Practical synthesis of naringenin

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Two routes for the synthesis of the flavanone naringenin are described. In the first, 3,5-dimethoxyphenol is converted to 2-hydroxy-4,6-dimethoxyacetophenone and then by condensation with anisaldehyde to 2′-hydroxy-4,4′,6′-trimethoxychalcone. The chalcone is then cyclised with aqueous hydrochloric acid and demethylated with pyridine hydrochloride to form naringenin in 45% overall yield. The condensation of 2-hydroxy-4,6-dimethoxyacetophenone with anisaldehyde could also directly produce 4′,5,7-trimethoxyflavanone, which was then converted into naringenin in 60% overall yield. In the second route, a single step for the preparation of the chalcone is used in which 1,3,5-trimethoxybenzene is acylated with *p*-methoxycinnamic acid. Although the synthesis of naringenin is achieved in a lower overall yield of 29%, the process is simpler.

Keywords: naringenin, taxicatigenin, anisaldehyde, *p*-methoxycinnamic acid, chalcone

Flavanones, 2-phenylchroman-4-ones, belong to the family of flavonoids, many of which are produced as secondary metabolites in the plant kingdom[1] and exhibit a broad spectrum of interesting biological activities.[2-5] Naringenin (5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, Fig. 1) is one of the most abundant flavanones present in grapefruits and citrus fruits.[6] It is well-known for its beneficial health-related properties, including anti-oxidant, anti-cancer, anti-atherogenic, anti-inflammatory and anti-proliferative activities.[7,8] Naringenin is reported to inhibit the assembly and long-term production of infectious hepatitis C virus particles in a dose-dependent manner.[9] Furthermore, naringenin potentiates intracellular signalling responses to low insulin doses, suggesting that naringenin sensitises hepatocytes to insulin.[10] Additionally, naringenin was shown to traverse the blood–brain barrier and exert a diverse array of neuronal effects through their ability to interact with the protein kinase C (PKC) signalling pathways.[11]

A number of syntheses of **1** have been reported because of its attractive biological characteristics. In 2006, Selenski *et al*.[12] described a synthesis of naringenin in three steps using tris-*o*-Boc salicylaldehyde as the starting material. However, whereas the key starting material tris-*o*-Boc salicylaldehyde could not be prepared easily and the yield was relatively low (32.5%). In 2009, Hamilton and coworkers[13] reported another route to naringenin in seven steps using phloroglucinol as the starting material. However, the route did not have the potential for industrial production on account of the complicated process, the presence of a side product and the low overall yield. Naringenin has also been prepared by others,[14-16] but most of these methods consist of long reaction times, low yields of the products, harsh reaction conditions, and the use of expensive and environmentally toxic reagents. As a result, there is a need for a more straightforward and cost-effective procedure for the synthesis of naringenin.

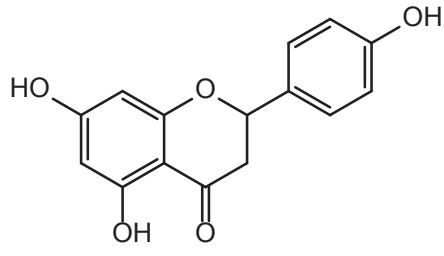

Fig. 1. Structure of naringenin.

We have reported the synthesis of naringenin in five steps from 1,3,5-trimethoxybenzene or phloroglucinol with a moderate overall yield.[17] As a continuation of our investigations on the synthesis of the bioactive natural flavonoids and their biological activity,[17,18-25] we have carried out further studies and we now report the preparation of **1** using commercially available starting materials, and by an improved procedure with satisfactory yields.

Results and discussion

As shown in Schemes 1 and 2, the last two steps of the routes involved cyclisation of the key intermediate **4** and demethylation of the precursor **5**. The first approach gave **1** in four steps. The remaining two pathways involve just three steps.

As shown in Scheme 1, the first step started with the acylation of **2** by acetic acid under the $ZnCl_2$ as a 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 decent yield (86%). Conversion of **4** to **5** was performed by 10% aqueous HCl (room temperature, r.t., 50 h), and the resulting product **5** (74%) was demethylated with pyridine hydrochloride under an N_2 atmosphere (180 °C, 6 h) to give the target natural product **1** in commendable yield (90%). Alternatively, in light of the report by Cui *et al*.,[17] a one-pot reaction directly produced a compound **5** (85%) *via* a Claisen–Schmidt condensation of compound **3** with anisaldehyde (KOH, r.t., 72 h) by increasing the concentration of KOH, which was subsequently converted into naringenin (r.t., 72 h) in good yield (90%).

Although compound **1** was prepared in a fairly good overall yield from taxicatigenin, we decided to improve the strategy by further shortening the total time of the synthesis of **1**. This was fulfilled by a single step via the treatment of the readily available 1,3,5-trimethoxybenzene **6** and *p*-methoxycinnamic acid **7** in BF_3–Et_2O (100 °C, 5 h) to give chalcone **4** (step f) in moderate yield (44%). Then, the following two steps were performed under identical conditions as same as above. Although this synthetic pathway gave a lower yield of **1** (29%), the reaction time was shorter and the workup was simplified.

In summary, two novel routes which used commercially available starting materials and reagents for the synthesis of naringenin have been described. The former improved procedures had better yields and the latter shortened the reaction time. Moreover, each step gave the product easily.

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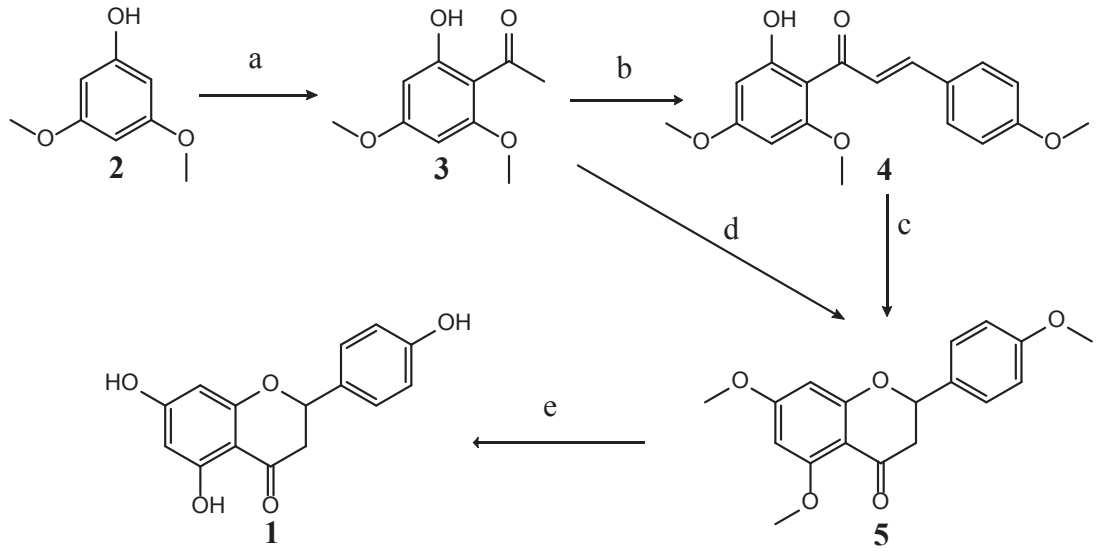
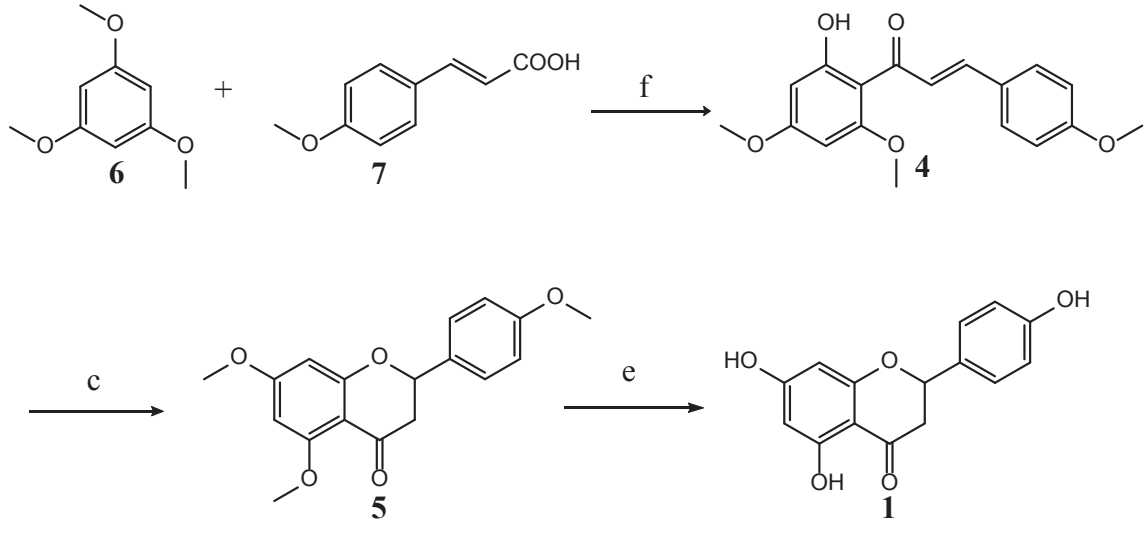


Scheme 1 Reagents and conditions: (a) $ZnCl_2$, CH_3COOH, 145 °C, 2 h, 79%; (b) anisaldehyde, KOH, r.t., 80 h, 86%; (c) 10% aqueous HCl, ethanol, r.t., 50 h, 74%; (d) anisaldehyde, 40% aqueous KOH, methanol, r.t., 72 h, 85%; (e) Py·HCl, 180 °C, 6 h, 90%.



Scheme 2 Reagents and conditions: (f) *p*-methoxycinnamic acid, BF_3–Et_2O, 100 °C, 5 h, 44%; (c) 10% aqueous HCl, ethanol, room temperature, 50 h, 74%; (e) Py·HCl, 180 °C, 6 h, 90%.

Compared to previous works of our team, we decreased the reaction procedures and raised the yield at the same time. Taken together, these advances significantly enhance opportunities for potential industrial scale-up of this important natural compound and could be a useful addition to the reported methods for the preparation of the flavanone.

Experimental

All glassware was thoroughly washed and dried in an oven at 120 °C. Teflon-coated magnetic stirring bars were washed with acetone and dried. 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 Impact 400 FT-IR instrument. Melting points were measured on a YRT-3 temperature apparatus, ^{1}H NMR spectral data were recorded on a Bruker Avance 400 NMR spectrometer or a Bruker DRX 500 NMR spectrometer, chemical shifts were reported in parts per million (ppm) against internal tetramethylsilane. Mass spectra were determined on VG Auto Spec-3000 spectrometer and reported as *m/z*. All reagents were purchased from Tansoole reagent, China, and used without further purification.

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 till 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, 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 using column chromatography over silica gel. Elution with a gradient solvent system of petroleum ether/ethyl acetate gave compound **4** as white powdery (15.5 g, yield 79%); m.p. 80–82 °C (lit.[26] 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*): Potassium hydroxide (11.2 g, 0.2 mol) was added to methanol (80 mL). After it had cooled to ambient temperature, 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. (2.7g, yield 86%).

(*Step f*): 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. The solution was left overnight and the red solid 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 being decolourised with active charcoal and cooled to 0 °C, the yellow crystals of compound **4** were filtered and dried to give 1.4 g (44%); m.p. 114–115 °C (lit.[27] 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-Trimethoxyflavanone (**5**); (*Step c*): Compound **4** (1.6 g, 5 mmol) and ethanol (10 mL) were placed in a dry round-bottomed flask, then 10% aqueous HCl (15 mL) was slowly added and the solution was stirred for 50 h at room temperature. The precipitate was filtered off and the solvent was removed under reduced pressure, and then recrystallised from H_2O to give compound **5** as a pale yellow crystals (1.16 g, yield 74%);

(*Step d*): A mixture of compound **3** (2.0 g, 0.01 mol) and anisaldehyde (1.5 g, 0.011 mol) was dissolved in methanol (20 mL), and 40% aqueous KOH (70 mL) was added dropwise at approximately 0 °C in an ice-bath. The mixture was stirred for 72 h at room temperature. Then the reaction mixture was neutralised to pH 5–6 with 10% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give compound **5** as pale yellow crystals (2.67 g, 85%); m.p. 121–123 °C (lit.[28] 124 °C); ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.52 (d, 2H, ArH), 6.98 (d, 2H, ArH), 6.10 (d,1H, ArH), 6.06 (d, 1H, ArH), 5.30 (dd, *J* = 12.8, 2.9 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.95 (dd, *J* = 16.8, 2.9 Hz, 1H), 2.70 (dd, *J* = 16.8, 13.0 Hz, 1H); MS (*m/z*): 315 [M+H]$^+$.

Naringenin (**1**): A mixture of compound **5** (3.1 g, 0.01 mol) and excess pyridine hydrochloride (11.6 g, 0.1 mol) was heated at 180 °C for 6 h under an N_2 atmosphere. Then 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 approximately 0 °C for several hours. The precipitate was filtered off, washed with cold ethanol and recrystallised from absolute ethanol to give compound **1** as a yellow crystals (2.46 g, yield 90%); m.p. 248–250 °C (lit.[29] 247–250 °C); ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 12.18 (s, 1H, OH), 10.82 (s, 1H, OH), 9.54 (s, 1H, OH), 7.55 (d, *J* = 8.4 Hz, 2H, ArH), 7.16 (d, *J* = 8.4 Hz, 2H, ArH), 5.85 (s, 2H, ArH), 5.41–5.34 (m, 1H), 3.15 (dd, *J* = 17.0, 12.9 Hz, 1H), 2.68 (dd, *J* = 17.0, 3.0 Hz, 1H); MS (*m/z*): 273 [M+H]$^+$.

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