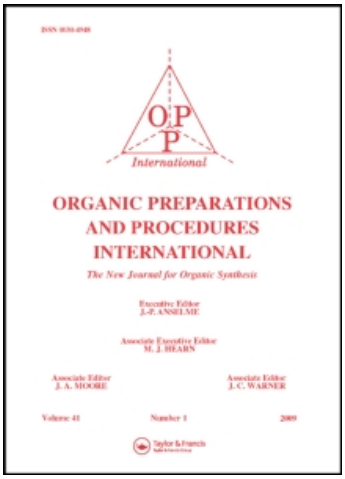

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New Synthetic Routes for the Preparation of 2-Amino-3-hydroxy-1,4-naphthoquinone

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New Synthetic Routes for the Preparation of 2-Amino-3-hydroxy-1,4-naphthoquinone

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On the basis of biological and structural properties, 1,2- and 1,4-naphthoquinones are considered privileged structures in medicinal chemistry.[1] The presence of a nitrogen atom in quinone compounds is also related with a wide range of biological properties, such as anticancer[2] and antimalarial[3] activities. In addition, the amino naphthoquinone moiety is a component of the molecular framework of several natural products (*e. g.* rifamycins, kinamycins, *etc.*).[4,5]

2-Amino-3-hydroxy-1,4-naphthoquinone (**2**) has been prepared by: i) catalytic hydrogenation of 2-hydroxy-3-nitro-1,4-naphthoquinone[6,7] in the presence of PtO_2,[8] or ii) reduction of 2-hydroxy-3-nitroso-1,4-naphthoquinone with $Na_2S_2O_4$ or $NaBH_4$,[9] resulting in low yields of quinone **2** (53% and 45%, respectively). We now report two new synthetic routes to 2-amino-3-hydroxy-1,4-naphthoquinone (**2**) in yields better than previously reported in the literature.[8,9]

Both routes start from 3-(4′-nitrophenylazo)-4-hydroxy-1,2-naphthoquinone (**1**) which was prepared from the coupling reaction of the diazonium salt of 4-nitroaniline with 2-hydroxy-1,4-naphthoquinone in basic medium, as described in the literature.[10] The product precipitates immediately and is obtained in a pure form in 92% yield. It is poorly soluble in usual organic solvents. This reaction is very clean and generates no by-products. The first route involves the reaction compound **1** in the presence of Raney nickel and formic acid, in MeOH, at room temperature. Protonation of the azo group of **1**, followed by cleavage of the N = N bond gives **2** and 4-nitroaniline. After extraction with $CHCl_3$ and washing with water we were able to recover part of the 4-nitroaniline used in the preparation of **1** and obtain the desired product **2** in good yield (82%). This methodology has been reported to selectively reduce aromatic nitro compounds.[11] The second route involves the reduction of

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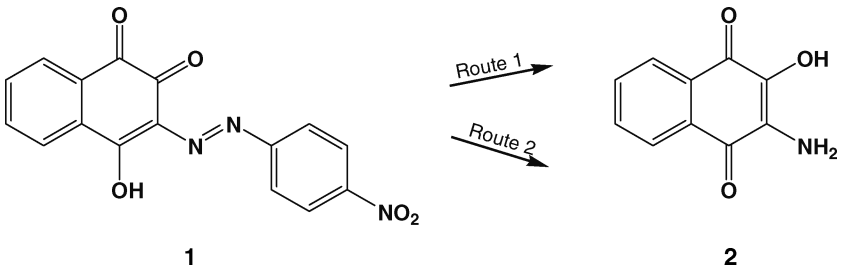
1 with Sn/HCl under reflux[12] which gives product **2** in 78% yield and 4-nitroaniline after the same work out procedure.



1 **2**

Scheme 1

Route 1. i) Raney Ni, MeOH, 1h.; ii) HCOOH at RT. *Route 2*. i) Sn/conc.HCl, EtOH, reflux, 2h; ii) NaOH.

The overall yields of product **2** from both routes are quite good (78%–82%), when compared to those described previously (53%–45%).[8,9] Furthermore another disadvantage of the catalytic hydrogenation of compound 2-hydroxy-3-nitro-1,4-naphthoquinone,[8] when compared to routes 1 and 2 described in this paper, is the use of expensive PtO_2.

Interestingly, reduction of 3-(phenylazo)-4-hydroxy-1,2-naphthoquinone[13] (mp 253–255°C, *lit*.[13] 253–254°C), which has been synthesized as described for **1** from 2-hydroxy-1,4-naphthoquinone and the diazonium salt of aniline, under the conditions of the two routes does not result in the formation of the desired product **2**.

Experimental Section

Mps were determined in capillary tubes on a Mel-Temp II, Laboratory Devices, USA and are uncorrected. The NMR spectra were recorded on a Varian 300 MHz spectrometer. Chemical shifts are reported in δ relative to TMS as internal reference. The IR spectrum was recorded on a FT-IR Spectrum One (Perkin-Elmer) (KBr). The UV-vis spectrum was obtained with a Diode Array 8452A (Hewlett Packard–HP) spectrometer, in spectroscopic grade chloroform and dimethyl sulfoxide.

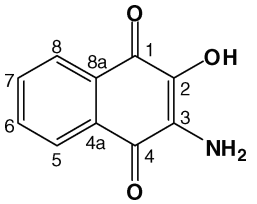
Preparation of Compound 1

A mixture of 0.915 g (6.63 mmol) of 4-nitroaniline, 3.5 mL of water and 3.5 mL of conc. HCl was stirred until dissolution. The solution was then cooled by the addition of crushed ice (1.00 g) to the solution. When the solution temperature reached 0°C, 0.303 g (4.39 mmol)

Table 1
Yields (%) of **2** from the two Synthetic Routes Described

Route	Product 2 from 1	Overall Yield from 2-hydroxy-1,4-naphthoquinone
1	89	82
2	85	78

Table 2
^{1}H NMR data ($CDCl_3$, 300 MHz) of 2-Amino-3-hydroxy-1,4-naphthoquinone



H5	H6	H7	H8
δ 7.97; 1H, dd J = 6.89 and 3.28 Hz	δ 7.61; 1H, dt J = 6.89, 6.89 and 2.40 Hz	δ 7.71; 1H, dt J = 6.89, 6.89 and 3.28 Hz	δ 8.04; 1H, dd J = 6.89 and 2.40 Hz

of $NaNO_2$ in 2 mL of cold water was added to the mixture. The solution was stirred at 0°C for 20 min., then added dropwise to a stirred solution of 2-hydroxy-1,4-naphthoquinone (0.635 g, 3.65 mmol) and sodium hydroxide (0.438 g, 10.95 mmol) in ethanol (28 mL) kept at 0°C. The resulting orange solid, mp 275–276°C, *lit.*[10] 273–274°C, was collected and washed with cold water and ethanol and dried under vacuum (1.08 g, 92%).

Preparation of 2-Amino-3-hydroxy-1,4-naphthoquinone (2)

Route 1. To a stirred suspension of 1.00 g (3.10 mmol) of **1** and 0.15 g of Raney nickel in 10 mL of MeOH at room temperature was added formic acid (90%) (4 mL). The reaction monitored by TLC (ethyl acetate/hexane 3:7) was completed in 1 h. The mixture was filtered through Celite to remove all the Raney nickel. The filtrate was extracted with $CHCl_3$ (3 × 30 mL). Following addition of a 2M solution of NaOH (12 mL) to the aqueous phase to adjust the pH to 9, 4-nitroaniline precipitated. The organic layer was dried over $MgSO_4$, and evaporation of the solvent gave 0.497 g (2.63 mmol, 86%) of 2-Amino-3-hydroxy-1,4-naphthoquinone (**2**) as a purple solid,[6] mp. 131–132°C, *lit.*[8] 130–149°C.

Route 2. To a stirred mixture of **1** (1.00 g, 3.10 mmol) in 13 mL of conc. hydrochloric acid and 20 mL of ethanol was added granulated tin (2.225 g, 20 mmol) and the reaction mixture was heated under reflux for 4 h. After the mixture had cooled, addition of water (100 mL) was followed by addition of solid NaOH (0.219 g, 5.47 mmol) to adjust the pH to 14. The tin oxide was filtered off through filter paper and the dark orange filtrate

Table 3
^{13}C NMR Data ($CDCl_3$, 75 MHz) of 2-Amino-3-hydroxy-1,4-naphthoquinone

C1	C2	C3	C4	C4a	C5	C6	C7	C8	C8a
177.7	135.9	133.2	181.9	130.3	125.1	132.5	133.8	124.9	130.1

(approximately 30 mL) was transferred to a separation funnel together with the same volume of dichloromethane; slow addition of 6M HCl led to extraction of the product to the organic phase. The extraction procedure was repeated twice again. The bright red extracts were combined and dried over $MgSO_4$. Evaporation of the solvent gave 0.497 g (86%) of 2-amino-3-hydroxy-1,4-naphthoquinone as a purple solid.[8]

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