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Convenient Synthesis of Wogonin, A Flavonoid Natural Product with Extensive Pharmacological Activity

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Wogonin (5,7-dihydroxy-8-methoxyflavone, **5**), a flavonoid natural product first isolated from *Scutellaria Radix*, is well-known for its anti-inflammation,[1] anti-allergy,[2] anti-tumor[3] and anti-hepatitis B virus[4] properties. Owing to its extensive applications in medical treatment, researchers have developed several synthetic pathways to obtain this important natural product since the early part of the last century.[5, 6] The initial total syntheses of *wogonin* were based on the common synthetic approaches to flavonoids through Baker-Venkataraman rearrangement[6, 7] or intramolecular Wittig reaction.[8] However, neither of these two strategies was efficient for large scale production of the compound. Recently Huang *et al*.[9] reported a simplified synthesis of *wogonin* (**5**) and *oroxylin A* (**6**) from 3,4,5-trimethoxyphenol (**1**) and cinnamoyl chloride (2). As shown in Figure 1, the flavone nucleus was obtained from intermediate **4** wherein the two hydroxyl groups compete for the addition to the α,β-unsaturated ketone moiety. Evidently, the C_6-OH is more active than C_2-OH since the yield of *oroxylin A* was nearly double that of *wogonin*. Moreover, this synthetic route is not an ideal process for industrial production because the two products are difficult to separate.

Prompted by this earlier report on the construction of the flavone nucleus, we launched our own studies, focusing on avoiding the undesired flavone derivative 6 in the total synthesis of pure *wogonin* (Figure 2). To avoid the competitive addition process while forming the flavone nucleus, we utilized intermediate **8** which has only one reactive position. Intermediate **8** was synthesized in >90% yield from 2,5-dimethoxybenzene-1,3-diol (**7**)

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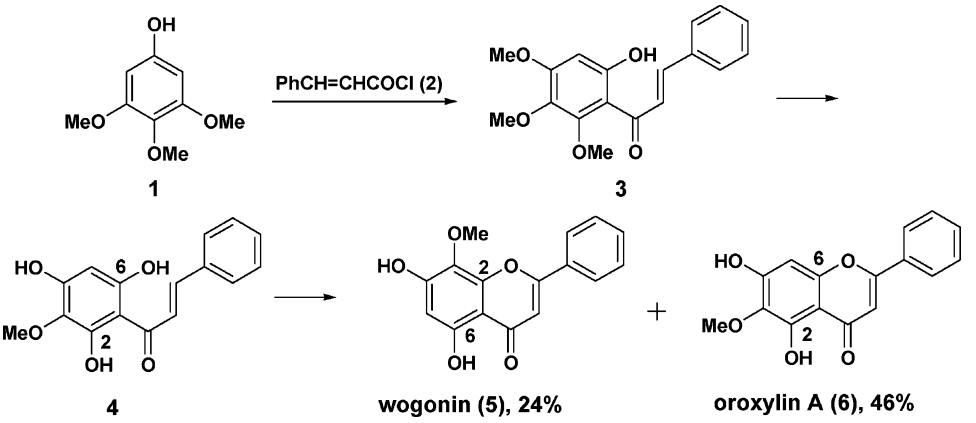

Figure 1

which was prepared according to Geissman *et al.*[10] and cinnamoyl chloride (**2**) in the presence of BF_3-Et_2O. Subsequently, 8 was smoothly cyclized with I_2 in dimethyl sulfoxide (DMSO) to afford 5-methoxywogonin (**9**) in > 90% yield.[11] Finally, *wogonin* was obtained after selective removal of the 5-methoxy group with anhydrous $AlCl_3$ in acetonitrile (CH_3CN) in good yield (84%). The overall yield of **5** from **7** was 68%.

After paying attention to the avoidance of the undesired flavone derivative **6** during the synthesis of *wogonin* following the method of Huang *et al*,[9] we evaluated two other literature approaches of the final intermediate 5-methoxywogonin (**9**). Suan *et al.* reported that **9** could be obtained from **7** by two steps: firstly acetylating and then reacting with sodium benzoate and benzoic anhydride.[12] Additionally, Rivaille *et al.*[13] reported that **9** could be obtained directly by cyclization of compound **7** with acetyl benzoylacetate. However, both of these methods have many drawbacks such as poor yields, high reaction temperature and long reaction time, all of which made these approaches unsuitable for scale up. Thus, our synthesis was comparatively more efficient and simple.

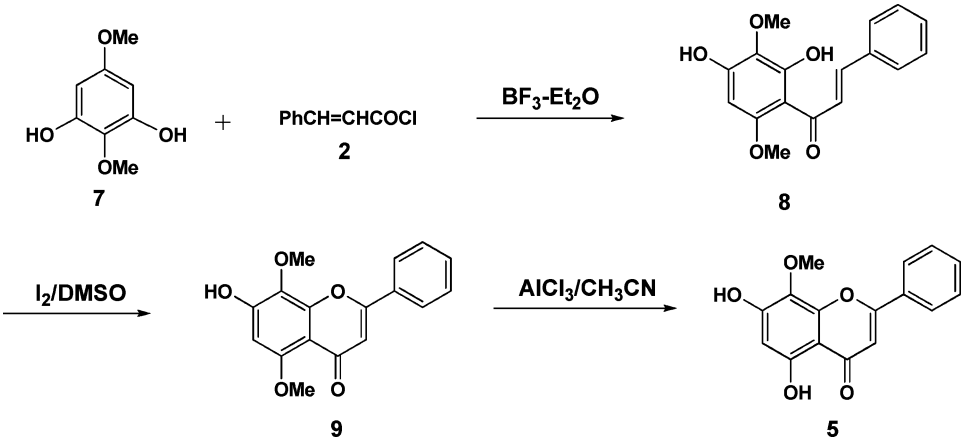

Figure 2

In conclusion, an improved strategy for the total syntheses of *wogonin* is reported. Compared with the previously reported methods, this synthetic route is more convenient and proceeds to give pure *wogonin* in an overall yield of 68%. This novel synthetic pathway to *wogonin* is of great value for the large scale and industrial preparation of this important flavonoid natural product.

Experimental Section

Reagents, solvents and starting materials were purchased from commercial sources and were used without further purification unless noted. Melting points were determined on a micro-melting point apparatus XT-4(Beijing Taike instrument company, China). ^{1}H-NMR spectra were recorded on a Brucker AMX-300 spectrometer. Chemical shifts are reported in δ values relative to TMS as an internal standard. Coupling constants were in units of Hertz (Hz). Mass spectra (EI) were obtained on Shimadzu GCMS-QP2010. IR spectra were collected using a Nicolet Impact 410 instrument. All of the reactions were performed under an inert atmosphere of nitrogen.

(E)-1-(2,4-Dihydroxy-3,6-dimethoxyphenyl)-3-phenylprop-2-en-1-one (8)

A solution of commercially available 2,5-dimethoxybenzene-1,3-diol (**7**, 10.0 g, 60 mmol) and cinnamoyl chloride (**2**, 18.0 g, 70 mmol) in BF_3-Et_2O solution (20 mL) was heated at reflux for 30 min, cooled and poured into water. The resulting solid was collected and recrystallized from methanol to give compound **8** (16.2 g, 94%) as reddish-yellow crystals, mp 210°C, *lit*.[14] 124–125°C. The literature report[14] indicates that compound **8** was separated from the seeds and leaves of *Polygonum senegalense* by chromatography on silica gel. However, we found that authentic **8** prepared by our method when mixed with authentic **2** and **7**, could not be separated and purified by chromatography on silica gel since it was totally adsorbed on the silica gel. This would explain the much lower mp. reported in the literature.[14]

^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.00 (6H, s), 6.13 (1H, s), 7.48–7.52 (3H, m), 7.68–7.70 (2H, m), 8.03 (1H, d, $J = 15.2$ Hz), 8.33(1H, d, $J = 15.2$ Hz). The OH hydrogens could not be observed neither in DMSO-d_6 nor in $CDCl_3$. The two methoxy groups appear to have identical chemical shifts. ^{13}C-NMR (75MHz, DMSO-d_6): δ 56.9, 60.2, 93.9, 104.3, 121.7, 129.3, 129.7, 130.1, 132.2, 134.1, 148.7, 158.2, 160.7, 165.6, 180.5. IR (KBr): 3400, 3216, 3011, 1606, 1526, 1445, 1374, 1250, 1129 cm^{-1}. EI-MS (*m/z*): 300 ($M+$), 285, 269, 230, 223, 196, 181, 167, 153.

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.92; H, 5.45.

7-Hydroxy-5,8-dimethoxy-2-phenyl-4H-chromen-4-one (9)

A solution of **8** (8.0 g, 27 mmol) and iodine (50 mg) in DMSO (35 mL) was stirred at 140°C for 1 h and then carefully poured onto crushed ice. The precipitate was collected and washed with 20% Na_2SO_3 solution and pure water. The crude product was recrystallized from aqueous methanol (3:1) to give **9** as a pale yellow solid (7.3 g, 95%), mp 287–288°C, lit.[12,13] 287–288°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.76 (3H, s), 3.85 (3H, s), 6.48 (1H, s), 6.77 (1H, s), 7.57–7.60 (3H, m), 8.01–8.05 (m, 2H). ^{13}C-NMR (75MHz, DMSO-d_6): δ55.7, 60.9, 96.9, 106.2, 107.8, 125.7, 128.8, 129.1, 131.1, 131.3, 151.5, 155.4, 155.7, 159.0, 175.7. IR (KBr): 3123, 1635, 1579, 1501, 1397, 1339, 1207, 1114 cm^{-1}. EI-MS (*m/z*): 298 (*M*+), 283, 255, 153.

Wogonin (5,7-Dihydroxy-8-methoxyflavone, 5)

A solution of **9** (5.0 g, 17 mmol) in acetonitrile (250 mL) was added anhydrous $AlCl_3$ (11.0 g, 17 mmol) at 0°C under a nitrogen atmosphere. The reaction mixture was heated at reflux for 4 h and then poured into 200 mL of 3N HCl. Extraction with ethyl acetate (200 mL), drying over anhydrous Na_2SO_4 followed by evaporation of the solvent gave the crude product which was recrystallized from ethanol to give a yellow solid (15.0 g, 84%), mp 201–202°C, *lit*.[7]198–199°C.

^{1}H-NMR (300MHz, DMSO-d_6): δ 3.86 (3H, d, J = 1.8 Hz), 6.32 (1H, s), 7.01 (1H, s), 7.61–7.64 (3H, m), 8.07–8.09 (2H, m), 10.82 (1H, s), 12.51 (1H, d, J = 1.8 Hz). ^{13}C-NMR (75MHz, DMSO-d_6): δ 61.0, 99.1, 103.7, 105.3, 126.2, 127.8, 129.2, 130.8, 132.0, 149.6, 156.2, 157.3, 163.0, 182.0. IR (KBr) : 3411, 1660, 1579 cm^{-1}. EI-MS (*m/z*): 284 (*M*+).

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