Synthesis of 3-Aroylcoumarin-Flavone Hybrids

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Abstract: A facile two step synthesis of 3-aroylcoumarin-flavone hybrids was achieved from 7-hydroxyflavone and α-oxoketene dithioacetals. In the first step 7-hydroxyflavone was regioselectively formylated under Duff reaction conditions. Resulting 8-formyl-7-hydroxy flavones were condensed with α-oxoketene dithioacetals in the presence of a catalytic amount of piperidine to furnish 3-aroylcoumarin-flavone hybrids.

Keywords: 7-hydroxyflavone, α-oxoketene dithioacetal, 8-formyl-7-hydroxy flavones, coumrain-flaovone hybrid, duff reaction.

INTRODUCTION

Both coumarins and flavones are widely distributed heterocyclic natural products with varied biological activities [1]. In technological and medicinal fields, coumarins and flavones, independently, find extensive use [2]. While coumarins, especially those having electronic push-pull characteristics, find applications as fluorescent probes and as triplet sensitizers, flavones, particularly those with several phenolic hydroxyl groups, are used as antioxidants. In continuation of our synthetic efforts towards 3-aroyl coumarins we contemplated the synthesis of 3-aroylcoumarin-flavone hybrids. Such hybrid molecules represent both 3-aroylcoumarin and flavones characteristics. Even though there were scattered reports on simple coumarin-flavone hybrid systems, no systematic synthesis or spectral characterization has been reported [3]. Moreover, 3-aroylcoumarin-flavone hybrids, target molecules of present study are not known. We have shown recently that α-oxoketene dithioacetals **1**, the three carbon push-pull systems, on condensation with 2-hydroxybenzaldehydes furnish a wide variety of 3-aroylcoumarins [4]. We have now extended this study by condensation of α-oxoketene dithioacetals **1** with 2-hydroxybenzaldehyde incorporated in a flavone scaffold eg., **2** to furnish 3-aroylcoumarin-flavone hybrids **3** (Scheme **1**). Synthesis of such heterocyclic entities holds promise for integrating medicinal and fluorescent properties.

7-Hydroxyflavones **4**, prepared from resacetophenone and aroyl chloride *via* Baker-Venkataraman rearrangement [5], were formylated with hexamethylenetetramine and acetic acid (Duff reaction) [6] to furnish 8-formyl-7-hydroxy flavones (2-(4-aryl)-7-hydroxy-4-oxo-4*H*-chromene-8-carbaldehydes **2a**, R^2 = H and **2b** R^2 = Cl) [3b]. Regioselectivity of formylation was ensured from the ^{1}H NMR spectra which displayed two doublets in the aromatic region for two 1,2-coupled hydrogens in **2**. Condensation of flavones **2a** and **2b**, independently, with one mole each of three α-oxoketene dithioacetals **1a-c** in presence of piperidine furnished a small combinatorial library of six 3-aroylcoumarin-flavone hybrids **3a-f** in good yield (Scheme **1**). Appearance of two singlet signals at about δ 8.8 and 6.9 ppm in the ^{1}H NMR spectra assignable to two olefinic CH of 3-aroylcoumarin-flavone hybrids **3** confirmed formation of the product. Moreover, the ^{13}C NMR spectra displayed two lactone carbonyls at about δ 177 and 163 ppm, in addition to one α,β-unsaturated carbonyl carbon at δ 191 ppm.

In conclusion we have described a short and facile two-step synthesis of 3-aroylcoumarin-flavone hybrids **3** from 7-hydroxy flavone **4** and α-oxoketene dithioacetals **1**.

EXPERIMENTAL SECTION

General

The progression of all the reactions was monitored by TLC using hexanes (60-80 °C boiling mixture) / ethyl acetate mixture as eluent. Column chromatography was carried on silica gel (100-200 mesh SRL chemicals) using increasing percentage of ethyl acetate in hexanes. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100MHz) and DEPT spectra were recorded for ($CDCl_3$ + CCl_4) solutions on a Bruker - 400 spectrometer with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. IR spectra were recorded as KBr pellets on a Nicolet-6700 spectrometer. UV spectra were recorded using Hitachi ratio-beam spectrometer. Melting points were recorded using open-ended capillary tubes on VEEGO VMP-DS instrument. High resolution mass spectra were recorded on a Waters Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Organic solvents were distilled and dried before use.

General Procedure for Formylation of 7-hydroxyflavone: 7-Hydroxy-4-oxo-2-phenyl-4*H*-chromene-8-carbaldehyde 2a

A solution of 7-hydroxyflavone (238 mg, 0.001 mol) dissolved in glacial acetic acid (5 mL), hexamethylen-etetramine (560 mg, 0.004 mol) was added and the resulting solution was heated on a water bath for12 h. To the rt cooled solution 4 mL of 6 N aq HCl was added and then heated on a

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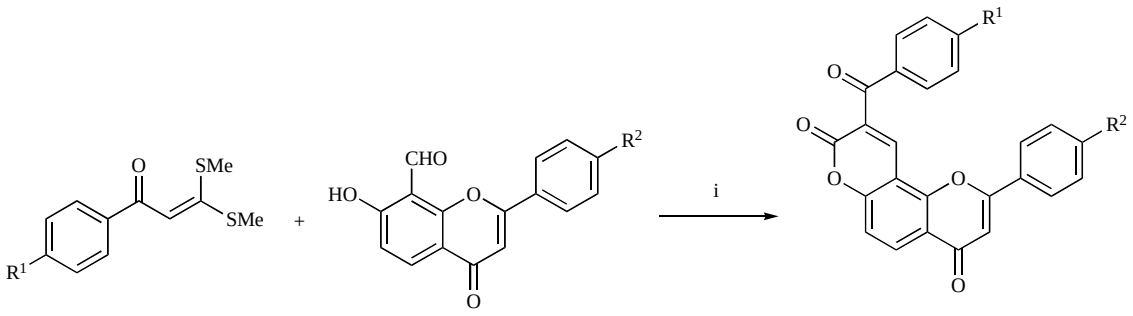

1a-c **2a-b** **3a-f**

1a: R^1 = H
1b: R^1 = Cl
1c: R^1 = Me

2a: R^2 = H
2b: R^2 = Cl

3a: $R^1 = R^2$ = H
3b: R^1 = H, R^2 = Cl
3c: R^1 = Cl, R^2 = H
3d: $R^1 = R^2$ = Cl
3e: R^1 = Me, R^2 = H
3f: R^1 = Me, R^2 = Cl

Scheme 1. Synthesis of coumarin-flavone hybrids **3** from α-oxoketene dithioacetals **1** and 8-formyl-7-hydroxyflavones **2**. *Reagents and conditions:* (i) piperidine, dry THF reflux, 8-32 h, 44-85%.

water bath for a further period of for 30 min. The reaction mixture was then diluted with water (10 mL) and left standing for 1 h at 5 °C in the refrigerator. The reaction mixture was extracted with dichloromethane (2 x 10 mL). Combined organic solution was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Column chromatographic purification on silica gel with increasing amount of ethyl acetate in hexanes provided 2a as a free flowing solid in 70% yield. Analytical samples were obtained by recrystallization from chloroform. mp = 181°C; UV (DCM), 343 nm (log ε = 3.28), 289 nm (log ε = 3.18); IR (KBr) υ_{max} 3065, 2959, 1642, 1597, 1444, 1405, 1376, 1302, 1215, 1173, 1077, 1026, 860, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 10.70 (s, 1H), 8.31 (d, *J* = 9.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.57-7.53 (m, 3H), 6.99 (d, *J* = 8.8, 2H), 6.80 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 191.9, 176.4, 167.6, 162.7, 158.1, 134.8, 131.2, 129.4, 126.1, 116.4, 109.0, 108.5 ppm. HRMS (ESI, m/z) $C_{16}H_{10}O_4$ calcd for (M+H) found 267. 0530 and 267.0523.

2-(4-Chlorophenyl)-7-hydroxy-4-oxo-4H-chromene-8-carbaldehyde 2b

Yellow color solid; Yield = 65%; mp = 190°C; UV (DCM) 349 nm (log ε = 3.46), 293 nm (log ε = 4.12); IR (KBr) υ_{max} 3453, 3078, 1657, 1594, 1412, 1315, 1294, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.35 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 1H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 176.1, 167.6, 161.6, 158.0, 138.3,134.8, 129.7, 129.6, 127.3, 116.5, 116.3, 108.9, 108.7 ppm; HRMS (ESI, m/z) $C_{16}H_9ClO_4$ calcd for (M+Na) found 323.0734 and 323.0729.

General Procedure for Synthesis of Coumarin-flavone Hybrids; 9-Benzoyl-2-phenylpyrano[2,3-f]chromene-4,8-dione 3a

To stirred solution of 7–hydroxyl-8-formyl flavone **2a** (50 mg, 0.187 mol) and 3,3-bis(methylthio)-1-phenylprop-2-en-1-one **1a** (42 mg, 0.187 mmol) in dry THF and piperidene (13 mg, 0.187 mmol) in dry THF (1.2 mL) was added drop wise at rt under a blanket of nitrogen. The reaction mixture was heated at reflux in a pre-heated oil bath (80 °C) for 36 h for completion of reaction (TLC, 20% dicholromethane in hexanes; R_f = 0.3). The reaction mixture was diluted with dichloromethane (10 mL) and the organic solution was washed with water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. Column chromatographic purification on silica gel with increasing amount of dichlormethane in hexanes provided **3a** as a free flowing solid in about 68% yield. Analytical samples were obtained by recrystallization from 5% DCM in hexanes. mp > 240°C; UV (DCM), 361 nm (log ε = 3.48), 293 nm (log ε = 3.35); IR (KBr) υ_{max} 3058, 2919, 1731, 1664, 1439, 1379, 1260, 1087, 865, 804 cm^{-1}; ^{1}H NMR (500 MHz, $DMSOD_6$) δ 8.93 (s, 1H), 8.31 (d, *J* = 5.5 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.59-7.55 (m, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, DMSO D_6) δ 190.7, 176.3, 163.1, 158.0, 157.9, 153.0, 138.0, 136.2, 134.6, 132.5, 130.2, 130.7, 129.7, 129.6, 127.9, 127.1, 120.0, 115.0, 109.7, 108.1 ppm; HRMS (ESI, m/z) calcd for $C_{25}H_{14}O_5$ (M+Na) 417.0734 found 417.0725.

9-Benzoyl-2-(4-chlorophenyl)pyrano[2,3-f]chromene-4,8-dione 3b

Colorless solid; Yield = 48%; mp = >240 °C. UV (DCM) 349 nm (log ε = 3.46), 293 nm (log ε = 4.12); IR (KBr) υ_{max} 3053, 1734, 1657, 1625, 1481, 1438, 1406, 1375, 1256, 1093, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.47 (d, *J* = 6.8 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 175.0, 165.0, 159.0, 154.0, 153.0, 145.03, 138.7, 134.1, 132.3, 131.7, 130.9, 129.6, 128.7, 127.9, 127.5, 126.5, 121.6, 114.0, 108.5, 107.9 ppm; HRMS (ESI, m/z) 451.0349 calcd for $C_{25}H_{13}ClO_5$ (M+Na) found 451.0345.

9-(4-Chlorobenzoyl)-2-phenylpyrano[2,3-f]chromene-4,8-dione 3c

Colorless solid; Yield = 53%; mp > 240°C; UV (DCM), 315 nm (log ε = 3.44), 298 nm (log ε = 4.18); IR (KBr) υ_{max} 2927, 1732, 1657, 1613, 1532, 1438, 1375, 1262, 1093, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78(s, 1H), 8.45 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 2.4 Hz, 2H), 7.57 (t, *J* = 9.9 Hz, 1H), 7.52 (d, *J* = 4.4 Hz, 2H), 7.50 (d, *J* = 6.7 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 177.0, 163.5, 158.4, 154.9, 153.0, 145.5, 139.0, 134.2, 132.2, 131.2, 130.9, 129.4, 129.1, 127.2, 126.2. 120.5, 114.6, 108.7 ppm; HRMS (ESI, m/z) 429.0530 calcd for $C_{25}H_{13}ClO_5$ (M+H) found 429.2375.

9-(4-Chlorobenzoyl)-2-(4-chlorophenyl)pyrano[2,3-f]chromene-4,8-dione 3d

Colorless solid; Yield = 44%; mp 240 °C above, UV (DCM), 335 nm (log ε = 3.44), 298 nm (log ε = 4.18); IR (KBr) υ_{max} 3071, 1738, 1663, 1625, 1412, 1368, 1262, 1093, 861, 830, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.48 (d, *J* = 5.2 Hz, 1H), 7.84 (d, *J* = 4.8Hz, 2H), 7.55(d, *J* = 4.4 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8 Hz, 1H), 6.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 176.9, 163.4, 158.9, 157.4, 153.6, 149.0, 138.0, 134.1, 132.4, 131.0, 130.7, 130.1, 129.7, 129.5, 127.9, 127.1, 120.3, 114.7, 108.8, 108.5 ppm; HRMS (ESI, m/z) 484.9959 calcd for $C_{25}H_{12}Cl_2O_5$ (M+Na) found 484.9963.

9-(4-Methylbenzoyl)-2-phenylpyrano[2,3-f]chromene-4,8-dione 3e

Colorless solid; Yield = 85% ; mp > 240°C; UV (DCM) 303.5 nm (log ε = 3.36), 340.5 nm (log ε = 4.18), IR (KBr) υ_{max} 3071, 2921, 1737, 1661, 1625, 1441, 1380, 1266, 1087, 867, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.48 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 9.6 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.59-7.45 (m, 3H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.31(d, *J* = 8 Hz, 2H), 6.90 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 176.8, 163.5, 158.4, 157.4, 153.0, 145.2, 138.0, 133.2, 132.2, 130.9, 130.7, 129.8, 129.5, 129.4, 127.8, 126.2, 120.3, 114.6, 108.7, 108.6, 21.90 ppm; HRMS (ESI, m/z) calcd $C_{26}H_{16}O_5$ for 431.0895 (M+Na) found 431.0898.

2-(4-Chlorophenyl)-9-(4-methylbenzoyl)pyrano[2,3-f]chromene-4,8-dione 3f

Colorless solid; Yield = 56%; mp > 240 °C, UV (DCM), 345 nm (log ε = 3.45), 296 nm (log ε = 4.04); IR (KBr) υ_{max} 3079, 2921, 1737, 1654, 1615, 1440, 1408, 1378, 1265,1182, 1092, 868, 782, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.46 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.8Hz, 2H), 7.81 (d, *J* = 8.8Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 6.87 (s, 1H), 2.45(s, 3H) ppm; $^{13}CNMR$ (100 MHz, $CDCl_3$) δ 190.7, 176.3, 162.3, 158.2, 157.4, 152.9, 145.5, 138.6, 137.9, 133.1, 130.6, 129.8, 129.7, 129.5, 129.3, 127.9, 127.4, 120.2, 114.8, 108.76, 108.73, 21.9 ppm; HRMS (ESI, m/z) 443.0630 calcd for $C_{26}H_{15}ClO_5$ (M+H) found 443.0625.

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CONFLICT OF INTEREST

Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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