A One-Step Synthesis of 2-Alkyl-5-hydroxychromones and 3-Alkoyl-2-alkyl-5-hydroxychromones

Sabrina Okombi,[a] Julien Schmidt,[a] Anne-Marie Mariotte,[a] Eric Perrier,[b] and Ahcène Boumendjel*,[a]

[a] *Département de Pharmacochimie Moléculaire UMR-CNRS 5063, Université Joseph Fourier de Grenoble, Faculté de Pharmacie; 5, avenue de Verdun 38240 Meylan–France: and* [b] *Coletica-Engelhard; 32 rue Saint Jean de Dieu, 69007 Lyon–France.* Received March 14, 2005; accepted June 12, 2005

2-Alkyl-5-hydroxychromones (2-alkyl-5-hydroxy-4-oxo-4*H*-1-benzopyran) and 3-alkoyl-2-alkyl-5-hydroxychromones (3-alkoyl-2-alkyl-5-hydroxy-4-oxo-4*H*-1-benzopyran) were prepared in one-step and one pot reaction by condensation of 2′,6′-dihydroxyacetophenone with an alkoyl chloride in the presence of K_2CO_3.

Key words 2-substituted chromone; 2,3-disubstituted chromone; one-step synthesis

The occurrence of a 5-hydroxychromone (5-hydroxy-4-oxo-4*H*-1-benzopyran) unit **1** (Fig. 1) in the structure of numerous natural products is frequent. The well known flavones and isoflavones are illustrative.[1)] It has been reported that the presence of a 5-hydroxy group in flavone and isoflavone structures is often correlated with higher biological activity. In enzymes, and especially in kinase inhibition, the higher activity of 5-hydroxychroman-4-one derivatives has been linked to the ability of 5-hydroxychromone **1** to occupy the site in which the adenine of ATP binds.[2—4)] In addition to flavones and isoflavones, the unit **1** is also found in the xanthones subfamily, such as the 8-hydroxy-2,3,4,9-1*H*-xanthene-1,9-dione **2** (Fig. 1). The dione **2** is of particular interest, as it features in a number of natural compounds[5)] such as xanthoquinodin (antibiotic),[6)] the beticolin toxin[7)] and the eumertin pigments.[8)]

Based on the biological activity of natural products derived from 5-hydroxychromen-4-one **1** and 8-hydroxy-2,3,4,9-1*H*-xanthene-1,9-dione **2**, the 2-alkyl-5-hydroxychromones **3** and 3-alkoyl-2-alkyl-5-hydroxychromones **4** (Fig. 1) have been investigated for their biological potential, for example as inhibitors of tyrosine kinase,[9)] as monoamine oxidase inhibitors and as antifungals.[10,11)] In addition, it is worth mentioning that analytical and environmental applications have been reported for derivatives of **3** and **4**.[12,13)]

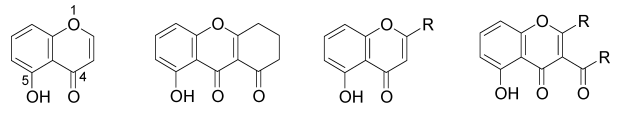

Fig. 1

Despite their potential use, synthetic strategies affording these compounds have been explored. A literature survey indicates that only three analogues of **3** (R=Me, Et and Pr) and one analog of **4** (R=Me) are known.[14,15)] More recently, analogs of **4** in which R=Ph (3-benzoylflavones) have been reported by Elguero and co-workers.[16)] Compounds **3** are obtained in two steps, according to the Baker–Venkataraman method.[17,18)] In this method, 2′,6′-dihydroxyacetophenone is converted to a dialkoylester. The ester is treated with a base to induce an intramolecular Claisen condensation, forming a 1,3-diketone which is cyclized to the corresponding chromone upon heating in glacial acetic acid containing sulfuric acid.

Results and Discussion

The purpose of the present study is to report the synthesis of 2-alkyl-5-hydroxychromones **3** and 3-alkoyl-2-alkyl-5-hydroxy-4-chromones **4** in one step and one reaction.[19)] This method is advantageous since it is short and takes place in mild conditions (K_2CO_3 in acetone) and does not require the use of pyridine or strong acidic conditions.

Condensation of 2′,6′-dihydroxyacetophenone with an alkoyl chloride in the presence of an excess of K_2CO_3 affords two new compounds which can be separated by chromatography (Chart 1). Based on their MS and ^{1}H-NMR spectra (Table 1), the two compounds were identified as 2-alkyl-5-hydroxychroman-4-one **3** and 3-alkoyl-2-alkyl-5-hydroxychroman-4-one **4**. They were obtained through the formation of intermediates 2-alkoylacetophenone **3′** and 2,2-dialkoylacetophenone **4′**, followed by *in situ* cyclodehydration, to give **3** and **4**.

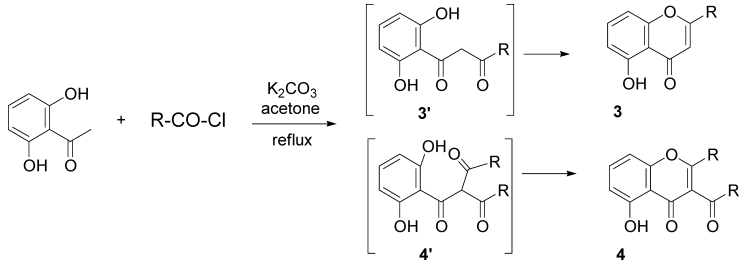

Chart 1

* To whom correspondence should be addressed. e-mail: Ahcene.Boumendjel@ujf-grenoble.fr

Table 1. 2-Alkyl-5-hydroxychromones **3** and 3-Alkoyl-2-alkyl-5-hydroxychromones **4** Prepared According to Chart 1

Entry	R–	Yield	Ratio **3**/**4**[a]	Product, mp (°C), ^{1}H-NMR,[b] MS[c]
a	CH_3–	34	1/0	mp 82—84 °C, literature: 92 °C (ref. 15)
b	H_2C=CH–$(CH_2)_2$–	60	0/1	**4b**: Amorphous, ^{1}H-NMR ($CDCl_3$) δ: 7.50 (1H, t, J=8.4 Hz), 6.82 (1H, d, J=8.4 Hz), 6.75 (1H, d, J=8.4 Hz), 5.82—5.73 (2H, m), 5.05—4.92 (4H, m), 3.01 (2H, t, J=7.2 Hz), 2.75 (2H, t, J=7.2 Hz), 2.48—2.36 (4H, m). MS m/z: 216 (M−80), 147, 137. *Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.16; H, 5.99.
c	CH_3–$(CH_2)_4$–	46	1/1	**3c**: Amorphous, ^{1}H-NMR ($CDCl_3$) δ: 7.43 (1H, t, J=8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 6.71 (1H, d, J=8.4 Hz), 6.05 (1H, s), 2.55 (2H, t, J=7.6 Hz), 1.65 (2H, m), 1.33 (4H, m), 0.86 (3H, t, J=6.8 Hz). MS m/z: 232 (M^+), 189, 176, 147, 137, 108. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.06; H, 6.53. **4c**: Amorphous, ^{1}H-NMR ($CDCl_3$) δ: 7.47 (1H, t, J=8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 6.74 (1H, d, J=8.4 Hz), 2.87 (2H, m), 2.61 (2H, m), 1.70—1.60 (4H, m), 1.36—1.28 (8H, m), 0.95—0.80 (6H, m). MS m/z: 331 $(M+1)^+$, 313, 259, 139. *Anal.* Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.49; H, 7.57.
d	CH_3–$(CH_2)_5$–	36	1/1	**3d**: Amorphous, ^{1}H-NMR ($CDCl_3$) δ: 7.43 (1H, t, J=8.4 Hz), 6.81 (1H, d, J=8.4 Hz), 6.71 (1H, d, J=8.4 Hz), 6.04 (1H, s), 2.55 (2H, t, J=7.2 Hz), 1.70—1.60 (2H, m), 1.34—1.24 (10H, m), 0.83 (3H, t, J=7.2 Hz). MS m/z: 246 (M^+), 203, 189, 176,137. *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.26. **4d**: ^{1}H-NMR ($CDCl_3$) δ: amorphous, 7.46 (1H, d, J=8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 6.73 (1H, d, J=8.4 Hz), 2.87 (2H, t, J=7.2 Hz), 2.61 (2H, t, J=7.2 Hz), 1.98—1.55 (4H, m), 1.36—1.18 (12H, m), 0.87 (6H, m). SM m/z: 358 (M^+), 301, 273, 231, 137. *Anal.* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.44; H, 8.12.
e	CH_3–$(CH_2)_6$–	22	1/2	**3e**: Amorphous. ^{1}H-NMR ($CDCl_3$) δ: 7.51 (1H, t, J=8.4 Hz), 6.88 (1H, d, J=8.4 Hz), 6.79 (1H, d, J=8.4 Hz), 6.13 (1H, s); 2.63 (2H, t, J=7.5 Hz), 1.76—1.73 (2H, m), 1.41—1.31 (8H, m), 0.91 (3H, t, J=6.4 Hz). SM m/z: 260 (M^+), 189, 176, 137. *Anal.* Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.61; H, 7.42. **4e**: ^{1}H-NMR ($CDCl_3$) δ: 7.55 (1H, d, J=8.4 Hz), 6.89 (1H, t, J=8.4 Hz), 6.82 (1H, d, J=8.4 Hz), 2.95 (2H, t, J=7.4 Hz), 2.69 (2H, t, J=7.4 Hz), 1.76—1.67 (4H, m), 1.36—1.30 (16H, m), 0.91—0.88 (6H, m). SM m/z: 386 (M^+), 315, 287, 231, 137. *Anal.* Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.37; H, 8.60.
f	CH_3–$(CH_2)_7$–	40	5/1	**3f**: Amorphous. ^{1}H-NMR ($CDCl_3$) δ: 7.45 (1H, t, J=8.4 Hz), 6.81 (1H, d, J=8.4 Hz), 6.71 (1H, d, J=8.4 Hz), 6.05 (1H, s), 2.55 (2H, t, J=8 Hz), 167 (2H, m), 1.33—1.21 (10H, m), 0.82 (3H, t, J=6.8 Hz). SM m/z: 274 (M^+), 189, 176, 137. *Anal.* Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.06; H, 7.96. **4f**: Amorphous, ^{1}H-NMR ($CDCl_3$) δ: 7.47 (1H, t, J=8.4 Hz), 6.82 (1H, d, J=8.4 Hz), 6.73 (1H, d, J=8.4 Hz), 2.87 (2H, t, J=7.6 Hz), 2.61 (2H, t, J=7.6 Hz), 1.70—1.59 (4H, m), 1.31—120 (20H, m), 0.82 (6H, m). SM m/z: 414 (M^+), 329, 301, 137. *Anal.* Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 74.00; H, 8.97.
g	CH_3–$(CH_2)_9$–	30	1/1	**3g**: Amorphous. ^{1}H-NMR ($CDCl_3$) δ: 7.43 (1H, t, J=8.4 Hz), 6.80 (1H, d, J=8.4 Hz), 6.70 (1H, d, J=8.4 Hz), 6.04 (1H, s), 2.55 (1H, t, J=7.6 Hz), 1.70—1.63 (2H, m), 1.31—1.20 (14H, m), 0.82 (3H, t, J=6.8 Hz). SM m/z: 302 (M^+), 189, 176, 137. *Anal.* Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.23; H, 8.38. **4g**: Amorphous. ^{1}H-NMR ($CDCl_3$) δ: 7.46 (1H, t, J=8.4 Hz), 6.81 (1H, d, J=8.4 Hz), 6.74 (1H, d, J=8.4 Hz), 2.87 (2H, t, J=7.6 Hz), 2.61 (2H, t, J=7.6 Hz), 1.72—1.61 (4H, m), 1.51—1.20 (28H, m), 0.86—0.80 (6H, m). SM m/z: 470 (M^+), 357, 329, 231, 137. *Anal.* Calcd for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.08; H, 9.43.
h	$(CH_3)_3C$–CH_2–	80	1/1	**3h**: Amorphous. ^{1}H-NMR ($CDCl_3$) δ: 7.41 (1H, t, J=8.4 Hz), 6.81 (1H, d, J=8.4 Hz), 6.71 (1H, d, J=8.4 Hz), 6.02 (1H, s), 2.42 (2H, s), 1.02 (9H, s). SM m/z: 232 (M^+), 217, 176, 137, 57. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.18; H, 6.77. **4h**: ^{1}H-NMR ($CDCl_3$) δ: 7.46 (1H, t, J=8.4 Hz), 6.78 (1H, d, J=8.4 Hz), 6.73 (1H, d, J=8.4 Hz), 2.81 (2H, s), 2.57 (2H, s), 1.03 (9H, s), 1.03 (9H, s). SM m/z: 330 (M^+), 315, 259, 203, 57. *Anal.* Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.49; H, 7.73.

a) The ratio determination is based on purified products. *b*) ^{1}H-NMR spectra were recorded on a Bruker AC-400 instrument using Me_4Si as an internal standard. *c*) EI and DCI mass spectra were recorded on a Fisons Trio 1000 instrument.

Experimental

Typical Procedure A mixture of 2′,6′-dihydroxyacetophenone (1 g, 6.57 mmol) and K_2CO_3 (35.85 mmol, 5 eq) in acetone (33 ml) was stirred at room temperature for 15 min, then the alkolyl chloride (1 eq) was added. The solution was refluxed for 24 h, then acetone was evaporated and water (30 ml) was added. The solution was acidified by HCl (1 N) until pH *ca.* 4 then extracted with ethyl acetate (2×50 ml). The organic layer was collected, dried over Na_2SO_4 and evaporated. The crude products were purified by a silica gel chromatography column eluted with ethyl acetate : cyclohexane (1 : 9) to afford **3** and **4** as amorphous compounds.

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