Pergamon

Tetrahedron Letters 41 (2000) 6631–6634

TETRAHEDRON LETTERS

A versatile synthesis of the 1,4-dihydroxynaphthoquinone nucleus

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Received 20 January 2000; revised 13 June 2000; accepted 20 June 2000

Abstract

The electrochemical oxidation of different methoxynaphthalenes to afford the corresponding 5,8-dihydroxy-1,4-naphthoquinones has been examined. This method constitutes a new alternative and efficient route for the synthesis of the 5,8-dihydroxy-1,4-naphthoquinone nucleus.

Keywords: electrochemistry; oxidation; naphthoquinones; antitumor compounds.

Naphthoquinone derivatives are widespread in nature and their biological and pharmacological activities are of interest.[1] Recently, a number of naturally occurring naphthoquinones have been isolated from various species of Boraginaceae family. In particular, alkannin and shikonin, two enantiomeric dyes extracted from *Alkanna tinctoria* and *Lithospermum erythrorhizon*, respectively, seem to have peculiar biological properties.[2] They have been known over many centuries as dyestuffs, wound healing, anti-inflammatory, antibacterial and antineoplastic substances.[3–11] From the pharmacological point of view, their mechanism of action seems to include inhibition of the Topoisomerase I enzyme (Topo I).[7,8,11–14] Moreover, cellular toxicity mediated by a redox process has also been suggested.[7,8,11–14]

Our aim was to synthesize new naphthoquinone derivatives with side chains different from that of alkannin and shikonin. In particular, we were interested in synthesizing new peptide–naphthoquinone structures as potential Topo I inhibitors such as 5,8-dihydroxy-2-(1-hydroxy-2-nitroethyl)-1,4-naphthoquinone.

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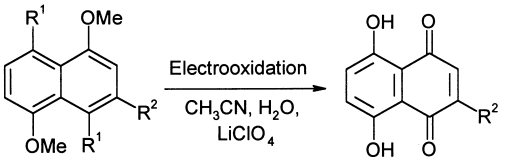
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01041-8

Generally, the last step in the preparation of the 5,8-dihydroxy-1,4-naphthoquinone nucleus involves the deprotection of the 5,8-methoxy groups. Many deprotection methods have been reported in the literature; however, it was found that those methods were not compatible with the protecting groups present in the side chain.[2,7,15,16] Ceric ammonium nitrate and aluminium chloride, or silver oxide–nitric acid, were evaluated with different reaction conditions, but the results were poor or unsatisfactory. The mixed chemical–electrochemical synthesis according to Torii and co-workers was not found to be suitable.[17]

We decided to investigate the electrochemical oxidation–deprotection more deeply to obtain the 5,8-dihydroxy-1,4-naphthoquinone core from the 1,4,5,8-tetramethoxynaphthalene. An electrolytic cell with two platinum electrodes separated by a glass sinter was used, with a saturated calomel electrode (SCE) as the reference electrode. The reaction medium was 10% aqueous acetonitrile containing 0.15 M lithium perchlorate as supporting electrolyte. The reaction is shown in Scheme 1.†



Scheme 1. $R^1 = H, OCH_3$; $R^2 = H, CH(OH)CH_2NO_2$

To understand the oxidation pathway better, we performed the electrooxidation in two steps: the first one at 0.90–1.30 V, and the second one at 1.50–2.00 V (versus SCE). As shown in the cyclic voltammograms of 2-(1-hydroxy-2-nitroethyl)-1,4,5,8-tetramethoxynaphthalene (see Figs. 1 and 2), during the first oxidative step the starting material was quantitatively transformed into the mono- or di-methoxy-1,4-naphthoquinone, with the consumption of 2 (for substrates **1**, **2** and **4**) and 4 (for substrate **3**) faraday/mole.

During the second oxidative step the methoxylated intermediates were transformed into the 5,8-dihydroxy-1,4-naphthoquinone derivatives, which have been completely characterized.‡ In the second oxidation step the charge was higher than the expected amount due to the contemporary

† General procedure: the methoxynaphthalene derivative (10^{-2} M) and the lithium perchlorate (0.15 M) dissolved in 30 ml of 10% aqueous acetonitrile were introduced in the electrolytic cell. The solution was electrolyzed in two steps at the potentials corresponding to the chemically irreversible oxidation peaks detected by cyclic voltammetry. The solvent was removed under reduced pressure to a reduced volume and the resulting solution extracted with ethyl acetate and water. The organic layer was washed several times with water and dried over anhydrous sodium sulphate. After the removal of the solvent and purification by column chromatography (when necessary) the pure 5,8-dihydroxy-1,4-naphthoquinone derivative was obtained. HPLC (reverse phase, 2 μ): A = water (0.05% TFA), B = 90% aqueous acetonitrile (0.05% TFA). The gradient started from A 100% ramped in 10 min to A = 40%.

‡ ^{1}H NMR ($CDCl_3$) (for 5,8-dihydroxy-2-(1-hydroxy-2-nitroethyl)-1,4-naphthoquinone) δ = 12.56, (1H, s, phenol OH), 12.44 (1H, s, phenol OH), 7.45 (1H, d, J 1 Hz, H^3), 7.20 (2H, s, H^6 and H′), 5.64–5.60 (1H, m, CHOH), 4.91–4.86 (1H, dd, J 3, 12 Hz, CH_2NO_2), 4.57–4.50 (1H, dd, J 9, 12 Hz, CH_2NO_2). ^{13}C NMR ($CDCl_3$) δ = 177.2, C=O; 175.8, C=O; 169.3, C^5-OH, C^8-OH; 147.1, C^2=C^3; 134, C^2=C^3; 133.7, C^{4a}; 133.5, C^{8a}; 112.1, C^6 and C^7; 80.0, CH_2NO_2; 65.6, *C*HOH: Elemental analysis, on a purified sample, (C, H, N) was within 0.40% of the calculated values. For the other compounds spectra and melting points were identical to that obtained from an authentic sample of naphthazarin.

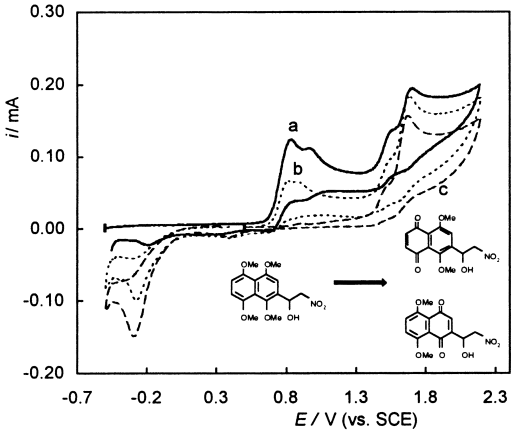


Figure 1. Cyclic voltammograms for the 2-(1-hydroxy-2-nitroethyl)-1,4,5,8-tetramethoxynaphthalene (on Pt, at 0.2 V s^{-1}) performed before and after the electrolysis carried out at the first oxidation step. (a) Starting reaction mixture; (b) after 1 faraday/mole at 0.9 V; (c) after 2 faraday/mole at 0.9 V

oxidation of water at the electrolytic potential. The oxidation potentials and the reaction yields for the four substrates investigated are reported in Table 1.

In conclusion, a new oxidation/deprotection method has been disclosed. Both experimental conditions and reaction yield are satisfactory. Other electrochemical oxidation experiments with a larger set of 1,4,5,8-tetramethoxynaphthalene derivatives and different reaction conditions are in progress to gain a better understanding into the oxidative mechanism.

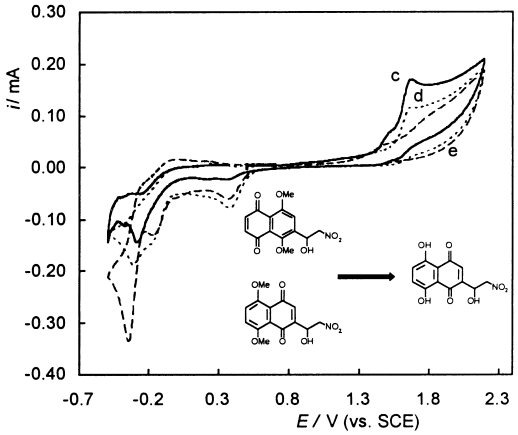
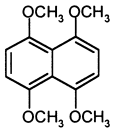
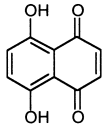
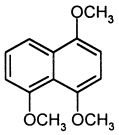
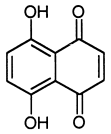
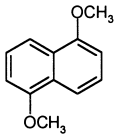
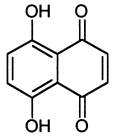
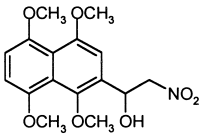
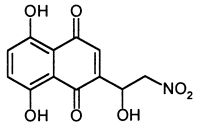


Figure 2. Cyclic voltammograms for the 2-(1-hydroxy-2-nitroethyl)-1,4,5,8-tetramethoxynaphthalene performed before and after the electrolysis carried out at the second oxidation step. (c) Reaction mixture at the end of the oxidation at 0.9 V; (d) after 0.6 faraday/mole at 1.7 V; (e) after 3.0 faraday/mole at 1.7 V

Table 1

Starting compound	Product	E_1 (V)	E_2 (V)	Yield
		1.00	1.50	96 %
		1.1	1.95	78 %
		1.3	2.00	54 %
		0.9	1.7	91 %

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