# The redeeming features of reaction of the 8-formyl-7-hydroxychromones with malononitrile

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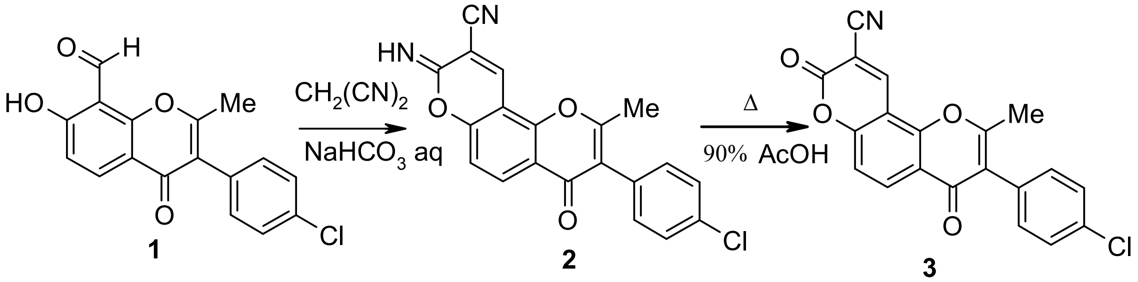
A range of 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones have been prepared using Knoevenagel reaction of the 8-formyl-7-hydroxychromones with malononitrile. The 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-dione derivative was also obtained through the acid hydrolysis of the 8-imino-4*H*,8*H*-pyrano[2,3-*f*]chromen-4-one. 8-Formyl-7-hydroxychromone **1** was found to add two molecules of malononitrile through Michael addition resulting in formation of the 2-[8-amino-3-(4-chlorophenyl)-9-cyano-2-methyl-4-oxo-4H,10H-pyrano[2,3-f]chromen-10-yl]malononitrile.

## Introduction

Chromene system is worth studying in view of a wide scope of transformations in which it is employed in organic synthesis. On the other hand, the introduction of the formyl group ortho to the hydroxyl group in the chromene cycle enables annulation reactions. Since annulated with α-pyrone cycle at the C7-C8 bound chromones occur naturally [1-4] and display bacteriostatic activity [5, 6] their synthesis is up-to-date problem in the Chemistry of natural compounds.

Notably, Knoevenagel reaction [7] as well as Perkin reaction [6, 8, 9] proved to be an effective mean to the access of 4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones. Furthermore we have previously reported the synthesis of the 9-hetaryl-4*H*,8*H*-pyrano[2,3-*f*]chromen-4,8-diones via the reaction of the 8-formyl-7-hydroxychromones with 2-hetarylacetonitriles [10-14]. As a part of our ongoing interest in the

Chemistry of chromones annulated at the C7-C8 bound with α-pyrone cycle, we addressed the problem of investigation the reaction of chromones with malononitrile. The variety of the products heavily depended on the ratio and conditions used in the reaction of 6-formyl-7-hydroxychromone with malononitrile [15]. Our attention was also drawn by the high reactivity of malononitrile in this reaction.



**Scheme 1.** The synthesis of 3-(4-chlorophenyl)-2-methyl-4,8-dioxo-4*H*,8*H*-pyrano[2,3-*f*]chromeno-9-carbonitrile.

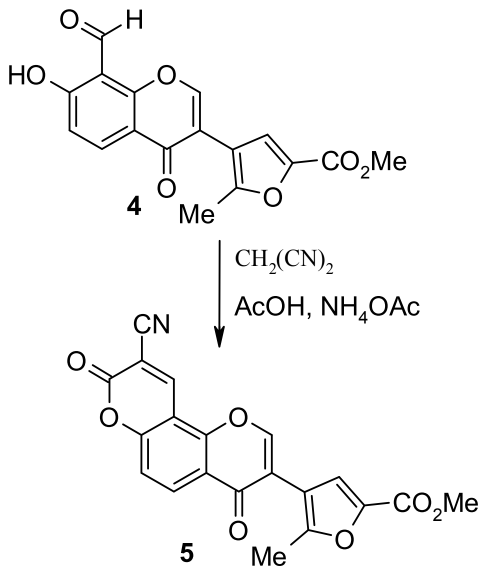
## Results and discussion

Upon the treatment of the 8-formyl-7-hydroxychromone **1** with malononitrile in aqueous solution of the $NaHCO_3$, 8-iminopyranochromone **2** was isolated in 66% yield. $^1H$ NMR spectrum of 4*H*,8*H*-pyrano[2,3-*f*]chromone **2** indicates the desired pyrane cycle formation which is consistent with the absence of the aldehyde proton resonances of formyl and hydroxyl groups at 10.55 ppm and 12.19 ppm. On the contrary, the new singlet of imino group appeared at 9.03 ppm and the resonance of H10 is upfield (as large as 1.78 ppm) of that one of aldehyde. IR spectrum showed absorbtion bends of NH group at 3298, CN at 2231 and C=O at 1622 $cm^{-1}$ respectively.

Subsequent hydrolysis of the **2** via refluxing it in AcOH resulted in pyranochromone **3** formation in 75% yield (**Scheme 1**). The complete absence of the resonance of NH group and the downfield shift of H10 (up to 0.62 ppm) support its successful hydrolysis. The presence of lactone carbonyl within α-pyrone cycle is evident because of the CO absorbtion bend at 1746 $cm^{-1}$ in IR spectrum.

Next it was disclosed that the using of the mixture of AcOH and $NH_4OAc$ may serve as an alternative way to the pyranochromone synthesis. Thus, reaction of 8-formylchromone **4** and malononitrile yielded the proper 4*H*,8*H*-pyrano[2,3-*f*]chromone **5** in 27% yield (**Scheme 2**).

We envisaged the 8-iminopyranochromone **2** would join another malononitrile molecule at C10 through Michael addition. Thus, using of the 2 equiv of malononitrile in reaction of the 8-formylchromone **1** in methanol and $Et_3N$ gave the product **6** in 60% yield (**Scheme 3**).



**Scheme 2.** The synthesis of methyl 4-(9-cyano-4,8-dioxo-4*H*,8*H*-pyrano[2,3-*f*]chromen-3-yl)-5-methyl-2-furoate .

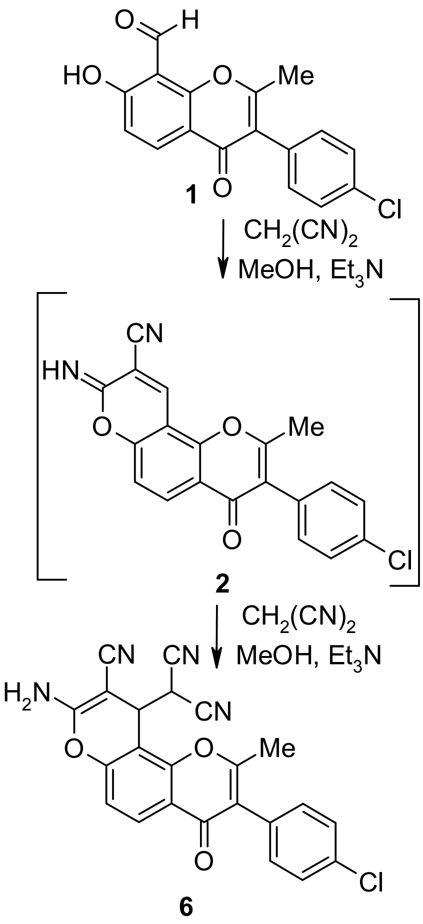
$^1$H NMR spectrum of the compound **6** reveals singlet of amino group at 7.69 ppm and the aliphatic proton resonances at 3.18 and 4.93 ppm. The presence of absorption bends at 3428, 3177 cm$^{-1}$ and 2199 cm$^{-1}$ in the IR spectrum of the compound **6** clearly indicates the formation of amino and cyano groups respectively.

Finally, the structure of **6** was confirmed by X-ray diffraction study (**Figure 1**). The compound **6** exists in the crystal phase as solvate with methanol in ratio 1:0.5. The pyran ring adopts a distorted boat conformation with deviation of the C17 and O3 atoms from the mean plane of the remaining atoms of the ring by 0.244(3) Å and 0.107(3) Å, respectively. The chlorobenzene ring is turned with respect to pyranochromene fragment (the C3-C4-C7-C8 torsion angle is -62.6(3)°) due to steric repulsion between geminal substituents (H9b…C4 (2.62 Å) and H9b…C3 (2.74 Å) intramolecular contacts are shorter than corresponding van der Waals radii sum 2.87 Å [16]). The dicyanomethyl group is turned in such way that the C18-C17-C21-H21 torsion angle is -174° leading to appearance of the C19…C22 (3.12 Å) and C14…C23 (3.38 Å) shortened intramolecular contacts (van der Waals radii sum is 3.42 Å [16]).

In crystal phase molecules **6** are bonded by intermolecular hydrogen bonds: N2-H2a…O1$^{i}$ [i: x, 2-y,-0.5+z] (H…O 2.04 Å, N-H…O 167°) and N2-H2b…N4$^{ii}$ [ii: 0.5-x, 2.5-y, 1-z] (H…N 2.37 Å, N-H…N 157°). The solvate methanol molecule is bonded with **6** by the O1s-H1s…N1$^{jj}$ [jj: x, 2-y, 0.5+z] hydrogen bond (H…N 2.42 Å, O-H…N 121°). In addition the Cl1…N3$^{j}$ [j: 1-x, -1+y, 1.5-z] intermolecular short contact was found (the distance is 3.27 Å as compared with van der Waals radii sum 3.40 Å [16]). The C-Cl…N angle is 171° what allows interpreting this interaction as σ-hole [17] between chlorine atom and π-system of cyano group.

## Conclusion

To conclude we have reported that the resultant structures of the products of 8-formyl-7-hydroxychromones and malononitrile reaction heavily depended on the components ratios and conditions.



**Scheme 3.** The synthesis 2-[8-amino-3-(4-chlorophenyl)-9-cyano-2-methyl-4-oxo-4*H*,10*H*-pyrano[2,3-*f*]chromen-10-yl]malononitrile.

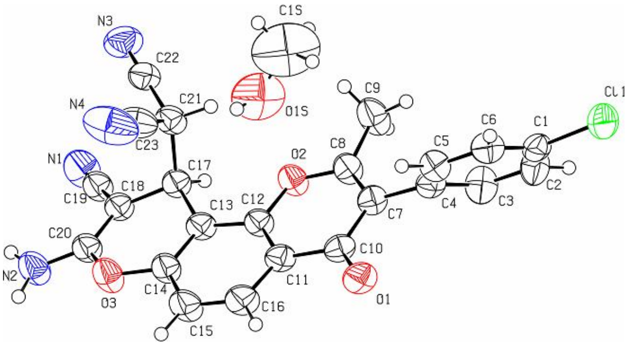


**Figure 1.** Molecular structure of compound **6** according to X-ray diffraction data.

## Experimental part

Reaction progress and purity of obtained compounds were monitored by TLC on Merc 60 $F_{254}$ silica gel plates using $CHCl_3$-MeOH (9:1) system. NMR spectra were recorded on Mercury-400 spectrometer (spectrometer frequency for $^1H$: 400 MHz) from DMSO-$d_6$ and $CDCl_3$ solns. The TMS signal was used as an internal standart. Elemental analyses for C, H, and N were performed using Perkin-Elmer C, H, N Analyser.

### X-Ray diffraction study of compound 6

The crystals of **6** ($C_{47}H_{30}N_8O_7Cl_2$) are monoclinic. At 293 K a = 24.5353(11), b = 9.2398(4), c = 18.7531(10) Å, β = 98.991(5)°, V = 4199.1(3) Å$^3$, $M_r$ = 889.69, Z = 4, space group C2/c, $d_{calc}$ = 1.407 g/cm$^3$, μ(Mo$K_\alpha$) = 0.219 mm$^{-1}$, F(000) = 1832. Intensities of 20297 reflections (4763 independent, $R_{int}$=0.0275) were measured on the «Xcalibur-3» diffractometer (graphite monochromated Mo$K_\alpha$ radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 55°). The structure was solved by direct method using SHELXTL package [18]. Positions of the hydrogen atoms were located from electron density difference maps and refined by “riding” model with $U_{iso}$ = $nU_{eq}$ (n= 1.5 for methyl groups and n=1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against $F^2$ in anisotropic approximation for non-hydrogen atoms using 4763 reflections was converged to $wR_2$ = 0.1592 ($R_1$ = 0.0533 for 3292 reflections with F>4σ(F), S = 1.03). The final atomic coordinates, and crystallographic data for molecule **6** have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 1024850). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

**3-(4-Chlorophenyl)-8-imino-2-methyl-4-oxo-4*H*,8*H*-pyrano[2,3-*f*]chromeno-9-carbonitrile (2).** To a stirred soln. of sodium bicarbonate (0.2 g) in water (20 mL) was added 3-(4-chlorophenyl)-7-hydroxy-2-methyl-4-oxo-4*H*-8-chromenecarbaldehyde (**1**) [10] (0.63 g, 2 mmol) and malononitrile (0.13 g, 2 mmol). The resulting solution was heated at 100°C until the product started precipitating. It was then cooled down, filtered off, washed with hot water, dried and recrystallized from DMF. Orange solid; yield: 0.48 g (66%); mp 238-239°C.

$^{1}H$ NMR (DMSO-$d_6$): δ=2.43 (s, 3H, 2-$CH_3$), 7.21 (s, 1H, $^{3}J_{HH}$=9.2 Hz, H6 ), 7.28 (d, 2H, $^{3}J_{HH}$= 8.0 Hz, H2', H6'), 7.44 (d, 2H, $^{3}J_{HH}$ =8.0 Hz, H3', H5'), 8.16 (d, 1H, $^{3}J_{HH}$ =9.2 Hz, H5), 8.77 (s, 1H, H10), 9.03 (s, 1H, NH).

IR spectrum (KBr, ν, cm$^{-1}$): 3298 (NH), 2231 (CN), 1622 (C=O).

Anal. Calcd for $C_{20}H_{11}ClN_2O_3$: C, 66.22; H 3.06; Cl, 9.77; N, 7.72. Found: C, 66.15; H 3.19; Cl, 9.70; N, 7.90.

**3-(4-Chlorophenyl)-2-methyl-4,8-dioxo-4*H*,8*H*-pyrano[2,3-*f*]chromeno-9-carbonitrile (3).** Compound **2** (0.36 g, 1 mmol) was dissolved in 2 ml of 90% acetic acid and the solution was heated at reflux for 15 min. The resulting solid was filtered off and washed with methanol.

Yellow solid; yield: 75%, m.p. 266-267°C.

$^{1}H$ NMR (DMSO-$d_6$): δ=2.47 (s, 3H, 2-$CH_3$), 7.36 (d, 2H, $^{3}J_{HH}$=8.0 Hz, H2', H6'), 7.50 (d, 2H, $^{3}J_{HH}$=8.0 Hz, H3', H5'), 7.55 (d, 1H, $^{3}J_{HH}$=9.2 Hz, H6), 8.39 (d, 1H, $^{3}J_{HH}$=9.2 Hz, H5), 9.39 (s, 1H, H10).

IR spectrum (KBr, ν, cm$^{-1}$): 2232 (CN), 1746 ($C=O_\alpha$), 1622 ($C=O_\gamma$).

Anal. Calcd for $C_{20}H_{10}ClNO_4$: C, 66.04; H 2.77; Cl, 9.75; N, 3.85. Found: C, 66.18; H 2.69; Cl, 9.67; N, 3.93

**Methyl 4-(9-cyano-4,8-dioxo-4*H*,8*H*-pyrano[2,3-*f*]chromen-3-yl)-5-methyl-2-furoate (4)**

A mixture of methyl 4-(8-formyl-7-hydroxy-4-oxo-4*H*-3-chromenyl)-5-methyl-2-furoate (**5**) [13] (0.33 g, 1 mmol), malononitrile (0.07 g, 1 mmol) and of ammonium acetate (0.24 g, 3 mmol) in AcOH (10 ml) was heated at reflux and left overnight. The resulting mixture was then diluted with water and the solid was filtered off and recristallized from DMF.

Pale yellow solid; yield 0.1 g (27%); mp 255°C.

$^{1}H$ NMR (DMSO-$d_6$): δ= 2.44 (s, 3H, 2'-$CH_3$), 3.84 (s, 3H, $CO_2CH_3$), 7.36 (s, 1H, H4'), 7.54 (d, 1H, $^{3}J_{HH}$=8.8 Hz, H6), 8.44 (d, 1H, $^{3}J_{HH}$=8.8 Hz, H5), 8.57 (s, 1H, H2), 9.16 (s, 1H, H10).

IR spectrum (KBr, ν, cm$^{-1}$): 2235 (CN), 1736 (C=O ester+α), 1623 ($C=O_\gamma$).

Anal. Calcd for $C_{20}H_{11}NO_7$: C, 63.67; H 2.94; N, 3.71. Found: C, 63.90; H 2.89; N, 3.80.

**2-[8-Amino-3-(4-chlorophenyl)-9-cyano-2-methyl-4-oxo-4*H*,10*H*-pyrano[2,3-*f*]chromen-10-yl]malononitrile (6).**

To a soln. of 3-(4-chlorophenyl)-7-hydroxy-2-methyl-4-oxo-4*H*-8-chromenecarbaldehyde (**1**)

(0.63 g, 2 mmol) and malononitrile (0.26 g, 4 mmol) in 20 ml of methanol $Et_3N$ (0.15 ml) was added dropwise. It was then left for 3 days at room temperature. The crystal solid was filtered off, washed with methanol and dried. Orange solid; yield 0.52 g (60%), mp. 225°C.

$^1$H NMR (DMSO-$d_6$): δ= 2.38 (s, 3H, 2-$CH_3$), 3.18 (s, 1H, $CH(CN)_2$), 4.93 (s, 1H, CH), 7.22 (d, 1H, $^3J_{HH}$=8.8 Hz, H6), 7.27 (d, 2H, $^3J_{HH}$=8.0 Hz, H2', H6'), 7.44 (d, 2H, $^3J_{HH}$=8.0 Hz, H3', H5'), 7.69 (s, 2H, $NH_2$), 8.09 (d, 1H, $^3J_{HH}$=8.8 Hz, H5).

IR spectrum (KBr, ν, $cm^{-1}$): 3428 ($NH_{2\ asym}$), 3177 ($NH_{2\ sym}$), 2199 (CN), 1630 (C=O).

Anal. Calcd for $C_{23}H_{13}ClN_4O_3$: C, 64.42; H 3.06; Cl, 8.27; N, 13.06. Found: C, 64.60; H 3.10; Cl, 8.19; N, 12.90.

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