A convenient and efficient synthesis of naphthazarin

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A convenient and efficient synthetic method of the important intermediate naphthazarin is presented starting from 1, 4, 5, 8-tetramethoxynaphthalene in an overall yield of 87%. Compared with the reported synthesis, this method has several advantages. Firstly, the reaction conditions are milder; secondly, the workup of each step is simpler and the yield is considerably higher; thirdly, all the reactions involved in the method are more suitable for large-scale preparations.

Keywords: naphthazarin, 1, 4, 5, 8-tetramethoxynaphthalene, synthesis

Naphthazarin (**1**), which is widely distributed in nature, has been used as a key intermediate for the construction of several pharmacologically active compounds.[1] It is a useful precursor for the syntheses of several natural products such as 2-hydroxyaklavinone,[2] 6-demethoxyaustocortirubin,[3] shikonin/alkannin and their derivatives[4,5]. It also acts as a chelating ligand that provides a rigid framework for the metal centre and might serve for a study of the oligomeric nature of metal alkoxides, as polyatomic titanium species, which are used for Lewis acids reagents and as catalysts for organic stereoselective synthesis.[6] More importantly, naphthazarin and its derivatives display various biological activities such as antifungal,[7] antibacterial,[8] anti-parasite[9] and inducing apoptosis activities.[10]

Naphthazarin has been prepared by several methods. Most approaches were based on the Friedel–Crafts cycloacylation of hydroquinones with dichloro- or dibromomaleic anhydrides and the subsequent reductive dehalogenation of the corresponding halo-substituted adducts.[11~14] Nevertheless, there were some serious disadvantages to these methods such as very low and poorly reproducible yields, drastic reaction conditions and troublesome purification. It was helpful if hydroquinone was replaced with 1,4-dimethoxybenzene, but it was found that the subsequent demethylation was inconvenient[15]. Demethylation using Lewis acids such as aluminium chloride, boron tribromide *etc.* was accompanied by side reactions. Silver (II) oxide-nitric acid as a demethylation agent was not pleasant with poor yields, costly reactants and was environmentally unsatisfactory.[16,17] In spite of the excellent experimental conditions and good yields, the electrochemical oxidation–deprotection demethylation of 1, 4, 5, 8-tetramethoxynaphthalene derivatives was confined to a microreaction.[18] Hence it was necessary to develop a convenient and efficient method favourable for the large-scale preparation of naphthazarin.

Recently, an efficient synthesis of 1, 4, 5, 8-tetramethoxynaphthalene from 1, 5-naphthalediol in bulk has been proposed by our group in 74% overall yield.[19] Inspired by this result, we have developed an efficient route to synthesize naphthazarin using 1, 4, 5, 8-tetremethoxynaphthalene as starting materials *via* four-step conventional reactions with the yield of 87%. A crucial step rested on the improvement of demethylation of the 5, 8-dimethoxynaphthoquinone bypassing the use of silver (II) oxide–nitric acid.

Results and discussion

Our synthetic approach, depicted in Scheme 1, began with 1, 4, 5, 8-tetramethoxy- naphthalene **2**, which was oxidized and demethylated to generate naphthoquinone **3** with cerium ammonium (IV) nitrate (CAN) in acetonitrile and several drops of water at room temperature in 98% isolated yield. The amount of water has a significant influence on the yield of naphthoquinone **3**, which has a high water solubility and is not easily separated by the reported method[20]. Subsequent reduction and acylation of **3** with zinc powder in the presence of excess acetic anhydride, triethylamine and catalytic amounts of 4-dimethylaminopyridine (DMAP) afforded the pale-yellow crystal of **4** in 91% yield. Many attempts to prepare the compound **4** were made using different reductive and acylating agents,but the results were unsatisfactory. Afterwards the acylated **4** was converted into the deep yellow compound **5** in a yield of 99% using the same demethylation method as 1, 4, 5, 8-tetramethoxynaphthalene **2**. The product was transformed into the title compound **1** in a high yield of 98% by hydrolysis. Therefore, although our synthetic route to the preparation of naphthazarin involves a four-step reaction sequence, the total yield reached 87% in terms of compound **2**. Furthermore, the workup of each step in the method is very simple.

In summary, we have developed a novel and efficient synthetic method suitable for the large-scale preparation of naphthazarin. This route has several advantages: firstly, the reaction conditions are mild; secondly, the workup of each step is simple and the yield is very high.

Experimental

Reagents and solvents were obtained from commercial supplies. Solvents were dried and purified using standard techniques. All reactions involving air or moisture sensitive or intermediates were carried out under nitrogen. Melting points were determined on a SGW X-4 micromelting point apparatus and are uncorrected. NMR spectra were recorded on Varian Mercury-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C), chemical shifts of ^{1}H and ^{13}C spectra were recorded with tetramethylsilane as internal standard. Mass spectra were recorded on a Shimadzu LCMS-2010EV mass spectrometer. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemical Factory.

5,8-Dimethoxynaphthalene-1,4-dione (**3**): Ceric ammonium nitrate (CAN) (32.9 g, 0.06 mol) was added in portions to a stirred solution of **2** (4.96 g, 0.02 mol) in acetonitrile (50 mL) at room temperature, and several drops of water were dropwise added, and stirred for additional 30 min, and then diluted with ethyl acetate (40 mL). The resulting reaction mixtures were concentrated to remove acetonitrile and ethyl acetate in *vacuo*, and the residue was dissolved with ethyl acetate (80 mL) again, and then filtrated. The filtrate was concentrated and re-crystallized with ether to provide 4.27 g of **3** (98%) as the red solid. m.p. 156–157 °C, (lit[21]. m.p. 157 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 2H), 6.77 (s, 2H), 3.95 (s, 6H). ESI-MS: 241.40 $(M+Na)^+$.

1,4- Diacetoxy-5,8-dimethoxynaphthalene (**4**): To a mixture of **3** (5.25 g, 0.025 mol), Ac_2O (12.5 mL), and Et_3N (2.5 mL) was added DMAP (60 mg, 0.5 mmol), the mixture was stirred for 1 h at room temperature. Afterwards zinc powder activated with HCl was added (16.25 g, 0.25 mol) in portions. After being stirred overnight, the mixture was poured into ice water and then extracted with ethyl

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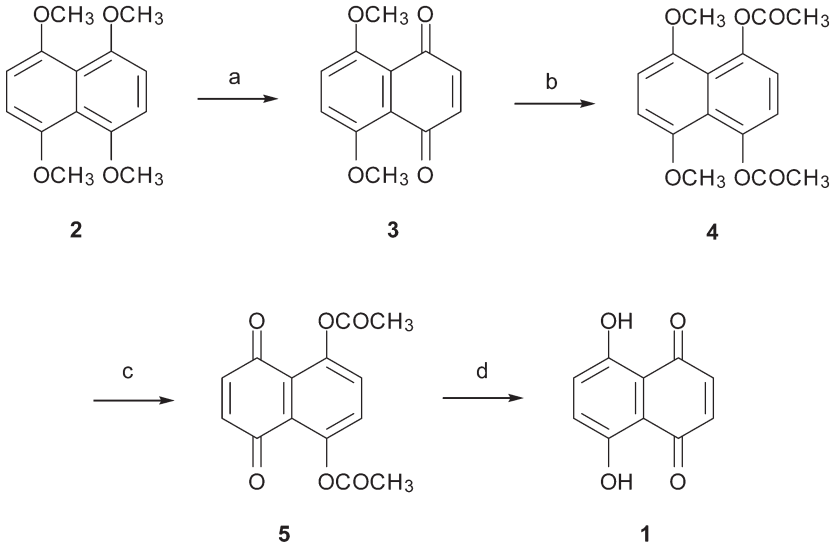

Scheme 1 a, CAN, CH_3CN, r. t., 98%; b, Zn, Ac_2O, $(Et)_3N$, DMAP, r. t. 91%; c, CAN, CH_3CN, r. t., 99%; d, 1 mol/L NaOH, 10% HCl, r.t., 98%.

acetate (80 mL). The organic layer was washed with aqueous $NaHCO_3$, water and brine respectively, and dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was re-crystallised from ether to give 6.92 g (91%) of **4** as pale-yellow crystals. m.p. 127–128 °C, (lit. m.p. 128 °C[22]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (s, 2H), 6.79 (s, 2H), 3.87 (s, 6H), 2.46 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.4, 169.4, 147.8, 138.7, 131.2, 124.5, 76.8, 21.2. ESI-MS: 327.28 $(M+Na)^+$.

1,4- Diacetoxy-5,8-dioxo-5,8-dihydronaphthalene (**5**): Compound **4** (6.08 g, 0.02 mol) was carried out according to the same procedure as compound **3**, and the residue was re-crystallised from ether to afford 5.43 g of **5** (99%) as the deep-yellow solid. m.p. 190–191 °C (lit. m.p. 192 °C[23]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 2H), 6.80 (s, 2H), 2.46 (s, 6H). ESI-MS: 297.22 $(M+Na)^+$.

Naphthazarin (**1**): Hydrolysis of **5** (5.48 g, 0.02 mol) in 1 mol/L sodium hydroxide (0.4 L) was performed with stirring at room temperature for 2 h under a nitrogen atmosphere, and acidified with 10% HCl until the color of the reaction solution changed to red, and then extracted with ethyl acetate (40 mL ×2). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was re-crystallised from petroleum ether or n-hexane to afford 3.72 g of **1** as the purple-red solid in 98% yield, m.p. 232–234 °C (lit. m.p. 234 °C[14]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.41 (s, 2H), 7.14 (s, 4H).

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