A convenient synthesis of 2-formyl-1,4,5,8-tetramethoxynaphthalene

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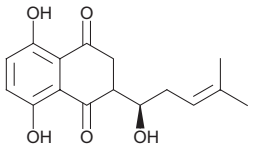
A convenient and concise synthesis of 1,4,5,8-tetramethoxynaphthalene can be achieved by methylation of 2,3-dihydronaphthazarin with dimethylsulfate in the presence of phase transfer catalytic in 90.3% yield, then formylation of 1,4,5,8-tetramethoxynaphthalene can afford 2-formyl-1,4,5,8-tetramethoxynaphthalene in 96.2% yield.

Keywords: phase transfer catalytic, 2-formyl-1,4,5,8-tetramethoxy naphthalene, formylation

2-Formyl-1,4,5,8-tetramethoxynaphthalene **1** was a key intermediate in the total synthesis of shikonin **2**, and alkannin **3**.[1] Shikonin and its derivatives have been reported to have antitumor,[2] anti-inflammatory,[3] antibacterial,[4] immunostimulatory,[5] angiostatic[6] and antithrombotic[7] activities, and can be used as raw material for cosmetics.[8] Several syntheses of 2-formyl-1,4,5,8-tetramethoxynaphthalene have been reported in the literature.[8] Most of methods are of low-yield and, therefore, impractical. In the past, we have reported a synthesis of 2-formyl-1,4,5,8-tetramethoxy-naphthalene utilising naphthazarin,[9] in this paper, we report a convenient and efficient synthesis of 2-formyl-1,4,5,8-tetramethoxy-naphthalene utilising 2,3-dihydronaphthazarin **5** as starting material.



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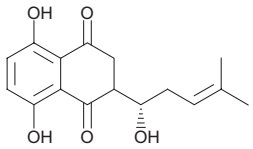

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Results and discussion

Recently we studied the total synthesis of shikonin, and found that the efficient synthesis of 1,4,5,8-tetramethoxynaphthalene **6** with 2,3-dihydronaphthazarin in the presence of a phase transfer catalyst afforded product **1** in very high yields. Meantime, we optimised the synthetic condition of 2,3-dihydronaphthazarin and formylation on a large-scale according to the reported procedure.[1,10,12]

Tetrabutylammonium bromide was used as a phase transfer catalyst. One-fifteenth molar equivalent of tetrabutyl-ammonium bromide was enough for 2,3-dihydronaphthazarin to proceed completely. Dimethyl sulfate and sodium hydroxide were in excess. The methylation reaction was monitored by TLC and took about 10–18 h at 45–50°C. The methylation could be carried out at room temperature, but the reaction time could exceed 24 hours. It can be seen that the yields of methylation were very high under the given reaction conditions. It was found that vigorous stirring was required for the successful methylation. The 1,4,5,8-tetramethoxynaphthalene could be obtained by simple Buchner filtration of the final water suspension mixture, and recrystallised from tetrahydrofuran. Treatment of **6** with Vilsmeier reagent ($POCl_3$,DMF) gave 2-formyl-1,4,5,8-tetramethoxy-naphthalene **1** in 96.2% yield.

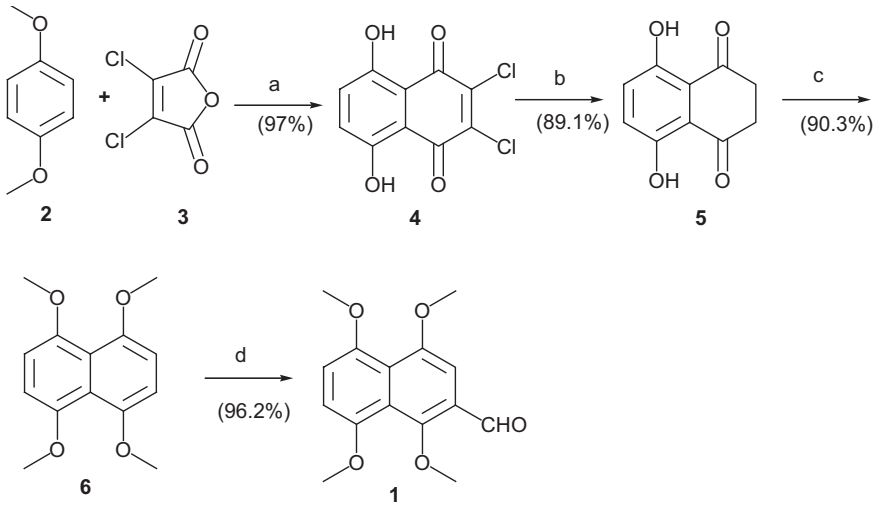
Conclusions

The present contribution describes the use of tetrabutylammonium bromide as an efficient catalyst for the methylation reaction of 2,3-dihydronaphthazarin. The current method presents a very promising synthetic process for 1,4,5,8-tetramethoxynaphthalene because of the following advantages: (1) very high yield, (2) simplicity of process, (3) simplicity of product purification, (4) recycling of solvent, and (5) that the protocol reported in this paper can be easily developed into large-scale preparation of 2-formyl-1,4,5,8-tetramethoxynaphthalene for total syntheses of shikonin and its derivatives.

Experimental

General

Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT34 binocular microscope (Beijing Tech



Scheme 1 a, $AlCl_3$, NaCl; b, $SnCl_2$, HCl; c, $(CH_3)_2SO_4$, $(C_4H_9)4NBr$, THF; d, DMF, $POCl_3$, $CHCl_3$

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Instrument Co., China) and were not corrected. ^{1}H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, chemical shifts (δ) 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 gel GF254, and silica gel H60, respectively.

2,3-Dichloronaphthazarin (**4**): This compound was prepared in 97% yield from dichloromaleic anhydride and 1,4-dimethoxybenzene according to the method described by Huor and Brassard.[10] Crystallisation from petrol ether (b.p. 90–120°C) gave the quinone m.p. 196.5–198.5°C (lit. m.p.198–199°C [10]).

2,3-Dihydronaphthazarin (**5**):[11] A mixture of 2,3-dichloronaphthazarin (13.1 g, 50 mmol), $SnCl_2{\cdot}H_2O$ (27.1 g, 120 mmol), 750 ml 4M HCl was refluxed for 5 h. The green solution was formed at 30 min of reflux. The reaction was monitored by TLC. After the reaction was completed, the mixture was filtered while heated and the filtrate was cooled to room temperature and filtered to give a green crystal 2,3-dihydronaphthazarin. (8.56 g, 89.1%), m.p.147–149°C (lit. m.p.148–151°C[11]).

1,4,5,8-Tetramethoxynaphthalene (**6**): A mixture of 2,3-dihydronaphthazarin (14.4 g, 75 mmol), tetrabutylammonium bromide (1.61 g, 5 mmol), 180 ml tetrahydrofuran (THF), 180 ml water was stirred at room temperature. After 10 min, the solution was alternatively treated with sodium hydroxide (15.0 g, 375 mmol) in water (30 ml) and dimethyl sulfate (22.5 g, 180 mmol) at 45–50°C for 3 h. The above-mentioned amounts of aqueous sodium hydroxide and dimethyl sulfate were again added to the solution; and the mixture was then stirred at 45–50°C for 10 h. The reaction was monitored by TLC. After the reaction was completed, the solvent, tetrahydrofuran, was evaporated. 1,4,5,8-tetramethoxynaphthalene was then recovered by filtration and recrystallised from tetrahydrofuran as colourless scale-like crystals (16.8 g, 90.3%), m.p. 167–168.5°C (lit. m.p. 167–168°C[1]). ^{1}H NMR ($CDCl_3$): δ = 6.84 (s,4H,ArH × 4), 3.89 (s, 12H,OCH_3 × 4).

2-Formyl-1,4,5,8-tetramethoxynaphthalene (**1**): A solution of 1,4,5,8-tetramethoxynaphthalene (16.8 g, 67.7 mmol) in chloroform (120 ml) was added to a mixture of phosphoryl chloride (69.0 g, 407 mmol) and N,N-dimethylfrmamide (29.7 g, 407 mmol) and the mixture was refluxed for 6 h. Evaporation of the solvent gave a residue. The residue was decomposed with ice water. 2-formyl-1,4,5,8-tetramethoxynaphthalene was filtered and recrystallised from hexane as yellow crystals (18.0 g, 96.2%), m.p. 124.5–125.5°C (lit. m.p. 124–125.5°C[1]). ^{1}H NMR ($CDCl_3$): δ 10.56 (s, 1H, ArCHO), 7.20 (s, 1H, ArH), 7.04 (d, *J* = 7.9, 1H, ArH), 6.93(d, *J* = 7.6, 1H, ArH), 3.99, 3.98, 3.92, 3.91(each s, 3H, OCH_3).

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