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

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

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Although 2-amino-3-cyano-4H-pyrans became recently readily obtainable via efficient synthetic routes [1-3] the chemistry of these versatile enaminonitriles has received very limited attention [4,5]. In conjunction of our effort directed toward exploring the synthetic potential of enaminonitriles [6,7], we report here on the chemistry of the 2-amino-3-cyano-4H-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 ¹H nmr which revealed a singlet at 4.1 ppm for pyran H-4 and did not show a multiplet for protons linked to Sp³ carbons at δ 2.3 ppm as would be anticipated for **3**.

Compound la reacted with malononitrile in refluxing ethanol to yield a product of molecular formula C,H,N,O (M⁺ = 148). ¹H 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 la 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 benzylidenemalononitrile 2a. The presence of 2a in reaction media was indicated via isolation of the 4H-pyrano[2,3-c]pyrazole (5) [8] on treatment of the mother liquor of reaction of la 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-dicyanomethyl-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 $C_{18}H_{13}N_3O_2$ (M⁺ = 303). The ¹H 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 Sp³ carbons as would be expected for 11. Compounds 1b,c were

OCH₃

recovered unreacted on treatment with 2a,c under conditions effected addition of 1a to 2a,c. This finding supports further the assumption that the reaction of the latter compounds (1a and 2a,c) involved addition of the $CH_3C=0$ to the double bond in 2a,c thus affording 12.

The reaction of 1a with ethyl acetoacetate afforded 1c. The formation of the latter is assumed to proceed via reaction of ethyl acetoacetate with 2a which is present in solution of 1a in ethanol as a result of existence of the latter in equilibrium with the acyclic tautomer 3a. Compound 3a is in equilibrium with its constituents (cf. eq. 1). Similar equilibrium has been suggested recently by us to account for some of the chemistry of 1c [2].

$$1a = 3a = 2a + CH_3COCH_2COCH_3$$
 eq. 1

In support of suggested tautomerism is the formation of **5** from reaction of **1a** with **6**.

In contrast to the behaviour of 1a, 1b reacted with 6 to yield a product of condensation via ethanol and water elimination. Two isomeric structures seemed possible for this product (cf. 13 and 14). Structure 13 was established based on ir spectra which revealed two CN bands and the absence of a NH_2 vibration. Moreover 1H nmr indicated a multiplet at δ 3-3.8 for two CH linked to Sp^3 carbons.

While benzalazine 15 was the only isolable product from reaction of 1a with hydrazine hydrate, compound 1b afforded the N-aminopyridine 16 on treatment with hydrazine hydrate in refluxing ethanol. The formation of 16 from 1b and hydrazine is in contrast to recently reported [2] formation of 5 from reaction of 1c and hydrazine. The discrepancy in behaviour between 1b and 1c can be rationalised by assuming that the chain tautomer of 1b is not in equilibrium with its constituents as in 1c. The presence of a methoxy substituent in the

1b
$$\frac{6}{-C_2H_6OH}$$
 $\frac{C_6H_4OCH_3-p}{CH_3}$ $\frac{C_6H_4OCH_3-p}{CN}$ $\frac{CH_3}{CN}$ \frac

former (1b) makes decomposition of the chain tautomer into constituents less facile reaction.

The pyrano[2,3-d]pyrimidine derivatives 17a-c were obtained on reacting 1a-c with benzoylisothiocyanates. The cyclic structure 17 was established based on ir which revealed absence of CN band. The benzoylamino form 17 was preferred over possible N-1 benzoylimino structure 18 based on the stability of the reaction products under conditions reported to effect debenzoylation or rearrangement of N-benzoylaminoheteroaromatics.

It is thus clear that the enaminonitrile moiety in **la-c** is inert toward nucleophilic reagents.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded in potassium bromide on a Pye-Unicam SP-1000 spectrophotometer. The $^1\mathrm{H}$ nmr were measured in DMSO on a varian A-90 Hz spectrophotometer and chemical shifts are expressed as δ ppm.

2-Amino-3-cyano-6-methyl-4-aryl-5-substituted-4H-pyrans.

A solution of each of **2a-c** (0.1 mole) in ethanol (150 ml) containing few drops of triethylamine was treated with acetylacetone (10.0 g) or ethyl acetoacetate (13.0 g). The reaction mixture was refluxed for three hours then allowed to cool to room temperature. The solid product, so formed, was collected by filtration and crystallized from ethanol.

Compound 1a formed colourless crystals mp 155°; yield, 70% ir: 3420, 3320 cm⁻¹ (NH₂), 2225 (CN), 1710 (CO) and 1640 (δ NH₂); ¹H nmr: 2.0 (s, 3H, CH₃), 2.3 (s, 3H, CH₃), 4.8 (s, 1H, pyran H-4), 5.4 (br, 2H, NH₂) and 7.3-7.5 (m, 5H, C₆H₃); ms: m/e = 254 (M⁴).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$ (254.3); C, 70.9; H, 5.5; N, 11.0. Found: C, 70.8; H, 5.3; N, 11.2.

Compound 1b formed colorless crystals; mp 130° yield 82%; ir: 3400, 3200 (NH₂), 2200 (CN), 1710 (CO) and 1640 (δ NH₂); ¹H nmr: 1.2 (t, 3H, CH₃), 2.4 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 4.2 (q, 2H, CH₂), 4.6 (s, 1H, H-4), 6.2 (s, 2H, NH₂), 7.2-7.6 (m, 4H, C₆H₄); ms: m/e = 314 (M*).

Anal. Calcd. for C₁₇H₁₈N₂O₄ (314.3): C, 65.0; H, 5.7; N, 8.9. Found: C, 65.0; H, 5.6; N, 8.7.

Compound 1c formed colorless crystals from ethanol, mp 177° (lit mp 176°) [2], yield 80%; ir: 3420, 3340, 3280 (NH₂), 2200 (CN) and 1700 (CO); ¹H nmr: 1.2 (t, 3H, CH₃), 2.2 (s, 3H, CH₃), 4.0 (q, 2H, CH₂), 4.5 (s, 1H, H-4),

6.9 (s, 2H, NH_2) and 7.2-7.4 (m, 5H, C_6H_3); 13 C nmr: 13.6 (CH_3), 18.1 (CH_3), 57.5 (pyran C-4), 60.0 (CH_2), 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 la with (a) Malononitrile.

A suspension of **la** (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); 'H nmr: 2.2 (s, 3H, CH₃), 2.3 (s, 3H, CH₃), 6.1 (s, 1H, CH), 12.3 (s, 1H, NH); ms: m/e = 148 (M*).

Anal. Calcd. for $C_0H_0N_2O$ (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); 'H nmr: 2.2 (s, 3H, CH₃), 2.3 (s, 3H, CH₃), 2.5 (d, 1H, CH), 2.8 (d, 1H, CH), 6.0 (s, H, H-4), 7.3-7.6 (m, 5H, C₆H₃); ms: m/e = 303 (M⁺).

Anal. Calcd. for $C_{18}H_{13}N_3O_2$ (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 (NH₂), 2220 (CN) 1700-1650 (δ NH₂ and C = C); ¹H nmr: 2.0 (s, 3H, CH₃), 2.2 (br, 4H, 2NH₂), 4.6 (s, 1H, pyran H-4), 5.0 (s, 1H, pyran H-4), 7.3-7.5 (m, 10H, 2C₆H₃); ms: m/e = 408 (M*).

Anal. Calcd. for $C_{25}H_{20}N_4O_2$ (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 (2NH₂), 3100-2800 (CH, CH₂ and CH₃), 1750 (ester CO), 1690-1660 (C=C, NH₂ deformation); ms: m/e = 455 (M*).

Anal. Calcd. for $C_{27}H_{25}N_3O_4$ (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 (2NH₂), 2220 (CN), 1710 (CO), 1660-1620 (δ NH₂ and C=C); ¹H nmr: 1.2 (t, 3H, CH₃), 2.2 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 4.1 (m, 4H, CH₂ and NH₂), 5.7 (s, 1H, H-4), 7.2-7.5 (m, 4H, C₆H₄), 8.6 (s, 2H, NH₂); ms: m/e = 363 (M*-17).

Anal. Calcd. for $C_{20}H_{20}N_4O_4$ (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- α -p-methoxyphenyl- β -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 $> 300^{\circ}$, yield 50%; ir: 3480-3340 (NH), 2220 (CN), 1670-1610 (CO, δ NH); ¹H nmr: 2.5 (s, 3H, CH₃), 3.4-3.9 (m, 8H, CH₃, OCH₃, (-C-H₂), 6.8-7.3 (m, 5H, NH, C₆H₄); ms: m/e = 346 (M⁺ -2).

Anal. Calcd. for C₁₉H₁₆N₄O₃ (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 (NH₂ and OH), 2195 (CN), 1650 (CO); ¹H nmr: 3.7 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 4.5 (s, 1H, pyridine H-4), 6.8-7.1 (m, 6H, arom protons and NH₂) and 7.8 (s, 1H, OH); ms: m/e = 315 (M*).

Anal. Calcd. for $C_{15}H_{17}N_5O_3$ (315.3): C, 57.1; H, 5.4; N, 22.2. Found: C, 57.0; H, 5.4; N, 22.0.

Reaction of la-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 $C_{23}H_{19}N_3O_3S$ (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 $C_{25}H_{23}N_3O_5S$ (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); 'H nmr: 1.3 (t, 3H, CH₃), 2.4 (s, 3H, CH₃), 3.4 (s, 1H, NH), 4.2 (q, 2H, CH₂), 5.0 (s, 1H, pyran H-4), 7.2-7.7 (m, 10H, 2C₆H₅), 8.2 (s, br, 1H, NH).

Anal. Calcd. for $C_{24}H_{21}N_3O_4S$ (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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