A convenient synthesis of 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene

Ai-Hong Zhao, De-Feng Xu, Wen Zhuo, Zhen Rao and Shao-Shun Li*

School of Pharmacy, Shanghai Jiaotong University, Minghang, Shanghai 200240, P.R.China

2,3-Dihydronaphazarin was prepared from 1,4-dimethoxybenzene and dichloromaleic anhydride. Reaction with bromochloromethane gave 1,8:4,5-bis(methylenedioxy)naphthalene which with NBS, gave 2-bromo-1,8:4,5-bis-(methylenedioxy)naphthalene. Reaction of the Grignard derivative with DMF afforded 2-formyl-1,8:4,5-bis(methylene-dioxy)naphthalene. This method had several advantages compared with the reported synthesis, including fewer steps, milder condition and higher yields.

Keywords: 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene, Grignard reagent, shikonin, intermediate, synthesis

Shikonin **8**, the active ingredient of the traditional Chinese medicine redroot gromwell, exhibits a wide variety of pharmacological effects, including antibacterial, anti-inflammatory, antivirus and anti-tumor activity.[1] Shikonin is a natural pigment which has been used in the food, cosmetics, printing and dyeing industries. Substantial quantities of shikonin are therefore required. The total synthesis of shikonin involves a key intermediate 2-formyl-1,4,5,8-tetramethoxy-naphthalene, which involves a tedious preparation.[2,3] Progress was made by Nicolaou *et al*. who used a naphthazarin intermediate protected by a methylene in the total synthesis of shikonin.[4,5]

The naphthazarin intermediate reported by Nicolaou was synthesised by the reaction of DMF with an organolithium compound obtained by the reaction of 2-bromo-1,8:4,5-bis(methylenedioxy)naphthalene and n-butylithium at –78°C. However, the harsh reaction condition and expensive reagent made it difficult to use this in multigram preparations. Kim has reported that[5] the intermediate **1** could be obtained from a formylation of 1,8:4,5-bis(methylenedioxy)naphthalene with Vilsmeier ($POCl_3$ and DMF) in $CHCl_3$. However we found that this reaction did not proceed smoothly. A new route based on the literature was designed as follows.

2,3-dihydronaphazarin **5** was obtained from 1,4-dimethoxybenzene and dichloromaleic anhydride, by Friedel–Crafts condensation and reduction. Compound **5** was then protected by methylene groups using bromochloromethane and reacted with NBS to give **6**. This was transformed into a Grignard reagent, and treated with DMF to afford the important intermediate 2-formyl-1,8:4,5-bis (methylenedioxy) naphthalene for the synthesis of shikonin **1**. This method had several advantages compared with the synthesis reported including fewer steps, mild condition and high yields. The overall yield was 39.9% based on **2**.

Experimental

General

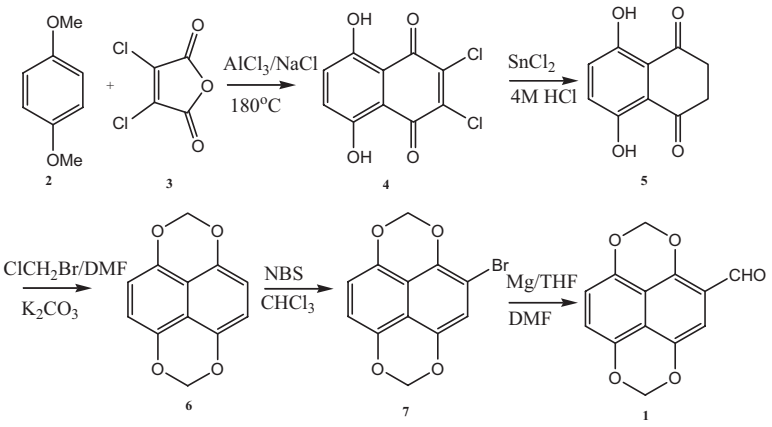
Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. ^{1}H NMR spectra were recorded on Mercuryplus 400 (300 MHz) spectrometer, 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 98.2% yield from dichloromaleic anhydride and 1,4-dimethoxybenzene according to the method described by Hour and Brasard.[6] Crystallisation fom petrolroleum ether gave the quinone m.p. 197–199°C (lit.[6] yield 97% m.p. 198-199°C).

2,3-Dihydronaphazarin (**5**): A mixture of 2, 3-dichloronaphthazarin (5.2 g, 0.02 mol), $SnCl_2.H_2O$ (31.2 g, 0.14 mol), 300 ml 4M HCl was refluxed for 5 h. The green solution was formed after 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 **5** (3.4 g, 89.1%), m.p. 147–149°C (lit.[7] yield 73% m.p. 148–151°C).

1,8:4,5-Bis(methylenedioxy)naphthalene (**6**): To a solution of 2,3-dihydronaphazarin **5** (2.0 g, 10.4 mmol) and dry K_2CO_3 (7.3 g, 52.9 mmol) in DMF (100 ml), bromochloromethane (3.3 g, 25.5 mol) was added dropwise under N_2. The reaction mixture was stirred for 24 h at 80–85°C. The solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, dried with $MgSO_4$ and recrystallised with petroleum ether to give white crystals **6** (1.61 g, 72.2%). m.p.149–151°C. ^{1}H NMR ($CDCl_3$): δ = 6.83 (s, 4H, ArH × 4), 5.58 (s,4H, –OCH_2O- × 2). (lit.[5] m.p. 154–156°C, ^{1}H NMR ($CDCl_3$): δ = 6.8 (s, 4H), 5.5 (s,4H)).

2-Bromo-1,8:4,5-bis(methylenedioxy)naphthalene (**7**):[8] NBS (1.9 g, 11.9 mol) was added. To 1,8:4,5-bis(methylenedioxy)naphthalene **6** (2.2 g, 11.5 mmol) in $CHCl_3$ (100 ml), The reaction mixture was



Scheme 1

* Correspondent. E-mail: ssli@sjtu.edu.cn

stirred at room temperature for 24 h. Then the solution was washed with 10% KOH (100 ml) and water (200 ml × 3), dried over anhydrous $MgSO_4$. and then evaporated to dryness. The residue was crystallised with isopropanol to give the white crystals **7** (2.65 g, 88.2%) m.p. 167–168°C. ^{1}H NMR ($CDCl_3$): δ = 6.84 (s, 1H, ArH), 6.82 (d, *J* = 3.6, 1H, ArH), 6.82 (d, *J* = 3.6, 1H, ArH), 5.53 (s, 2H, OCH_2O), 5.52 (s, 2H, OCH_2O).

2-Formyl-1,8:4,5-bis(methylenedioxy)naphthalene (**1**): To the mixture of Mg (240 mg, 10 mmol) and I_2 which was heated and activated for 1 hr in anhydrous THF (30 ml), the solution of 2-bromo-1,8:4,5-bis(methylenedioxy)naphthalene (200 mg, 0.68 mmol) in THF (10 ml) was added dropwise. After 3 h, DMF (10 ml) was added and the reaction mixtue was stirred for 8 h. Then the solution was hydrolysed with aq. NH_4Cl (15 ml) and extracted by ethyl acetate (50 ml × 3). The organic phase was dried by $MgSO_4$ and condensed. The residue was crystallised with isopropanol to give light crystal **1** (117 mg, 71.2%). m.p. 190–191°C. ^{1}H NMR($CDCl_3$): δ = 10.52 (s, 1H, ArCHO), 7.25 (s, 1H, ArH), 7.03 (d, *J* = 7.6, 1 H, ArH), 6.95 (d, *J* = 7.6, 1H, ArH), 5.63 (s, 2H, OCH_2O), 5.51 (s, 2H, OCH_2O). (lit.[5] m.p. 184°C, ^{1}H NMR($CDCl_3$): δ = 10.52 (s, 1H), 7.25 (s, 1H), 7.04 (d, *J* = 8.34, 1 H), 6.96 (d, *J* = 8.34, 1H), 5.64 (s, 2H), 5.52 (s, 2H)).

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