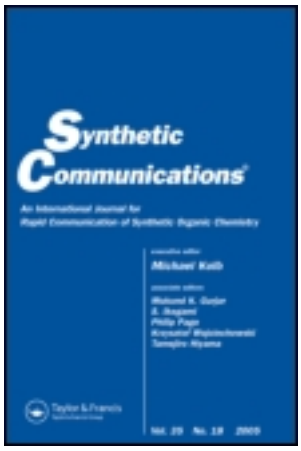

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ENAMINONES AS BUILDING BLOCKS IN ORGANIC SYNTHESIS: SYNTHESIS OF NEW POLYFUNCTIONAL PYRIDINES, CONDENSED PYRIDINES, AND PENTA SUBSTITUTED BENZENE

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ENAMINONES AS BUILDING BLOCKS IN ORGANIC SYNTHESIS: SYNTHESIS OF NEW POLYFUNCTIONAL PYRIDINES, CONDENSED PYRIDINES, AND PENTA SUBSTITUTED BENZENE

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ABSTRACT

Several new thienopyridine and methylthioether derivatives have been synthesized. New synthesis of pyrido[2,3-b]-thieno[3,2-d]pyrimidine and penta substituted benzene were achieved.

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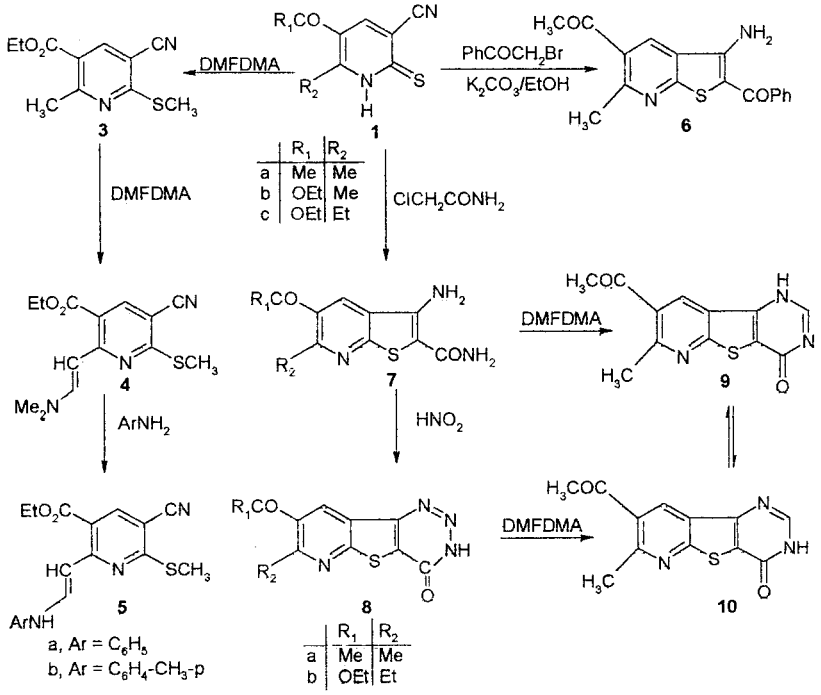
The considerable activity of polyfuctionally substituted pyridines[1–3] as calcium channel blockers and as antiviral agent has stimulated considerable interest in developing synthesis of pyridines derivatives.[4–9] Thus, we recently reported[10,11] efficient synthesis of **1a–c** via reacting **2a–c** with cycanothioacetamide. In this article we report on the utility of these compounds for synthesis of polyfunctionally condensed pyridines such as **3–10** (Sch. 1). Moreover, results of our effort to extend synthetic approach for **1** functionally substituted pyridones to enable is also reported.

Thus methylation of 3-cyano-5-carbethoxy-6-methylpyridine-2(1*H*)-thione **1b** with Dimethylformamidedimethylacetal (DMFDMA) afforded the corresponding methylthioether **3**. Treatment of **3** with DMFDMA in anhydrous DMF afforded the corresponding *N*,*N*-dimethylenamine **4** which is assigned the configuration based on the presence of two doublet at δ 8.10, and 6.47 ppm corresponding to the two *trans* vinyl protons, with coupling constant 12.4 Hz. Treatment of **4** with aromatic amines[12] in glacial acetic acid gave the corresponding *N*-arylenamines **5a**,**b** without cyclization



Scheme 1.

(Sch. 1), ^{1}H NMR of **5a** shows triplet at δ 1.38, quartet at δ 4.32 for ethyl group and doublet at δ 10.97 pm, exchangeable for NH group.

The pyridine-2(1*H*)-thione **1a** reacted with phenacyl bromide in the presence of K_2CO_3 under reflux in ethanol to give the thieno[2,3-b]pyridine derivative **6**. Also pyridine-2(1*H*)-thione derivatives **1a–c** reacted with chloroacetamide in the presence of K_2CO_3 under reflux in ethanol to give thieno[2,3-b]pyridine derivatives **7a–c** (Sch. 1). Treatment of **7a**,**c** with nitrous acid afforded the pyrido[2,3-b]thieno[3,2-b]-1,2,3-triazine derivatives **8a**,**b** in good yield. Also, compound **7a** on treatment with DMFDMA afforded a product that is formulated as pyrido[2,3-b]thieno[3,2-d]pyrimidine-4(3*H*)-one **9** and it's tautomer **10** (Sch. 1). Tautomer **9** 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 **9**, whereas the NH of **10** would normally appear at $\sim$12 ppm.

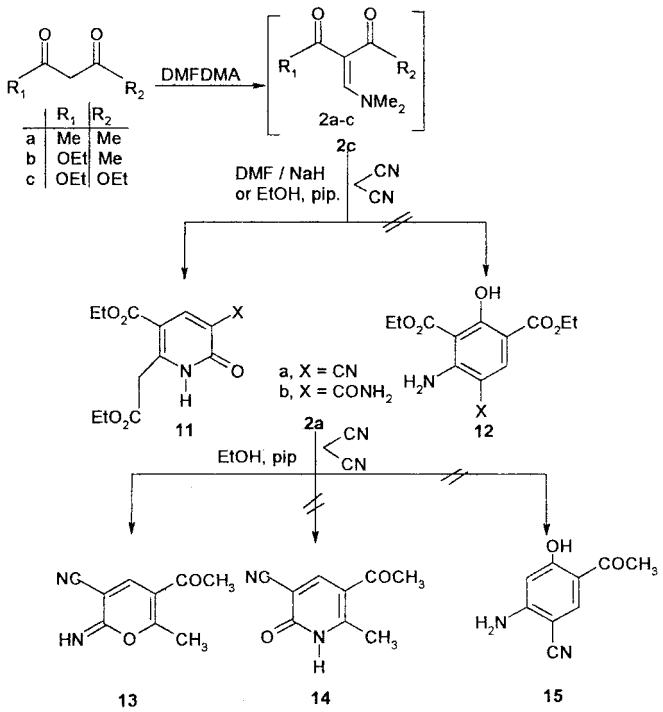
The reaction of enamine **2c** (prepared via condensation of diethyl-1,3-acetondicarboxylate with DMFDMA) with malononitrile, sodium hydride in DMF produced the pyridone derivative **11a** rather than pentasubstituted benzene derivative **12a**, (Sch. 2). When the reaction was reported using pipyridine, ethanol, as medium compound **11b** was separated. ^{1}H NMR spectrum for compound **11a** shows the methylene group (a) at δ 4.03 ppm as a singlet. IR spectrum for **11b** shows the disappearance of the cyano group.

The most likely route to the formation of pyridone derivatives **11a**,**b** is outlined in (Sch. 2). While the reaction of enamine **2a** with malononitrile, pipyridine in ethanol furnish the pyran derivative **13** but not the pyridone derivative **14** or tetrasubstituted benzene derivative **15**, (Sch. 2), it's ^{1}H NMR shows two singlets at δ 2.55 and 2.37 for the two methyls in the structure **13**, NH of pyridone **14** would normally appear at $\sim$12 ppm in ^{1}H NMR.

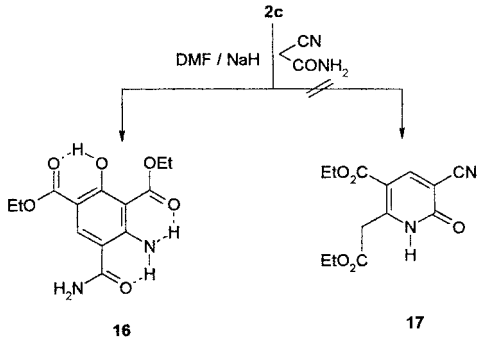
The reaction of **2c** with cyanoacetamide afforded the pentasubstituted benzene **16** rather than the expected pyridone derivative[13] **17**. The structure of **16** was confirmed by ^{1}H NMR spectrum which an exchangeable signal for one proton at δ 12.27 ppm for the intramolecular hydrogen bonded OH, a broad exchangeable signal at δ 8.22 ppm for two protons of the amide NH_2 group, a singlet δ 8.19 ppm for the ring proton and two broad exchangeable signals at δ 7.82 and 7.02 ppm for two proton of the amino group.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer for Nujol mulls. ^{1}H NMR



Scheme 2.



spectra were recorded on a Bruker AC 300 spectrometer at 300 MHz spectrometer with DMSO-d_6 and $CDCl_3$ as solvent and TMS as internal standards. Mass spectra were obtained on a Finnigan 4500 (low resolution) and Kratos Concept (high resolution, HRMS)

Table 1. Analytical Data and Physical Characteristic of New Compounds

Compound	M.P. (°C) (solvent)	Yield (%)	Elemental Analysis (Calcd.) C	H	N
3	135–137 EtOH	97	55.89 (55.93)	5.09 (5.02)	11.93 (11.86)
4	172–174 EtOH	79	57.69 (57.76)	6.11 (5.84)	13.96 (14.43)
5a	210–211 EtOH	94	63.17 (63.71)	5.05 (5.01)	12.06 (13.38)
5b	210–211 EtOH	96	64.77 (64.58)	5.59 (5.38)	11.62 (11.90)
6	185–186 AcOH	86	65.75 (65.80)	4.40 (4.51)	9.25 (9.70)
7a	270–271 AcOH	93	53.25 (53.01)	4.48 (4.41)	16.70 (16.86)
7b	245–247 AcOH	95	51.80 (51.61)	4.80 (4.65)	15.16 (15.05)
7c	210–212 AcOH	93	53.10 (53.24)	5.16 (5.12)	14.31 (14.33)
8a	210 AcOH	83	50.69 (50.77)	2.91 (30.7)	21.25 (21.54)
8b	178–180 AcOH	82	51.39 (51.13)	3.85 (3.94)	18.27 (18.42)
9	317–319 AcOH	82	55.38 (55.59)	3.42 (3.47)	16.42 (16.21)
11a	240 EtOH	67	65.01 (56.11)	5.15 (5.03)	10.25 (10.07)
11b	217 EtOH	59	52.96 (52.70)	5.80 (5.40)	9.20 (9.45)
13	250 EtOH	60	61.54 (61.36)	4.35 (4.54)	15.75 (15.90)
16	221–223 MeOH	35	52.90 (52.70)	5.25 (5.40)	9.61 (9.45)

spectrometers using electron impact (EI) or chemical ionization with amonia (CI). Microanalyses were carried out in the Micro-analytical laboratory at the Department of Chemistry, Manchester University, U.K.

Table 2. Spectral Data of New Compounds

Compound	IR (cm^{-1})	^1H NMR (δ: ppm)	m/z (M^+)
3	2230 (CN), 1716 (C=O)	1.37 (t, 6 Hz, 3H, $OCH_2\underline{CH_3}$), 2.63 (s, 3H, ring-$\underline{CH_3}$), 2.84 (s, 3H, $S\underline{CH_3}$), 4.33 (q, 6 Hz, 2H, $O\underline{CH_2}CH_3$), 8.28 (s, 1H, ring-H)	236
4	2215 (CN), 1702 (C=O)	1.34 (t, 7 Hz, 3H, $OCH_2\underline{CH_3}$), 2.57 (s, 3H, $S\underline{CH_3}$), 3.03 (s, H, br, Me_2N), 4.27 (q, 7 Hz, 2H, $O\underline{CH_2}CH_3$), 6.47 (s, 1H, vinyl-H, $J = 12.5$ Hz), 8.10 (d, 1H, vinyl-H, $J = 12.5$ Hz), 8.12 (s, 1H, ring-H)	291
5a	2214 (CN), 1700 (C=O)	1.38 (t, 6 Hz, 3H, $OCH_2\underline{CH_3}$), 2.79 (s, 3H, $S\underline{CH_3}$), 4.32 (q, 6 Hz, 2H, $O\underline{CH_2}CH_3$), 7.0 (d, 1H, vinyl-H), 7.02–7.07 (m, 3H, Ar-H), 7.23–7.35 (m, 3H, Ar-H), 8.22 (s, 1H, ring-H), 10.97 (d, 1H, br, exch. NH, $J = 12.5$ Hz)	339
5b	2212 (CN), 1702 (C=O)	1.37 (t, 3H, $OCH_2\underline{CH_3}$), 2.30 (s, 3H, $\underline{CH_3}$), 2.77 (s, 3H, $S\underline{CH_3}$), 4.32 (q. 2H, $O\underline{CH_2}CH_3$), 6.60 (d, 1H, vinyl-H), 6.89 (m, 2H, Ar-H, $J = 8.38$), 7.13 (d, 2H, Ar-H, $J = 8.38$), 7.25 (d, 1H, vinyl-H), 8.21 (s, 1H, ring-H), 10.98 (d, 1H, br, exch. NH, $J = 12.5$ Hz)	353
6	3425,3326 (NH_2), 1695 (C=O)	2.62 (s, 3H, $\underline{CH_3}$), 2.83 (s, 3H, $CO\underline{CH_3}$), 7.21 (s, 2H, exch. NH_2), 7.43–7.60 (m, 3H, Ar-H), 7.82–7.91 (m, 2H, Ar-H), 8.26 (s, 1H, ring-H)	311
7a	3400, 3325 (NH_2), 1715, 1685 (C=O)	2.62 (s, 3H, $\underline{CH_3}$), 2.71 (s, 3H, $CO\underline{CH_3}$), 6.94 (br, 2H, exch. NH_2), 7.21 (br, 2H, exch. NH_2), 8.26 (s, 1H, ring-H)	249
7b	3400, 3325 (NH_2), 1715, 1685 (C=O)	1.36 (t, 3H, $OCH_2\underline{CH_3}$), 2.69 (s, 3H, $\underline{CH_3}$), 4.32 (q, 2H, $O\underline{CH_2}CH_3$), 6.37 (br, 2H, exch. NH_2), 7.01(br, 2H, exch NH_2), 8.79 (s, 1H, ring-H)	279

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7c	2443, 3347, 3172 (NH_2), 1710, 1686 (C=O)	1.24 (t, 3H, $CH_2\underline{CH_3}$), 1.37 (t, 3H, OCH_2 $\underline{CH_3}$), 3.14 (q, 2H, $\underline{CH_2}CH_3$), 4.34 (q, 2H, $O\underline{CH_2}CH_3$), 6.93 (br, 2H, exch. NH_2), 7.22 (br, 2H, exch. NH_2), 8.84 (s, 1H, ring-H)	293
8a	3286 (NH), 1695 (C=O)	2.7 (s, 3H, ring $\underline{CH_3}$), 2.77 (s, 3H, $CO\underline{CH_3}$), 9.02 (d, 1H, $J = 0.96$ Hz ring-H), 15.55 (br, 1H, exch. NH)	260
8b	3305 (NH), 1715 (C=O)	1.39 (t, 7 Hz, 3H, $CH_2\underline{CH_3}$), 1.45 (t, 7 Hz, 3H, $OCH_2\underline{CH_3}$), 3.38 (q, 2H, 7.4 Hz, $\underline{CH_2}CH_3$), 4.46 (q, 2H, 7 Hz, $O\underline{CH_2}CH_3$), 9.26 (s, 1H, ring-H), 13.56 (br, 1H, exch. NH)	304
9	3354 (NH), 1725, 1690 (C=O)	2.08 (s, 3H, $\underline{CH_3}$), 2.87 (s, 3H, $CO\underline{CH_3}$), 8.43 (s, 1H, CH), 8.93 (s, 1H, ring-H), 10.75 (br, 1H, exch. NH)	259
11a	3341 (NH), 2231 (CN), 1749, 1710 (C=O)	1.29 (t, 3H, $OCH_2\underline{CH_3}$), 1.36 (t, 3H, OCH_2 $\underline{CH_3}$), 4.23 (q, 2H, $O\underline{CH_2}CH_3$), 4.26 (s, 2H, $\underline{CH_2}$), 4.32 (q, 2H, $O\underline{CH_2}CH_3$), 8.30 (s, 1H, ring-H), 12.75 (br, 1H, exch. NH)	278
11b	3385, 3190 (NH), 1730, 1705, 1660 (C=O)	1.17 (t, 3H, $OCH_2\underline{CH_3}$), 1.25 (t, 3H, OCH_2 $\underline{CH_3}$), 4.03 (s, 2H, $\underline{CH_2}$), 4.08 (q, 2H, $\underline{OCH_2}$ CH_3), 4.19 (q, 2H, $\underline{OCH_2}$ CH3), 8.84 (s, 1H, ring-H), 8.9 (br, 2H, exch. Amide-H), 12.76 (br, 1H, exch. NH)	296
13	3330 (NH), 2210 (CN), 1670 (C=O)	2.37 (s, 3H, $\underline{CH_3}$), 2.55 (s, 3H, $CO\underline{CH_3}$), 6.04–6.12 (br, 2H, exch. NH), 8.23 (s, 1H, ring-H)	176
16	3447, 3367 (OH), 1687 (C=O)	1.28–1.36 (2t, 6H, $2OCH_2\underline{CH_3}$), 4.27–4.37 (2q, 4H, $2O\underline{CH_2}CH_3$), 7.02 (br, 1H, exch. NH), 7.82 (br, 1H, exch. NH), 8.19 (s, 1H, ring-H), 8.22 (br, 2H, exch. Amide-H), 12.27 (s, 1H, exch. OH)	296

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Ethyl-5-cyano-2-methyl-6-methylthiopyridine-3-carboxylate (3): Equimolar amount of **1b** (1.93 g, 10 mmol), and DMFDMA (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 crystallized from ethanol.

Ethyl-5-cyano-2-[2(*N*,*N*-dimethylamino)ethyl]-6-methylthiopyridine-3-carboxylate (4): A mixture of **3** (2.36 g, 10 mmol) and DMFDMA (1.19 g, 10 mmol) in anhydrous DMF (10 mL) were 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-water, and the solid obtained was recovered by filtration and purified by crystallization from ethanol.

General method for the reaction of 4 with aniline derivatives to prepare, Ethyl-5-cyano-2-[2(*N*-phenylamino)ethyl]-6-methylthiopyridine-3-carboxylate (5a) and Ethyl-5-cyano-2-[2(*N*-*p*-tolylamino)ethyl]-6-methylthiopyridine-3-carboxylate (5b): Equimolar amount of **4** (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 crystallization from ethanol.

5-Acetyl-3-amino-2-benzyl-6-methylthieno[2,3-b]pyridine (6): Equimolar amount of **1a** (1.92 g, 10 mmol) and phenacyl bromide (1.99 g, 10 mmol), anhydrous potassium carbonate (2 g, 15 mmol) in absolute ethanol (30 mL), were heated under reflux for 3 h. The reacion mixture was diluted with water, and the product was collected by filtration and recystallized from acetic acid.

General method for the reaction of pyridine-2(1H)-thione derivative (1a–c) with chloroacetamide to prepare, 5-Acetyl-3-amino-6-methylthieno[2,3-b]pyridine-2-carboxamide (7a), 3-Amino-5-carbethoxy-6-methylthieno[2,3-b]pyridine-2-carboxamide (7b), and 3-Amino-5-carbethoxy-6-ethylthieno [2,3-b]pyridine-2-carbox-amide (7c): Equimolar amount of pyridine-2(1H)-thione (**1a–c**), chloroacetamide (0.66 g, 10 mmol) and anhydrous potassium carbonate (2 g, 15 mmol) in absolute ethanol (30 mL), were heated under reflux for 3 h. The reacion mixture was diluted with water, and the product was collected by filtration and recrystallized from acetic acid.

General method for the reaction of 3-aminothieno[2,3-b]pyridine-2-carboxamide derivatives (7a,c) with nitrous acid to prepare, 8-Acetyl-7-methyl-3,4-dihydropyrido[2,3 : 5,4]thieno[2,3-d]triazine-4-one (8a) and Ethyl-7-ethyl-3,4-dihydropyrido[2,3 : 5,4]thieno[2,3-d]triazine-4-one 8-carboxylate (8b): A solution of **7a** or **7c** (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 h. The solid was collected and purified by crystalisation from acetic acid.

8-Acetyl-7-methylpyrido[2,3-b]thieno[3,2-d]pyrimidine-4(3H)-one (9): A solution of **7a** (0.30 g, 1 mmol) in dry DMF (10 mL) was treated with DMFDMA (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 recrystallization from acetic acid.

Ethyl-3-cyano-6-(carboxymethyl)pyridine-2(1H)-one-5-carboxylate (11a): A mixture of diethyl 1,3-acetone dicarboxylate (2.02 g, 10 mmol) and DMFDMA (1.19 g, 10 mmol) in anhydrous DMF (10 mL) in a dry flask under argon was stirred at room temperature for 24 h. In a second flask, a mixture of sodium hydride (0.48 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in anhydrous DMF (10 mL) was stirred under argon at room temperature for 10 min. The content 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 acidified with conc. HCl to pH 4, and stirring was continued for 24 h. The product so formed was recovered by filtration and purified by crystallization from ethanol.

Ethyl-3-carbamoyl-6-(carbethoxymethyl)pyridine-2(1H)-one-5-carboxylate (11b): The reaction was carried out as described above using diethyl 1,3-acetone dicarboxylate (2.02 g, 10 mmol) and DMFDMA (1.19 g, 10 mmol) and malononitrile (0.66 g, 10 mmol), pipyridine (1 mL) in absolute ethanol (30 mL) solvent.

5-Acetyl-3-cyano-6-methyl-2-iminopyran (13): The reaction was carried out as described above using acetylacetone (1 g, 10 mmol), DMFDMA (1.19 g, 10 mmol) and malononitrile (0.66 g, 10 mmol), pipyridine (1 mL) in absolute ethanol, (30 mL) solvent.

3-Amino-2,6-*bis*(carbethoxy)-4-carbamoylphenol (16): The reaction was carried out as described above using diethyl 1,3-acetone dicarboxylate (2.02 mL, 10 mmol) and DMFDMA (1.19 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol), in anhydrous DMF (10 mL).

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