Syrris Tech Note - Photooxygenation of 1,5-dihydroxynaphthalene for obtention of Juglone

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1 Summary

This technical note demonstrates how to use the Asia Photochemical Reactor to carry out the photooxygenation of 1,5-dihydroxynaphthalene (**1**) for the synthesis of the natural product Juglone (**2**).

The use of the Asia Photochemical Reactor for this application shows both an increased efficiency and a safer practical method for this transformation.

2 Introduction

Molecular oxygen is an attractive oxidant due to its atom efficiency, reduced cost, and sustainable nature. Singlet oxygen $O_2(^1\Delta_g)$ can be produced starting from "ground state", triplet oxygen $O_2(^1\Sigma_g)$, by light irradiation in the presence of a suitable photosensitizer, such as methylene blue, Rose Bengal, and tetraphenylporphyrin (TPP) (*Figure 1*).[1, 2]

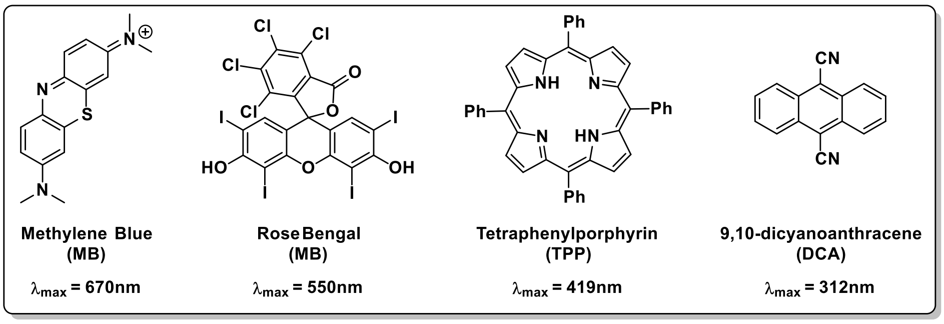
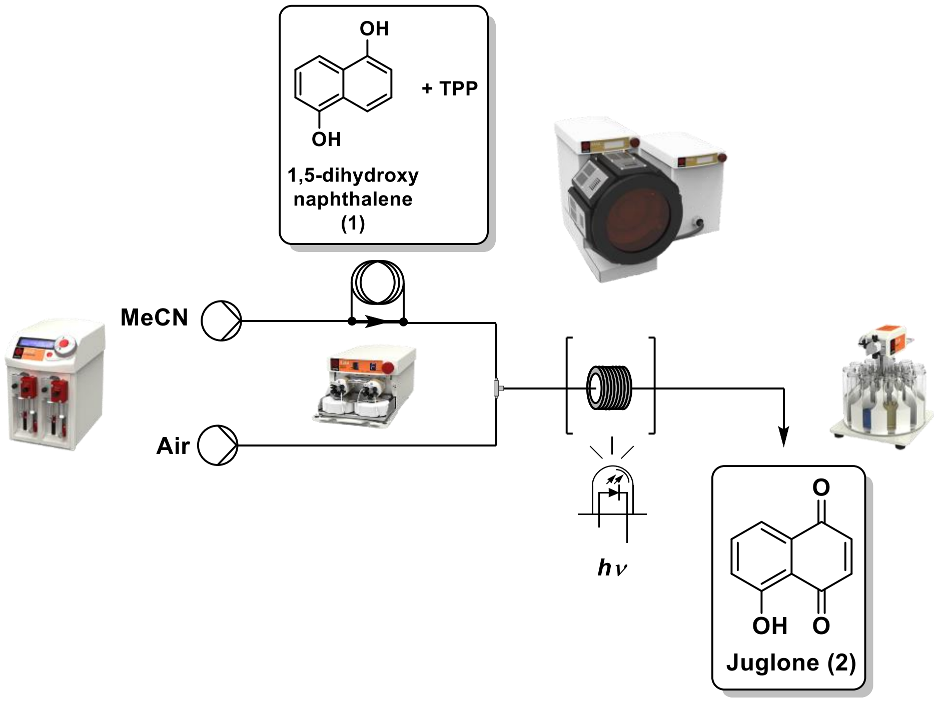


Figure 1. Common photosensitizers for the $^1O_2$ generation.

Compared to triplet oxygen, singlet oxygen shows higher electrophilicity, which allows substrates to be oxidized which are otherwise unreactive to oxygen.[2]

In this technical note we present a photocatalysed protocol under continuous flow conditions using the Asia Photochemical Reactor for the photooxygenation of 1,5-dihydroxynaphthalene (**1**) for obtention of juglone (**2**) (*Scheme 1*).



*Scheme 1. Fluidic setup for synthesis of juglone (**2**).*

Juglone occurs naturally in the leaves, roots, husks, fruit (the epicarp), and bark of plants in the *Juglandaceae* family, particularly the black walnut (*Juglans nigra*). It has several uses, as an herbicide, a dye for cloth and inks, and as a colouring agent for foods and cosmetics.[3].

There are several methods for synthetic obtention of juglone mainly using environmental problematic metallic oxidants (Ag_2O, MnO_2) or organic congeners (2,3-dichloro-5,6-dicyano-1,4-benzoquinone – DDQ).[2]

The generation and use of singlet oxygen $^1O_2$ can be facilitated through the application of photochemical techniques. The presented methodology opens-up the possibility to work in process intensification regime (scaling-up), using oxygen gas as a cost-effective reagent. This offers a reproducible, cleaner, and robust process, while reducing the associated hazards of handling oxygen under traditional batch-wise processes.

3 Material and Method

System Setup

To perform the experiments were used the Asia Flow Chemistry System using the following modules:

- Asia Pump (part number 2200292)
- Asia Blue Syringes (part number 2200393)
- Asia Reagent Injector Fitted with 5ml Sample Loops (part number 2200520)
- Asia Photochemistry Control Module (240V) (part number 2202089)
- Asia Photochemistry Assembly (for Asia Heater) (part number 2202091)
- Asia 525 nm LED modules (Green) (part number 2202099)
- Asia 450 nm LED modules (Blue) (part number 2202098)
- Asia 405 nm LED modules (Violet) (part number 2202096)
- Asia 365 nm LED modules (UV) (part number 2202094)
- Asia Heater (part number 2200527)
- Asia Heater Tube Reactor Adaptor (part number 2200530)
- Asia 4 ml Tube Reactor Fluoropolymer (part number 2200541)
- IDEX non-metallic inline check-valves (IDEX cat. no. CV-3324)
- Asia Product Collector (part number 2200534)
- Asia Manager PC Software (part number 2200537)

Reagent Preparation

The following chemicals were needed for the experiments:

- 1,5 dihydroxynaphthalene (CAS 83-56-7) (1)
- meso-Tetraphenylporphyrin (TPP) (CAS 917-23-7)
- Acetonitrile (CAS 75-05-8)
- Dichloromethane (CAS 75-09-2)

A solution of TPP (5.2 mg; 0.09 mmol; 0.03 eq.) in DCM (10 mL) was added to a solution of substrate **1** (52.6 mg; 3 mmol, 1.0 eq.) in MeCN (90 mL).

Aliquots of 5 mL were introduced to the sample loop of Reagent Injector and the reaction was carried out pumping MeCN and air.

Schematic of Setup

The fluidic setup is shown in Figure 2. The Asia Pump was used to pump acetonitrile (MeCN) (carrier fluid) and atmospheric air (source of O_2), The Asia Reagent Injector (RIM) was used to introduce the reagent solution into the fluidic network. The carrier solvent and air were combined and passed through the Asia Photochemistry Reactor fitted with a 4 mL Asia Tube Reactor. The system was kept at ambient temperature with no back-pressure applied. Collection was carried out using the Asia Product Collector. Note. IDEX check-valves were fitted to the output of the Asia Syringe pump pressure sensor to prevent back flow. Off-line quantitative analyses were carried out allowing to calculate reaction yields.

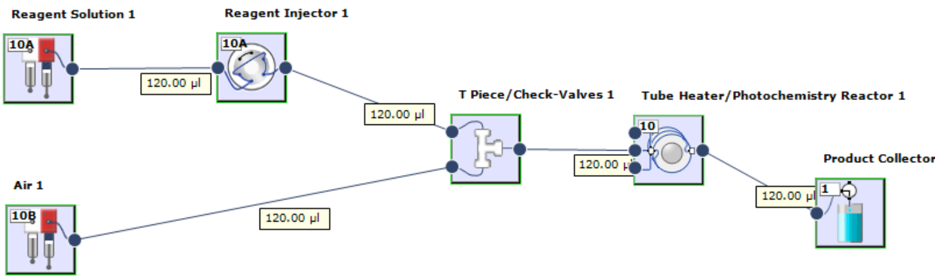


Figure 2. Fluid network for the photooxygenation reactions.

The results were determined by a qualitative analyses of the verification of colour change under different conditions. The reagent solution presents a purple colour, and the product solution has a yellow/orange colour (Figure 3).

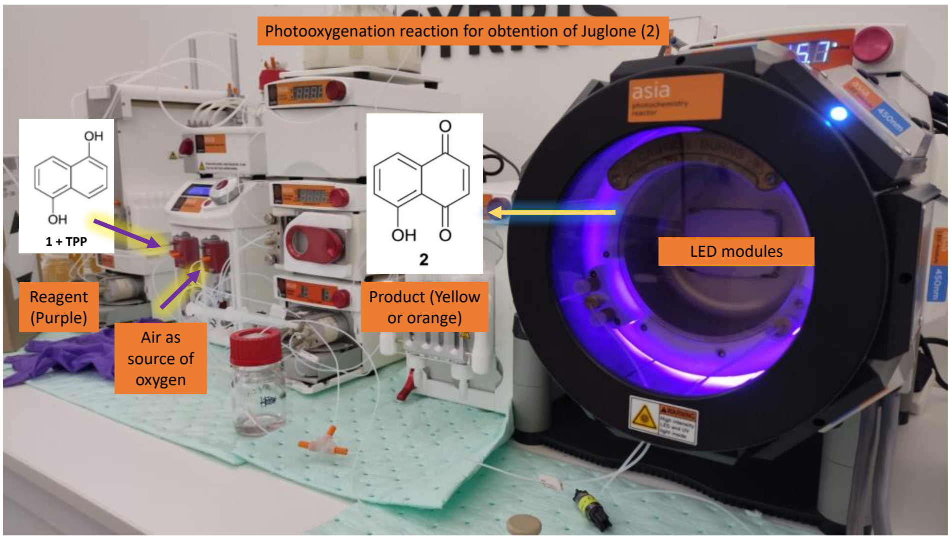


Figure 3. Experimental set-up used in the experiment.

System Parameters

Automated experiments were performed using Asia Manager software. The residence times and light intensity were explored. Light intensity was varied by changing both the number of LED modules used and the percentage of input power selected on the Asia Photochemistry Reactor. The reaction conditions are shown in Table 1.

Table 1 – System parameters.

Exp #	LED wavelength (nm)	Number modules	Power %	Total Flow rate (mL/min)	Residence Time (min)
1	450	8	100	0.0625	64.0
2*	450	8	100	0.0625	64.0
3	450	8	50	0.0625	64.0
4	450	4	100	0.400	10.0
5	525	4	100	0.400	10.0
6	405	4	100	0.400	10.0
7	365	4	100	0.400	10.0
8**	N/A	0	0	0.400	10.0

*no air pumped; ** no light

Table 1. Experimental conditions used in the reaction optimization.

4 Results

A series of eight experiments were used to perform the method development performed on Asia Photochemical Reactor.

The range of residence times, light intensity and LED wavelengths were explored as shown in Table 1.

TPP absorbs light in most of the UV-Vis spectrum, and all tested wavelengths promoted the photooxygenation reaction and as such a change in the reagent solution colour was observed (from purple to yellow or orange) in all experiments where light was irradiated.

Experiment 8 shows the reaction where no light was used to irradiate the reaction. This benchmark shows no colour change from the starting solution (Figure 4).

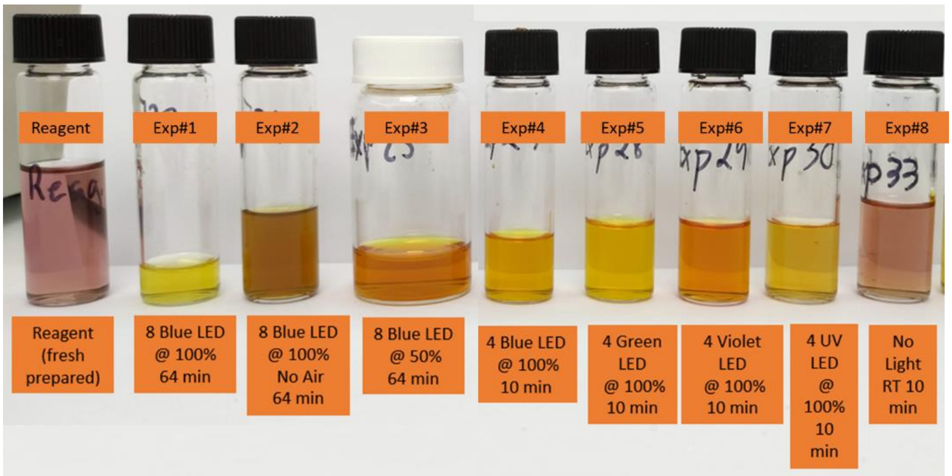


Figure 4. Qualitative results of set experiments.

Experiment 2 was performed with no air being pumped through channel 2 and therefore no oxygen being delivered to the reaction. The resulting reaction mixture showed a turbid, brown solution containing some particulate. When compared to all other experiments where air was introduced (showing a clear yellow/orange colour) the result of this experiment confirmed the need to pump air and hence oxygen, creating the proper biphasic flow stream for generation of singlet oxygen and the correct chemical environment allowing the reaction to take place.

Experiment 1 performed with a greater light intensity (8x LED modules, 100% power) showed the conversion of the purple starting solution to a bright yellow product solution compared with 50% power as shown in expt.3. This indicates the greater conversion to the desired product and highlights the requirement of a photochochemistry reactor to enable a variable power input and scalable light intensity.

It should be noted that reducing the residence time to 10mins showed a good colour conversion as shown in expt. 4 -7.

These results are in complete agreement with the literature[2] and is worth mentioning that the previous studies made use a supply of neat oxygen gas. In this technical note, the pumping of atmospheric air, containing approximately 20% of oxygen, was enough to generate singlet oxygen and promote the reaction in mere 10 min. These findings demonstrate the high power and excellent efficiency of the LED arrays used in the Asia Photochemical Reactor.

5 Conclusions

It was demonstrated the proof-of-concept of the Asia Photochemistry Reactor by a photooxygenation reaction for obtention of juglone (**2**). In addition, we have shown the applicability and safety of this device which can be used in process intensification by using mild and cost-competitive conditions to produce valuable compounds.

6 References

[1] Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.*, **2016**, *116* (17), 10276–10341. https://doi.org/10.1021/acs.chemrev.5b00707.

[2] de Oliveira, K. T.; Miller, L. Z.; McQuade, D. T. Exploiting Photooxygenations Mediated by Porphyrinoid Photocatalysts under Continuous Flow Conditions. *RSC Adv.*, **2016**, *6* (16), 12717–12725. https://doi.org/10.1039/C6RA00285D.

[3] Strugstad, M. P.; Despotovski, S. And Potential Uses of Juglone : A Literature Review. *J. Ecosyst. Manag.*, **2012**, *13* (3), 1–16.