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SYNTHESIS AND REACTIVITY OF METHYL 3-ACYL-6-AMINO-4-ARYL-5-CYANO-4H-PYRAN-2-CARBOXYLATES

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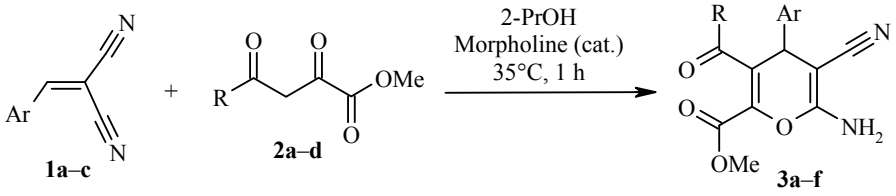
By treating arylidenemalononitriles with methyl 2,4-dioxobutanoates, derivatives of 4H-pyrans - methyl 3-acyl-6-amino-4-aryl-5-cyano-4H-pyran-2-carboxylates - are obtained, which are novel, promising structural components for the synthesis of carbo- and heterocycles. The reactions of these pyrans with sulfuric and hydrochloric acids, acetic anhydride, and alcohols have been studied. Novel methods have been developed for the preparation of substituted derivatives of cyclopentenone, pyrano[2,3-d]-pyrimidine, 5-oxo-3-phenylpentanoic acid, and nicotinic acid nitrile.

Keywords: cyclopentenones, 5-oxopentanoic acid, 4*H*-pyrans, pyridines, ring opening.

The synthesis of novel 4*H*-pyrans is a current problem in organic chemistry. Different classes of organic compounds can be obtained on their basis. 4*H*-Pyrans, including 2-amino-3-cyano-4*H*-pyrans, exhibit antimicrobial [1, 2], antiviral [3], analgesic [4], antitumor [5-8], fungicidal [9, 10], and herbicidal [11] activity.

We have used arylidenemalononitriles and methyl 2,4-dioxobutanoate in the synthesis of novel 2-amino-3-cyano-4*H*-pyrans. Methyl 2,4-dioxobutanoates have been used before in the synthesis of five- and six-membered nitrogen-containing heterocycles [12-15]. The reactions of arylidenemalononitriles with these esters have not been studied before.



1 a Ar = Ph, **b** Ar = 3-ClC_6H_4, **c** Ar = 2-ClC_6H_4; **2 a** R = Me, **b** R = Ph, **c** R = 4-$MeOC_6H_4$, **d** R = 4-MeC_6H_4; **3 a** R = Me, Ar = Ph; **b** R = Ph, Ar = Ph; **c** R = 4-$MeOC_6H_4$, Ar = Ph; **d** R = 4-MeC_6H_4, Ar = Ph; **e** R = Me, Ar = 3-ClC_6H_4; **f** R = 4-MeC_6H_4, Ar = 2-ClC_6H_4

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We have used our previously discovered method for the preparation of methyl 3-acyl-6-amino-4-aryl-5-cyano-4*H*-pyran-2-carboxylates [16] from arylidenemalononitriles and methyl 2,4-dioxobutanoates in propan-2-ol in the presence of a catalytic amount of morpholine for the differently substituted starting compounds **1a-c** and **2a-d**.

The structure of the synthesized pyrans **3a-f** was confirmed by the X-ray structural data for compound **3a** (Fig. 1).

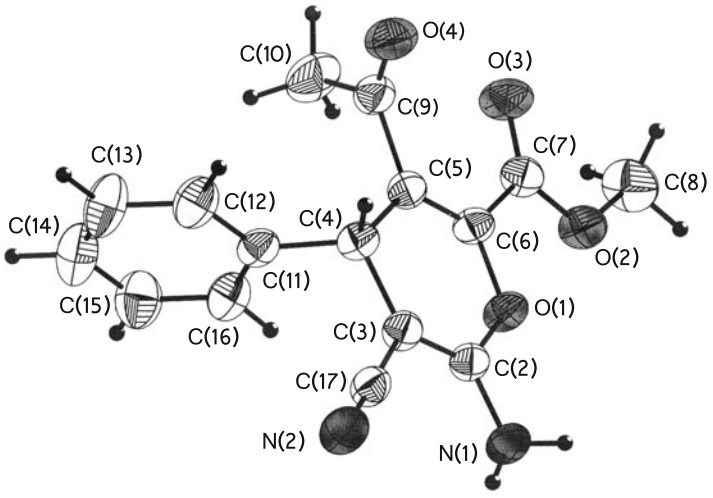
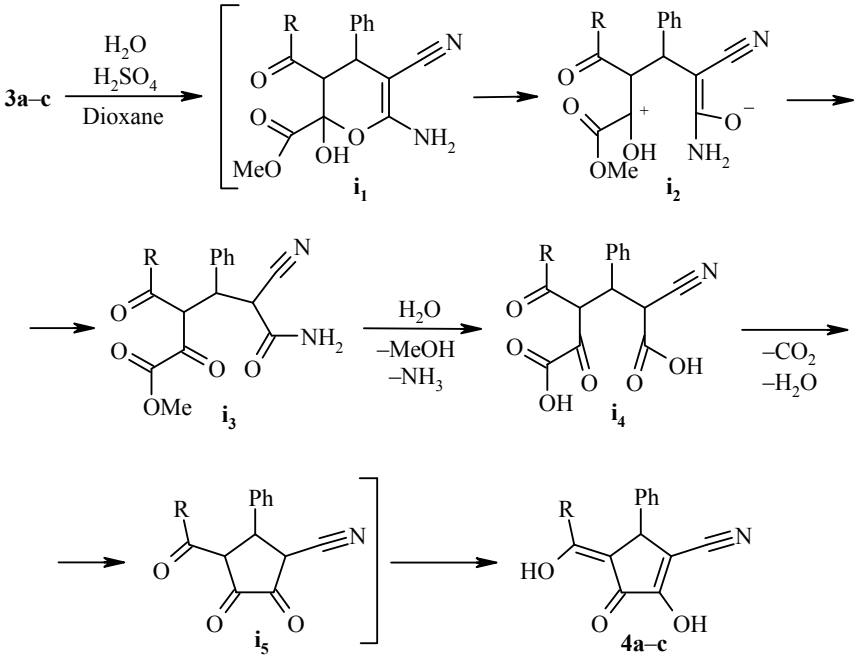


Fig. 1. Molecular structure of compound **3a** with atoms represented by thermal vibration ellipsoids of 50% probability.

This unique combination of different functional groups in the methyl 3-acyl-6-amino-4-aryl-5-cyano-4*H*-pyran-2-carboxylates **3** and their susceptibility to ring opening gives them novel and unusual properties.



4 a R = Me, **b** R = Ph, **c** R = 4-MeOC$_6$H$_4$

We have found that heating the pyrans **3a-c** for 4-6 h in a mixture of 10% aqueous H_2SO_4–dioxane gives the cyclopentenones **4a-c**. The structure of the cyclopentenones was confirmed from the X-ray structural analysis of compound **4c** (Fig. 2).

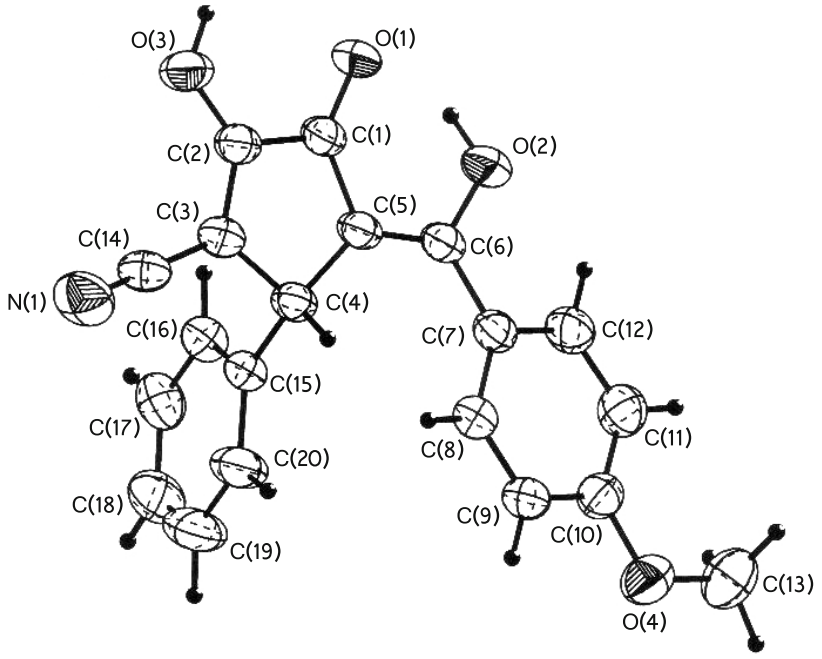
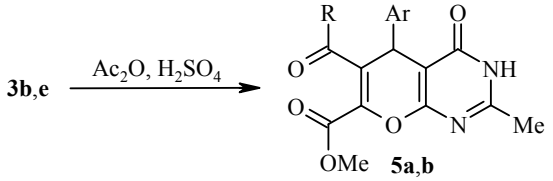


Fig. 2. Molecular structure of compound **4c** with atoms represented by thermal vibration ellipsoids of 50% probability.

We propose that water at first adds to the C=C double bond of the pyran ring. The following stages are: opening of the ring in intermediate $\mathbf{i_1}$ to $\mathbf{i_2}$, hydrolysis of intermediate $\mathbf{i_3}$ to $\mathbf{i_4}$, dehydration, decarboxylation, and cyclization of intermediate $\mathbf{i_4}$ to $\mathbf{i_5}$ to give the cyclopentenones **4a-c**.

Novel methods for the synthesis of substituted cyclopentenones have a high value since the cyclopentenone fragment is an important component in natural compounds and their analogs [17-19]. Known routes for the formation of 3-oxo-2-hydroxycyclopentene-1-carbonitrile unit involve three stages with the use of organometallic reagents and low temperatures, and the yields are low (16-22%) [19].

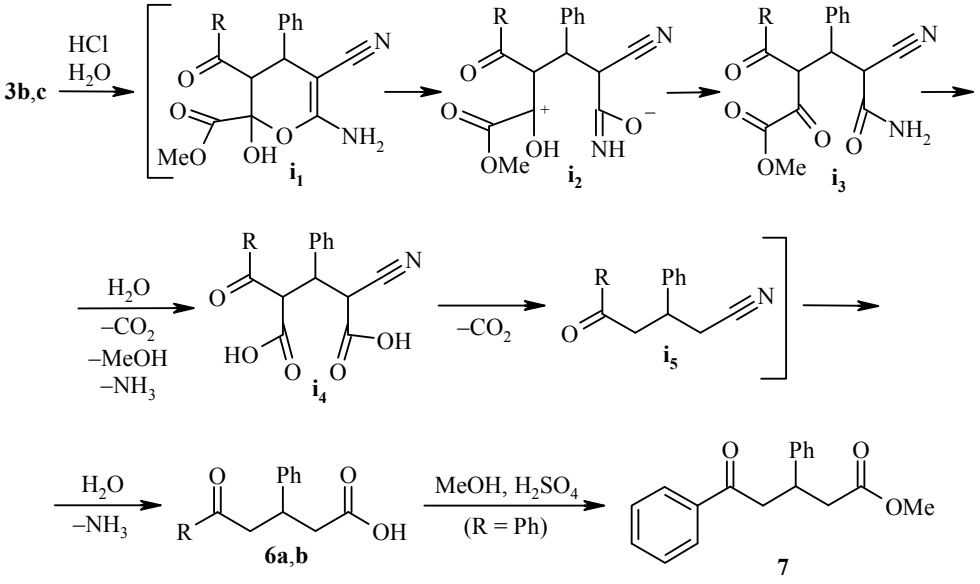
A high reactivity of the 4*H*-pyrans **3** is indicated by their reactions with acetic anhydride in the presence of sulfuric acid. For example, heating compounds **3b**,**e** to 80-90ºC for 1 min gives the pyrano[2,3-*d*]pyri-midines **5a,b**. Similar known reactions of 4*H*-pyrans take 6-10 h [2].



5 a R = Ph, Ar = Ph; **b** R = Me, Ar = 3-ClC_6H_4

Different transformations occur when refluxing the pyrans **3b**,**c** in concentrated hydrochloric acid over 12 h. Hydrolysis gives the acids **6a**,**b**.

We propose that water initially adds to the pyran ring C=C bond to give the intermediate **i**$_1$, which opens to **i**$_2$. It is likely that hydrolysis and decarboxylation of **i**$_3$ then gives **i**$_4$, followed by decarboxylation of intermediate **i**$_4$ to **i**$_5$. The final stage is the hydrolysis of intermediate **i**$_5$ to form the acids **6a**,**b**.

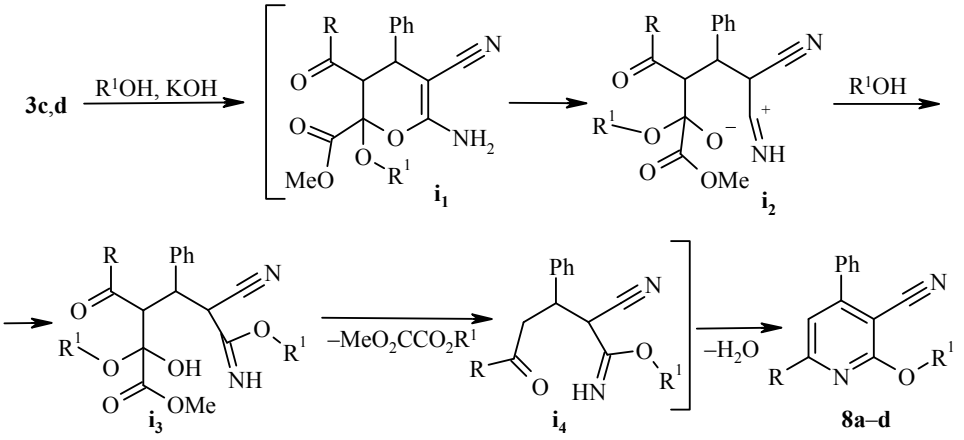


6 a R = Ph, **b** R = 4-MeOC$_6$H$_4$

In order to confirm the conversion of pyrans **3b**,**c** to acids **6a**,**b**, we carried out a reaction of the acid **6a** with methanol in the presence of sulfuric acid to give the ester **7**. Synthesis of compounds **6a, 7** had been carried out previously from 4-phenyldihydro-2*H*-pyran-2,6(3*H*)-dione [20]. However, this method is laborious, involves the use of phenylmagnesium bromide, and needs cooling to -78ºC.

This more profound transformation of pyrans **3** to acids **6** occurs when using concentrated hydrochloric acid (reaction time 12 h, acid concentration 35%), compared with the reaction of **3→4** (reaction time 4-6 h, acid concentration 10%), and is likely due to the more forcing conditions.

Another route using the pyrans **3** as promising synthons is a reaction in the presence of a base. We have found that short (1 min) heating of pyrans **3c**,**d** in an alcohol (methanol, ethanol, or ethylene glycol) in the presence of potassium hydroxide gives the pyridinecarbonitriles **8a-d**.



8 a R = 4-MeOC$_6$H$_4$, R^1 = Me; **b** R = 4-MeOC$_6$H$_4$, R^1 = C$_2$H$_4$OH;
c R = 4-MeC$_6$H$_4$, R^1 = Me; **d** R = 4-MeC$_6$H$_4$, R^1 = Et

Evidently there initially occurs an addition of alcohol to the C=C double bond of the pyran ring. The subsequent stages are: opening of the cyclic intermediate $\mathbf{i_1}$ to $\mathbf{i_2}$, addition of the alcohol to intermediate $\mathbf{i_2}$, elimination of an oxalate ester from intermediate $\mathbf{i_3}$, cyclization and aromatization of intermediate $\mathbf{i_4}$ to the nicotinic acid nitrile **8**. Processes analogous to transformations of intermediate $\mathbf{i_4}$ to the pyridines **8** have been described in study [21]. The reactions **3→8** that we have carried out represent a novel approach to the preparation of nicotinic acid nitriles. The known method of preparing 2-alkoxynicotinic nitriles is more laborious and lengthy [22].

Hence we have found that reactions of arylidenemalononitriles with methyl 2,4-dioxobutanoates give the methyl 3-acyl-6-amino-4-aryl-5-cyano-4*H*-pyran-2-carboxylates, providing a novel route to highly reactive pyrans. The ability of methyl 3-acyl-6-amino-4-aryl-5-cyano-4*H*-pyran-2-carboxylates to undergo ring opening and also their diverse functionality are decisive factors in their single-stage transformations to substituted cyclopentenones, pyran[2,3-*d*]pyrimidines, 5-oxopentanoic acids, and nicotinic acid nitriles. In fact, we propose that these structures are the most reactive and promising synthons amongst known 4*H*-pyrans.

EXPERIMENTAL

IR spectra were recorded for a thin film of vaseline oil suspension on an FSM-1201 instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 (500 and 125 MHz, respectively) for DMSO-d_6 solutions with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (70 eV electron impact). Monitoring of the reaction course and the purity of the prepared compounds was carried out by TLC on Silufol UV-254 plates, which were eluted with EtOAc and visualized with UV radiation, iodine vapor, and also by thermal decomposition. Elemental analysis was carried out on a Carlo-Erba apparatus. Melting points were determined with a capillary instrument.

Methyl 3-Acyl-6-amino-4-aryl-5-cyano-4*H*-pyran-2-carboxylates (3a-f) (General Method). Morpholine (1 drop) was added to a mixture of arylidenemalononitrile **1a-c** (1 mmol) and methyl 2,4-dioxobutanoate **2a-d** (1 mmol) in 2-PrOH (8 ml). The reaction mixture was stirred for 1 h at 35ºC and maintained for 10-12 h at room temperature. The precipitate formed was filtered off, washed with a mixture of 2-PrOH and hexane (1:1), and recrystallized from 2-PrOH.

Methyl 3-Acetyl-6-amino-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate (3a). Yield 0.24 g (82%). White crystals, mp 185-186ºC. IR spectrum, ν, cm^{-1}: 3399, 3317, 2198, 1734, 1691, 1647, 1602. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.91 (3H, s, CH_3CO); 3.78 (3H, s, $COOCH_3$); 4.47 (1H, s, C<u>H</u>Ph); 7.11 (2H, s, NH_2); 7.19-7.21 (2H, m, H-2,6 Ph); 7.29-7.31 (1H, m, H-4 Ph); 7.46-7.49 (2H, m, H-3,5 Ph). Mass spectrum, *m/z* (I_{rel}, %): 298 $[M]^+$ (21). Found, %: C 64.14; H 4.88; N 9.44. $C_{16}H_{14}N_2O_4$. Calculated, %: C 64.42; H 4.73; N 9.39.

Methyl 6-Amino-3-benzoyl-5-cyano-4-phenyl-4*H*-pyran-2-carboxylate (3b). Yield 0.31 g (87%). White crystals, mp 184-185ºC. IR spectrum, ν, cm^{-1}: 3428, 3310, 2197, 1733, 1658, 1642, 1593. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.47 (3H, s, OCH_3); 4.43 (1H, s, C<u>H</u>Ph); 7.11-7.14 (2H, m, H-2,6 Ph); 7.15-7.17 (1H, m, H-4 Ph); 7.19 (2H, s, NH_2); 7.22-7.25 (2H, m, H-3,5 Ph); 7.36-7.39 (2H, m, H-2,6 Ph); 7.53-7.55 (1H, m, H-4 Ph); 7.61-7.64 (2H, m, H-3,5 Ph). Mass spectrum, *m/z* (I_{rel}, %): 360 $[M]^+$ (12). Found, %: C 70.15; H 4.31; N 7.87. $C_{21}H_{16}N_2O_4$. Calculated, %: C 69.99; H 4.48; N 7.77.

Methyl 6-Amino-5-cyano-3-(4-methoxybenzoyl)-4-phenyl-4*H*-pyran-2-carboxylate (3c). Yield 0.33 g (85%). White crystals, mp 170-171ºC. IR spectrum, ν, cm^{-1}: 3440, 3325, 2194, 1736, 1674, 1642, 1600. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.48 (3H, s, $COOCH_3$); 3.79 (3H, s, C<u>H</u>$_3$OC$_6$H$_4$); 4.39 (1H, s, C<u>H</u>Ph); 6.91 (2H, d, *J* = 8.9, H-3,5 Ar); 7.11-7.14 (2H, m, H Ph); 7.15 (2H, s, NH_2); 7.15-7.17 (1H, m, H-4 Ph); 7.23-7.26 (2H, m, H Ph); 7.38 (2H, d, *J* = 8.9, H-2,6 Ar). Mass spectrum, *m/z* (I_{rel}, %): 390 $[M]^+$ (5). Found, %: C 67.75; H 4.84; N 7.02. $C_{22}H_{18}N_2O_5$. Calculated, %: C 67.69; H 4.65; N 7.18.

Methyl 6-Amino-5-cyano-3-(4-methylbenzoyl)-4-phenyl-4*H*-pyran-2-carboxylate (3d). Yield 0.30 g (79%). White crystals, mp 160-161ºC. IR spectrum, ν, cm^{-1}: 3402, 3327, 2197, 1737, 1676, 1648, 1602.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, C<u>H</u>$_3$C$_6$H$_4$); 3.46 (3H, s, COOCH$_3$); 4.31 (1H, s, C<u>H</u>Ph); 7.11 (2H, d, *J* = 8.1, H-3,5 Ar); 7.11-7.14 (2H, m, H Ph); 7.15-7.17 (1H, m, H-4 Ph); 7.18 (2H, s, NH$_2$); 7.21-7.24 (2H, m, H Ph); 8.01 (2H, d, *J* = 8.1, H-2,6 Ar). Mass spectrum, *m/z* (I_{rel}, %): 374 [M]$^+$ (4). Found, %: C 70.97; H 4.65; N 7.51. $C_{22}H_{18}N_2O_4$. Calculated, %: C 70.58; H 4.85; N 7.48.

Methyl 3-Acetyl-6-amino-4-(3-chlorophenyl)-5-cyano-4*H*-pyran-2-carboxylate (3e). Yield 0.24 g (72%). White crystals, mp 150-151ºC. IR spectrum, ν, cm^{-1}: 3455, 3294, 2176, 1692, 1671, 1634, 1595. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (3H, s, CH$_3$CO); 3.78 (3H, s, COOCH$_3$); 4.54 (1H, s, C<u>H</u>Ar); 7.17 (2H, s, NH$_2$); 7.18-7.20 (1H, m, H Ar); 7.27 (1H, s, H Ar); 7.37-7.39 (1H, m, H Ar); 7.40-7.42 (1H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 332 [M]$^+$ (9). Found, %: C 57.63; H 4.02; N 8.29. $C_{16}H_{13}ClN_2O_4$. Calculated, %: C 57.76; H 3.94; N 8.42.

Methyl 6-Amino-4-(2-chlorophenyl)-5-cyano-3-(4-methylbenzoyl)-4*H*-pyran-2-carboxylate (3f). Yield 0.29 g (71%). White crystals, mp 210-211ºC. IR spectrum, ν, cm^{-1}: 3409, 3324, 2196, 1657, 1600. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, C<u>H</u>$_3$C$_6$H$_4$); 3.78 (3H, s, OCH$_3$); 4.59 (1H, s, C<u>H</u>Ar); 7.15 (2H, s, NH$_2$); 7.13-7.15 (2H, m, H Ar); 7.17-7.19 (1H, m, H Ar); 7.19-7.21 (2H, m, H Ar); 7.22-7.24 (1H, m, H Ar); 7.33-7.35 (1H, m, H Ar); 7.38-7.40 (1H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 408 [M]$^+$ (7). Found, %: C 64.69; H 4.12; N 6.94. $C_{22}H_{17}ClN_2O_4$. Calculated, %: C 64.63; H 4.19; N 6.85.

2-Hydroxy-4-[hydroxy(R)methylene]-3-oxo-5-phenylcyclopent-1-enecarbonitriles (4a-c) (General Method). A mixture of the pyran **3a-c** (1 mmol), water (30 ml), conc. H_2SO_4 (1.8 ml), and dioxane (1 ml) was heated for 4-6 h. After cooling to room temperature the mixture was diluted with water (20 ml) and left for 24 h. The precipitate formed was washed with water (2×25 ml) and dissolved in EtOAc (15 ml). The ethyl acetate layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was separated on a silica gel column eluting with a mixture of EtOAc and hexane (3:1).

2-Hydroxy-4-(1-hydroxyethylidene)-3-oxo-5-phenylcyclopent-1-enecarbonitrile (4a). Yield 0.067 g (28%). Yellow crystals, mp 179-180ºC. IR spectrum, ν, cm^{-1}: 3435, 3205, 2222, 1650, 1638, 1603. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, CH$_3$); 4.92 (1H, s, C<u>H</u>Ph); 7.19-7.22 (2H, m, H-3,5 Ph); 7.37-7.40 (2H, m, H-2,6 Ph); 7.40-7.42 (1H, m, H-4 Ph); 12.56 (2H, br. s, OH). Mass spectrum, *m/z* (I_{rel}, %): 241 [M]$^+$ (12). Found, %: C 69.42; H 4.67; N 5.96. $C_{14}H_{11}NO_3$. Calculated, %: C 69.70; H 4.60; N 5.81.

2-Hydroxy-4-[hydroxy(phenyl)methylene]-3-oxo-5-phenylcyclopent-1-enecarbonitrile (4b). Yield 0.12 g (41%). Yellow crystals, mp 172-173ºC. IR spectrum, ν, cm^{-1}: 3410, 3250, 2211, 1664, 1640, 1596. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.90 (1H, s, C<u>H</u>Ph); 7.23-7.52 (10H, m, H Ph); 12.76 (2H, br. s, OH). Mass spectrum, *m/z* (I_{rel}, %): 303 [M]$^+$ (17). Found, %: C 75.52; H 4.39; N 4.51. $C_{19}H_{13}NO_3$. Calculated, %: C 75.24; H 4.32; N 4.62.

2-Hydroxy-4-[hydroxy(4-methoxyphenyl)methylene]-3-oxo-5-phenylcyclopent-1-enecarbonitrile (4c). Yield 0.14 g (43%). Yellow crystals, mp 169-170ºC. IR spectrum, ν, cm^{-1}: 3440, 3250, 2209, 1670, 1640, 1610. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 (3H, s, CH$_3$); 4.87 (1H, s, C<u>H</u>Ar); 7.23-7.39 (9H, m, H Ar); 12.76 (2H, br. s, OH). Mass spectrum, *m/z* (I_{rel}, %): 333 [M]$^+$ (11). Found, %: C 72.36; H 4.42; N 4.07. $C_{20}H_{15}NO_4$. Calculated, %: C 72.06; H 4.54; N 4.20.

Methyl 6-Acyl-5-aryl-2-methyl-4-oxo-4,5-dihydro-3*H*-pyrano[2,3-*d*]pyrimidine-7-carboxylates 5a,b (General Method). The pyran **3b**,**e** (1 mmol), Ac_2O (1.5 ml), and conc. H_2SO_4 (15 mg, 0.15 mmol) were mixed. The reaction mixture was heated for 1 min at 80-90ºC, cooled to room temperature, and water (2 ml) was added. After 24 h the residue was filteredb off and washed with water (10 ml) and a 1:1 mixture of 2-PrOH and hexane (5 ml). The product was recrystallized from 2-PrOH.

Methyl 6-Benzoyl-2-methyl-4-oxo-5-phenyl-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-7-carboxylate (5a). Yield 0.37 g (91%). White crystals, mp 255-256ºC. IR spectrum, ν, cm^{-1}: 3200, 1738, 1668, 1642, 1596. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, 2-CH$_3$); 3.51 (3H, s, COOCH$_3$); 4.69 (1H, s, C<u>H</u>Ph); 7.09-7.12 (2H, m, H-2,6 Ph); 7.13-7.15 (1H, m, H-4 Ph); 7.20-7.23 (2H, m, H-3,5 Ph); 7.37-7.40 (2H, m, H-2,6 Ph); 7.54-7.56 (1H, m, H-4 Ph); 7.62-7.65 (2H, m, H-3,5 Ph); 12.64 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 402 [M]$^+$ (13). Found, %: C 68.39; H 4.58; N 6.78. $C_{23}H_{18}N_2O_5$. Calculated, %: C 68.65; H 4.51; N 6.96.

Methyl 6-Acetyl-5-(3-chlorophenyl)-2-methyl-4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidine-7-carboxylate (5b). Yield 0.33 g (87%). White crystals, mp 221-222ºC. IR spectrum, ν, cm^{-1}: 3150, 1727, 1706, 1669, 1644, 1598. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, CH_3CO); 2.28 (3H, s, 2-CH_3); 3.81 (3H, s, $COOCH_3$); 4.79 (1H, s, C<u>H</u>Ar); 7.20-7.22 (1H, m, H Ar); 7.30 (1H, s, H Ar); 7.31-7.33 (1H, m, H Ar); 7.34-7.36 (1H, m, H Ar); 12.64 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 374 $[M]^+$ (9). Found, %: C 57.80; H 4.16; N 7.38. $C_{18}H_{15}ClN_2O_5$. Calculated, %: C 57.69; H 4.03; N 7.47.

5-Aryl-5-oxo-3-phenylpentanoic Acids (6a,b) (General Method). Conc. HCl (10 ml) was added to the pyran **3b,c** (0.5 mmol) and refluxed for 12 h. The precipitate formed was washed with a 1:1 mixture of 2-PrOH and hexane and recrystallized from 2-PrOH.

5-Oxo-3,5-diphenylpentanoic Acid (6a). Yield 97 mg (72%). White crystals, mp 126-128ºC. IR spectrum, ν, cm^{-1}: 1697, 1679, 1670. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (1H, dd, *J* = 15.8, *J* = 8.6) and 2.70 (1H, dd, *J* = 15.8, *J* = 6.4, C<u>H</u>$_2$COOH); 3.37 (1H, dd, *J* = 11.1, *J* = 6.4) and 3.45 (1H, dd, *J* = 11.1, *J* = 7.8, PhCOC<u>H</u>$_2$); 3.65-3.67 (1H, m, C<u>H</u>Ph); 7.13-7.15 (1H, m, H Ph); 7.23-7.25 (2H, m, H Ph); 7.28-7.31 (2H, m, H Ph); 7.48-7.50 (2H, m, H Ph); 7.60-7.62 (1H, m, H Ph); 7.91-7.93 (2H, m, H Ph); 12.06 (1H, s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 268 $[M]^+$ (21). Found, %: C 76.15; H 6.04. $C_{17}H_{16}O_3$. Calculated, %: C 76.10; H 6.01.

5-(4-Methoxyphenyl)-5-oxo-3-phenylpentanoic Acid (6b). Yield 100 mg (70%). White crystals, mp 153-155ºC. IR spectrum, ν, cm^{-1}: 1698, 1672, 1602, 1505. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (1H, dd, *J* = 15.8, *J* = 8.6) and 2.68 (1H, dd, *J* = 15.8, *J* = 6.3, C<u>H</u>$_2$COOH); 3.28 (1H, dd, *J* = 16.7, *J* = 6.3) and 3.38 (1H, dd, *J* = 16.7, *J* = 7.9, ArCOC<u>H</u>$_2$); 3.63-3.65 (1H, m, C<u>H</u>Ph); 3.82 (3H, s, OCH_3); 6.99-7.02 (2H, m, H Ar); 7.13-7.15 (1H, m, H Ph); 7.23-7.25 (2H, m, H Ph); 7.29-7.31 (2H, m, H Ph); 7.89-7.91 (2H, m, H Ar); 12.02 (1H, s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 298 $[M]^+$ (15). Found, %: C 72.44; H 6.03. $C_{18}H_{18}O_4$. Calculated, %: C 72.47; H 6.08.

Methyl 5-Oxo-3,5-diphenylpentanoate (7). One drop of conc. H_2SO_4 was added to a solution of 5-oxo-3,5-diphenylpentanoic acid (**6a**) (1.34 g, 5 mmol) in MeOH (15 ml) and refluxed for 8 h. Water (15 ml) was added. The white precipitate obtained was filtered off, washed with water, and recrystallized from a 1:1 mixture of 2-PrOH and hexane. Yield 1.07 g (76%). White crystals, mp 73-75ºC. IR spectrum, ν, cm^{-1}: 1730, 1679, 1598. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.62 (1H, dd, *J* = 15.3, *J* = 7.3) and 2.80 (1H, dd, *J* = 15.3, *J* = 7.3, C<u>H</u>$_2$COOMe); 3.36 (1H, dd, *J* = 16.7, *J* = 6.9) and 3.41 (1H, dd, *J* = 16.7, *J* = 6.9, PhCOC<u>H</u>$_2$); 3.59 (3H, s, COOC<u>H</u>$_3$); 3.75-3.76 (1H, m, C<u>H</u>Ph); 7.13-7.15 (1H, m, H Ph); 7.25-7.28 (2H, m, H Ph); 7.28-7.30 (2H, m, H Ph); 7.50-7.52 (2H, m, H Ph); 7.61-7.63 (1H, m, H Ph); 7.90-7.92 (2H, m, H Ph). Mass spectrum, *m/z* (I_{rel}, %): 282 $[M]^+$ (33). Found, %: C 76.61; H 6.47. $C_{18}H_{18}O_3$. Calculated, %: C 76.57; H 6.43.

2-Alkoxy-4,6-diaryl-3-pyridinecarbonitriles (8a-d) (General Method). The pyran **3c**,**d** (1 mmol) was added to a solution of potassium hydroxide (0.2 g, 3.5 mmol) in an alcohol (methanol, ethanol, or ethylene glycol) (10 ml) and heated for 1 min at 64ºC. The mixture was cooled to room temperature, diluted with water (20 ml), and neutralized with 10% HCl to pH 7. The precipitate formed was filtered off, washed with water (2×25 ml), and recrystallized from 2-PrOH (compounds **8a**,**c**) or from a 1:1 mixture of 2-PrOH and hexane (compounds **8b**,**d**).

2-Methoxy-6-(4-methoxyphenyl)-4-phenylnicotinonitrile (8a). Yield 0.25 g (78%). White crystals, mp 145-146ºC. IR spectrum, ν, cm^{-1}: 2220, 1583, 1549. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, C<u>H</u>$_3$OC$_6$H$_4$); 4.14 (3H, s, 2-OCH_3); 7.19 (2H, d, *J* = 8.8, H-3,5 Ar); 7.57-7.60 (3H, m, H-3,4,5 Ph); 7.63 (2H, m, H-2,6 Ph); 7.65 (1H, s, H-5); 8.24 (2H, d, *J* = 8.8, H-2,6 Ar). ^{13}C NMR spectrum, δ, ppm: 54.4; 55.5; 91.2; 112.8; 114.3; 115.6; 128.6; 128.9; 129.1; 129.2; 130.0; 136.0; 156.2; 157.2; 161.5; 164.3. Mass spectrum, *m/z* (I_{rel}, %): 316 $[M]^+$ (78). Found, %: C 76.22; H 5.19; N 8.75. $C_{20}H_{16}N_2O_2$. Calculated, %: C 75.93; H 5.10; N 8.85.

2-(2-Hydroxyethoxy)-6-(4-methoxyphenyl)-4-phenylnicotinonitrile (8b). Yield 0.25 g (71%). White crystals, mp 190-191ºC. IR spectrum, ν, cm^{-1}: 3306, 2214, 1683, 1642. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.58 (2H, d, *J* = 6.9, C<u>H</u>$_2$OH); 3.64 (1H, s, OH); 3.83 (3H, s, C<u>H</u>$_3$OC$_6$H$_4$); 4.37 (2H, d, *J* = 6.9, 2-OCH_2); 7.18 (2H,

d, J = 8.8, H-3,5 Ar); 7.57-7.59 (3H, m, H-3,4,5 Ph); 7.63-7.64 (2H, m, H-2,6 Ph); 7.64 (1H, s, H-5); 8.21 (2H, d, J = 8.8, H-2,6 Ar). ^{13}C NMR spectrum, δ, ppm: 55.5; 60.0; 71.1; 91.2; 112.8; 114.4; 115.4; 128.4; 128.9; 129.1; 129.2; 130.1; 136.0; 156.2; 157.2; 161.5; 165.0. Mass spectrum, *m/z* (I_{rel}, %): 346 $[M]^+$ (51). Found, %: C 72.59; H 5.12; N 7.97. $C_{21}H_{18}N_2O_3$. Calculated, %: C 72.82; H 5.24; N 8.09.

2-Methoxy-6-(4-methylphenyl)-4-phenylnicotinonitrile (8c). Yield 0.24 g (81%). White crystals, mp 159-160ºC. IR spectrum, ν, cm^{-1}: 2221, 1677, 1588, 1546. ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.39 (3H, s, C$\underline{H}_3$C$_6$H$_4$); 4.17 (3H, s, 2-OCH$_3$); 7.36 (2H, d, J = 8.1, H-3,5 Ar); 7.58-7.61 (3H, m, H-3,4,5 Ph); 7.74-7.75 (2H, m, H-2,6 Ph); 7.79 (1H, s, H-5); 8.19 (2H, d, J = 8.1, H-2,6 Ar). ^{13}C NMR spectrum, δ, ppm: 21.3; 54.5; 91.6; 112.9; 114.4; 124.2; 127.2; 128.8; 129.0; 129.3; 130.6; 136.1; 138.5; 156.3; 157.3; 164.5. Mass spectrum, *m/z* (I_{rel}, %): 300 $[M]^+$ (100). Found, %: C 80.02; H 5.49; N 9.24. $C_{20}H_{16}N_2O$. Calculated, %: C 79.98; H 5.37; N 9.33.

2-Ethoxy-6-(4-methylphenyl)-4-phenylnicotinonitrile (8d). Yield 0.25 g (79%). White crystals, mp 150-151ºC. IR spectrum, ν, cm^{-1}: 2222, 1674, 1588, 1544. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.45 (3H, t, J = 7.1, OCH$_2$C$\underline{H}_3$); 2.39 (3H, s, C$\underline{H}_3$C$_6$H$_4$); 4.64 (2H, q, J = 7.1, OC$\underline{H}_2$CH$_3$); 7.35 (2H, d, J = 8.1, H-3,5 Ar); 7.56-7.59 (3H, m, H-3,4,5 Ph); 7.73-7.75 (2H, m, H-2,6 Ph); 7.75 (1H, s, H-5); 8.15 (2H, d, J = 8.1, H-2,6 Ar). ^{13}C NMR spectrum, δ, ppm: 14.9; 21.3; 63.4; 91.7; 112.9; 114.4; 124.2; 127.9; 128.8; 129.1; 129.6; 130.6; 136.1; 138.4; 156.3; 157.3; 164.2. Mass spectrum, *m/z* (I_{rel}, %): 314 $[M]^+$ (100). Found, %: C 80.33; H 5.82; N 9.01. $C_{21}H_{18}N_2O$. Calculated, %: C 80.23; H 5.77; N 8.91.

X-ray Structural Study of Compounds 3a and 4c. Crystals of compounds **3a** and **4c** were grown for the X-ray structural analysis by evaporation from acetonitrile at room temperature. The diffraction data was gathered at room temperature (295(2) K) on a CAD-4 diffractometer with graphite monochromator, MoKα radiation, and ω-scanning. The standard WinGX procedure was used for data processing [23]. Control measurements were taken every 120 min. Correction for absorption was not performed. The structures of the compounds were analyzed by a direct method and refined using the SHELX software [24]. The refinement of the positional and thermal parameters for the non-hydrogen atoms was carried out in a full-matrix, anisotropic approximation. Hydrogen atoms were localized by Fourier difference synthesis and refined in the isotropic approximation. Thermal parameters for the hydrogen atoms occurred in the range of 0.054-0.126 and 0.036-0.103 Å^2 for compounds **3a** and **4c**, respectively. R factors, calculated for $F^2 > 2\sigma(F^2)$, were 0.045 (2140 reflections) for compound **3a** and 0.044 (2850 reflections) for the compound **4c**. The images for the molecular structures were prepared using the DIAMOND software [25].

X-ray crystallographic data for compound **3a**: $C_{16}H_{14}N_2O_4$. M 298.29, triclinic symmetry. Unit cell parameters: a 7.194(2), b 10.090(1), c 11.075(2) Å, α 105.74, β 94.63, γ 75.05(2)º, V 747.5(3) Å^3; space group P-1; Z 2; d_{calc} 1.325 g·cm^{-3}; μ(MoKα) 0.097; 2926 reflections gathered, of which 2140 had $I > 2\sigma(I)$; probability factor R 0.045.

X-ray crystallographic data for compound **4c**: $C_{20}H_{15}NO_4$. M 333.33, triclinic symmetry. Unit cell parameters: a 9.5147(12), b 10.0778(14), c 9.5877(13) Å, α 91.01, β 81.52, γ 113.13(2)º, V 835.3(2) Å^3; space group P-1; Z 2; d_{calc} 1.325 g·cm^{-3}; μ(MoKα) 0.092; 4020 reflections gathered, of which 2850 had $I > 2\sigma(I)$; probability factor R 0.044.

The crystallographic data has been submitted to the Cambridge Crystallographic Data Center (deposit CCDC-764770 for compound **3a** and CCDC-764769 for compound **4c**).

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