

# Studies on Heterocyclic Enamines: New Syntheses of 4*H*-Pyranes, Pyranopyrazoles and Pyranopyrimidines

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The behaviour of several 2-amino-3-cyano-4*H*-pyran derivatives toward a variety of nucleophilic reagents is reported.

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Although 2-amino-3-cyano-4*H*-pyrans became recently readily obtainable *via* efficient synthetic routes [1-3] the chemistry of these versatile enaminnitriles has received very limited attention [4,5]. In conjunction of our effort directed toward exploring the synthetic potential of enaminnitriles [6,7], we report here on the chemistry of the 2-amino-3-cyano-4*H*-pyran derivatives **1a-c**. Compounds **1a-c** were prepared by addition of acetylacetone and ethyl acetoacetate to arylidenemalononitrile **2a,b** as has been recently reported.

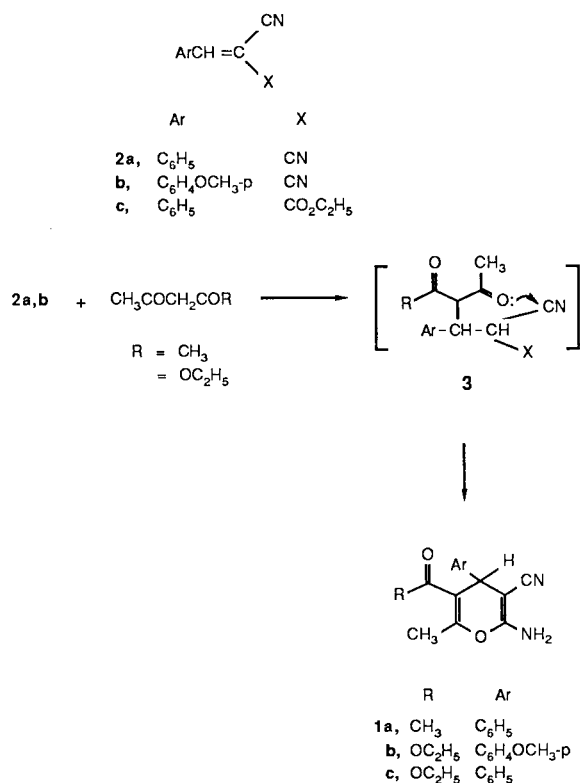
Although the Michael adducts may be also formulated as the acyclic derivatives **3a-c**, the pyran structure was

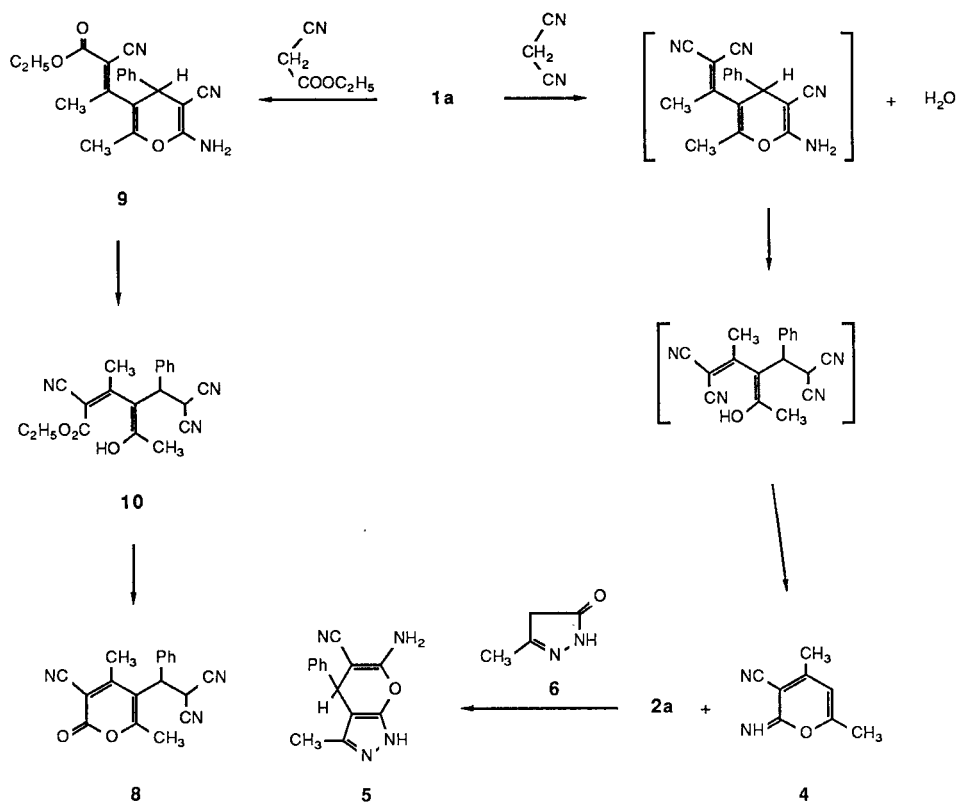
established for the reaction products based on <sup>1</sup>H nmr which revealed a singlet at 4.1 ppm for pyran H-4 and did not show a multiplet for protons linked to Sp<sup>3</sup> carbons at δ 2.3 ppm as would be anticipated for **3**.

Compound **1a** reacted with malononitrile in refluxing ethanol to yield a product of molecular formula C<sub>9</sub>H<sub>8</sub>N<sub>2</sub>O (M<sup>+</sup> = 148). <sup>1</sup>H nmr of this product revealed two methyl signals at δ 2.2 and 2.3 ppm in addition to two one proton signals at δ 6.1 ppm and δ 12.3 ppm. The signal at δ 12.3 ppm disappeared on deuterium oxide exchange. Thus structure **4** was assigned for this product. The formation of **4** from reaction of **1a** and malononitrile is assumed to proceed *via* initial formation of a condensation product which undergoes ring opening and recyclization in presence of water eliminated during reaction to yield acyclic intermediate which affords **4** and benzylidene-malononitrile **2a**. The presence of **2a** in reaction media was indicated *via* isolation of the 4*H*-pyran[2,3-*c*]pyrazole (**5**) [8] on treatment of the mother liquor of reaction of **1a** and malononitrile with 3-methyl-2-pyrazolin-5-one (**6**). It is of value to report that **4** cannot be produced *via* condensation of malononitrile with acetylacetone in presence of basic catalyst. Under these conditions 5-cyano-6-dicyano-methyl-2,4-dimethylpyridine was the only reported isolable product [9].

Similar to the recently reported behaviour of **1c**, compound **1b** reacted with malononitrile to yield the pyranopyridine derivative **7**.

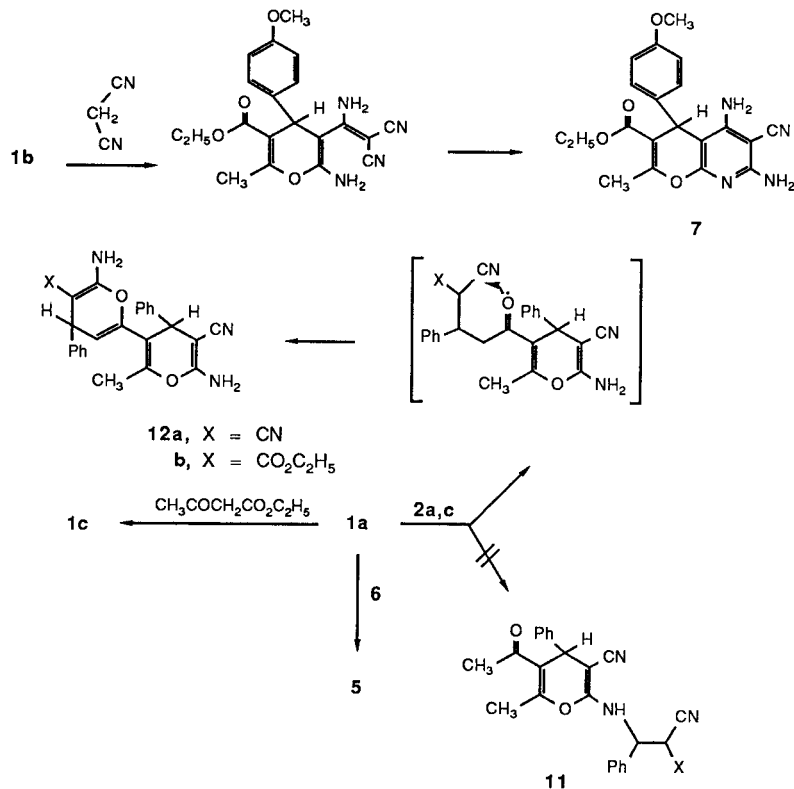
Fusion of **1a** with ethyl cyanoacetate in presence of piperidine at 120° afforded a product of molecular formula C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> (M<sup>+</sup> = 303). The <sup>1</sup>H nmr of this product revealed two methyl signals and two one proton doublets at δ 2.5 and δ 2.8 ppm. Structure **8** was assumed for reaction product and is assumed to be formed *via* condensation with **1a** to form the condensation product **9**. This undergoes ring opening affording **10** then cyclizes readily into **8** *via* ethanol elimination.





Compound **1a** reacted with **2a,c** to yield 1:1 adducts which can be formulated as **11** or isomeric **12**. Structure **12** was assumed for these products based on spectral

evidence which revealed only one methyl signal and absence of any multiplets for protons linked to  $Sp^3$  carbons as would be expected for **11**. Compounds **1b,c** were





6.9 (s, 2H, NH<sub>2</sub>) and 7.2-7.4 (m, 5H, C<sub>6</sub>H<sub>5</sub>); <sup>13</sup>C nmr: 13.6 (CH<sub>3</sub>), 18.1 (CH<sub>2</sub>), 57.5 (pyran C-4), 60.0 (CH<sub>2</sub>), 107 (pyran C-3), 119.5 (CN), 126.0-135.5 (arom carbons), 144 (C-5), 157 (C-6), 159 (C-2) and 169.5 (CO).

Reaction of **1a** with (a) Malononitrile.

A suspension of **1a** (2.6 g, 0.01 mole) in ethanol (30 ml) containing a catalytic amount of triethylamine was treated with malononitrile (0.66 g, 0.01 mole). The reaction mixture was refluxed for five hours then evaporated to half its volume and left to stand at room temperature. The solid product, formed on cooling was collected by filtration and crystallized from ethanol.

2,4-Dimethyl-5-cyano-6-imino-2H-pyran (**4**) formed colorless crystals from ethanol, mp 260° yield 80%; ir: 3150-2600 (chelated NH), 2220 (CN), 1670-1630 (C=N and C=C); <sup>1</sup>H nmr: 2.2 (s, 3H, CH<sub>3</sub>), 2.3 (s, 3H, CH<sub>3</sub>), 6.1 (s, 1H, CH), 12.3 (s, 1H, NH); ms: m/e = 148 (M<sup>+</sup>).

Anal. Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O (148.2): C, 64.8; H, 5.4; N, 18.9. Found: C, 64.9; H, 5.4; N, 18.5.

The filtrate from the reaction of **1a** with malononitrile was treated with **6** (1.0 g, 0.01 mole) then refluxed for one hour. The reaction mixture was allowed to cool to room temperature and the solid product, so separated was collected by filtration and identified (mp and mixed mp) as **5**.

(b) With Ethyl Cyanoacetate.

A mixture of **1a** (2.6 g, 0.01 mole) and ethyl cyanoacetate (1.1 ml, 0.01 mole) was treated with piperidine then heated at 120° (bath temperature) for five minutes. The reaction mixture was then triturated with ethanol and the so formed solid was collected by filtration.

2,4-Dimethyl-5-cyano-3-(1-phenyl-2-dicyanoethyl)-2H-pyran-6-one (**8**) formed yellow crystals from methanol, mp 225°, yield 80%; ir: 2220 (CN), 1670 (CO) and 1630 (C=C); <sup>1</sup>H nmr: 2.2 (s, 3H, CH<sub>3</sub>), 2.3 (s, 3H, CH<sub>3</sub>), 2.5 (d, 1H, CH), 2.8 (d, 1H, CH), 6.0 (s, H, H-4), 7.3-7.6 (m, 5H, C<sub>6</sub>H<sub>5</sub>); ms: m/e = 303 (M<sup>+</sup>).

Anal. Calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> (303.3): C, 71.3; H, 4.3; N, 13.9. Found: C, 71.3; H, 4.2; N, 13.6.

(c) With **2a,c**.

A suspension of **1a** (2.6, 0.01 mole) in ethanol (30 ml) was treated with each of **2ac** (0.01 mole) then with few drops of triethylamine. The reaction mixture was refluxed for three hours. The solid product so formed, was collected by filtration and crystallized from ethanol.

2-Amino-3-cyano-4-phenyl-5-(2-amino-3-cyano-4-phenyl-4H-pyran-6-yl)-6-methyl-4H-pyran (**12a**) formed colorless crystals, mp 265°, yield 70%; ir: 3500-3280 (NH<sub>2</sub>), 2220 (CN) 1700-1650 (δ NH<sub>2</sub> and C=C); <sup>1</sup>H nmr: 2.0 (s, 3H, CH<sub>3</sub>), 2.2 (br, 4H, 2NH<sub>2</sub>), 4.6 (s, 1H, pyran H-4), 5.0 (s, 1H, pyran H-4), 7.3-7.5 (m, 10H, 2C<sub>6</sub>H<sub>5</sub>); ms: m/e = 408 (M<sup>+</sup>).

Anal. Calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub> (408.4): C, 73.5; H, 4.9; N, 13.7. Found: C, 73.4; H, 5.0; N, 13.8.

2-Amino-3-cyano-4-phenyl-5-(2-amino-3-ethoxycarbonyl-4-phenyl-4H-pyran-6-yl)-6-methyl-4H-pyran (**12b**) formed colorless crystals from ethanol, mp 258°, yield 63%; ir: 3420-3380 (2NH<sub>2</sub>), 3100-2800 (CH, CH<sub>2</sub> and CH<sub>3</sub>), 1750 (ester CO), 1690-1660 (C=C, NH<sub>2</sub> deformation); ms: m/e = 455 (M<sup>+</sup>).

Anal. Calcd. for C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> (455.5): C, 71.2; H, 5.5; N, 9.2. Found: C, 71.4; H, 5.5; N, 9.2.

(d) With Ethyl Acetoacetate.

A suspension of **1a** (2.6 g, 0.01 mole) in ethanol (30 ml) was treated with ethyl acetoacetate (1.30 g) then with few drops of triethylamine. The reaction mixture was refluxed for three hours then allowed to cool to room temperature. The solid product, formed on standing, was collected by filtration and identified (mp and mixed mp) as **1c**.

(e) With **6**.

A suspension of **1a** (2.6 g, 0.01 mole) in pyridine (30 ml) was treated with **6** (1.0 g, 0.01 mole). The reaction mixture was refluxed for three hours then left to cool. The solid product, so formed, was collected by filtration and identified (mp and mixed mp) as **5**.

(f) With Hydrazine Hydrate.

A suspension of **1a** (2.6 g, 0.01 mole) in ethanol (30 ml) was treated with hydrazine hydrate (1.3, 98%). The reaction mixture was refluxed for three hours then evaporated *in vacuo*. The resulting solid product was collected by filtration and identified (mp and mixed mp) as benzalazine.

5,7-Diamino-6-cyano-2-methyl-4-*p*-methoxyphenyl-3-ethoxycarbonyl-4H-pyrano[2,3-*b*]pyridine (**7**).

A solution of **1b** (3.1 g, 0.01 mole) in ethanol (30 ml) was treated with malononitrile (0.66 g) then with three drops of triethylamine. The reaction mixture was refluxed for four hours then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filtration.

Compound **7** formed yellow crystals from ethanol mp 191°, yield 60%; ir: 3430, 3360, 3240 (2NH<sub>2</sub>), 2220 (CN), 1710 (CO), 1660-1620 (δ NH<sub>2</sub> and C=C); <sup>1</sup>H nmr: 1.2 (t, 3H, CH<sub>3</sub>), 2.2 (s, 3H, CH<sub>3</sub>), 3.8 (s, 3H, OCH<sub>3</sub>), 4.1 (m, 4H, CH<sub>2</sub> and NH<sub>2</sub>), 5.7 (s, 1H, H-4), 7.2-7.5 (m, 4H, C<sub>6</sub>H<sub>4</sub>), 8.6 (s, 2H, NH<sub>2</sub>); ms: m/e = 363 (M<sup>+</sup>-17).

Anal. Calcd. for C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub> (380.4): C, 63.1; H, 5.3; N, 14.7. Found: C, 63.1; H, 5.1; N, 14.9.

3,6-Dimethyl-5- $\alpha$ -*p*-methoxyphenyl- $\beta$ -dicyanoethyl-4-oxo-4H-pyrano[2,3-*c*]1H-pyrazole (**13**).

A solution of **1b** (3.1 g, 0.01 mole) in pyridine was treated with **6** (1.0 g, 0.01 mole). The reaction mixture was refluxed for three hours then evaporated *in vacuo*. The remaining product was triturated with water and hydrochloric acid. The resulting solid product was collected by filtration.

Compound **13** formed yellow crystals from dioxane and water mp > 300°, yield 50%; ir: 3480-3340 (NH), 2220 (CN), 1670-1610 (CO, δ NH); <sup>1</sup>H nmr: 2.5 (s, 3H, CH<sub>3</sub>), 3.4-3.9 (m, 8H, CH<sub>3</sub>, OCH<sub>3</sub>, (-C-H)<sub>2</sub>), 6.8-7.3 (m, 5H, NH, C<sub>6</sub>H<sub>4</sub>); ms: m/e = 346 (M<sup>+</sup>-2).

Anal. Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub> (348.4): C, 65.5; H, 4.6; N, 13.9. Found: C, 65.3; H, 4.6; N, 13.6.

1-Amino-5-cyano-6-hydroxy-2-methyl-4-*p*-methoxyphenyl-1,4-dihydropyridine-3-carbohydrazide (**16**).

A solution of **1b** (3.1 g, 0.01 mole) in ethanol (50 ml) was treated with hydrazine hydrate (0.5 ml, 0.01 mole). The reaction mixture was refluxed for one hour then left to cool. The crystals, separated on standing, were collected by filtration and crystallized.

Compound **16** formed colorless crystals from ethanol, mp 200°, yield 60%; ir: 3500-3200 (NH<sub>2</sub> and OH), 2195 (CN), 1650 (CO); <sup>1</sup>H nmr: 3.7 (s, 3H, CH<sub>3</sub>), 3.8 (s, 3H, OCH<sub>3</sub>), 4.5 (s, 1H, pyridine H-4), 6.8-7.1 (m, 6H, arom protons and NH<sub>2</sub>), and 7.8 (s, 1H, OH); ms: m/e = 315 (M<sup>+</sup>).

Anal. Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> (315.3): C, 57.1; H, 5.4; N, 22.2. Found: C, 57.0; H, 5.4; N, 22.0.

Reaction of **1a-c** with Benzoyl Isothiocyanate.

A mixture of each of **1a-c** (0.01 mole) and benzoyl isothiocyanate (0.01 mole) was refluxed in dry dioxane (30 ml) for 4 hours. The reaction mixture was triturated with water. The oil so formed was triturated with benzene and petroleum ether. The solid product, so formed, was collected by filtration.

6-Acetyl-4-*N*-benzoylamino-1,2-dihydro-7-methyl-5-phenyl-2-thioxo-5H-pyrano[2,3-*d*]pyrimidine (**17a**) formed yellow crystals from chloroform and petroleum ether, mp 180°, yield 75%; ir: 3460-3260 (2NH), 1690-1580 (CO, δ NH).

Anal. Calcd. for C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S (417.4): C, 66.2; H, 4.6; N, 10.1; S, 7.7. Found: C, 66.5; H, 4.6; N, 10.0; S, 7.5.

Ethyl 4-*N*-benzoylamino-1,2-dihydro-7-methyl-5-*p*-methoxyphenyl-2-thioxo-5H-pyrano[2,3-*d*]pyrimidine-6-carboxylate (**17b**) formed yellow crystals from benzene-petroleum ether, mp 192°, yield 70%; ir: 3210, 3130 (NH), 1710-1690 (CO).

Anal. Calcd. for C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>S (477.5): C, 62.9; H, 4.6; N, 8.8; S, 6.7. Found: C, 62.9; H, 4.5; N, 8.6; S, 6.7.

Ethyl 4-*N*-benzoylamino-1,2-dihydro-7-methyl-5-phenyl-2-thioxo-5H-pyrano[2,3-*d*]pyrimidine 6-carboxylate (**17c**) formed yellow crystals from

ethanol, yield 75%, mp 110°; ir: 3210 (NH); 1710-1695 (CO); <sup>1</sup>H nmr: 1.3 (t, 3H, CH<sub>3</sub>), 2.4 (s, 3H, CH<sub>3</sub>), 3.4 (s, 1H, NH), 4.2 (q, 2H, CH<sub>2</sub>), 5.0 (s, 1H, pyran H-4), 7.2-7.7 (m, 10H, 2C<sub>6</sub>H<sub>5</sub>), 8.2 (s, br, 1H, NH).

*Anal.* Calcd. for C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>S (447.4): C, 64.4; H, 4.7; N, 9.4; S, 7.2. Found: C, 64.2; H, 4.5; N, 9.3; S, 7.2.

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