

A New Strategy for Synthesis of 9-Benzoyl-4-methylpyrano[2,3-f]chromene-2,8-dione Using L-Proline as a Novel and Efficient Catalyst¹

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Abstract—We report the high yield synthesis of novel 9-benzoyl-4-methylpyrano[2,3-f]chromene-2,8-dione derivatives obtained by the reaction of 8-formyl-7-hydroxy-4-methylcoumarin with various active methylene compounds. A mechanism of the tandem Knoevenagel condensation and cyclisation reaction is proposed. Structures of all compounds were elucidated on the basis of ¹H and ¹³C NMR, and mass spectrometry, and elemental analysis.

Keywords: substituted 3-oxo-3-phenylpropanenitrile, L-proline, coumarin derivatives

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INTRODUCTION

Various synthetic coumarin derivatives constitute a widely used group of anti-HIV [1], anti-inflammatory [2–4], and antioxidant [5, 6] agents. They have been studied as potential anticancer [7–10] and antiviral [11] agents. A broad number of coumarin derivatives have been synthesized mostly on the basis of Perkin or Knoevenagel reactions [12–18]. Further development of synthesis of novel coumarin based scaffolds is of high demand.

RESULTS AND DISCUSSION

Herein we report synthesis of some novel coumarin derivatives **8a–8j** (Schemes 1–3). Resorcinol **1** reacted with ethylacetoacetate in presence of sulfuric acid and gave 7-hydroxy-4-methyl coumarin (**2**). Refluxing of **2** and hexamethylenetetramine in glacial acetic acid for 6 h afforded 8-formyl-4-methyl-7-hydroxy coumarin **3**. Refluxing of substituted benzoates **5** with acetonitrile in the presence of NaOH provided 3-oxo-3-phenylpropanenitrile derivatives **6**. Condensation of **3** and **6** in ethanol using catalytic amount of L-proline gave corresponding coumarin derivatives **8a–8j** in 2–3 h with 75–90% yield (see table).

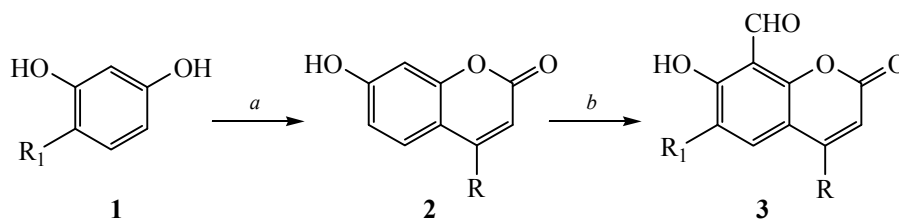
A possible mechanistic pathway of the process can be presented as follows (Scheme 4). Initially L-proline in its zwitterionic form reacts with **6** to form a corresponding iminium intermediate followed by proton abstraction from benzoyl acetonitrile with formation of the corresponding carbanion. The latter attacks the iminium intermediate and the following elimination of proline produces the cyano intermediate. This intermediate undergoes rearrangement with formation of the imine intermediate, which upon acidic hydrolysis at 60°C gives a corresponding 9-benzoyl-4-methylpyrano[2,3-f]chromene-2,8-dione (**8a–8j**).

EXPERIMENTAL

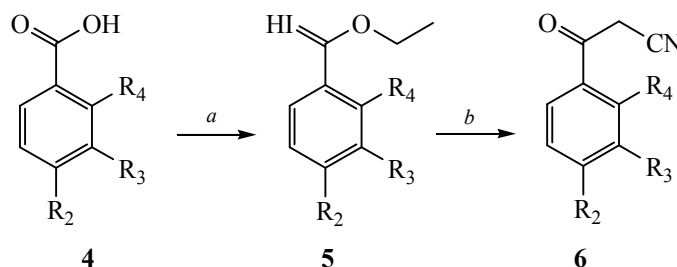
All chemicals were purchased from Aldrich and Merk. Melting points were measured in open capillary tubes. IR spectra were recorded as KBr pellets on a Shimadzu FT-IR 8400s spectrophotometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were measured on a Bruker Avance II 400 spectrometer in CHCl₃ using TMS as the internal standard. Mass spectra were measured on a Hewlett-Packard 1100 LC/MSD spectrometer.

4-Methyl-7-hydroxy coumarin (2) [19]. Concentrated sulfuric acid (20 mL) was added to a 100 mL round bottom flask and cooled down to 0–5°C in an

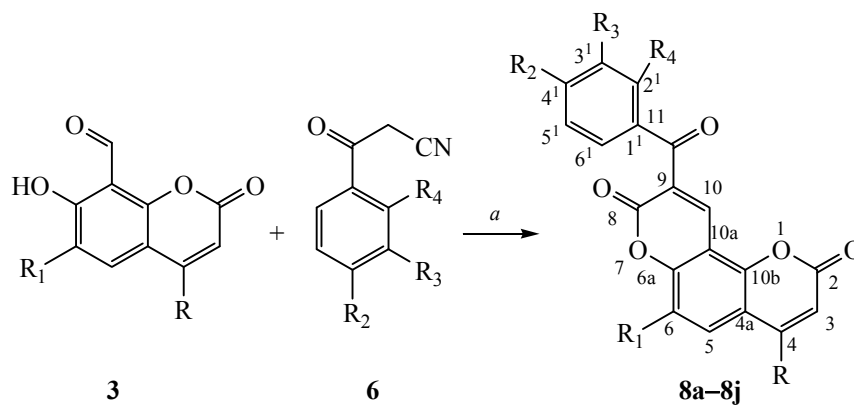
¹ The text was submitted by the authors in English.

Scheme 1. Synthesis of 4-methyl-7-hydroxy-8-formyl coumarin.

a: H₂SO₄, ethylacetoacetate, 15 min; *b*: hexamethylenetetramine, AcOH, 6 h, HCl, 30 min, 80–85°C.

Scheme 2. Synthesis of 3-oxo-3-phenylpropanenitrile derivatives.

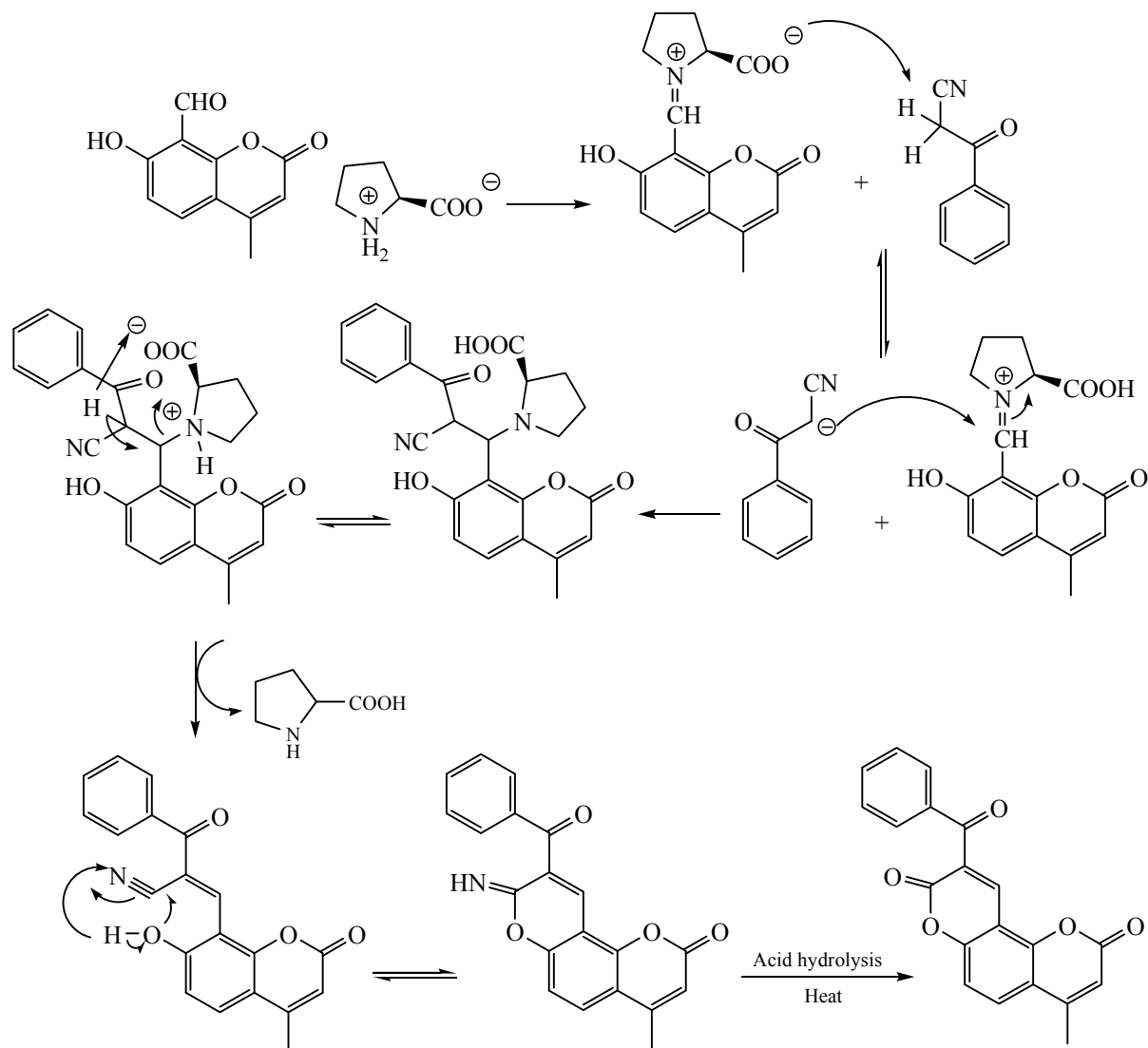
a: H₂SO₄, EtOH, 15 min; *b*: CH₃CN, NaH, THF, room temperature, 40–80%.

Scheme 3. Synthesis of **8a–8j** by the Knoevenagel condensation of **3** and **6a–6j**.

a: L-Proline, EtOH reflux, 2–3 h.

ice bath. A solution of resorcinol **1** (0.001 mol) in ethyl acetoacetate (0.0015 mol) was added to sulfuric acid under constant stirring at 0°C. The reaction mixture was stirred over night at room temperature and poured on to crushed ice with vigorous stirring. An off-white solid obtained was filtered off and recrystallized from ethanol. mp 180–182°C. IR spectrum, ν , cm⁻¹: 3423 (OH), 1733 (CO), 1555 (C=C). ¹H NMR spectrum, δ , ppm: 2.49 s (3H, C⁴CH₃), 6.31 s (1H, C³H), 6.92 d (1H, C⁶H, *J* = 9.0 Hz), 6.94 s (1H, C⁸H), 7.57 d (1H, C⁵H, *J* = 9.0 Hz).

4-Methyl-7-hydroxy-8-formyl coumarin (3) [20]. To a solution of 7-hydroxy-4-methyl-coumarin **2** (0.001 mol) in glacial acetic acid (20 mL) hexamethylenetetramine (0.003 mol) was added. The mixture was heated at 80–85°C in a water bath for 6 h. A hot solution of 5 mL water and 30 mL hydrochloric acid was added to the reaction mixture, stored for 30 min and cooled down to room temperature. It was extracted with diethyl ether, the solvent evaporated to give a pale yellow solid. Yield 22%, mp 176–178°C. IR spectrum, ν , cm⁻¹: 3442 (OH), 1742 (CO), 1644

Scheme 4. A possible mechanism for formation of 9-benzoyl-4-methylpyrano[2,3-*f*]chromene-2,8-dione (**8a–8j**).

(CHO), 1594 (C=C). ^1H NMR spectrum, δ , ppm: 2.44 s (3H, C^4CH_3), 6.22 s (1H, C^3H), 6.90–6.93 d (1H, C^6H , $J = 9\text{Hz}$), 7.73–7.76 d (1H, C^5H , $J = 9\text{Hz}$), 10.63 s (1H, HCO), 12.28 s (1H, OH).

Synthesis of 8a–8j by the Knoevenagel condensation of 3 with 6a–6j [21, 22]. 8-Formyl-4-methyl-7-hydroxy coumarin **3** (0.001 mol) was dissolved in 10 mL of ethanol solution of a derivative of 3-oxo-3-phenylpropanenitrile **6a–6j** (0.001 mol) and catalytic amount of L-proline. Upon refluxing for 2–3 h the mixture was cooled down to 0–5°C and filtered off (see table).

9-Benzoyl-4-methylpyrano[2,3-*f*]chromene-2,8-dione (8a). mp 174°C. IR spectrum, ν , cm^{-1} : 3442 (OH), 1765.0 and 1716.0 (C=O), 1742 (CO), 1644 (CHO), 1594 (C=C). ^1H NMR spectrum, δ , ppm: 2.51

d (3H, CH_3 , $J = 1.255\text{ Hz}$), 6.35 d (1H, 3-H, $J = 1.255\text{ Hz}$), 7.35 d (1H, 6-H, $J = 9.035, 0.502\text{ Hz}$), 7.51 m (2H, 3¹,5¹-H), 7.65 t.t.t (1H, 4¹-H), 7.860 d (1H, 5-H, $J = 8.784\text{ Hz}$), 7.89 d (1H, 6¹-H, $J = 1.506\text{ Hz}$), 7.89 d (1H, 1¹-H, $J = 1.255\text{ Hz}$), 8.62 s (1H, 10-H). ^{13}C NMR spectrum, δ_{C} , ppm: 19, 108, 112.9, 114.4, 116.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 157.2, 159, 190.8. DIPMS [$M + \text{H}$]: m/z 333.07603. Found, %: C 72.25, H 3.62. $\text{C}_{20}\text{H}_{12}\text{O}_5$. Calculated, %: C 72.29, H 3.64.

9-(*p*-Chlorobenzoyl)-4-methylpyrano[2,3-*f*]chromene-2,8-dione (8b). mp 232–233°C. IR spectrum, ν , cm^{-1} : 3442 (OH), 1755.0 and 1716.0 (C=O), 1742 (CO), 1644 (CHO), 1615 (C=C), 1594 (C=C). ^1H NMR spectrum, δ , ppm: 2.51 d (3H, CH_3 , $J = 1.255\text{ Hz}$),

6.35 d (1H, 3-H, $J = 1.255$ Hz), 6.93 d (1H, 6-H, $J = 9.035$ Hz), 7.16 d (1H, 5-H, $J = 8.784$ Hz), 7.45 d (2H, 3¹,5¹-H, $J = 1.506$ Hz), 7.72 d (1H, 6¹,2¹-H, $J = 1.506$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 108, 112.9, 114.4, 118.3, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 140, 150.8, 152.2, 156.3, 157.2, 159, 190.8. Mass spectrum: m/z 367 [$M + H$]⁺. Found, %: C 65.44, H 3.0. C₂₀H₁₁ClO₅. Calculated, %: C 65.50, H 3.02. M 366.75.

9-(*p*-Nitrobenzoyl)-4-methyl-pyrano[2,3-*f*]chromene-2,8-dione (8c). mp 232–234°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 2.51 d (3H, CH₃, $J = 1.25$ Hz), 6.35 d (1H, 3-H, $J = 1.25$ Hz), 7.35 d (1H, 6-H, $J = 9.03$ Hz), 7.86 d (1H, 5-H, $J = 8.78$ Hz), 8.96 d (2H, 6¹,2¹-H, $J = 1.25$ Hz), 8.30 d (2H, 3¹,5¹-H, $J = 8.784$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 108, 112.9, 114.4, 118.2, 125.1, 127.8, 129, 129.7, 134.2, 135.5, 140.4, 150.8, 152.2, 156.3, 159.5, 160, 191.2. Mass spectrum: m/z 378 [$M + H$]⁺. Found, %: C 63.63, H 2.98, N 3.69. C₂₀H₁₁NO₇. Calculated, %: C 63.67, H 3.02, N 3.71. M 377.30.

9-(*o*-Methylbenzoyl)-4-methyl-pyrano[2,3-*f*]chromene-2,8-dione (8d). mp 190–192°C. IR spectrum, ν , cm⁻¹: 2925 (C–H), 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 2.51 d (3H, CH₃, $J = 1.255$ Hz), 2.6 s (*o*-CH₃), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.35 d (1H, 6-H, $J = 9.035$ Hz), 7.60 d (1H, 5-H, $J = 8.784$ Hz), 7.51, 7.65 m (4H, 4¹3¹,5¹,6¹-H), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 21, 110, 112.9, 117.4, 1187.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 159.2, 160.5, 190.8. Mass spectrum: m/z 348 [$M + H$]⁺. Found, %: C 72.80, H 4.02. C₂₁H₁₄O₅. Calculated, %: C 72.83, H 4.07. M 346.33.

9-Benzoyl-6-chloro-4-methylpyrano[2,3-*f*]chromene-2,8-dione (8e). mp 162–164°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 2.51 d (3H, CH₃, $J = 1.255$ Hz), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.860 s (1H, 5-H), 7.51 m (2H, 3¹,4¹-H), 7.65 t.t.t (1H, 4¹-H), 7.89 d (1H, 6¹-H, $J = 1.506$ Hz), 7.89 d (1H, 2¹-H, $J = 1.255$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 108, 112.9, 114.4, 116.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 157.2, 159, 190.8. Mass spectrum: m/z 332.31 [$M + H$]⁺. Found, %: C 65.46, H 3.01. C₂₀H₁₂O₅. Calculated, %: C 65.50, H 3.02. M 366.75.

9-Benzoyl-6-chloro-4-(chloromethyl)pyrano[2,3-*f*]chromene-2,8-dione (8f). mp 182–184°C. IR spectrum,

Synthetic data for 9-benzoyl-4-methylpyrano[2,3-*f*]chromene-2,8-diones (**8a–8j**)

Entry	R	R ₁	R ₂	R ₃	R ₄	Time, h	Yield, %
8a	CH ₃	H	H	H	H	2	90
8b	CH ₃	H	Cl	H	H	2	87
8c	CH ₃	H	NO ₂	H	H	2	85
8d	CH ₃	H	H	H	CH ₃	3	80
8e	CH ₃	Cl	H	H	H	3	85
8f	CH ₂ Cl	Cl	H	H	H	3	78
8g	CH ₂ Cl	H	H	H	H	2	87
8h	CH ₂ Cl	H	Cl	H	H	2	80
8i	CH ₃	Cl	H	H	CH ₃	3	85
8j	CH ₃	Cl	NO ₂	H	H	3	75

ν , cm⁻¹: 1765.0 and 1710.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 4.51 s (2H, CH₂), 6.35 s (1H, 3-H), 7.51 m (2H, 3¹,5¹-H), 7.65 t.t.t (1H, 4¹-H), 7.860 s (1H, 5-H), 7.89 d (1H, 6¹-H, $J = 1.506$ Hz), 7.89 d (1H, 2¹-H, $J = 1.255$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 112, 119.9, 125.4, 126.2, 127.1, 129.1, 129.5, 129.7, 134.2, 135.5, 140.4, 150.8, 152.2, 156.3, 157.2, 159, 190.8. Mass spectrum: m/z 367 [$M + H$]⁺. Found, %: C 59.81, H 2.48. C₂₀H₁₀Cl₂O₅. Calculated, %: C 59.87, H 2.51. M 401.20.

9-Benzoyl-4-(chloromethyl)pyrano[2,3-*f*]chromene-2,8-dione (8g). mp 170°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 4.51 s (2H, CH₂), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.35 d (1H, 6-H, $J = 9.035$ Hz, $J = 0.502$ Hz), 7.51 m (2H, 3¹,5¹-H), 7.65 t.t.t (1H, 4¹-H), 7.860 d (1H, 5-H, $J = 8.784$ Hz), 7.89 d (1H, 6¹-H, $J = 1.506$ Hz), 7.89 d (1H, 2¹-H, $J = 1.255$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_c , ppm: 19, 110.8, 112.9, 114.4, 116.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 159.2, 160.2, 190.8. Mass spectrum: m/z 367 [$M + H$]⁺. Found, %: C 65.49, H 2.98. C₂₀H₁₁ClO₅. Calculated, %: C 65.50, H 3.02. M 366.50.

9-(*p*-Chlorobenzoyl)-4-(chloromethyl)pyrano[2,3-*f*]chromene-2,8-dione (8h). mp 228°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 4.51 s (2H, CH₂), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.35 d (1H, 6-H, $J = 9.035$ Hz), 7.51 m (2H, 3¹,5¹-H), 7.860 d (1H, 5-H, $J = 8.784$ Hz), 7.89 d

(1H, 2¹,6¹-H, $J = 1.506$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_C , ppm: 19, 110.5, 112.9, 114.4, 116.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 159.2, 160.2, 190.8. Mass spectrum: m/z 401. Found, %: C 59.84, H 2.49. C₂₀H₁₀Cl₂O₅. Calculated, %: C 59.87, H 2.51.

9-(*o*-Methylbenzoyl)-6-chloro-4-methylpyrano-[2,3-*f*]chromene-2,8-dione (8i). mp 233°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 2.51 d (3H, CH₃, $J = 1.255$ Hz), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.860 s (1H, 5-H), 7.51 m (2H, 3¹,5¹-H), 7.65 t.t.t (1H, 4¹-H), 7.89 d (1H, 6¹-H, $J = 1.506$ Hz), 7.89 d (1H, 2¹-H, $J = 1.255$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_C , ppm: 19, 21, 110, 112.9, 117.4, 1187.2, 127.1, 128.8, 129, 129.7, 134.2, 135.5, 138.4, 150.8, 152.2, 156.3, 159.2, 160.5, 190.8. Mass spectrum: m/z 381 [M + H]⁺. Found, %: C 66.20, H 3.42. C₂₁H₁₃ClO₅. Calculated, %: C 66.24, H 3.44. M 381.78.

9-(*p*-Nitrobenzoyl)-6-chloro-4-methylpyrano-[2,3-*f*]chromene-2, 8-dione (8j). mp 240°C. IR spectrum, ν , cm⁻¹: 1765.0 and 1716.0 (C=O), 1613 (C=C). ¹H NMR spectrum, δ , ppm: 2.51 d (3H, CH₃, $J = 1.255$ Hz), 6.35 d (1H, 3-H, $J = 1.255$ Hz), 7.860 s (1H, 5-H), 8.96 d (2H, 6¹, 2¹-H, $J = 1.255$ Hz), 8.30 d (2H, 3¹,5¹-H, $J = 8.784$ Hz), 8.62 s (1H, 10-H). ¹³C NMR spectrum, δ_C , ppm: 19, 108, 112.9, 114.4, 118.2, 125.1, 127.8, 129, 129.7, 134.2, 135.5, 140.4, 150.8, 152.2, 156.3, 159.5, 160, 191.2. Mass spectrum: m/z 412 [M + H]⁺. Found, %: C 58.30, H 2.43, N 3.37. C₂₀H₁₀ClNO₇. Calculated, %: C 58.34, H 2.45, N 3.40. M 411.75.

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