Total synthesis of luteolin

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Luteolin is a naturally-occurring polyphenolic flavonoid compound which has received considerable attention because of its wide range of biological and pharmacological properties. Efficient methods are reported for preparing luteolin, based on the acylation of 1,3,5-trimethoxybenzene and condensation with 3,4-dimethoxybenzaldehyde or the reaction of 3,4-dimethoxycinnamic acid with 1,3,5-trimethoxybenzene. The first of these is the better method.

Keywords: flavonoid, luteolin, Claisen–Schmidt condensation, one-pot reaction

The flavonoids are polyphenolic compounds possessing a C6–C3–C6 skeleton (Fig. 1)[1], which occur widely in fruits and vegetables, and exhibit a broad spectrum of interesting biological activities against cancer, cardiovascular, and neurodegenerative diseases.[2] They are divided into several sub-groups based on structural differences in their ring C involving its oxidation state.[3] The A and B-rings of naturally occurring flavonoids are usually functionalised by OH, OMe, isoprenyl, and glycosyl groups. The OH and glycosyl residues can be further functionalised by acyl, glycosyl or other flavonoid moieties.[3] They exert antioxidant and biological activities due to their aromatic moieties and the presence of oxygen functions.

Luteolin (Fig. 2) is a polyphenolic flavonoid compound which has attracted considerable attention owing to its biological and pharmacological activities.[4–6] However, only a small amount of luteolin is available for biological studies because it is difficult to obtain. Among the published syntheses of luteolin,[7–9] none is attractive for large-scale synthesis due to drawbacks such as the use of expensive starting materials that are not easily accessible. Therefore, a simple and efficient synthetic method of luteolin is very desirable. We now report an efficient synthetic route for the preparation of luteolin (Scheme 1) based on our previous work.[10–15]

Results and discussion

As shown in Scheme 1, compound **6** is the key intermediate for the synthesis of luteolin and quercetin, which prepared by a reaction sequence starting from the commercially available 1,3,5-trimethoxybenzene *via* Friedel–Crafts acylation, demethylation selectively, Claisen–Schmidt condensation with compound **4**. It was also afforded by using 1,3,5-trimethoxybenzene and 3,4-dimethoxycinnamic **5** as starting materials in the presence of excess of BF_3–Et_2O through one-pot reaction, but its yield is lower than the previous one within three steps.

Compound **6** was heated with iodine in DMSO at 130 °C, which gave the compound **7.** Compound **7** was then completely demethylated in the presence of pyridine hydrochloride for 6.5 h to afford **8**.

In conclusion, a short route for the synthesis of the compound **8** has been achieved in an overall yield 47.2%. This synthesis of **8** is a green and convenient approach. Moreover, this method not only has the advantages of mild conditions, easily accessible starting materials and facile separation, and it is also less expensive, more practical, and environmentally friendly. Hence, we believe that this procedure could be an efficient synthetic approach for a scaled-up synthesis of luteolin.

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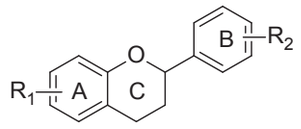
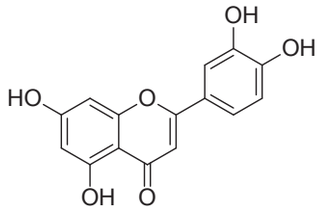


Fig. 1 Flavonoid skeleton.



luteolin

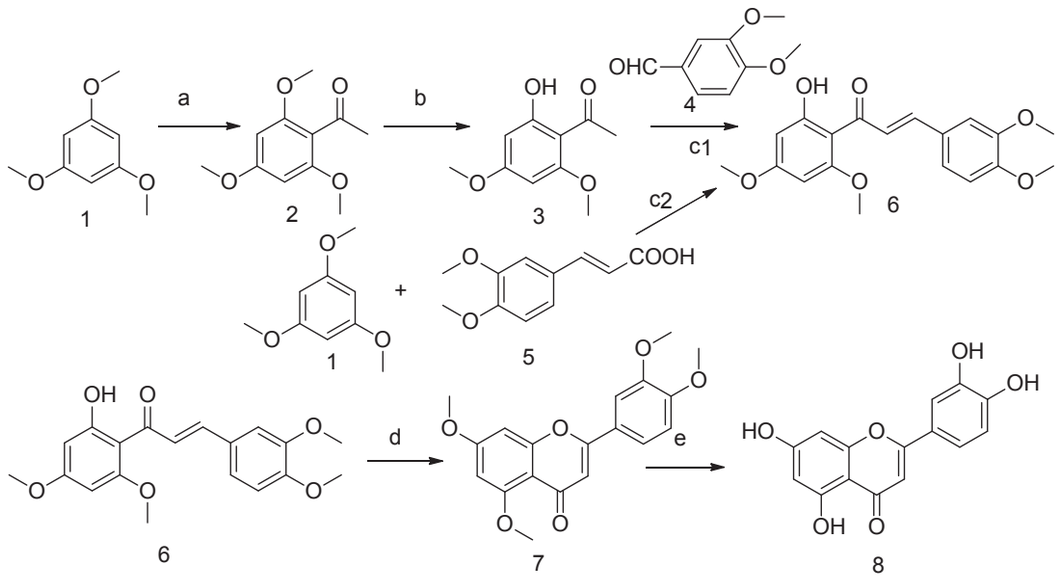
Fig. 2 Structure of luteolin.

Experimental

All reactions were monitored by TLC on silica gel GF254. Melting points were measured on a YRT-3 temperature apparatus and are uncorrected. ^{1}H NMR spectral data were recorded on a Bruker DRX 500 NMR spectrometer and chemical shifts are reported in ppm (δ) relative to TMS as internal standard. IR spectra were recorded on Impact 400 FT-IR instrument. All reagents were purchased from Aladdin-reagent, China, and used without further purification.

2,4,6-Trimethoxyacetophenone (**2**): 1,3,5-Trimethoxybenzene **2** (8.4 g, 0.05 mol) and acetic anhydride 7 mL (7.6 g, 0.075 mol) were dissolved in ethyl acetate (30 mL) and BF_3–Et_2O 3.8 mL (4.3 g, 0.025 mol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Then, H_2O (50 mL) was added and the reaction mixture was extracted with ethyl acetate (2 × 50 mL) The organic layers were combined and washed sequentially with H_2O (100 mL × 2), saturated sodium bicarbonate (100 mL × 2) and H_2O (100 mL × 1) and then dried with anhydrous sodium sulfate overnight. Removal of the solvent under reduced pressure gave a solid residue, which was recrystallised from ethanol to afford the compound **3** as white crystals (9.8 g); yield 93%, m.p. 101–102 °C (lit.[16] 101–103 °C) ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 2.46 (s, 3H, $COCH_3$), 3.79 (s, 6H, OCH_3), 3.83 (s, 3H, OCH_3), 6.10 (s, 2H, ArH). IR ν_{max} (KBr/cm^{-1}): 1704 (C=O).

2-Hydroxy-4,6-dimethoxyacetophenone (**3**): A solution of the compound **2** (4.2 g, 0.02 mol) in dichloromethane (20 mL) at approximately 0 °C was treated with 1 mol L^{-1} BCl_3 in dichloromethane (24 mL, 0.024 mol) dropwise for about 1 h, and then the reaction mixture was stirred at room temperature for another 1 h. H_2O (100 mL) was added, the mixture was stirred for another hour and extracted with dichloromethane twice (50 mL × 2). The organic layers were combined and washed sequentially with H_2O (100 mL × 2), saturated sodium bicarbonate (100 mL × 2) and H_2O (100 mL × 1) and then dried with anhydrous sodium sulfate overnight. The solvent was removed under reduced pressure, and the residue was recrystallised from ethanol to give compound **3** (3.24 g); yield 87%, white crystals, m.p. 79–80 °C (lit.[17] 80–81 °C) ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 2.61



Scheme 1 Reagents and conditions: (a) BF_3–Et_2O, EtOAc, r.t., 2 h, 93%; (b) BCl_3, CH_2Cl_2, 0 °C, r.t., 2 h, 87%; (c1) KOH, r.t., 72 h, 83% (c2) BF_3–Et_2O, 100 °C, 6 h, 45%; (d) DMSO, I_2, 130 °C, 4 h, 80%; (e) pyridine HCl, 180 °C, 6.5 h, 88%.

(s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.93 (s, 1H, ArH), 6.06 (s, 1H, ArH), 14.03 (s, 1H, OH). IR ν_{max} (KBr/cm^{-1}): 3461 (OH), 1619(C=O).

2'-Hydroxy-3,4,4',6'-trimethoxychalcone (**6**): *Method (c1)*: A mixture of compound **3** (3.0 g, 0.015 mol), anisaldehyde **4** (2.98 g, 0.018 mol) and methanol (100 mL) was placed in a dry round-bottomed flask. Potassium hydroxide (15.0 g, 0.27 mol) was slowly added and the solution was stirred for 72 h at room temperature. Then the reaction mixture was neutralised to pH 7 with 37% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from EtOH to give compound **6** (4.28 g); yield 83%; yellow crystals, 149–151 °C (lit[17]. 154–156 °C) ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 14.29 (s, 1H, OH), 8.07 (d, J = 15.2 Hz, 1H), 7.75 (d, J = 15.6 Hz, 1H), 7.26 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 6.12 (d, J = 2.4 Hz, 1H), 5.96 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). IR ν_{max} (KBr/cm^{-1}): 3420 (OH), 1625 (C=O).

Method (c2): A mixture of 1,3,5-trimethoxybenzene (**1**) (0.8 g, 5 mmol) and 3,4-dimethoxycinnamic **5** (1.56 g, 7.5 mmol) in BF_3–Et_2O (15 mL) was heated at 100 °C for 4 h. After one night at room temperature, the red solid was filtered and dried to give red needles. A suspension of the needles in EtOH was heated at reflux for 2 h to give a clear orange solution. After the solution was decolourised with active charcoal and cooled to 0 °C, the precipitate was filtered and dried to give compound **6** (0.77 g); yield 45%, yellow crystals, 149–151 °C (lit[17]. 154–156 °C) ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 14.29 (s, 1H, OH), 8.07 (d, J = 15.2 Hz, 1H), 7.75 (d, J = 15.6 Hz, 1H), 7.26 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 6.12 (d, J = 2.4 Hz, 1H), 5.96 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3). IR ν_{max} (KBr/cm^{-1}): 3420 (OH), 1625 (C=O).

3',4',5,7 -Tetramethoxyflavone (**7**): Compound **6** (2.7 g, 8.0 mmol) and iodine (0.2 g, 0.8 mmol) in DMSO (25 mL) were heated at 130 °C for 4.5 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 to give compound **7** (2.2 g); yield 80%, white crystals, m.p. 192–194 °C (lit[7]. 190–194 °C) ^{1}H NMR (500 MHz, $CDCl_3$) (δ, ppm): 7.51 (dd, J = 2.1 Hz / 8.5 Hz, 1H), 7.32 (d, J = 2.1 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.61 (s, 1H), 6.56 (d, J = 2.3 Hz, 1H), 6.38 (d, J = 2.3 Hz, 1H), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). IR ν_{max} (KBr/cm^{-1}): 1637 (C=O), 1595 (C=C).

3',4',5,7-Tetrahydroxyflavone (**8**): A mixture of compound **7** (2.0 g, 5.8 mmol) and excess pyridine hydrochloride (6.9 g, 0.06 mol) was heated at 180 °C for 6.5 h under a N_2 atmosphere. The mixture was then cooled to room temperature and H_2O (100 mL) was added. The mixture was stirred for another 1 h. The precipitate was filtered off, washed with water and recrystallised from ethyl acetate to give compound **8** as yellow crystals (1.46 g); yield 88%, m.p. 326 °C (lit[18]. 328–330 °C) ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 12.97 (s, 1H, OH), 10.83 (s, 1H, OH), 9.91 (s, 1H, OH), 9.40 (s, 1H, OH), 7.40 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.66 (s, 1H), 6.43 (s, 1H), 6.18 (s, 1H). IR ν_{max} (KBr/cm^{-1}): 1655 (C=O), 1437 (C=C).

This work was supported by National Natural Science Foundation of China (NSFC) (No.21062009) and the Natural Science Foundation of Yunnan Province (No. 2011FZ059), which are gratefully acknowledged.

Received 9 November 2013; accepted 23 November 2013
Paper 1302277 doi: 10.3184/174751914X13867643876192
Published online: 8 January 2014

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