SUPPLEMENTARY MATERIAL

Efficient synthesis of 9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione derivatives in ionic liquid and the study of their antioxidant activity .

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Abstract

Ionic liquid *N,N,N',N'*-tetramethylguanidinium trifluoroacetate (TMGT) has been applied as a green and reusable catalyst for one-pot synthesis of 10-aryl substituted-9,10-dihydropyrano[2,3-*h*]chromene-2,8-diones via reaction of various aromatic aldehydes, 5,7-dihydroxycoumarin derivatives and Meldrum's acid. The reactions were rapid, clean, and the products were prepared in good yield. The ionic liquid was stable during the reaction process and reused without significant loss of its activity. The synthesized compounds were evaluated for their antioxidant activity by a 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay

Keywords: *N,N,N',N'*-tetramethylguanidinium trifluoroacetate; meldrum's acid; 5,7-dihydroxycoumarin; aromatic aldehyde; antioxidant activity

2.3. The proposed mechanism

According to the literature survey (Karami et al. 2012; Rad-Moghadam et al. 2012), the suggested mechanism for the synthesis of product **4** has been shown in Scheme 3. First, Knoevenagel condensation between Meldrum's acid **1** and aromatic aldehyde **2** occurred and arylidene Meldrum's acid **5** was formed. 4-hydroxy-6-methyl-2H-pyran-2-one **1** subsequently undergoes a Michael type addition with arylidene Meldrum's acid **5** to produce the intermediate **6**. In the end, intramolecular nucleophilic attack of enol type intermediate **6** after releasing the acetone and carbon dioxide, product **4** was obtained.

Scheme S1. The suggested mechanism for the synthesis of coumarin fused dihydropyran-2-ones (**4**) using TMGT.

3. Experimental

3.1. General

All chemicals and reagents were purchased from Merck and Aldrich Chemical Companies in high purity. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^1H and 100.6 MHz for ^{13}C) with DMSO as solvent. IR spectra were recorded on an FT-IR Bruker Tensor 27 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were carried on a Perkin-Elmer 2400II CHNS/O Elemental Analyzer.

3.2. Typical experimental procedure for the synthesis of 10-aryl substituted-9,10-dihydropyrano[2,3-*h*]chromene-2,8-diones (**4**)

A mixture of aromatic aldehyde (1mmol), Meldrum's acid (1 mmol), and 5,7-dihydroxycoumarin (1 mmol) in TMGT (1 mL) was stirred at 80 °C. After completion of the reaction, as indicated by TLC, the residue was washed with cold water (2 × 10 mL) to extract the ionic liquids. The solid residues were recrystallized from ethanol (95.5%) to afford pure products **4a–l**. The ionic liquid was recovered from the aqueous extracts by evaporation of water in reduced pressure and reused in the next cycles. The structure of products was determined on the basis of their elemental analysis, ¹H and ¹³C NMR, IR and mass spectroscopic data.

3.2.1. 5-Hydroxy-4-methyl-10-phenyl-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (**4a**)

Yield 290 mg (90%). white powder. mp > 300 °C (Karami et al. 2012). IR (KBr) cm⁻¹: 3265, 1784, 1683, 1621, 1603, 1382, 1152, 1091. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.48 (3H, s, CH₃), 2.88 (1H, d, *J* = 16.0 Hz, CH₂), 3.36 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.74 (1H, d, *J* = 7.2 Hz, CH), 6.08 (1H, s, CH), 6.57 (1H, s, CH), 6.96-7.18 (5H, m, 5Ar-H), 11.10 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 24.0 (CH₃), 34.3 (CH₂), 37.1 (CH), 99.5, 109.3, 111.8, 126.8, 127.9, 129.0, 129.4, 152.5, 154.7, 155.4, 156.9, 158.5, 160.5, 167.0. MS (EI, 70 eV): *m/z* 322.0 [M]⁺. Anal. Calcd for C₁₉H₁₄O₅ (322.3): C 70.80, H 4.38. Found: C 70.71, H 4.42.

3.2.2. 5-Hydroxy-4-methyl-10-(2-methoxyphenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (**4b**)

Yield 310 mg (89%). white powder. mp > 300 °C (Karami et al. 2012). IR (KBr) cm⁻¹: 3361, 1785, 1681, 1623, 1602, 1385, 1153, 1097. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.54 (3H, s, CH₃), 2.80 (1H, d, *J* = 15.8 Hz, CH₂), 3.30 (1H, dd, *J* = 15.8, 7.8 Hz, CH₂), 3.81 (3H, s, OCH₃), 4.82 (1H, d, *J* = 7.8 Hz, CH), 6.05 (1H, s, CH), 6.57 (1H, s, CH), 6.74 (1H, d, *J* = 6.4 Hz, 1Ar-H), 6.81 (1H, t, *J* = 7.2 Hz, 1Ar-H), 7.02 (1H, d, *J* = 1.6 Hz, 1Ar-H), 7.23 (1H, t, *J* = 7.8 Hz, 1Ar-H), 11.10 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 24.0 (CH₃), 30.8 (CH₂), 35.1 (CH), 55.6 (OCH₃), 99.7, 103.1, 106.4, 111.8, 120.9, 127.9, 129.0, 129.2, 152.6, 154.7, 155.3, 156.9, 157.5, 159.5, 167.0. MS (EI, 70 eV): *m/z* 352.1 [M]⁺. Anal. Calcd for C₁₉H₁₆O₆ (352.3): C 68.18, H 4.58. Found: C 68.23, H 4.49.

3.2.3.5-Hydroxy-4-methyl-10-(3-chlorophenyl)-9,10-dihydropyrano[2,3-h]chromene-2,8-dione (4c)

Yield 330 mg (92%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3285, 1787, 1680, 1621, 1601, 1432, 1385, 1123, 1097. ¹H NMR (400 MHz, DMSO-d₆): δ 2.55 (3H, d, *J* = 1.2 Hz, CH₃), 2.97 (1H, dd, *J* = 16.0, 2.0 Hz, CH₂), 3.41 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.76 (1H, d, *J* = 6.0 Hz, CH), 6.08 (1H, d, *J* = 1.2 Hz, CH), 6.60 (1H, s, CH), 7.01 (1H, dt, *J* = 6.4, 1.6 Hz, 1Ar-H), 7.21 (1H, t, *J* = 1.2 Hz, 1Ar-H), 7.30-7.36 (2H, m, 2Ar-H), 11.19 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.0 (CH₃), 34.0 (CH₂), 37.0 (CH), 99.9, 103.4, 106.5, 111.9, 125.6, 127.0, 127.8, 131.4, 134.0, 144.1, 152.5, 154.3, 155.3, 157.8, 159.5, 167.0. MS (EI, 70 eV): *m/z* 356.1 [M]⁺. Anal. Calcd for C₁₉H₁₃ClO₅ (356.7): C 63.97, H 3.67. Found: C 63.93, H 3.62.

3.2.4.5-Hydroxy-4-methyl-10-(4-chlorophenyl)-9,10-dihydropyrano[2,3-h]chromene-2,8-dione (4d)

Yield 330 mg (93%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3301, 1789, 1681, 1625, 1603, 1383, 1156, 1097. ¹H NMR (400 MHz, DMSO-d₆): δ 2.55 (3H, s, CH₃), 2.91 (1H, dd, *J* = 16.0, 1.6 Hz, CH₂), 3.29 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.73 (1H, d, *J* = 6.8 Hz, CH), 6.09 (1H, s, CH), 6.59 (1H, s, CH), 7.12 (2H, d, *J* = 8.4 Hz, 2Ar-H), 7.37 (2H, d, *J* = 8.4 Hz, 2Ar-H), 11.17 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.0 (CH₃), 33.8 (CH₂), 37.0 (CH), 99.9, 103.7, 106.5, 111.9, 128.9, 129.4, 132.3, 140.5, 152.5, 154.3, 155.3, 157.7, 159.5, 167.0. MS (EI, 70 eV): *m/z* 356.1 [M]⁺. Anal. Calcd for C₁₉H₁₃ClO₅ (356.7): C 63.97, H 3.67. Found: C 63.91, H 3.74.

3.2.5.5-Hydroxy-4-trifluoromethyl-10-(4-chlorophenyl)-9,10-dihydropyrano[2,3-h]chromene-2,8-dione (4e)

Yield 360 mg (88%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3311, 1785, 1683, 1629, 1604, 1388, 1150, 1096. ¹H NMR (400 MHz, DMSO-d₆): δ 2.92 (1H, dd, *J* = 16.0, 2.0 Hz, CH₂), 3.30 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.76 (1H, d, *J* = 6.8 Hz, CH), 6.61 (1H, s, CH), 6.85 (1H, s, CH), 7.13 (2H, d, *J* = 8.0 Hz, 2Ar-H), 7.36 (2H, d, *J* = 8.0 Hz, 2Ar-H), 11.21 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 33.7 (CH₂), 36.7 (CH), 96.9 (q, ³*J*_{CF} = 5.7 Hz), 99.8, 106.2, 116.3 (q, ³*J*_{CF} = 2.6 Hz), 121.2 (q, ¹*J*_{CF} = 275.7 Hz, CF₃), 127.1, 129.3, 132.1, 134.0, 142.3 (q, ²*J*_{CF} = 34.5), 154.1, 156.5, 159.0, 160.5, 167.0. MS (EI, 70 eV): *m/z* 356.1 [M]⁺. Anal. Calcd for C₁₉H₁₀ClF₃O₅ (410.7): C 55.56, H 2.45. Found: C 55.63, H 2.38.

3.2.6. 5-Hydroxy-4-methyl-10-(3-bromophenyl)-9,10-dihydropyrano[2,3-h]chromene

-2,8-dione (**4f**)

Yield 360 mg (91%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3264, 1788, 1684, 1613, 1605, 1378, 1122, 1096. ¹H NMR (400 MHz, DMSO-d₆): δ 2.56 (3H, d, *J* = 0.8 Hz, CH₃), 2.95 (1H, dd, *J* = 16.0, 1.6 Hz, CH₂), 3.38 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.75 (1H, d, *J* = 6.0 Hz, CH), 6.10 (1H, d, *J* = 1.2 Hz, CH), 6.60 (1H, s, CH), 7.03 (1H, d, *J* = 7.6 Hz, 1Ar-H), 7.27 (1H, t, *J* = 8.0 Hz, 1Ar-H), 7.36 (1H, t, *J* = 1.6 Hz, 1Ar-H), 7.46 (1H, d, *J* = 8.0 Hz, 1Ar-H), 11.19 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.0 (CH₃), 34.0 (CH₂), 37.0 (CH), 99.9, 103.4, 106.5, 112.0, 122.7, 126.0, 130.0, 130.7, 131.7, 144.4, 152.5, 154.3, 155.3, 157.8, 159.5, 167.0. MS (EI, 70 eV): *m/z* 401.0 [M]⁺. Anal. Calcd for C₁₉H₁₃BrO₅ (401.4): C 56.88, H 3.27. Found: C 56.96, H 3.32.

3.2.7.5-Hydroxy-4-methyl-10-(4-bromophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (**4g**)

Yield 360 mg (90%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3268, 1785, 1683, 1611, 1603, 1379, 1120, 1092. ¹H NMR (400 MHz, DMSO-d₆): δ 2.56 (3H, d, *J* = 1.2 Hz, CH₃), 2.94 (1H, dd, *J* = 16.0, 2.0 Hz, CH₂), 3.37 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.73 (1H, d, *J* = 5.6 Hz, CH), 6.09 (1H, d, *J* = 1.2 Hz, CH), 6.59 (1H, s, CH), 7.14 (2H, d, ³*J*_{HH} = 7.2 Hz, 2Ar-H), 7.40 (2H, d, ³*J*_{HH} = 7.2 Hz, 2Ar-H), 11.17 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.0 (CH₃), 33.6 (CH₂), 37.2 (CH), 99.9, 104.0, 106.5, 111.9, 128.9, 129.4, 132.3, 140.5, 152.5, 154.3, 155.3, 157.7, 160.5, 167.0. MS (EI, 70 eV): *m/z* 401.0 [M]⁺. Anal. Calcd for C₁₉H₁₃BrO₅ (401.2): C, 56.88, H, 3.27. Found: C, 56.81, H, 3.34.

3.2.8.5-Hydroxy-4-trifluoromethyl-10-(4-bromophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (**4h**)

Yield 380 mg (85%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3301, 1789, 1681, 1625, 1603, 1386, 1159, 1093. ¹H NMR (400 MHz, DMSO-d₆): δ 2.91 (1H, dd, *J* = 16.0, 1.6 Hz, CH₂), 3.28 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 5.01 (1H, d, *J* = 6.8 Hz, CH), 6.60 (1H, s, CH); 6.87 (1H, s, CH), 7.15 (2H, d, *J* = 8.4 Hz, 2Ar-H), 7.38 (2H, d, *J* = 8.4 Hz, 2Ar-H), 11.25 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 33.6 (CH₂), 36.5 (CH), 96.8 (q, ³*J*_{CF} = 5.7 Hz), 99.9; 106.3, 116.6 (q, ³*J*_{CF} = 2.6 Hz), 121.5 (q, ¹*J*_{CF} = 275.6 Hz, CF₃), 127.6, 129.3, 132.4, 134.5, 142.1 (q, ²*J*_{CF} = 34.5), 154.5, 156.2, 159.1, 160.6, 167.3. MS (EI, 70 eV): *m/z* 455.1 [M]⁺. Anal. Calcd for C₁₉H₁₀BrF₃O₅ (455.18): C 50.13, H 2.21. Found: C 50.07, H 2.28.

*3.2.9. 5-Hydroxy-4-methyl-10-(4-fluorophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (4i)*

Yield 300 mg (89%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3319, 1798, 1684, 1601, 1513, 1362, 1246, 1091. ¹H NMR (400 MHz, DMSO-d₆): δ 2.51 (3H, d, *J* = 1.2 Hz, CH₃), 2.94 (1H, dd, *J* = 16.0, 1.6 Hz, CH₂), 3.34 (1H, dd, *J* = 16.0, 7.8 Hz, CH₂), 4.71 (1H, d, *J* = 6.8 Hz, CH), 6.06 (1H, d, *J* = 1.2 Hz, CH), 6.53 (1H, s, CH), 6.98-7.02 (m, 2Ar-H), 7.31-7.35 (m, 2Ar-H), 11.10 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 23.9 (CH₃), 33.5 (CH₂), 37.1 (CH), 99.5, 102.3, 109.3, 115.7 (d, ²*J*_{CF} = 21.5 Hz), 128.7, 129.3 (d, ³*J*_{CF} = 8.1 Hz), 134.7 (d, ⁴*J*_{CF} = 3.0 Hz), 152.1, 155.4, 156.1, 158.0, 160.4, 162.1 (d, ¹*J*_{CF} = 245.0 Hz), 167.2. MS (EI, 70 eV): *m/z* 340.1 [M]⁺. Anal. Calcd for C₁₉H₁₃FO₅ (340.3): C 67.06, H 3.85. Found: C 67.13, H 3.91.

*3.2.10. 5-Hydroxy-4-methyl-10-(4-cyanophenyl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (4j)*

Yield 310 mg (90%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3289, 2229, 1791, 1684, 1603, 1501, 1365, 1243, 1094. ¹H NMR (400 MHz, DMSO-d₆): δ 2.55 (3H, s, CH₃), 2.98 (1H, d, *J* = 16.0 Hz, CH₂), 3.43 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.83 (1H, d, *J* = 6.4 Hz, CH), 6.09 (1H, s, CH), 6.59 (1H, s, CH), 7.31 (2H, d, *J* = 8.0 Hz, 2Ar-H), 7.79 (2H, d, *J* = 8.0 Hz, 2Ar-H), 11.24 (1H, br s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.0 (CH₃), 34.4 (CH₂), 36.6 (CH), 100.0, 103.0, 106.5, 110.6, 112.0, 119.0, 128.1, 133.4, 147.2, 152.5, 154.3, 155.3, 158.0, 159.4, 167.0. MS (EI, 70 eV): *m/z* 347.0 [M]⁺. Anal. Calcd for C₂₀H₁₃NO₅ (347.3): C 69.16, H 3.77, N 4.03. Found: C 69.23, H 3.69, N 4.11.

*3.2.11. 5-Hydroxy-4-methyl-10-(pyridine-3-yl)-9,10-dihydropyrano[2,3-*h*]chromene-2,8-dione (4k)*

Yield 294 mg (91%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3293, 1794, 1686, 1611, 1584, 1367, 1249, 1092. ¹H NMR (400 MHz, DMSO-d₆): δ 2.52 (3H, s, CH₃), 2.96 (1H, d, *J* = 16.0 Hz, CH₂), 3.42 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.81 (1H, d, *J* = 7.2 Hz, CH), 6.12 (1H, s, CH), 6.58 (1H, s, CH), 7.38 (1H, dd, *J* = 5.0, 4.0 Hz, 1Ar-H), 8.25 (1H, dd, *J* = 4.0, 1.2 Hz, 1Ar-H), 8.37 (1H, dd, *J* = 5.2, 1.2 Hz, 1Ar-H), 8.71 (1H, d, *J* = 0.4 Hz, 1Ar-H), 11.20 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.1 (CH₃), 34.5 (CH₂), 36.4 (CH), 102.0, 105.1, 106.8, 112.3, 129.1, 136.3, 143.2, 147.0, 149.2, 152.3, 154.5, 151.1, 158.3, 161.2, 167.5. MS (EI, 70 eV): *m/z* 323.1

[M]⁺. Anal. Calcd for C₁₈H₁₃NO₅ (323.3): C 66.87, H 4.05, N 4.33. Found: C 66.92, H 4.10, N 4.27.

3.2.12. 5-Hydroxy-4-methyl-10-(furan-2-yl)-9,10-dihydropyrano[2,3-h]chromene-2,8-dione (4l)

Yield 275 mg (88%). white powder. mp > 300 °C. IR (KBr) cm⁻¹: 3290, 1791, 1682, 1613, 1584, 1365, 1241, 1145, 1090. ¹H NMR (400 MHz, DMSO-d₆): δ 2.51 (3H, s, CH₃), 2.97 (1H, d, *J* = 16.0 Hz, CH₂), 3.43 (1H, dd, *J* = 16.0, 7.2 Hz, CH₂), 4.85 (1H, d, *J* = 7.2 Hz, CH), 6.12 (1H, s, CH), 6.60 (1H, s, CH), 7.48 (1H, d, *J* = 4.8 Hz, 1Ar-H), 7.56-7.67 (2H, m, 2Ar-H), 11.21 (1H, brs, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ 24.2 (CH₃), 34.3 (CH₂), 36.5 (CH), 101.1, 105.3, 106.8, 112.4, 113.5, 115.9, 137.8, 143.2, 153.8, 154.6, 155.1, 158.4, 161.3, 167.2. MS (EI, 70 eV): *m/z* 312.0 [M]⁺. Anal. Calcd for C₁₇H₁₂O₆ (312.3): C 65.39, H 3.87. Found: C 65.43, H 3.82.

3.3. Antioxidant activity

Radical scavenging activity of coumarin fused dihydropyran-2-ones **4a-l** was determined against stable DPPH radical spectrophotometrically (Blois 1958). A stock solution (1 mg mL⁻¹) of compounds was prepared in dimethyl sulfoxide (DMSO). Then, 1 mL of each compound solution was added to 1.0 mL of a 0.004% methanol solution of the DPPH radical and shaken vigorously. After 30 min of incubation in the dark at room temperature, the absorbance was observed against a blank at 517 nm. The assay was carried out in triplicate and the percentage of inhibition was calculated using the following formula:

$$\% \text{ inhibition} = \frac{(A_c - A_s)}{A_c} \times 100$$

Where *A_c* is the absorbance value of the control sample and *A_s* is the absorbance value of the tested sample.

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