An efficient synthesis of chrysin

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Two routes for the synthesis of the flavones chrysin are described. In the first 1,3,5-trimethoxybenzene was converted to 2-hydroxy-4,6-dimethoxyacetophenone and then by condensation with benzaldehyde to 2'-hydroxy-4',6'-dimethoxychalcone. The latter was cyclised with iodine and demethylated with pyridine hydrochloride to form chrysin in 53% overall yield. In the second route, 1,3,5-trimethoxybenzene was acylated with cinnamic acid to form the chalcone which was then converted to chrysin in 30.7% overall yield.

Keywords: chrysin, 1,3,5-trimethoxybenzene, benzaldehyde, cinnamic acid

Chrysin (5,7-dihydroxy-2-phenyl-4H-chromen-4-one) (Fig. 1), a naturally occurring flavone, is widely distributed and has previously been isolated from Populus, Pinus and Prunus species.[1] It has been reported to have extensive pharmacological activities, such as anti-tumour,[2,3] antiallergic,[4] and aromatase inhibitory activity,[5] as well as anti-inflammatory,[6] antiviral,[7] anti-microbial,[8] and hypoglycaemic[9] activity.

Owing to its wide pharmacological activity, a number of syntheses of **1** have been reported. Recently, chrysin has been synthesised by Kun Hu *et al*.[10] in five steps using 2,4,6-trihydroxyacetophenone as the starting material in a low overall yield (26.3%). It has also been prepared by other authors,[11] but most of these methods have low yields or use special reagents. Two approaches to the synthesis of **1** have been developed.

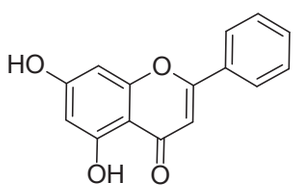


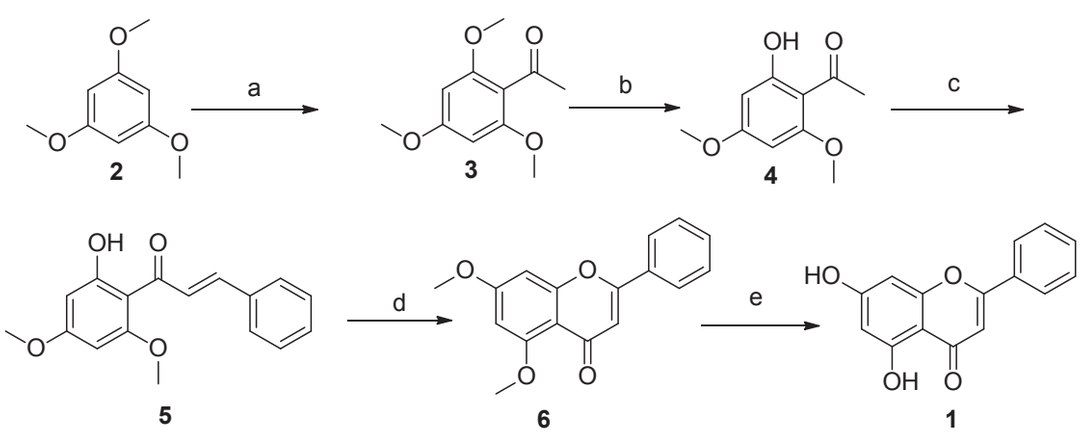
Fig. 1 Structure of chrysin.

Results and discussion

As shown in Schemes 1 and 2, the last two steps of the routes involved cyclisation of the key precursor **5** and demethylation of the precursor **6**. The first approach gave **1** in five steps. The second shorter pathway can be carried out in just three steps.

As shown in Scheme 1, the first step started with the acylation of **2** under mild conditions (BF_3–Et_2O, r.t., 2 h) to give acetophenone **3** in great yield (93%). 2-Hydroxy-4,6-dimethoxyacetophenone (**4**) was obtained by the selective demethylation with BCl_3 (0 °C, 2 h) in a yield of 89%. Aldol condensation of **4** with benzaldehyde (KOH, r.t., 80 h) gave the chalcone **5** in good yield (88%). Conversion of **5** to **6** was catalysed by I_2 in dimethyl sulfoxide (120 °C, 4 h), and the resulting product **6** (85%) was demethylated with pyridine hydrochloride under N_2 atmosphere (180 °C, 6 h) to give the desired natural product **1** in good yield (86%).

Although compound **1** was prepared in a fairly good overall yield (53.1%) from 1,3,5-trimethoxybenzene, we decided to improve the strategy by shortening the conversion of **2** to **1** in a three-step procedure. The second route (Scheme 2) began with the treatment of the readily available cinnamic acid **7** and **2** in BF_3–Et_2O (100 °C) to give chalcone **5** in moderate yield (42%). Then, the following two steps were performed under identical conditions as shown in Scheme 2. Although this synthetic pathway gave a lower yield of **1** (30.7%), the method was shorter and the workup was simplified.



Scheme 1 The first approach to chrysin: (a) BF_3–Et_2O, EtOAc, r.t., 2 h, 93%; (b) BCl_3, CH_2Cl_2, 0 °C,2 h, 89%; (c) benzaldehyde, KOH, r.t., 80 h, 88%; (d) DMSO, I_2, 120 °C, 4 h, 85%; (e) Py·HCl, 180 °C, 6 h, 86%.

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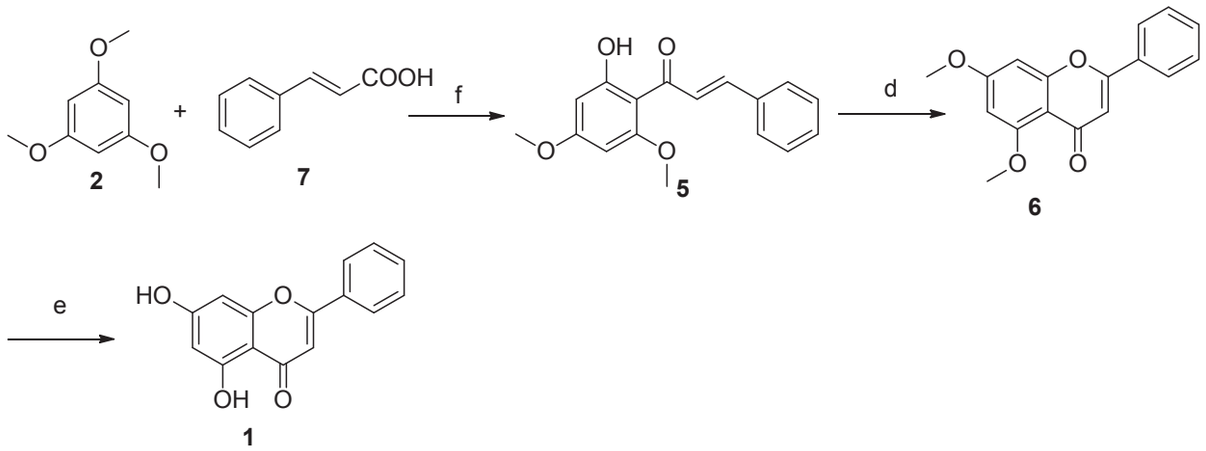

Scheme 2 The second approach to chrysin: (f) BF_3–Et_2O, 100 °C, 4 h, 42%; (d) DMSO, I_2, 120 °C, 4 h, 85%; (e) Py·HCl, 180 °C, 6 h, 86%.

In conclusion, two novel routes which used commercially available starting materials and reagents for the synthesis of chrysin were described. The first improved procedures had better yields and the second one shortened the reaction time. Moreover, each step gave the product easily. Hence, we believe that this improved procedure could be an efficient approach for a scaled-up synthesis of chrysin.

Experimental

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 and chemical shifts were 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*. All reagents were purchased from Aladdin-reagent, China, and used without further purification.

2,4,6-Trimethoxyacetophenone (**3**): BF_3–Et_2O 2.0 mL (2.3 g, 0.013 mol) was added to a solution of 1,3,5-trimethoxybenzene (**2**): (4.2 g, 0.025 mol) and Ac_2O 3.6 mL (3.8 g, 0.038 mol) in EtOAc (20 mL) over 30 minutes. The mixture was stirred at room temperature for 2 h. Then water (50 mL) was added and the mixture was extracted with ethyl acetate twice (50 × 2 mL). The combined organic layers were washed with H_2O (50 mL), Saturated Na_2CO_3 solution (50 mL), brine (50 mL), dried with anhydrous sodium sulfate overnight. Then the solution was concentrated under reduced pressure to give a solid residue, which was recrystallised from methanol/H_2O to afford the compound **3** as white powders (4.8 g, 93%); m.p. 100–102 °C (lit.[12] 101–103 °C); IR, $\tilde{\nu}$/cm^{-1}: 1704 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.46 (s, 3H, $COCH_3$), 3.79 (s, 6H, OCH_3-2,6), 3.83 (s, 3H, OCH_3-4), 6.10 (s, 2H, H-3,5). MS (*m/z*): 211 $[M+1]^+$.

2-Hydroxy-4,6-dimethoxyacetophenone (**4**): A solution of compound **3** (3.2 g, 0.015 mol) in dichloromethane (15 mL), was treated with 1 mol L^{-1} BCl_3 in dichloromethane (18 mL, 0.018 mol) for 1 h at approximately 0 °C. After the reaction mixture had been stirred at 0 °C for another 2 h, H_2O (50 mL) was added and the mixture stirred for another 1 hour and extracted with dichloromethane twice (50 mL × 2). The combined organic layers were washed with H_2O (50 mL), saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried with anhydrous magnesium sulfate overnight. The solvent was removed under reduced pressure and the residue was recrystallised from ethanol to give compound **4** as white crystal (2.6 g, yield 89%); m.p. 79–80 °C (lit.[13] 82–83 °C); IR, $\tilde{\nu}$/cm^{-1}: 2952 (OH), 1619 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.61 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3-6), 3.85 (s, 3H, OCH_3-4), 5.93 (s, 1H, H-3), 6.06 (s, 1H, H-5), 14.03 (s, 1H, OH-2). MS (*m/z*): 197 $[M+1]^+$.

2′-Hydroxy-4′, 6′-dimethoxychalcone (**5**); *Step c* (Scheme 1): Potassium hydroxide (11.2 g, 0.200 mol) was added to methanol (80 mL). After it had cooled to ambient, compound **4** (2.0 g, 0.010 mol) and benzaldehyde (1.2 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 with 5% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give yellow crystals of compound **5** (2.5 g, yield 88%).

Step f (Scheme 2): A mixture of 1,3,5-trimethoxybenzene (**2**) (0.84 g, 0.005 mol) and cinnamic acid (**7**) (1.1 g, 0.008 mol) in BF_3·Et_2O (15 mL) was stirred at 100 °C for 4 h. The red solid was filtered and dried to give red needles. A suspension of the needles in EtOH/H_2O (10 : 1) 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 **5** were filtered and dried to give 0.6 g (42%); m.p. 80–82 °C (lit.[14] 78–80 °C); IR, $\tilde{\nu}$/cm^{-1}: 1630 (C=O), 1589 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.83 (s, 3H, OCH_3-4′), 3.91 (s, 3H, OCH_3-6′), 6.14 (d, J = 1.6 Hz, 1H, H-3′), 6.17 (d, J = 1.6 Hz, 1H, H-5′), 7.45–7.49 (m, 3H, H-3,4,5), 7.65 (d, 1H, J = 16 Hz, H-α), 7.72–7.74 (m, 2H, H-2,6), 7.78 (d, J = 16 Hz, 1H, H-β), 13.41 (s,1H, OH-2′). MS (*m/z*): 285 $[M+1]^+$.

5,7-Dimethoxyflavone (**6**): Compound **5** (2.8 g, 0.010 mmol) and iodine (0.2 g) in DMSO (25 mL) were stirred at 120 °C for 4 h and then it was added to 2.0% $NaHSO_3$ (100 mL). The precipitate was filtered off, washed with water and recrystallised from methanol to give almost white crystals of **6** (2.4 g, yield 85%); m.p. 143–146 °C (lit.[15]148–149 °C); IR, $\tilde{\nu}$/cm^{-1}: 1651(C=O); ^{1}H NMR (400 MHz, DMSO-d_6), δ 3.83 (s, 3H, OCH_3-7), 3.90 (s, 3H, OCH_3-5), 6.50 (d, 1H, J = 2.4 Hz, H-8), 6.76 (s, 1H, H-3), 6.85 (d, 1H, J = 2.4 Hz, H-6), 7.56 (m, 3H, H-4′,5′,6′), 8.03 (m, 2H, H-2′,3′). MS (*m/z*): 283 $[M+1]^+$.

Chrysin (**1**): The mixture of the compound **6** (1.4 g, 0.005 mol) and excess pyridine hydrochloride (5.0 g) 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 5 °C for several hours. The precipitate was filtered off, washed with cold ethanol and recrystallised from absolute ethanol to give a light yellow powdery (1.1 g, yield 86%); m.p. 280–284 °C (lit.[16] 282–285 °C); IR, $\tilde{\nu}$/cm^{-1}: 3410 (OH) 1654 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6), δ 6.23 (d, 1H, J = 2.0 Hz, H-6), 6.53 (d, 1H, J = 2.0 Hz, H-8), 6.97 (s, 1H, H-3), 7.55–7.62 (m, 3H, H-4′,5′,6′), 8.06 (m, 2H, H-2′,3′), 10.94 (s, 1H, OH-7),12.83 (s, 1H, OH-5). MS (*m/z*): 255 $[M+1]^+$.

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