An efficient improvement on total synthesis of shikonin

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The problem associated with electrolytic deprotection, which is a concern in the total synthesis of shikonin, is solved by the addition of Cu^{2+} to the electrolysis system. The improvement has three advantages: first, it practically increased the yield from 40 to 85%; second, the isolation of shikonin became much easier. Third, the reaction time was significantly shortened.

Keywords: anodic oxidation, shikonin, electrolysis, deprotection

Shikonin, the major component of the traditional Chinese medicine redroot gromwell, exhibits a wide variety of pharmaceutical effects, including antibacterial,[1] anti-inflammatory,[2] analgesic[3] and anti-tumour[4] activities. Furthermore, it can also be used in food, cosmetics and dyes.[5] Because of the high medical and industrial value, it is necessary to devise an efficient synthesis of shikonin.

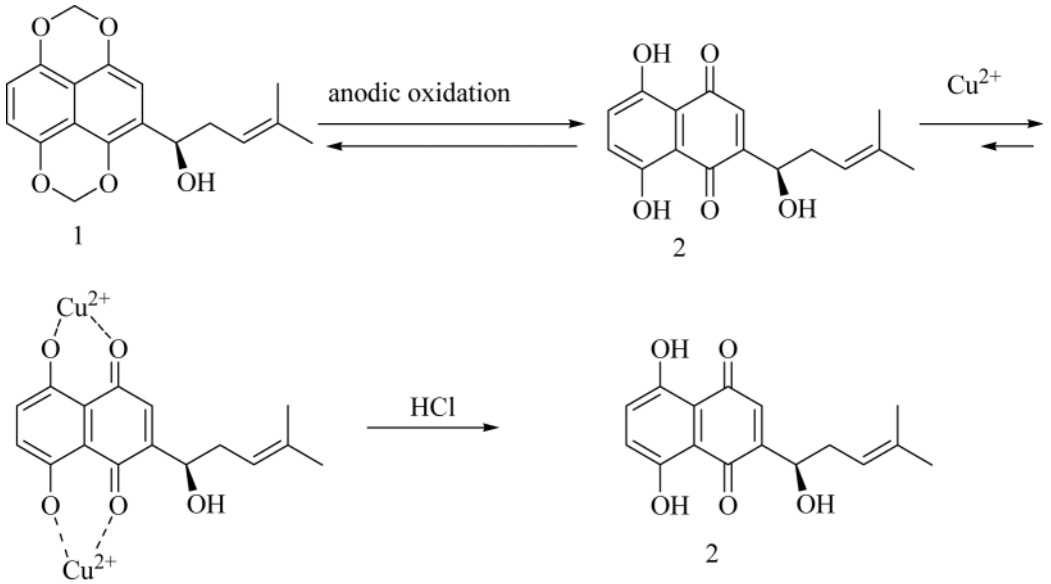
Most total syntheses[6,7] of shikonin have been achieved through the use of 2-formyl-1, 4, 5, 8-tetramethoxynaphthalene bearing a methyl-protected naphthazarin core. Those routes involve tedious steps and costly reagents. Moreover, the poor yield of less than 20% in the deprotection step makes it impractical for synthesis of shikonin in quantity.

To solve the problem, the Nicolaou group reported a new strategy[8] which introduced the methylene protecting group for the naphthazarin core. The total synthesis utilised commercially viable reagents and had fewer steps. More importantly, the protecting group could be cleaved by a mild anodic oxidation in the last step. The deprotection was performed with a simple experimental set-up and much better yield (80% yield at *ca* 50% conversion).

However, there was a big problem unsolved according to Nicolaou's report: at less than 50% conversion, TLC showed clean conversion to the desired product, and side products began to appear as the reaction proceeded to higher conversion. Indeed, our experiment confirmed the report that when the conversion was over 50%, side products began to appear, and meanwhile the reactant **1** and product **2** decreased simultaneously along with the accumulation of side product. When the reactant was exhausted, the desired product nearly disappeared. However, it is impractical to isolate the product at 50% conversion because it virtually cuts the yield of 80% in half; second it is difficult to isolate the product by column chromatography since the polarities of shikonin and its precursor were similar. Therefore, it is necessary to develop a method which makes the reaction complete and the product stable.

To achieve the aim, a series of experiments were devised. At the beginning, variants like voltage control and electrolyte concentration were taken into consideration. But the results were disappointing in that increasing or decreasing the voltage or electrolyte concentration changes the speed of reaction and side-reactions at the same time. It turned out that the when the reactant was exhausted, little desired product remained.

The reason why this attempt failed was that the product shikonin was unstable under electrolysis conditions. If we want the reactant used up and the product to be stable in the reaction, a solution must be found to preserve the product *in situ*. According to Papageorgious's patent[9], Cu^{2+} was used to complex shikonin when extracting it from a plant. Inspired by this, it was devised that Cu^{2+} could be added to the electrolysis system to preserve shikonin. To our satisfaction, the expected result was achieved. $Cu(OAc)_2$ was added to the reaction system using the Nicolaou-suggested experimental set-up: an undivided cell with graphite electrodes, a constant external voltage across the cell (3V), 50% aqueous acetonitrile as solvent, and 1M $LiClO_4$ as electrolyte. The reaction proceeded smoothly till the disappearance of reactant. The mixture turned red soon after the addition of 1M HCl. After work-up and chromatography, shikonin **2** was obtained in 85% yield with



Scheme 1

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total conversion of reactant. More interestingly, the reaction time (100% conversion) was shortened from 10h to 3h. The reason could be that the strong affinity between shikonin and Cu^{2+} made the electrolysis reaction equilibrium shift toward the right. Once shikonin emerged in the electrolysis, it soon complexed Cu^{2+} to yield a stable compound. The electrolytic equilibrium shifted along with the conversion of the product shikonin. The procedure is shown in Scheme 1.

In conclusion, we have solved the problem associated with electrolytic deprotection, which was a difficulty in the total synthesis of shikonin. The improvement has three advantages: first, it made the reaction complete, as practically the yield increased from 40 to 85%; second, owing to the 100% conversion of reactant, the isolation of shikonin became much easier since the reactant and product were similar in polarity. Third, the reaction time was significantly shortened from 10h to 3h.

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.

General procedure

Shikonin (**2**): To a three-necked round-bottom flask was successively added water (2.5 mL), acetonitrile (2.5 mL), $LiClO_4$ (530 mg), $Cu(OAc)_2.H_2O$ (400 mg) and **1** (25 mg). The mixture turned into a dark-blue solution after stirring. Two graphite electrodes with a constant voltage (3V) were inserted and fixed in the side-necks of flask. The mixture was stirred and the reaction progress was monitored by TLC. After completion (*ca* 3h), to the dark-blue suspension was added aqueous HCl (5 mL, 1M) and it soon turned red. The mixture was extracted with EtOAc (15 mL), and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (8 mL) and water (8 mL). The organic layer was dried and evaporated, and flash chromatography of the crude afforded product **2** (19.5 mg, 85%). M. p. 148–149 °C[1]; ^{1}H NMR (300M Hz, $CDCl_3$)[7]: δ 12.60 (s,1H), 12.49 (s,1H), 7.19 (s, 2H), 7.14 (s,1H), 5.21 (1H, dd, *J* = 8.0, 6.8), 4.91 (1H, dd, *J* = 7.2, 4.0), 2.67–2.62 (m,1H), 2.39–2.30 (m, 1H), 1.76 (s,3H), 1.64 (s, 3H)

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