Total synthesis of apigenin

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An efficient method for the synthesis of apigenin (4′,5,7-trihydroxyflavone, a traditional medicine) from phloroglucinol and anisaldehyde has been developed. This transformation features a green method for hydroxyl protection as methyl ethers and a different way for cyclisation using iodine in DMSO. The overall yield of 40% is satisfactory.

Keywords: phloroglucinol, apigenin, hydroxyl protection, cyclisation, demethylate

Apigenin (Fig. 1) is a flavonoid which is used in traditional or alternative medicine for its pharmacological activity. Human exposure to apigenin occurs primarily through the consumption of chamomile and through its presence as a glycoside in many fruits and vegetables including mint, parsley and celery.[1,2] Apigenin, like most flavonoids, has antioxidant, anti-inflammatory, and anti-tumour properties[3]. Several methods are available for the synthesis of apigenin.[4,5] Yeole *et al.*[4] reported a route to apigenin in three steps. However, the second step could not be achieved easily and the overall yield was only 27.6%, which restricted large-scale production. Seijas *et al.*[5] described another synthetic route to apigenin via microwaves irradiation of β-ketoester as the starting material to give a yield of 81%. However, the key starting β-ketoester could not be obtained easily.

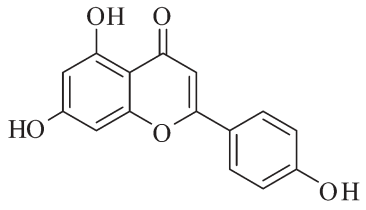


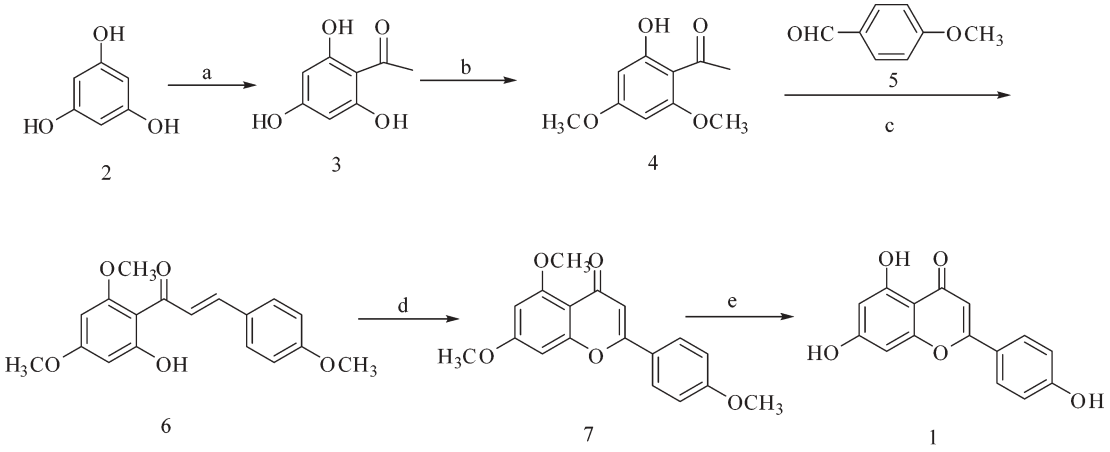
Fig. 1 Structure of apigenin (**1**).

We now report a convenient and efficient synthesis of **1** from the commercially available phloroglucinol **2**. The synthetic route is shown in Scheme 1.

Results and discussion

As shown in Scheme 1, apigenin **1** has been synthesised from phloroglucinol **2** in five steps. First, phloroglucinol **2** was acylated to 1-(2,4,6-trihydroxy-phenyl)-ethanone **3** by a Fries rearrangement.[6] The efficiency of this transformation was found to depend mainly on the amount of $BF_3{\cdot}Et_2O$ that was used. Second, treatment of **3** with 2.5 equivalents of methyl p-toluene sulfonate ($TsOCH_3$) instead of dimethylsulfate (Me_2SO_4)[7] in the presence of potassium carbonate in ethanol solution at 80 °C for 3 h afforded **4** in good yield. Third, condensation of **4** with anisaldehyde **5** using ethanolic potassium hydroxide resulted in the chalcone **6**,which was then treated with iodine in DMSO to afford flavone **7**, as previously reported.[8] Finally, the flavone **7** was treated with pyridine hydrochloride to achieve demethylation to obtain apigenin **1** in good yield.

In conclusion, a convenient and efficient synthesis of **1** has been achieved in overall yield(40%). The synthesis of **4** was a green and convenient approach.[9,10] Moreover, this is a relatively simple procedure, using easily accessible reagents and an easy separation, with good yields of products which are its main advantages.[11,12] Hence, we believe that this synthetic approach could be a useful addition to the reported methods for the preparation of flavone analogues.



Scheme 1 Reagents and conditions: (a) Ac_2O, $BF_3{\cdot}Et_2O$, 50 °C,10h, 86%; (b) $TsOCH_3$, K_2CO_3, 80 °C, 3h, 68%; (c) KOH, room temperature, 72h, 87%; (d) DMSO,I_2, 100 °C,4h, 86%; (e) pyridine HCl, 180–190 °C, 6 h, 90%.

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Experimental

All reactions were monitored by TLC, melting points were measured on a YRT-3 temperature apparatus and are uncorrected. IR spectra were recorded on Impact 400 FT-IR instrument. NMR spectral data were recorded on a Bruker DRX 500 NMR spectrometer.

1-(2,4,6-Trihydroxy-phenyl)-ethanone (**3**): Phloroglucinol **2** (10g, 79.4 m mol) and acetic anhydride 18 mL (19.4 g,190.0 m mol)were dissolved in ethyl acetate (40 mL), and BF_3·Et_2O 12 mL (13.8 g, 97.2 m mol) was added dropwise. The reaction mixture was heated at 50 °C for 10 h. Then, H_2O (150 mL) was added and the reaction mixture was extracted with ethyl acetate, After evaporation of the solvent the raw material was recrystallised from H_2O to give compound **3** (12 g); yield 86%, yellow crystals, m.p. 219–220 °C (lit.[13] 221 °C); IR (KBr/cm^{-1}):3201 (OH), 1616 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$):12.23 (s, 2H, OH), 10.38 (s, 1H, OH),5.79 (s, 2H, ArH),2.50 (s, 3H, $COCH_3$).

2-Hydroxy-4,6-dimethoxyacetophenone (**4**): Compound **3** (16.8 g, 0.1 mol), K_2CO_3 (28 g, 0.2 mol),and methyl p-toluenesulfonate (40.8 mL, 50.3 g, 0.27 mol) in ethanol (250 mL) were heated at 80 °C for 3 h. Then the mixture was poured into H_2O (500 mL), and the precipitate was filtered and recrystallised from methanol to give compound **4** (13.3g); yield 68%, white crystals, m.p. 79–80 °C (lit.[14] 80–81 °C); IR ν_{max} (KBr/cm^{-1}): 3461 (OH),1619(C=O); ^{1}H NMR (400 MHz, acetone-d_6): 13.79 (s, 1H,OH), 6.10 (s, 1H,ArH), 6.07 (s, 1H,ArH), 3.84 (s, 3H,OCH_3), 3.79 (s, 3H,OCH_3), 2.53 (s, 3H,$COCH_3$).

2'-Hydroxy-4,4',6'-trimethoxychalcone (**6**): Compound **4** (3.0 g, 0.015 mol), anisaldehyde **5** (2.5 g, 0,018 mol), and KOH (12.0 g, 0.21 mol) in methanol (250 mL) were stirred at room temperature for 72 h. Then the reaction mixture was neutralised to pH 7 with 37% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **6** (3.32 g); yield 87%, yellow crystals, m.p. 114–115 °C (lit.[8] 113–114 °C); IR ν_{max} (KBr/cm^{-1}):3648 (OH), 1622 (C=O), 1580 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): 14.42 (s, 1H, OH), 7.83 (s, 1H), 7.80 (s, 1H), 7.57–7.56 (d, *J* = 8.3 Hz, 2H), 6.94–6.92 (d, *J* = 8.3Hz, 2H), 6.11 (s, 1H), 5.96 (s, 1H), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3).

4',5,7-Trimethoxyflavone (**7**): Compound **6** (2.5g, 8.0 m mol), iodine (0.2g, 0.8 m mol) in DMSO (25 mL) were heated at 100 °C for 4 h. Then 0.5% $NaHSO_3$ (50 mL) was added to remove the iodine. The precipitate was filtered off, washed with water and recrystallised from ethanol/H_2O(1:1) to give compound **7** (2.15 g); yield 86%; off-white crystals, m.p. 153–154 °C, (lit.[8] 153–155 °C); IR ν_{max} (KBr/cm^{-1}): 1647 (C=O), 1607 (C=C); ^{1}H NMR (400 MHz, MeOD): 7.96–7.94 (d, *J* = 8.8 Hz, 2H), 7.12–7.10 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz,1H), 4.07 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H).

4',5,7-Trihydroxyflavone (**1**): The mixture of compound **7** (6.2 g, 0.02 mol) and excess pyridine hydrochloride (22.8 g, 0.20 mol) were heated at 180–190 °C for 6 h under an N_2 atmosphere. Then the mixture was cooled to room temperature and ethanol (20 mL) and H_2O (100 mL) were added. The reaction mixture was stirred for 10 min. The precipitate was filtered off, washed with ethanol and recrystallised from ethanol to give compound **1** (4.9 g); yield 90%, yellow crystals, m.p. 345–346 °C (lit.[3] 348–350 °C); IR ν_{max} (KBr/cm^{-1}): 3527 (OH), 1656 (C=O), 1445 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$): 12.95 (s, 1H, OH), 10.84 (s, 1H, OH), 10.36 (s, 1H, OH), 7.92 (d, 2H, *J* = 8.5 Hz), 6.92 (d, *J* = 8.5 Hz, 2H), 6.78 (s, 1H), 6.47 (s, 1H), 6.18 (s, 1H).

This study was supported by Natural Science Foundation of China (No. 21062009), Science Foundation of Department of Education of Yunnan Province (No. 2011J077), and Analysis and Testing Foundation of Kunming University of Science and Technology (No. 2011293).

Received 7 January 2012; accepted 20 January 2012
Paper 1201089 doi:10.3184/174751912X13285269293913
Published online: 22 March 2012

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