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Alkylazinylcarbonitriles as building blocks in heterocyclic synthesis: a route for the synthesis of 4-methyl-2-oxopyridines

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The reaction of **1** with active methylene reagents afforded the enaminoamides **2** which readily cyclised to the pyridones **5**. Compound **5** condensed with DMFDMA to afford the dimethylamino pyridones **8**. These coupled with aryldiazonium chloride to give hydrazonoals **10**. Compound **2** coupled with aromatic diazonium salts to yield the arylazopyridines **4**.

1. Introduction

The elaboration of efficient synthetic protocols for a variety of condensed systems as potential bio-active agents, have been a major area of research interest in our laboratories, over the past several years [1–4]. Our recent endeavors in this domain have successfully demonstrated the use of alkyl-azinylcarbonitriles as a building block for the synthesis of polyfunctionalised hetero-aromatics and other related condensed systems [5–10]. In conjunction with this and in view of the reported activity of alkylpyridones as HIV-1 reverse transcriptase inhibitars [11, 12], herein we report the utilization of the recently synthesized compound **1** [13] for the synthesis of 4-methyl-2-oxopyridine-3-carbonitrile (**5a**) and ethyl 4-methyl-2-oxo-pyridine-3-carboxylate (**5b**), and their utility for the synthesis of various pyridone derivatives.

2. Synthesis of the compounds

The facile transformation of **1** to the 1:1 adduct of malononitrile and ethyl cyanoacetate is shown in Scheme 1. Although the addition of active methylene reagents to an enone is well established to proceed via initial addition at the double bond and subsequent cyclization into pyrans [14, 15] **3** (vide infra), ^{1}H NMR and ^{13}C NMR did not match for this structure. In the ^{1}H NMR there are two olefine doublets with J = 13 Hz which were observed at $\delta = 8.21$, 8.05 and 5.63, 5.47 ppm indicating that the *trans* olefinic moiety in **1** has not been involved in the reaction. ^{13}C NMR indicated the presence of an sp^3 carbon at $\delta = 15.95$ which is assignable for the methyl carbon. Thus, structure **2** has been considered for this product. Formation of **2** is assumed to occur via the addition of the active methylene reagent to carbonyl groups in **1** and subsequent water elimination to furnish α,β-unsaturated nitriles. Water eliminated in this process then hydrolyses the cyano group in this intermediate to afford **2**. The behavior of **1** towards active methylene reagents is thus similar to the recently reported behaviour of aryl and other heteroaryl enaminone derivatives towards malononitrile [2].

When **2a** was refluxed in an acetic acid/hydrochloric acid mixture it was cyclized almost quantitatively to the pyridones **5a**. However attempts to achieve cyclization of **2b** (X = COOEt) to **5b** using this reagent gave intractable mixtures. Therefore, it was decided to effect cyclization by taking advantage of the close proximity of amide NH_2 group to the dimethyl amino moiety. Cyclization could be achieved in excellent yields by fusion of **2b** above its melting point. Thus, when **2b** was kept above its melting point, the pyridone ester **5b** sublimed out as white crystalline solid whose spectral and analytical data fully supported the proposed structure (Scheme 2).

Compound **5a** condensed with excess of DMFDMA to yield a mixture of the methoxy pyridine **6** and the dimethylamino vinylpyridone **8** which is believed to be formed via the intermediacy of **7** (Scheme 3).

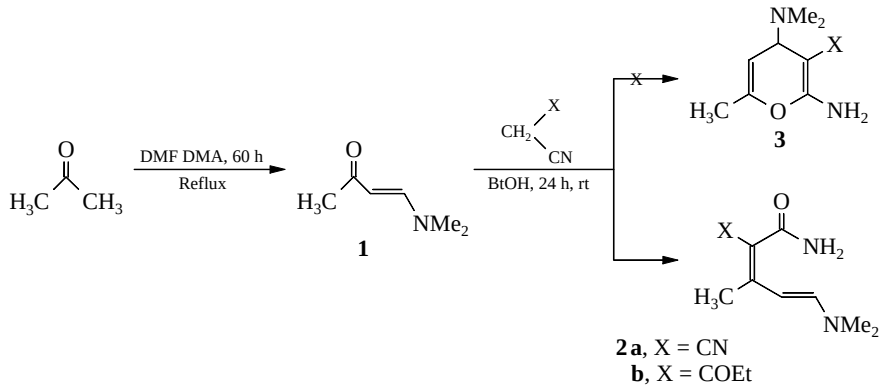
The structural assignment of **6** and **8** were made on the basis of the positions of methyl function chemical shifts in the ^{1}H NMR spectrum. The O-methoxy compound **6** revealed an O–Me signal at δ 4.2 ppm while the *N*-methyl product **8** revealed a *N*-methyl signal at 3.2 ppm.

As shown in Scheme 4, compound **8** reacted with various aromatic amines in the presence of catalytic amounts of concentrated HCl to afford the enamines **9** in good yields.

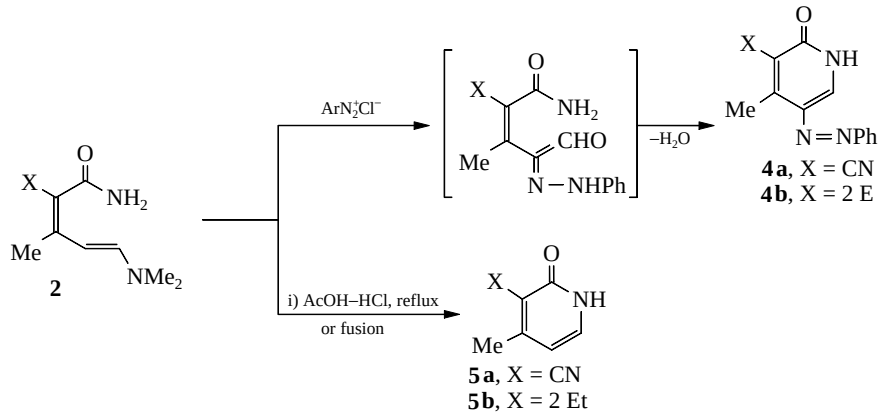
Table 1: Physical data of the synthesized compounds

Compd.	Yield (%)	mp (°C)	Cryst. Solvent	Formula (M.Wt.)
2a	62	236–238	MeOH	$C_9H_{13}N_3O$ (179.2)
2b	27	154–156	$CH_3COOC_2H_5$	$C_{11}H_{18}N_2O_3$ (226.1)
4a	23	180–185	MeOH	$C_{13}H_{10}N_4O$ (238.0)
4b	48	246–250	MeOH	$C_{15}H_{15}N_3O_3$ (285.1)
5a	75	290–295	CH_3COOH	$C_7H_6N_2O$ (134.0)
5b	75	138–140	$CH_3COOC_2H_5$	$C_9H_{11}NO_3$ (181.1)
6		158–160	C_6H_{12}	$C_8H_8N_2O$ (148.0)
8	80	185–190	EtOH	$C_{11}H_{13}N_3O$ (203.1)
9a	71	128–130	MeOH and CHC_3	$C_{15}H_{13}N_3O$ (251.1)
9b	61	245–248	MeOH and CHC_3	$C_{16}H_{15}N_3O$ (265.1)
9c	71	245–248	MeOH and CHC_3	$C_{16}H_{15}N_3O_2$ (281.1)
9d	64	215–218	MeOH and CHC_3	$C_{17}H_{17}N_3O_3$ (311.1)
10a	59	248–250	MeOH	$C_{15}H_{12}N_4O_2$ (280.1)
10b	18	180–182	MeOH	$C_{16}H_{14}N_4O_3$ (310.1)
10c	69	305–306	MeOH	$C_{15}H_{11}N_5O_4$ (325.1)

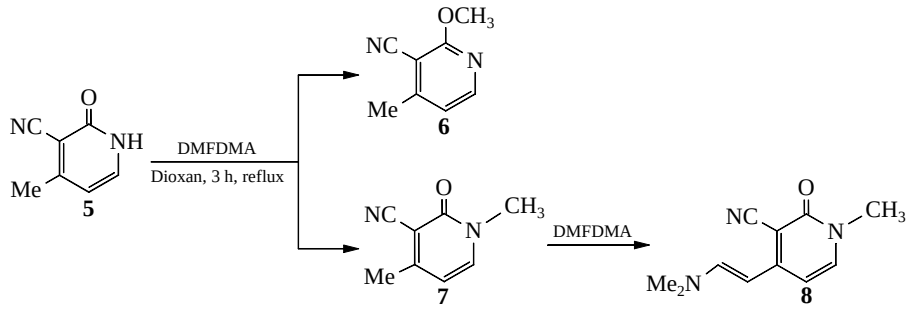
Scheme 1



Scheme 2



Scheme 3



Scheme 4

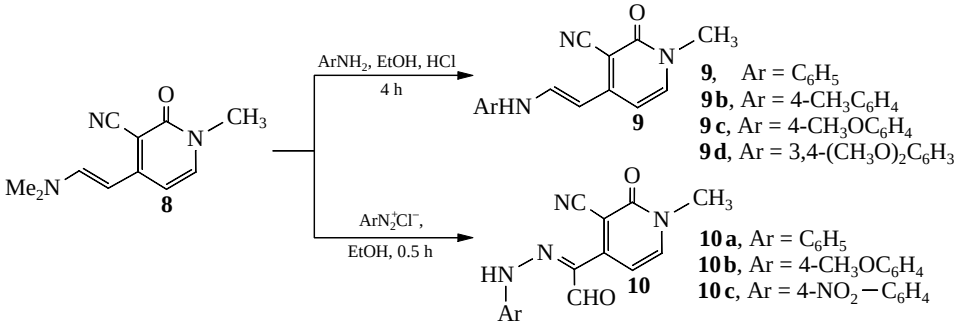


Table 2: Spectral data of the synthesized compounds

Compd.	IR (cm^{-1})	^1H NMR, ^{13}C NMR
1		δ 2.27 (s, 3 H, $-COCH_3$), 2.88 (s, 6 H, $-N(CH_3)$, 5.00 (d, 1 H, $-CH=C\underline{H}-N$, J = 12 Hz), 7.46 (d, 1 H, $-COC\underline{H}=CH-$, J = 12 Hz)
2a	3419, 3174, 2209, 1664, 1611, 1571	2.20 (s, 3 H, $-CH_3$), 3.10 (s, s, 6 H, $-N(CH_3)_2$), 5.47, 5.63 (d, 1 H, $-CH=CH-N$, J = 13 Hz), 6.06 (br, 2 H, NH_2, exchangeable with D_2O), 8.05, 8.21 (d, 1 H, $-C\underline{H}=CH-N$, J = 13 Hz). 15.95 (CH_3), 40.98 ($N(CH_3)_2$), 87.30, 95.51 (C=C), 119.78 (CN), 150.47, 162.96 (CH=CH), 166.31 (C=O)
2b	3372, 1651, 1634, 1566, 1526	1.30 (t, 3 H, $-CH_2-C\underline{H}_3$), 2.18 (s, 3 H, $-CH_3$), 3.12 (s, 6 H, $-N(CH_3)_2$), 4.22 (q, 2 H, $-C\underline{H}_2-CH_3$), 6.33, 6.50 (d, 1H, $-CH=C\underline{H}-N$, J = 13 Hz), 8.50, 8.67 (d, 1 H, $-C\underline{H}=CH-N$, J = 13 Hz). 14.82, 15.15 ($CH_3 \times 2$), 41.02 ($N(CH_3)_2$), 59.48 (CH_2), 99.09, 101.90 (C=C), 150.23, 163.79 (CH=CH), 168.68, 169.23 ($C=O \times 2$)
4a	3500, 2186, 1657	2.75 (s, 3 H, $-CH_3$), 7.40–7.80 (m, 6 H, C_6H_5- & Py–H–), 8.44 (s, 1 H, –OH)
4b	3488,1743, 1643	1.34 (t, 3 H, $-CH_2-C\underline{H}_3$), 2.77 (s, 3 H, $-CH_3$), 4.31 (q, 2 H, $-C\underline{H}_2CH_3$), 7.52–7.80 (m, 6 H, C_6H_5- & Py–H), 8.54 (s, 1 H, –OH)
5a	3465, 2244, 1671, 1624, 1577	2.27 (s, 3 H, $-CH_3$), 6.19 (d, 1 H, olefinic), 7.99 (d, 1 H, olefinic), 12.51 (br, 1 H, NH, exchangeable with D_2O). 19.53 (CH_3), 99.89, 105.45 (C=C), 117.15 (CN), 149.21, 154.16 (CH=CH), 161.09 (C=O)
5b	3375, 1737, 1690, 1663, 1620, 1554	1.38 (t, 3 H, $C\underline{H}_3CH_2-$), 2.46 (s, 3 H, $-CH_3$), 4.35 (q, 2 H, $CH_3C\underline{H}_2-$), 6.24, 8.15 (d, d, 2 H, Py–H)
6	3467, 2231, 1592, 1471, 1382, 1303	2.52 (s, 3 H, $-CH_3$), 4.04 (s, 3 H, $-OCH_3$), 6.86 (d, 1 H, Py–H), 7.69 (s, 1 H, Py–H)
8	3442, 2186, 1629, 1571, 1560	3.05 (s, 3 H, $-NCH_3$), 3.32, 3.44 (s, s, 6 H, $N(CH_3)_2$), 4.90, 5.06 (d, 1 H, olefinic, J = 13 Hz), 6.40, 7.50 (d, d, 2 H, Py–H–), 7.57, 7.72 (d, 1 H, olefinic, J = 13 Hz)
9a	3446, 2210, 1624, 1620, 1207	3.44 (s, 3 H, $-NCH_3$), 5.75, 5.91 (d, 1 H, olefinic, J = 13.50 Hz), 6.83 (d, 1 H, Py–H), 7.0–7.4 (m, 5 H, C_6H_5-), 7.71 (d, 1 H, Py–H), 8.26 (t, 1 H, olefinic, J = 13.5 Hz), 10.00 (br, d, –NH)
9b	3438, 3294, 2210, 1620, 1528	3.04 (s, 3 H, Ar–CH_3), 3.46 (s, 3 H, $-NCH_3$), 5.66, 5.82 (d, 1 H, olefinic, J = 13 Hz), 6.34–7.40 (m, 7 H, C_6H_4-, Py-H_2 & olefinic, J = 13 Hz)
9c	3464, 3294, 2211, 1643, 1618, 1529	3.34 (s, 3 H, NCH_3), 3.72 (s, 3 H, $-OCH_3$), 5.65, 5.80 (d, 1 H, olefinic, J = 13 Hz), 6.71 (d, 1 H, Py–H), 6.72–6.94 (m, 4 H, C_6H_4-), 7.68 (d, 1 H, Py–H), 8.11 (t, 1 H, olefinic, J = 13 Hz), 10.10 (d, 1 H, –NH)
9d	3437, 3288, 2208, 1643, 1612, 1562, 1516	3.47 (m, 3 H, $-NCH_3$), 3.72, 3.80 (s, s, 6 H, $-OCH_3 \times 2$), 5.66, 5.82 (d, 1 H, olefinic, J = 13 Hz), 6.80–7.10 (m, 4 H, C_6H_3- & Py–H), 7.65, 7.81 (t, 1 H, olefinic, J = 13 Hz), 10.06 (d, 1 H, –NH)
10a	3463, 3185, 2233, 1678, 1641, 1557	3.31 (s, 3 H, $-NCH_3$), 6.44 (d, 1 H, Py–H), 7.09–7.38 (m, 5 H, C_6H_5-), 8.20 (d, 1 H, Py–H), 9.55 (s, 1 H, –CHO), 11.19 (s, 1 H, –NH)
10b	3455, 2234, 1697, 1642, 1563	3.20 (s, 3 H, $-NCH_3$), 3.73 (s, 3 H, $-OCH_3$), 6.42 (d, 1 H, Py–H), 6.92–7.40 (d, d, 4 H, C_6H_4-), 8.20 (d, 1 H, Py–H), 9.50 (s, 1 H, –CHO), 11.14 (s, 1 H, –NH)
10c	3465, 2232, 1698, 1640, 1560	3.28 (s, 3 H, $-NCH_3$), 6.50 (d, 1 H, Py–H), 7.45–8.35 (m, 5 H, C_6H_4- & Py–H), 9.61 (s, 1 H, –CHO), 11.52 (s, 1 H, –NH). 33.57 ($-NCH_3$), 104.48, 108.61 (C=C), 115.54 (CN), 126.00 (C=N), 138.25, 144.65, 144.67, 147.64, 148.32 (Ar–C and C=C), 161.30 (C=O), 188.67 (CHO)

This class of compounds received much current interest due to their potential application in the preparation of non linear optical materials [16].

Compound **8** also coupled with aryl diazonium chloride, the hydrazonals **10** were obtained in good yields (Scheme 4). To the best our knowledge the coupling of **8** with benzene diazonium salts is the first reported example of such a reaction although coupling with enaminones and with dimethylaminodicyano-butadiene has recently been reported [4].

In view of the current importance of condensed pyrido-pyridinones and pyrido-pyridazines in pharmaceutical application it was felt that cyclization of enamines **8** or hydrazonals **10** would give novel condensed pyridines. However under a variety of cyclization conditions employed by us earlier, compounds **8** or **10** failed to cyclize. It seems that the hydrazone moiety is strongly hydrogen bonded with the aldehydic group. As a result it cannot adopt necessary geometry for cyclization [17].

In summary, we have demonstrated the potential use of the relatively simple molecule **1** as a building block for the preparation of a variety of pharmaceutically important functionalized pyridones and pyridinals.

3. Experimental

Melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-740 spectrometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer using TMS as the internal standard. Chemicals shifts are reported as δ units (ppm). Microanalysis were performed on a LECO CHNS-932 analyzer and gave satisfactory values.

3.1. 1-Methyl-3-dimethylaminoprop-2-enone (1)

The procedure used earlier was adopted [11]. Thus, a mixture of dry acetone (250 ml) and DMFDMA (75 ml) were refluxed for 60 h. The volatile compounds were evaporated in vacuo leaving an oil which was used directly without further purification for the subsequent steps. Yield: 32 g (40%).

3.2. (4E)-2-Cyano-3-methyl-5-dimethylamino-2,4-pentadienoic amide (2a)

To a stirred solution of enaminone **1** (23.5 g, 208 mmol) and malononitrile (13.8 g, 209 mmol) in abs. EtOH (250 ml), a few drops of piperidine (~0.5 ml) were added. The reaction mixture was kept stirred for 24 h at room temperature during which the orange yellow solid formed was filtered, and washed with EtOH.

3.3. (4E)-Ethyl 2-carboxamido-3-methyl-5-dimethylamino-2,4-pentadienoate (2b)

A mixture of enaminone **1** (4.25 g, 37.61 mmol), ethyl cyanoacetate (3.0 g, 26.55 mmol) and a few drops of piperidine (~0.5 ml) in abs. EtOH (25 ml) were refluxed for 4 h. The reaction mixture was cooled to room

temperature, evaporated to dryness and the residue re-dissolved in ethylacetate (25 ml) and kept overnight. The yellow solid formed was separated and crystallized.

3.4. 1,2-Dihydro-2-oxo-4-methyl-5-phenylazopyridine-3-carbonitrile (**4a**)

Compound **4a** was prepared from **2a** (1.00 g, 5.59 mmol) in dioxan (50 ml) and EtOH (25 ml) [contains NaOH 400 mg, in 2 ml H_2O], by treating with an ice cooled solution of diazonium chloride derived from aniline (520 mg, 5.59 mmol, in 6 ml conc. HCl) and $NaNO_2$ (400 mg, 6.223 mmol). The reaction mixture was stirred for 1 h during which the brown solid formed was filtered and crystallized from the proper solvent.

3.5. Ethyl 1,2-dihydro-2-oxo-4-methyl-5-phenylazopyridine-3-carboxylate (**4b**)

Compound **4b** was prepared by diazotization of **2b** (1.00 g, 4.42 mmol) in EtOH (25 ml containing NaOH, 180 mg, 4.5 mmol, in 2 ml H_2O) using diazonium chloride derived from aniline (410 mg, 4.42 mmol dil. HCl, 6 ml) and $NaNO_2$ (300 mg, 4.6 mmol). The yellow solid formed was filtered and crystallized from the proper solvent.

3.6. 1,2-Dihydro-2-oxo-4-methylpyridine-3-carbonitrile (**5a**)

A stirred suspension of **2a** (5 g, 28 mmol) in acetic acid/HCl mixture (50 ml, 2 : 1) was refluxed for 1 h. The reaction mixture was allowed to reach room temperature, the solid formed was filtered and crystallized from the proper solvent.

3.7. Ethyl 1,2-dihydro-2-oxo-4-methylpyridine-3-carboxylate (**5b**)

Compound **5b** was prepared by fusing **2b** (750 mg, 3.32 mmol) above its melting point for 3 h during which the crystalline white solid sublimed was collected and crystallized from the proper solvent.

3.8. Reaction of DMFDMA on 5a: Isolation of 2-methoxy-4-methylpyridine-3-carbonitrile (**6**) *and 2-methoxy-4-(2-dimethylaminoethylene)-pyridine-3-carbonitrile* (**8**)

A stirred suspension of **5a** (1.00 g, 7.46 mmol) and DMFDMA (1.80 g, 15.12 mmol) in dry dioxan (15 ml) was refluxed for 4 h during which an intense green colored solution was formed. The reaction mixture was cooled to room temperature and kept overnight. The greenish yellow solid formed was filtered and crystallized from the proper solvent. The filtrate upon evaporation under vacuo gave a brown residue which was crystallized from the proper solvent.

3.9. 1,2-Dihydro-1-methyl-4-(2-anilinoethylene)-2-oxopyridine-3-carbonitrile (**9a**)

A mixture of **8** (250 mg, 1.32 mmol) and aniline (123 mg, 1.32 mmol) in dry EtOH was refluxed in presence of concentrated HCl (0.5 ml) for 3 h. The reaction mixture was cooled, the solid formed was filtered and crystallized from the proper solvent.

3.10. 1,2-Dihydro-1-methyl-4-[2-(4-methylphenyl)aminoethylene]-2-oxopyridine-3-carbonitrile (**9b**)

Compound **9b** was prepared from **8** and *p*-toludine by an analogous procedure as described for **9a**.

3.11. 1,2-Dihydro-1-methyl-4-[2-(4-methoxyphenyl)aminoethylene]-2-oxopyridine-3-carbonitrile (**9c**)

Compound **9c** was prepared from **8** and *p*-methoxy aniline using the same procedure as described for **9a**.

3.12. 1,2-Dihydro-1-methyl-4-[2-(3,4-dimethoxyphenyl)aminoethylene]-2-oxopyridine-3-carbonitrile (**9d**)

Compound **9d** was prepared from **8** and 3,4-dimethoxy aniline using the same procedure as described for **9a**.

3.13. 1-Phenylhydrazono-1-(3-cyano-1,2-dihydro-1-methyl-2-oxopyridin-4-yl)-glyoxal (**10a**)

A cold solution of benzene diazonium chloride [was prepared by adding an ice cold solution of $NaNO_2$ 1.2 g, 18.69 mmol in H_2O (10 ml) to a cold solution of aniline 1.2 g, 12.90 mmol in 7 ml conc. HCl with stirring such that temperature does not exceed above 5 °C] was added at once to a stirred solution of enamine **8** (2.4 g, 11.82 mmol) in EtOH (100 ml) containing (550 mg, 12.5 mmol) in 4 ml H_2O. The reaction mixture was kept stirred at room temperature for 1 h, crushed ice was added (50 g), the solid separated was filtered and crystallized from the proper solvent.

3.14. (4-Methoxyphenylhydrazono-1-(3-cyano-1,2-dihydro-1-methyl-2-oxopyridin-4-yl)-glyoxal (**10b**)

Compound **10b** was prepared from **8** and *p*-methoxy benzene diazonium chloride using the same procedure as described for **10a**.

3.15. (4-Nitrophenylhydrazono-1-(3-cyano-1,2-dihydro-1-methyl-2-oxopyridin-4-yl)-glyoxal (**10c**)

Compound **10c** was prepared from **8** and *p*-nitrobenzene diazonium chloride using the same procedure as described for **10a**.

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