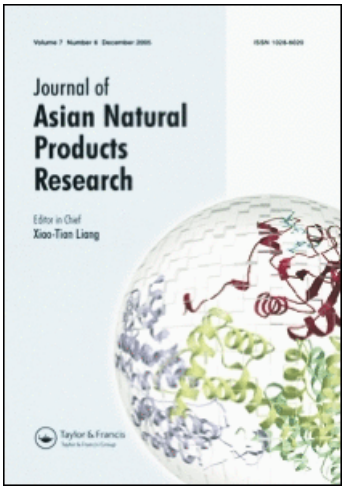

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Total synthesis of baicalein

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ORIGINAL ARTICLE

Total synthesis of baicalein

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In this paper, a simple and novel synthesis of baicalein is described. This transformation features the novel synthesis of helilandin B and a different way to demethylate. The overall yield of 59% is acceptable.

Keywords: baicalein; helilandin B; demethylate; synthesis

1. Introduction

Baicalein (5,6,7-trihydroxyflavone, **1**; Scheme 1) is a flavone with certain pharmacological and biological activities such as antihypertensive effect [1], decreasing LDH release of the cultured neuron [2], activation of gene estrogenicity [3], and so on. Until now, several synthetic routes have been reported. In 1973, Agasimundin and Siddappa [4] first reported a route to synthesize baicalein starting from 1-(2,4,6-trihydroxyphenyl)ethanone and 1-ethyl-3-phenyl-1,3-propanedione to get 6-acetyl-5,7-dihydroxyflavone, which was treated with H_2O_2 to give baicalein. In 2004, Shaw *et al.* [5] utilized the reaction of 3,4,5-trimethoxyphenol and cinnamoyl chloride to get helilandin B (**4**), and then treated with HBr–HOAc to obtain compound **1**. Furthermore, Zhang *et al.* [6] also reported a procedure to synthesize **1** from nitrogen-containing flavonoid by the Mannich reaction.

Herein, we report a novel and effective procedure to synthesize baicalein with a new preparation of **4** and a different way to demethylate.

2. Results and discussion

As shown in Scheme 2, the title compound (**1**) has been synthesized from 3,4,5-trimethoxyphenol (**2**) in four steps. First, compound **2** was acetylated to get 2-acetyl-3,4,5-trimethoxyphenol (**3**) by Fries rearrangement. Second, **3** is condensed with benzaldehyde to afford 2′-hydroxy-4′,5′,6′-tetramethoxychalcone (**4**). Third, 5,6,7-trimethoxyflavone (**5**) was acquired through cyclization. In the last step, **5** was treated with pyridine hydrochloride for demethylation to obtain baicalein (**1**) in good yield.

The efficiency of conversion from **2** to **3** was found to depend mainly on the amount of BF_3–Et_2O. When an excess amount of BF_3–Et_2O was used, an ideal transformation could be obtained even in a short reaction time.

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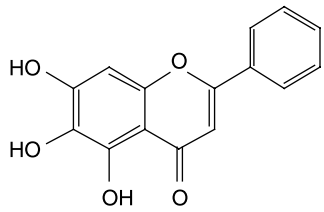

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Scheme 1. Structure of baicalein (**1**).

Optimization studies in the second step revealed that 3.0–3.8 eq. of KOH was not enough to achieve an ideal conversion. Especially, less than 3.5 eq. of KOH was observed to result in the worst yield and purity. As shown in Table 1, 4.0 eq. was eventually found to be the optimal value for this transformation.

In the cyclization, the yield and purity of compound **5** were determined depending on the number of equivalence of I_2. An amount of 0.22 eq. of iodine was optimal for the preparation of **5**. The optimization results are summarized in Table 2.

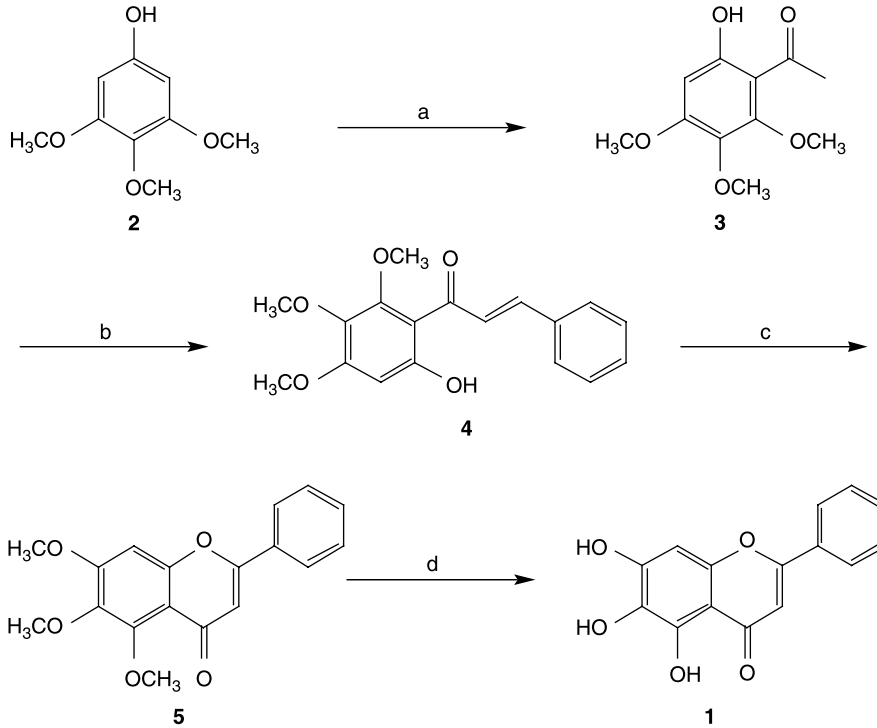
Demethylation in the last step mainly depended on the quantity of pyridine hydrochloride. In this study, the ideal equivalence of pyridine hydrochloride is found to be 9 (as shown in Table 3).

Finally, the total yield of compound **1**, i.e. 59% baicalein, has been obtained. Moreover, the synthesis of compound **4** was demonstrated as a convenient and efficient approach.

3. Experimental

3.1 General experimental procedure

Melting points were measured on a YRT-3 temp apparatus and are uncorrected. NMR spectra and MS data were recorded on a Bruker DRX 500 NMR spectrometer and a ZAB-2F mass spectrometer, respectively.



Scheme 2. The synthesis route of baicalein. Reagents and conditions: (a) acetic anhydride and BF_3–Et_2O, 60°C, 3 h, 86%; (b) KOH, 70 h, 88%; (c) I_2, DMSO, 100°C, 2.5 h, 93%; (d) pyridine hydrochloride, 190°C, 6.5 h, 85%.

Table 1. Quantification of KOH in the conversion of **3** to **4**.

Entry	Input **3** (mol)	KOH (eq.)	Time (h)	Yield (%)
1	0.2	3.0	70	76.5
2	0.2	3.3	70	78.2
3	0.2	3.5	70	79.9
4	0.2	3.8	70	85.3
5	*0.2*	*4.0*	*70*	*91.2*
6	*0.5*	*4.0*	*70*	*91.4*

Table 2. Quantification of I_2 in the conversion of **4** to **5**.

Entry	Input **4** (mol)	I_2 (eq.)	Yield (%)
1	0.1	0.15	85.3
2	0.1	0.17	86.4
3	0.1	0.20	84.6
4	*0.1*	*0.22*	*93.2*
5	0.1	0.30	90.1

Table 3. Quantification of pyridine hydrochloride in the conversion of **5** to **1**.

Entry	Input **5** (mol)	Pyridine hydrochloride (eq.)	Yield (%)
1	0.1	14	80.3
2	0.1	11	82.4
3	*0.1*	*9*	*85.3*

TLC was carried out on silica gel layers (Qingdao Haiyang Chemical Co., Ltd, Qingdao, China).

3.2 Synthesis procedure

3.2.1 2-Acetyl-3,4,5-trimethoxyphenol (3)

A dry round-bottomed flask charged with compound **2** (92 g, 0.5 mol), acetic anhydride (150 ml), and BF_3–Et_2O (5 ml) was heated at 60°C for 2 h, and then cooled to the ambient temperature. Subsequently, ethyl acetate (300 ml) was added and stirred for a minute. The mixture was kept in the refrigerator for 2 h. Then, it was filtered to get the cake which was poured into the solution of H_2O (400 ml) and ethanolamine (40 ml). The mixture was kept under stirring for 1 h and then extracted with ethyl acetate (300 ml). The extract was dried with anhydrous magnesium sulfate overnight and the solvent was evaporated to obtain compound **3** (97 g, 86%). ^{1}H NMR ($CDCl_3$): δ 13.43 (s, 1H), 6.22 (s, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 2.63 (s, 3H).

3.2.2 2′-Hydroxy-4′,5′,6′-tetramethoxychalcone (4)

A mixture of compound **3** (45.2 g, 0.2 mol), benzaldehyde (26.5 g, 0.25 mol), and methanol (300 ml) was charged into a dry round-bottomed flask. Potassium hydroxide (45 g, 0.8 mol) was slowly added and the solution was stirred for 70 h at room temperature. Then, diluted hydrochloric acid was added to make the pH to 6–7 to precipitate much yellow crystal. The reaction mixture was filtered and the cake was washed by water (200 ml). The solid was recrystallized from ethanol to give compound **4** (55 g, 88%); mp 103–105°C; ^{1}H NMR ($CDCl_3$): δ 13.80 (s, 1H), 8.00 (d, 1H, $J = 15.6$ Hz), 7.86 (d, 1H, $J = 15.6$ Hz), 7.67 (d, 2H, $J = 7.5$ Hz), 7.49–7.54 (m, 3H), 6.38 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H); MS (FAB+) *m/z*: 315 $[M+1]^+$.

3.2.3 5,6,7-Trimethoxyflavone (5)

A dry round-bottomed flask equipped with a reflux condenser was charged with compound **4** (31.4 g, 0.1 mol), DMSO (200 ml), and iodine (2.8 g, 0.22 mol), and heated at 100°C for 2.5 h. The mixture was then poured into sodium hydrogen sulfite solution (300 ml, 10%) and left to stand overnight. Then, the mixture was filtered and the cake was recrystallized from ethanol to give compound **5** as light yellow crystals (29 g, 93%); mp 164–165°C ([6] 165–167°C); ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 2H, $J = 5.0$ Hz),

7.49–7.54 (m, 3H), 6.84 (s, 1H), 6.70 (s, 1H), 3.86–3.97 (m, 9H).

*3.2.4 5,6,7-Trihydroxyflavone (baicalein, **1**)*

A three-necked round-bottomed flask equipped with a reflux condenser was charged with excess pyridine hydrochloride (102.6 g, 0.9 mol) and compound **5** (31.2 g, 0.1 mol) under N_2 atmosphere. The mixture was then heated at 190°C and refluxed for 6.5 h. The resultant hot, dark mixture was diluted with ethanol and poured into water (300 ml), and the reaction mixture was stirred for 1 h and then filtered. The solid so obtained was washed with water to give a yellow solid (**1**) (23 g, 85%); mp 263–266°C ([5] 264–265°C); ^{1}H NMR ($CDCl_3$): δ 12.63 (s, 1H), 11.84 (br, 1H), 10.39 (br, 1H), 8.04, 8.05 (d, 2H, $J = 7.5$ Hz), 7.55–7.59 (m, 3H), 6.92 (s, 1H), 6.61 (s, 1H); HR-ESI-TOF-MS *m/z*: 269.0456 $[M-H]^-$ (calcd for $C_{15}H_9O_5$, 269.0449).

4. Conclusion

In conclusion, this is an efficient, simple, and novel synthesis of baicalein. Relatively simple reaction procedure, utilization of cheap and readily available reagents, and ideal yields of products are some main advantages of the present approach.

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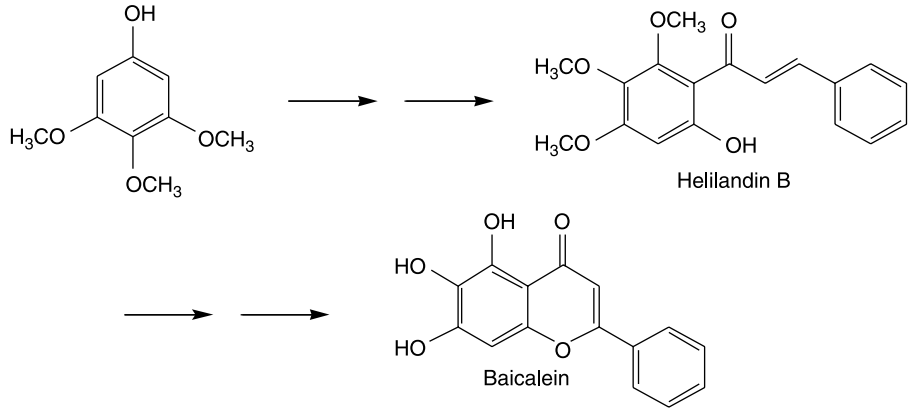

Preparation of baicalein through a modified process is described.

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