An efficient synthesis of 2-formyl-1,4,5,8-tetramethoxynaphthalene

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An improved synthetic method of 2-formyl-1,4,5,8-tetramethoxynaphthalene in 73% overall yield is described. This method has several advantages compared with the reported synthesis: first, the reactant is cheaper and the yield is higher; second, the reaction condition is milder and the reagent used is more friendly to environment; third, the work-up of each step is simpler; fourth, the protocol reported is more suitable for large-scale preparation.

Keywords: shikonin, 2-formyl-1,4,5,8-tetramethoxynaphthalene, synthesis, methylation

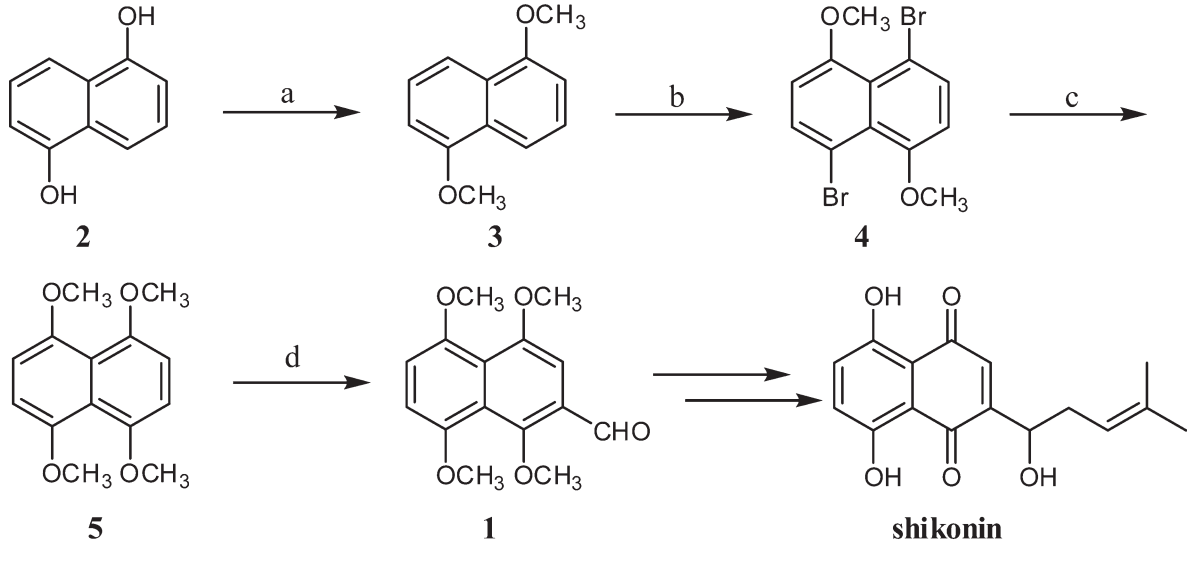
Shikonin, one of the major active components of the traditional Chinese medicine redroot gromwell, exhibits a wide variety of pharmacological effects, including anti-bacterial,[1] anti-inflammatory,[2] antiviral,[3] analgesic,[4] immunostimulatory,[5] angiostatic,[6] anti-thrombotic[7] and anti-tumour[8] activities. Furthermore, it is also a natural pigment which has been used in the food, cosmetics and dyeing industries.[9] Therefore, substantial quantities of shikonin are required. Most processes for the total synthesis of shikonin involve the reactant 2-formyl-1,4,5,8-tetramethoxynaphthalene **1** as a key intermediate. Although several synthetic routes of **1** have been reported,[10–13] most of these routes have drawbacks such as low-yield, expensive materials, high temperature, operational difficulties, and pollute the environment. It is, therefore, necessary to develop a new process. A convenient and efficient way to synthesise 2-formyl-1,4,5,8-tetramethoxynaphthalene is now reported using 1,5-dihydroxynaphthalene **2** as starting material (Scheme 1).

Result and discussion

A convenient and efficient method to synthesise 1,4,5,8-tetramethoxynaphthalene was developed. Compared with the method reported by Terada,[10] 1,5-dimethoxynaphthalene 3 was synthesised with increased yield from 80 to 98% and decreased reaction temperature from reflux to stirring at room temperature. Moreover, the work-up was simpler. Product **3** of adequate purity can be obtained by filtration without further recrystallisation and the acetonitrile used in this step can be recovered; When preparing 1,5-dibromo-4,8-dimethoxynaphthalene **4** according to Terada's method, it was found that the yield of this step in practice was very low (20–30%) and the toxic reagent CCl_4 and reactant Br_2 was used. In this study, NBS was used instead of Br_2 as a bromination reagent at low temperature affording a yield of 88%. The best ratio of 1,5-dimethoxynaphthalene **3** to NBS (1: 2.5) was established by the analysis of a series of experimental conditions. The reaction temperature of this step appeared to be very critical and should be carefully controlled. If not, some monobromo-substituent was produced and the yield decreased by 10–20%. The 1,4,5,8-tetramethoxynaphthalene **5** was obtained by refluxing with sodium methoxide (86%); Treatment of **5** with Vilsmeier reagent ($POCl_3$, DMF) gave 2-formyl-1,4,5,8-tetramethoxynaphthalene **1** in 99% yield.

Conclusion

An improved synthesis of 2-formyl-1,4,5,8-tetramethoxynaphthalene in 73% total yield is described. 1,5-Dimethoxynaphthalene was synthesised almost quantitatively under mild and friendly condition. This methylation method is also available for other similar preparations. This overall method has several advantages: first, the material and reactant is cheaper and the yield is higher; second, the reaction condition is milder and more friendly to environment, avoiding using toxic solvent



Scheme 1 a, $(CH_3)_2SO_4$, NaOH, $(C_4H_9)_4Br$, THF-H_2O, 98%; b, NBS, CH_3CN, 88%; c, CH_3ONa, CuI, DMF-CH_3OH, 86%; d, DMF, $POCl_3$, CH_2Cl_2, 99%.

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CCl_4 and reactant Br_2; third, the work-up of each step is simpler and the solvent can be recovered; fourth, the protocol reported in this paper is more suitable for large-scale preparation of 2-formyl-1,4,5,8-tetramethoxynaphthalene for total synthesis of shikonin and its derivatives.

Experimental

Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on XT34 binocular microscope (Beijing Tech Instrument Co., China). ^{1}H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, chemical shifts were reported in parts per million relative to tetramethylsilane. Splitting patterns were designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical shifts were reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ = 7.16 ppm). Analytical TLC and column chromatography were performed on silica GF254, and silica gel H60, respectively.

1,5-Dimethoxynaphthalene (**3**): Tetrabutylammonium bromide (1.6 g, 5 mmol), sodium dithionite (1 g, 5 mmol) sodium hydroxide (7.2 g, 180 mmol) were added to the solution of 1,5-dihydroxynaphthalene (12 g, 75 mmol) in THF-H_2O 150 mL (2:1) in portions under N_2. Then dimethyl sulfate (14.3 mL, 150 mmol) was added dropwise to the solution keeping the temperature below 30 °C. The resulting mixture was stirred at room temperature. After 4 h, the solid was collected by filtration to give 13.8 g yellow solid of **3** (98%). m.p. 183–185 °C, (lit.[10] 183–184 °C). ^{1}H NMR(CDCl3): δ 6.86 (s, 4H, ArH × 4), 3.75 (s, 12H, OCH_3 × 4).

1,5-Dibromo-4,8-dimethoxynaphthalene (**4**): A solution of N-bromosuccinimide (22.2 g, 125 mmol) in acetonitrile (150 mL) was added dropwise to a suspension of 1,5-dimethoxynaphthalene (9.4 g, 50 mmol) in acetonitrile (100 mL), which was cooled in a salt-ice bath. The resulting mixture was stirred at 10 °C under N_2 for 2 h. The resulting solid was collected by filtration, washed with methanol and then with petroleum ether to afford 15.2 g greenish powder of **4** (88%). m.p. 183–185 °C (lit.[14] 185–187 °C).

1,4,5,8-Tetramethoxynaphthalene (**5**): A mixture of 1,5-dibromo-4,8-dimethoxynaphthalene (11 g, 32 mmol), sodium methoxide (5.7 g, 106 mmol), copper (I) iodide (20 g, 106 mmol), N, N-dimethylformamide (150 mL) and methanol (150 mL) was refluxed for 36 h. The mixture was filtered when it was hot. The filtrate was poured into ice water and the resulting precipitate was filtered. The residue was recrystallised from ethyl acetate to afford 6.78 g white needles of **5** (86%). m.p. 166–167 °C (lit.[10] 167–168 °C). δ 6.86 (s, 4H, ArH × 4), 3.75(s, 12H, OCH_3 × 4).

2-Formyl-1,4,5,8-tetramethoxynaphthalene (**1**): A solution of 1,4,5,8-tetramethoxynaphthalene (6 g, 24.3 mmol) in chloroform (40 mL) was added to a mixture of phosphoryl chloride (18.2 g, 120.8 mmol) and N, N-dimethylformamide (8.8 g, 120.8 mmol) and the mixture was refluxed for 10 h. Evaporation of the solvent gave a residue. The residue was decomposed with ice water. The mixture was filtered and recrystallised from hexane to obtain 6.63 g yellow crystals of **1** (99%), m.p. 124–125 °C (lit.[10] 124–125.5 °C). δ 10.56 (s, 1H, ArCHO), 7.16 (s, 1H, ArH), 7.01 (d, J = 7.8, 1H, ArH), 6.93 (d, J = 7.4, 1H, ArH), 3.99 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3).

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