Modified syntheses of the dietary flavonoid luteolin

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Two novel syntheses of the flavone luteolin are described. In the first, 3,5-dimethoxyphenol was converted to 2-hydroxy-4,6-dimethoxyacetophenone and then by condensation with 3,4-dimethoxybenzaldehyde to 2′-hydroxy-3,4,4′,6′-tetramethoxychalcone. In the second, the chalcone step was prepared in which 3,5-dimethoxyphenol was acylated with 3,4-dimethoxycinnamoyl chloride. The chalcone was then cyclised with iodine and demethylated with pyridine hydrochloride to form luteolin in 47% and 40% overall yield, respectively. Several disadvantages of previous syntheses like long reaction time, harsh reaction conditions and low overall yield have been overcome.

Keywords: luteolin, 3,5-dimethoxyphenol, 3,4-dimethoxybenzaldehyde, 3,4-dimethoxycinnamoyl chloride, chalcone

Luteolin (3′,4′,5,7-tetrahydroxyflavone, see Fig. 1) is a widespread naturally occurring dietary flavonoid[1,2] and possesses a range of biological activities such as antioxidant,[3-4] antiallergic,[5] anti-inflammatory,[5] antibacterial,[6] antiviral,[7] anti-Alzheimer's Disease,[8] antimutagenic,[9] anti-angiogenesis,[10] anti-chikungunya,[11] anticancer,[12-15] neuroprotective[16] and anti-amnesic properties.[17,18] Luteolin also has potential for effective treatment of liver fibrosis[19] and amelioration of the deleterious effects of diet-induced obesity[20] and protect against diabetes-induced retinal neurodegeneration.[21]

Consequently, numerous methods exist for the synthesis of luteolin. In 2010, Barontini *et al.*[22] described a synthesis of luteolin by treating 4′,5,7-trihydroxyflavone with 2-iodoxybenzoic acid to give a excellent yield of 95%. However, the key starting 4′,5,7-trihydroxyflavone could not be prepared easily and the hypervalent iodine oxidant was poorly accessible. It has also been prepared by other groups,[23-25] but most of these methods consist of long reaction times, low yields of the products, accompanying of the side products and the use of expensive and environmentally toxic reagents. As a result, a more concise synthesis of the natural product is desirable.

We have reported the synthesis of luteolin from 1,3,5-trimethoxybenzene using two routes in 47% and 32% yield, respectively.[26] As a continuation of our investigations on the synthesis of the bioactive natural flavonoids and their biological activities,[26,27-36] we have carried out further studies and we now report the preparation of luteolin **1** using easily available starting materials, and by an improved procedure with satisfactory yields.

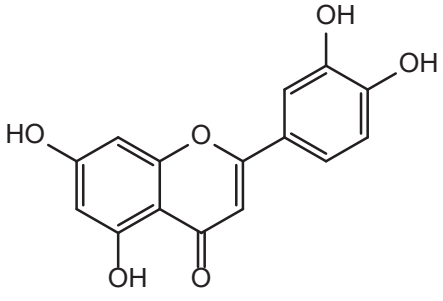

Fig. 1 Structure of luteolin.

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Results and discussion

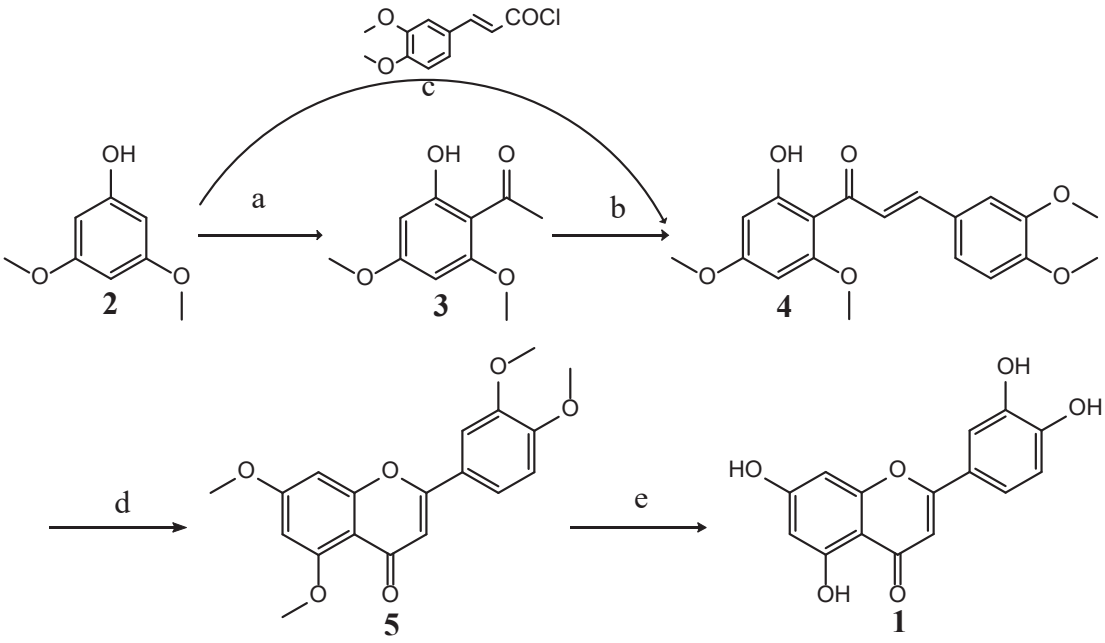
As shown in Scheme 1, the last two steps of the routes involved cyclisation of the key intermediate **4** and demethylation of the precursor **5**. The first approach gave **1** in four steps. The second route involved, instead of two steps for the preparation of the chalcone **4**, just a single step.

The initial step of the first route was the preparation of 2-hydroxy-4,6-dimethoxyacetophenone **3** which has been decribed previously.[34-36] Aldol condensation of **3** with 3,4-dimethoxybenzaldehyde (room temperature, 78 h) gave the chalcone **4** in decent yield (81%). The conversion of **4** to **5** was catalysed by iodine in dimethyl sulfoxide (120 °C, 5 h), and the resulting product **5** (82%) was demethylated with pyridine hydrochloride under an N_2 atmosphere (190 °C, 6 h) to give the target natural product **1** in good yield (89%). Although compound **1** had been prepared in four steps in fairly good overall yield (47%), 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 (55%) by treatment of the readily available 3,5-dimethoxyphenol **2** with freshly prepared 3,4-dimethoxycinnamoyl chloride in BF_3-Et_2O (reflux, 1.5 h) (step c). Although this synthetic pathway gave a lower yield of **1** (40%), the method was shorter and the workup was simplified.

In summary, two novel routes which used easily available starting materials and reagents for the synthesis of luteolin have been developed. The advantages of these synthetic pathways are improved procedures, shorter reaction time and higher yield. Futhermore, they are operationally simple, easy to workup and take place under mild reaction conditions. Compared to our previous work, we shortened procedures by selecting 3,5-dimethoxyphenol as starting material and raised the yield by replacing 3,4-dimethoxycinnamic acid with 3,4-dimethoxycinnamoyl chloride. 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 flavone.

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 FTIR instrument. Melting points were measured on a YRT-3



Scheme 1 Reagents and conditions:(a) $ZnCl_2$, CH_3COOH, 145 °C, 2 h, 79%; (b) 3,4-dimethoxybenzaldehyde, KOH, room temperature, 78 h, 81%; (c)3,4-dimethoxycinnamoyl chloride, $BF_3{\cdot}Et_2O$, reflux, 1.5 h, 55%; (d) I_2, DMSO, 120 °C, 5 h, 82%; (e) Py·HCl, 190 °C, 6 h, 89%.

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 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-3,4,4′,6′-tetramethoxychalcone (***4***)*

(Scheme 1, *Step b*): Potassium hydroxide (11.2 g, 0.2 mol) was added to methanol (90 mL). After cooling to room temperature, compound **3** (2.0 g, 0.01 mol) and 3,4-dimethoxybenzaldehyde (1.8 g, 0.011 mol) were added to the solution. It was stirred for 78 h at room temperature. Then the mixture was acidified to pH 5 with 10% aqueous HCl. The precipitate was filtered off, washed with water and recrystallised from ethanol to give yellow crystals of compound **4** (2.8 g, yield 81%).

(Scheme 1, *Step c*): A mixture of 3,5-dimethoxyphenol **2** (3.1 g, 0.02 mol) and 3,4-dimethoxycinnamoyl chloride (5.0 g, 0.022 mol) was dissolved in BF_3–Et_2O complex (20 mL) and heated to reflux for 1.5 h, and then quenched with water (100 mL). Filtration and recrystallisation from ethanol gave yellow crystals of compound **4** (3.8 g, 55%); m.p. 154–156 °C (lit.[37] 154–155 °C); IR ν_{max} (KBr/cm^{-1}): 3516 (OH), 1684 (C=O), 1625 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 14.17(s, 1H, OH), 7.68 (d, *J* = 15.5 Hz, 1H), 7.32 (d, *J* = 15.6 Hz, 1H), 7.23 (dd, *J* = 8.3,1.9 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.96 (d, *J* = 2.3 Hz, 1H), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); MS (*m/z*): 345 $[M+H]^+$.

3′,4′,5,7-Tetramethoxyflavone (**5**): Compound **4** (3.4 g, 0.01mol) and iodine (0.3 g) in DMSO (20 mL) were stirred at 120 °C for 5 h and then 2.0% $NaHSO_3$ (50 mL) was added to remove the iodine. The precipitate was filtered off, washed with water and recrystallised from ethanol to give white crystals of compound **5** (2.8 g, 82%); m.p. 192–193 °C (lit.[38] 193 °C); IR ν_{max} (KBr/cm^{-1}): 1647 (C=O), 1632 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 7.52 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.63 (s, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 3.98 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); MS (*m/z*): 343 $[M+H]^+$.

Luteolin (**1**): A mixture of compound **5** (1.7 g, 5 mmol) and excess pyridine hydrochloride (5.8 g, 0.05 mol) was heated at 190 °C for 6 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 and cooled to approximately 0 °C for several hours. The precipitate was filtered off, washed with water and recrystallised from ethyl acetate to give compound **1** as yellow crystals (1.3 g, 89%); m.p. 329–330 °C (lit.[39] 328–330 °C); IR ν_{max} (KBr/cm^{-1}): 3490 (OH), 1664 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 12.95 (s, 1H, OH), 10.86 (s, 1H, OH), 9.95 (s, 1H, OH), 9.44 (s, 1H, OH), 7.43–7.41 (m, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.68 (s, 1H), 6.44 (d, *J* = 1.9 Hz, 1H), 6.19 (d, *J* = 1.9 Hz, 1H); MS (*m/z*): 309 $[M+Na]^+$.

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