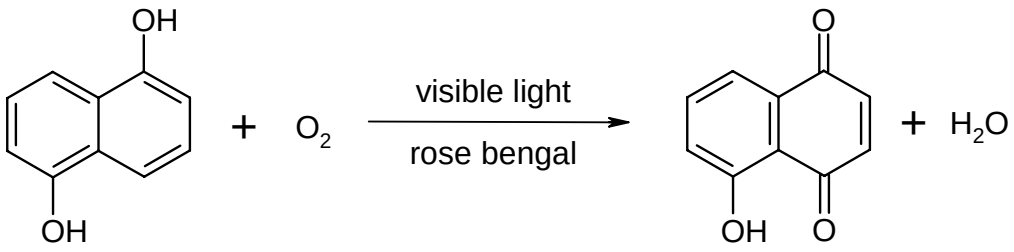
7001 Synthesis of 5-hydroxy-1,4-naphthoquinone (Juglone)



$C_{10}H_8O_2$ (160.2)

$C_{10}H_6O_3$ (174.2)

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Classification

Reaction types and substance classes

[4+2] cycloaddition; photooxygenation
naphthoquinone, natural product

Techniques

photochemical reaction, sensitization, photooxygenation, heterogeneous reaction

Instructions (1 mmol scale)

Equipment

100 mL modified Schlenck flask with 2 side arms and cold finger, suba seals, 500 W halogen lamp, 1/8" tubing, HPLC inlet filter, 50 mL round-bottom flask, rotary evaporator, chromatography column. For a detailed description of the setup, see below.

Substances

1,5-dihydroxynaphthalene (mp. 259–261 °C)	160 mg (1.00 mmol)
2-methyl-2-butanol (bp. 102 °C)	100 mL
rose bengal (bis-sodium salt)	approx. 0.05 mg
silica gel 60 for column chromatography	about 60 g
cyclohexane : ethyl acetate = 3 : 1 (mobile phase in chromatography)	

Reaction

1,5-Dihydroxynaphthalene (160 mg, 1 mmol) was dissolved in 100 mL of 2-methyl-2-butanol and was placed into a 100 mL Schlenck flask. Rose bengal (bis-sodium salt, a spatula tip, approx. 0.05 mg, 0.05 mmol) was dissolved in 0.1 mL H_2O and added to the photo reactor. The Schlenck flask was placed in front of a common 500 W halogen lamp. The solution was cooled via a cold finger while air was bubbled through the solution. This was done using a 1/8 inch diameter tubing and a HPLC inlet filter to generate small bubbles (see attached figure). The reaction was initiated by turning on the halogen lamp. The reaction was followed via TLC analysis using silica plates and a 3:1 mixture of cyclohexane/ethyl acetate

as the mobile phase. R_f(Product) ~ 0.52. ^{1}H NMR analysis can be alternatively used for reaction monitoring. The reaction was completed after approximately 2 hours.

Note: The reaction can also be carried out under direct sunlight by placing the reaction setup (excluding 500 W halogen lamp) in the bright sunlight.[1,2,3]. This ultimately saves on approximately 1000 W of power needed to run the halogen lamp. This is enough energy to run an average 40 W household bulb for 25 hours.

Work up

The solvent (2-methyl-2-butanol) was subsequently removed via rotary evaporation (30 mbar and 40 °C). The crude product is dissolved in 1 mL $CHCl_3$ and added onto the column. The crude product was then purified via column chromatography using silica gel as the solid phase and a 3:1 mixture of cyclohexane: ethyl acetate as mobile phase. The eluted vials were compared via TLC analysis and similar vials were combined. R_f(Product) = 0.52. The solvent was removed via rotary evaporation and the product collected.

Yield pure product: 109 mg (0.62 mmol, 62% yield) of product, bright orange solid, mp 152ºC, (lit: 151-154 ºC)

Note: The product Juglone is the first fraction to be eluted. During the purification process two columns were prepared using different mobile phases in order to compare yields. Chloroform, a traditional choice for purification of Juglone despite its high degree of toxicity to the environment, was used for comparison. A 3:1 mixture of cyclohexane/ethyl acetate was used as alternative. Chloroform showed shorter elution times and gave a slightly higher yield of 64%. However, due to the highly environmentally unfriendly nature of the solvent the slight reduction in percentage yield is justified in using the cyclohexane/ethyl acetate mixture.

The solvent used for the reaction, 2-methyl-2-butanol was recycled from previous reactions. Once the solvent has been removed via rotary evaporation it can be decolourised by stirring over activated charcoal overnight and vacuum filtration. ^{1}H NMR analysis of the solvent can be used to prove its purity before reuse.

Waste management

Recycling

The solvent 2-methyl-2-butanol can be reused in subsequent reactions to synthesize Juglone. The mobile phase from the column chromatography can also be reused after collection from rotary evaporation. However this is limited to purification methods requiring the same mobile phase as previously described. Both solvents can be dried using magnesium sulphate and can be decolourised using charcoal and vacuum filtration. The sensitizer rose Bengal is usually not recovered. However, it can be attached to a solid support (e.g. Sensitox©) for easy recovery and reuse. The reaction rate usually decreases under the latter conditions.[2]

Suggestions for Disposal

Solid waste is the only waste generated in this experiment. This consists of silica gel and rose bengal dye. This can be disposed of in the solid waste container within the laboratory.

Note: All solvents used can be collected via rotary evaporation and recycled.

Duration of Experiment

The conversion of 1,5-dihydroxynaphthalene to Juglone was completed after about 2.5 hours. The time to purify the crude product via column chromatography was in the region of 2-3 hours.

Where can I stop the Experiment?

The reaction can be stopped at any stage. Once the reaction solution is placed in complete darkness the reaction will cease. The reaction will recommence once light is reapplied. The most appropriate time to stop the reaction is after conversion of the dihydroxynaphthalene to Juglone and evaporation. The resulting solution can be left in the dark indefinitely before column chromatography.

Degree of Difficulty

Medium

Analytical Data:

NMR Spectra:

^{1}H-NMR (400 MHz; $CDCl_3$): 6.94 (2 H, s, Hquin.), 7.27 (1 H, dd, J 2.2 and 7.5 Hz, Harom.), 7.60-7.65 (2 H, m, Harom.) and 11.90 ppm (1 H, s, OH).

^{13}C-NMR (100 MHz, $CDCl_3$): 114.0, 118.1, 123.5, 130.8, 135.5, 137.6, 138.6, 160.6, 183.2 and 189.3 ppm.

IR Spectrum:

IR: n (KBr) 3400, 3058, 1662, 1641, 1590, 1448, 1289, 1225, 1151, 1098, 1081, 863, 827, 762 and 703 cm^{-1}.

Mass Spectrometry:

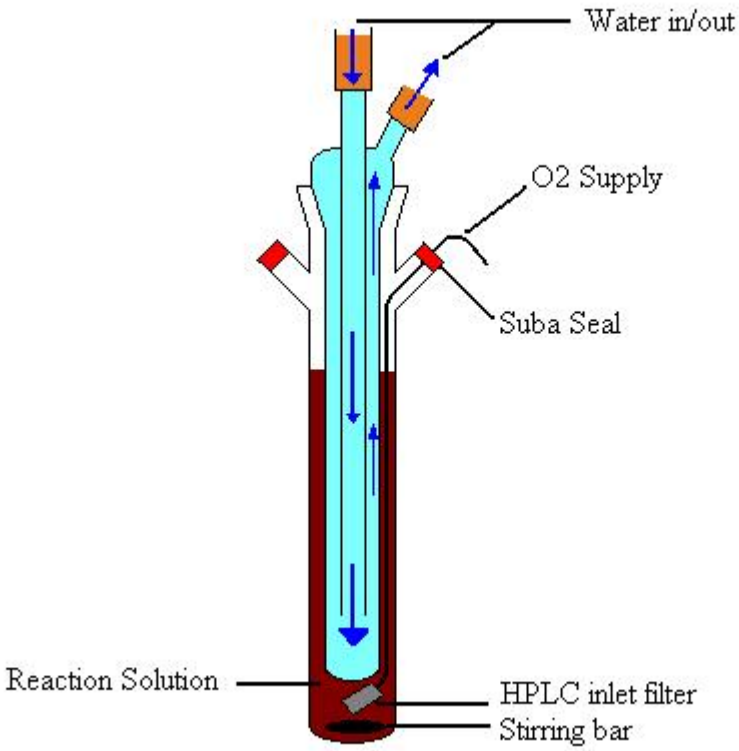
MS: m/z (EI, 70 eV) 174 (M^+, 100%), 146, 118, 90, 63 and 39.

CHN- Analysis:

Found: C, 68.25; H, 3.70. Calc. for C10H6O3: C, 68.97; H, 3.47.

Experimental Setup

The reaction container is a modified Schlenck-flask with two side-arms for air inlet and outlet. A cold finger of appropriate length is inserted into the flask. A common HPLC inlet filter may be used to generate small bubbles. A commercially available standard 500W halogen lamp (purchased in a home centre) was used as light source.



References

[1] M. Oelgemöller, C. Jung, J. Mattay, *Pure Appl. Chem*, 2007, **79**, 1939-1947
[2] M. Oelgemöller, N. Healy, *Green Chem*, 2006, **8**, 831-834
[3] M. Oelgemöller, C. Jung, *Green Chem*, 2005, **7**, 35-38