An improved synthesis of apigenin

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Two routes for the synthesis of the flavone apigenin are described. In the first, taxicatigenin was converted to 2-hydroxy-4,6-dimethoxyacetophenone and then by condensation with anisaldehyde to 2'-hydroxy-4,4',6'-trimethoxychalcone. The latter was cyclised with iodine and demethylated with pyridine hydrochloride to form apigenin in 53% overall yield. In the second route, a single step for the preparation of the chalcone was used in which 1,3,5-trimethoxybenzene was acylated with *p*-methoxycinnamic acid. Although the synthesis of apigenin was achieved in a lower overall yield of 34%, the process was simpler.

Keywords: apigenin, taxicatigenin, anisaldehyde, 1,3,5-trimethoxybenzene, *p*-methoxycinnamic acid

Flavonoids are a group of common phenolic plant pigments composed of a C_6–C_3–C_6 backbone which occur widely in higher plants and exhibit a broad spectrum of interesting biological activities including anticancer, antioxidant, neuroprotective and antihypertensive activities.[1] Apigenin (4′,5,7-trihydroxyflavone) is a flavone which is abundantly present in common fruits, vegetables and plant-derived beverages (*e.g.* tea and wine),[2] which has anti-inflammatory, free radical scavenging and anticancer effects.[3]

Owing to its attractive biological characteristics and commercial utility, apigenin has attracted much attention and sparked tremendous efforts on its total synthesis. Yeole *et al.*[4] reported a route to apigenin in three steps. However, the second step was difficult to achieve and the route did not have the potential of industrial production on account of the low overall yield. Seijas and co-workers[5] described another synthetic route to apigenin *via* microwave irradiation of a β-ketoester as starting material to give a good yield of 81%. However, the key starting β-ketoester could not be prepared easily and the microwave irradiation signified harsh terms to a number of researchers because of the inconsistent laboratory conditions in China. Apigenin has also been prepared,[6–8] but almost all of the published methods have in common, problems of low yields and poorly accessible starting materials.

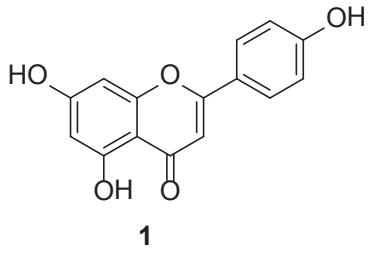

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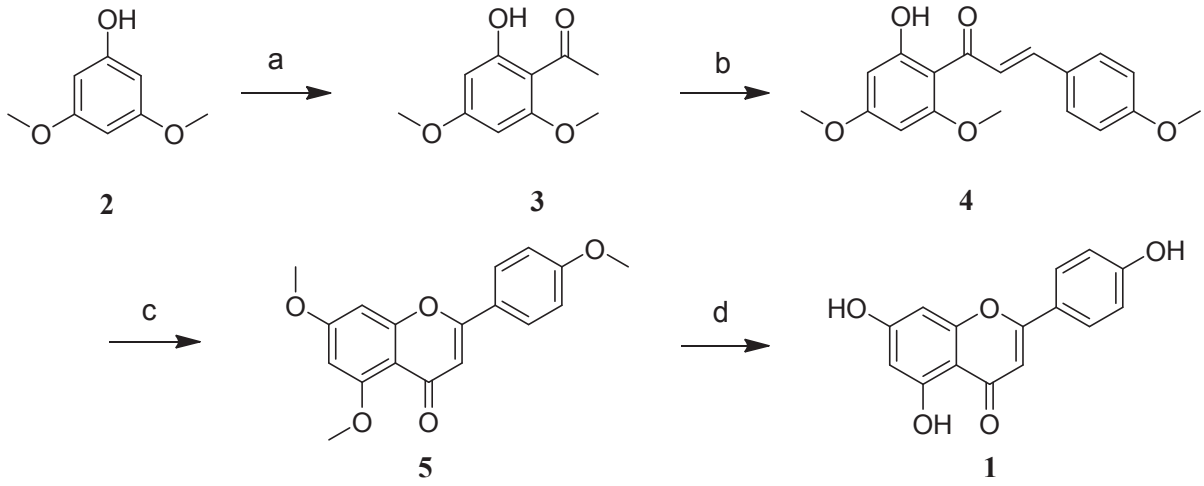
Fig. 1 Structure of apigenin.

We have already reported two methods for the synthesis of apigenin. In the first, apigenin was synthesised in five steps[9] with an overall yield of 40%. In the second, the yield was increased to 55%, also in five steps.[10] Building on these two approaches, we have carried out further studies and we report here a shorter, improved synthesis of apigenin **1** (Fig. 1) in satisfactory yield using commercially available starting materials.

Results and discussion

The first route (Scheme 1) gave **1** in four steps. The second route involved, instead of two steps for the preparation of the chalcone **4**, just a single step (Scheme 2).



Scheme 1 Reagents and conditions: (a) $ZnCl_2$, CH_3COOH, 145 °C, 2 h, 79%; (b) anisaldehyde, KOH, room temperature, 80 h, 86%; (c) DMSO, I_2, 120 °C, 4 h, 86%; (d) Py·HCl, 180 °C, 6 h, 90%.

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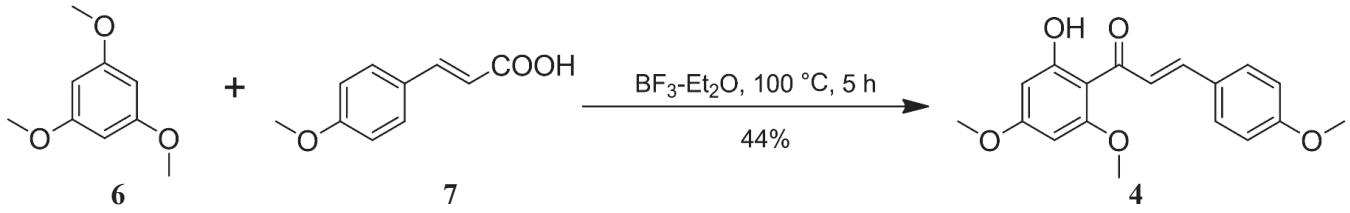

Scheme 2

As shown in Scheme 1, the initial step of the first route was the acylation of 3,5-dimethoxyphenol **2** by acetic acid using $ZnCl_2$ as catalyst (145 °C, 2 h) to give acetophenone **3** in good yield (79%). Aldol condensation of **3** with anisaldehyde (KOH, r.t., 80 h) gave the chalcone **4** in a very good yield (86%). Conversion of **4** to **5** was catalysed by I_2 in dimethyl sulfoxide (120 °C, 4 h), and the resulting product **5** (86%) was demethylated with pyridine hydrochloride under a N_2 atmosphere (180 °C, 6 h) to give the target natural product **1** in commendable yield (90%).

Although apigenin **1** had been prepared in four steps in fairly good overall yield (53%) from taxicatigenin **2** (Scheme 1), we decided to simplify the process by shortening the synthesis of **1** to a three-step procedure. This was accomplished by the single-step preparation of chalcone **4** in moderate yield (44%) by treatment of the readily available *p*-methoxycinnamic acid **7** with 1,3,5-trimethoxybenzene **6** in BF_3–Et_2O (100 °C, 5 h) (Scheme 2). Although this synthetic pathway gave a lower yield of **1** (34%), the method was shorter and the workup was simpler.

In conclusion, two novel routes using commercially available starting materials and reagents for the synthesis of apigenin are described. The former improved procedure had a better yield and the latter shortened the reaction time; moreover, each step gave the product easily. Compared to our previous work, we decreased the reaction procedures and kept the satisfactory yield at the same time. Consequently, we believe that this improved procedure could be an efficient approach for a scaled-up synthesis of apigenin. Further study towards a synthesis of apigenin-7-O-β-D-glucuronide (a known flavonoid glycoside with excellent pharmacological activities) is ongoing, and will be reported in due course.

Experimental

All reagents were purchased from Aladdin-reagent, China, and used without further purification. All reactions were monitored and the purity of the products was checked by TLC performed on GF-254 silica gel plates with visualisation by UV light. IR spectra were recorded on an Impact 400 FTIR instrument. Melting points were measured on a YRT-3 temperature apparatus. ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer and chemical shifts are reported in ppm (δ) relative to TMS as internal standard. Mass spectra were determined on VG Auto Spec-3000 spectrometer and reported as *m/z*.

2-Hydroxy-4,6-dimethoxyacetophenone (**3**): A mixture of fused $ZnCl_2$ (13.6 g, 0.1 mol) and acetic acid (6 mL, 0.1 mol) was heated slowly with stirring until the solution became homogeneous. Compound **2** (15.4 g, 0.1 mol) was added and the reaction mixture was kept for about 2 h at 145 °C. The reaction mixture was cooled and poured over crushed ice containing hydrochloric acid (1 : 1). The solid that separated out was filtered and washed separately with water and sodium bicarbonate solution. The crude product was purified by column chromatography over silica gel; elution was effected with a gradient solvent system of petroleum ether/ethyl acetate to give compound **4** as white powder (15.5 g, yield 79%); m.p. 80–82 °C (lit.[11] 82–83 °C); IR ν_{max} (KBr/cm^{-1}): 3448 (OH), 1613 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.88 (s, 1H, OH), 6.12 (s, 1H), 5.97 (s, 1H), 3.82 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.60 (s, 3H, $COCH_3$); MS (*m/z*): 197 $[M+H]^+$.

2′-Hydroxy-4,4′,6′-trimethoxychalcone (**4**): *Step b* (Scheme 1): Potassium hydroxide (11.2 g, 0.2 mol) was added to methanol (80 mL). After it had cooled to ambient, compound **3** (2.0 g, 0.01 mol) and anisaldehyde (1.5 g, 0.011 mol) were added to the solution. It was stirred for 80 h at room temperature. Then the mixture was neutralised to pH 5–6 by adding 5% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **4** as yellow crystals. (2.7 g, yield 86%).

2′-Hydroxy-4,4′,6′-trimethoxychalcone (**4**): (Scheme 2): A mixture of 1,3,5-trimethoxybenzene (**6**) (1.7 g, 0.01 mol) and *p*-methoxycinnamic acid (**7**) (2.7 g, 0.015 mol) in BF_3–Et_2O (30 mL) was stirred at 100 °C for 5 h. After overnight standing, the resulting mixture was filtered and dried to give red needles. A suspension of the needles in alcohol was refluxed for 2 h to give a clear orange solution. After decolourising with active charcoal and cooling to 0 °C, the yellow crystals of compound **4** were filtered off and dried to give 1.4 g (44%); m.p. 114–115 °C (lit.[12] 113–114 °C); IR ν_{max} (KBr/cm^{-1}): 3622 (OH), 1635 (C=O), 1564 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 13.98 (s, 1H, OH), 7.96–7.89 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.88–6.86 (d, J = 8.5 Hz, 2H), 6.02 (s, 1H), 5.94 (s, 1H), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3); MS (*m/z*): 315 $[M+H]^+$.

4′,5,7-Trimethoxyflavone (**5**): Compound **4** (3.1 g, 0.01 mol) and iodine (0.2 g, 0.008 mol) in DMSO (25 mL) were stirred at 120 °C for 4 h and then the reaction mixture was added to 1.0% $NaHSO_3$ solution (100 mL). The precipitate was filtered off, washed with water and recrystallised from ethanol/H_2O (1 : 1) to give off-white crystals of **5** (2.7 g, yield 86%); m.p. 154–155 °C (lit.[13] 157 °C); IR ν_{max} (KBr/cm^{-1}): 1662 (C=O), 1619 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.90–7.86 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.9 Hz, 2H), 6.76 (s, 1H), 6.63(d, J = 2.0 Hz, 1H), 6.22 (d, J = 2.0 Hz, 1H), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); MS (*m/z*): 313 $[M+H]^+$.

Apigenin (**1**): Compound **5** (1.4 g, 0.005 mol) and excess pyridine hydrochloride (5.0 g, 0.04 mol) were heated at 180 °C for 6 h under a N_2 atmosphere. The mixture was cooled to room temperature and H_2O (100 mL) was added. The mixture was stirred for another 30 min and cooled to below 5 °C for several hours. The precipitate was filtered off, washed with cold ethanol and recrystallised from absolute ethanol to give compound **1** as yellow crystals (1.2 g, yield 90%); m.p. 347–348 °C (lit.[8] 348–350 °C); IR ν_{max} (KBr/cm^{-1}): 3508 (OH), 1629 (C=O), 1432 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6), δ 12.92 (s, 1H, OH), 10.62 (s, 1H, OH), 10.54 (s, 1H, OH), 7.85 (d, J = 8.4 Hz, 2H), 6.97(d, J = 8.4 Hz, 2H), 6.64(s, 1H), 6.36 (s, 1H), 6.20 (s, 1H); MS (*m/z*): 271 $[M+H]^+$.

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