Application Note 71:

Photochemistry Process development and scale up to kilos/day

Produced by Vapourtec

Abstract

This application note demonstrates a 385 % increase in throughput in the ene-like reaction of singlet oxygen with citronellol, by increasing the photon molar output. By using Vapourtec's UV-150 photochemical reactor equipped with a 420 nm High Power LED, a throughput of 59 g/h (1.4 kg / day or over half a tonne a year) can be achieved.

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Background

Oxygen gas, the most accessible oxidant, is not widely used in organic chemistry as its most common form, ground state, is unreactive. Singlet oxygen, on the other hand, is an excited state of molecular oxygen which is unstable and highly reactive [1].

Singlet oxygen has been generated in the past via decomposition of peroxides (hydrogen peroxide, organic peroxide) [2]. Flow photochemistry offers a cleaner and more efficient alternative. By using photosensitizers such as rose Bengal or tertraphenylporphyrin (TPP), highly reactive oxygen species can be generated in-situ via dye-sensitized photoexcitation of triplet oxygen, reacting with organic substrates [1].

Singlet oxygen can be used to oxidize alkenes, by adding a peroxy group to the substrate. These can then subsequently be reduced to the corresponding alcohol. This chemical path can be used to create high added value products from inexpensive reagents, such as terpenes. Any excess oxidant will be degassed from the crude product.

François Lévesque and Peter Seeberger explored this reaction in the oxidation of a variety of terpenes, including citronellol, achieving a productivity of >1.0 mmol/min [1].

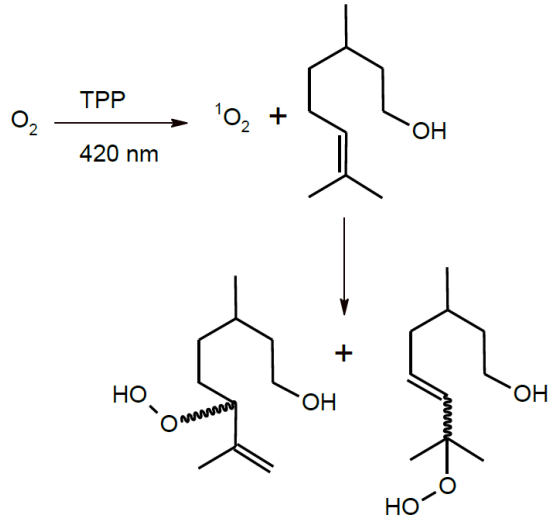

Figure 1 – Citronellol oxidation's mechanism via singlet oxygen

In 2015, Vapourtec explored this reaction using the UV-150 photochemical reactor [3]. A 420 nm LED was used to match the absorption of TPP, as shown in Figure 2. By using the right UV source, each emitted photon could be used to excite TPP efficiently.

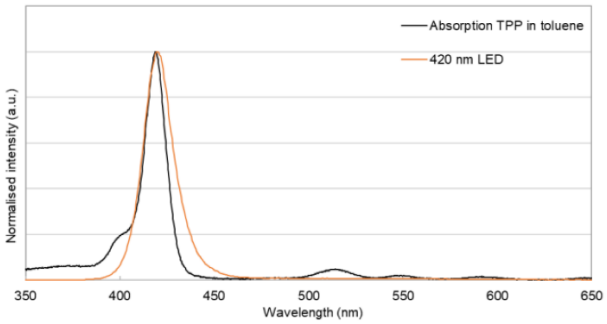

Figure 2 - Absorption of TPP with the output spectra of the 420 nm LED

Application Note 43 focused on the optimization of this ene-like reaction using the UV-150 photochemical reactor. Catalyst concentration, temperature and oxygen excess were evaluated. Catalyst concentration and oxygen excess were critical to maximize the throughput of the reaction to 15 g/h (96 mmol/h).

When carrying out photochemical reactions with gaseous reagents, it is important to minimize the amount of excess gas as this can impact the reaction performance. If the amount of gas used is close to stoichiometric ratio, it can become the limiting reagent, as not all gas will be dissolved in the solution.

On the other hand, too great stoichiometric excess will affect how many photons irradiate the solution. As more gas pockets pass through the photochemical reactor, the photons irradiating gas will not reach the photosensitizer and therefore will not be utilized. This becomes critical when using gases with low solubility coefficients in organic solvents, as it is the case with oxygen.

Reaction scale-up is an important area in process development which is not always easy to achieve. Non-thermally mediated reactions, such as photochemistry, can be even more challenging, as any change in the photon delivery efficiency will impact yield.

With Vapourtec's new family of high-power LED UV sources, photochemical reactions can be explored and scaled up with the UV-150 photochemical reactor.

Setup

A Vapourtec RS-300 equipped with a UV-150 photochemical reactor was used for this work. The R2S+ pump modules were selected as they can deliver both solutions and gas. Gas is delivered as standard cubic centimemetres (scc) per min (scc/min). scc is a unit of flow measurement indicating the volume of gas in standard conditions for temperature and pressure.

Pump D was set as active BPR at 8 bar, and the product was collected in a single vial. Figure 3 shows a schematic of the system.

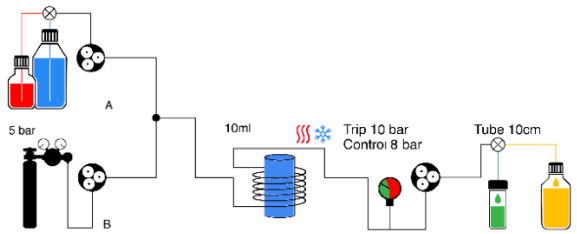

Figure 3 – Schematic of the R-Series system used during this application note

Reagents

All reagents and solvents used were purchased from commercial suppliers. Citronellol, TPP, chloroform were purchased from Sigma Aldrich. Compressed oxygen cylinder was rented from BOC.

System Parameters

System solvent: Chloroform

Reagent A: of 0.2 - 0.8 M citronellol and catalytic TPP (1:1600) in chloroform

Flow rate A: 6.8 ml/min

Reagent B: Oxygen

Flow rate B: 35-140 scc/min

Reactor volume: 10 ml

UV source: *Gen-1 420 nm (60 W input power, 18 W radiant power) and 420 nm high-power LED (150 W input power, 70 W radiant power)*

Reactor temperature: 40 °C

Back pressure regulator: 8 bar

Results and Discussion

Gen-1 420 nm LED

A solution of 0.2 M citronellol and 125 µM TPP was pumped at 6.8 ml/min, while pump B delivered 35 scc/min of O_2.

With these conditions, a throughput of 15.3 g/h was achieved with a conversion of 99.5 %.

High power LED

As the 420 nm high power LED has 3.9 times the radiant power, the moles per minute of reagents would need to be quadrupled to match these excess photons. To achieve this, citronellol solution's flowrate was maintained to 6.8 ml/min, but its concentration was quadrupled to 0.8 M citronellol and 500 µM TPP. O_2 flowrate was increased to 140 scc/min, ensuring it would not become the limiting reagent.

With these conditions, the photon flux was matched, and the reaction throughput was increased to 58.6 g/h, yielding 1.4 kg per day.

Figure 4 and Table 1 compile the results of both experiments.

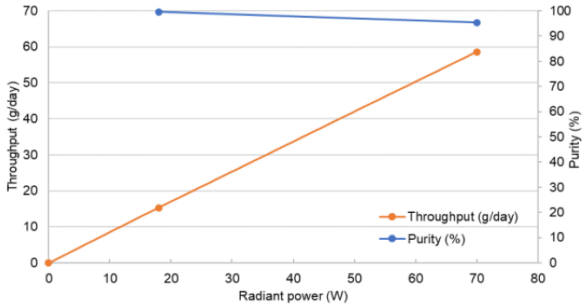

Figure 4 – Throughput and purity achieved at different UV LED radiant power

Table 1 – Reaction conditions and throughput on the oxidation of citronellol

	Gen-1 LED	High power LED
Radiant power (W)	18	70
Citronellol concentration (M)	0.2	0.8
TPP concentration (µM)	125	500
O_2 (scc/min)	35	140
Purity (%)	99.5	95.4
Throughput (g/h)	15.3	58.6

Conclusions

This application note demonstrates the versatility of the UV-150 photochemical reactor using the ene-like reaction between singlet oxygen and citronellol as example. By simply exchanging UV sources, the UV-150 can be used for both reaction optimization and scale up of photochemical reactions.

When using the high power LED, a throughput of 58.6 g/h (1.4 kg/day) of the terpene hydroperoxide was achieved under mild conditions.

References

[1] F. Lévesque and P. H. Seeberger, "Highly Efficient Continuous Flow Reactions Using Singlet Oxygen as a 'Green' Reagent," *Org. Lett.*, vol. 13, no. 19, pp. 5008–5011, Oct. 2011, doi: 10.1021/ol2017643.

[2] W. Tian, W. Shi, H. Yang, R. Cui, and L. Deng, "Production of singlet oxygen by the reaction of non-basic hydrogen peroxide with chlorine gas," *Phys. Chem. Chem. Phys.*, vol. 14, no. 38, pp. 13344–13349, 2012, doi: 10.1039/C2CP41690E.

[3] Vapourtec Ltd, "Application Note 43 – Singlet oxygen reaction in continuous flow, an example of an ene reaction," 2015.

Supporting Information

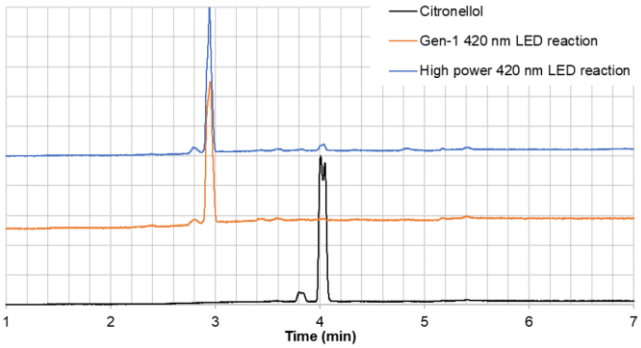

Figure S1 – HPLC chromatograms of Citronellol and crude products after solvent evaporation

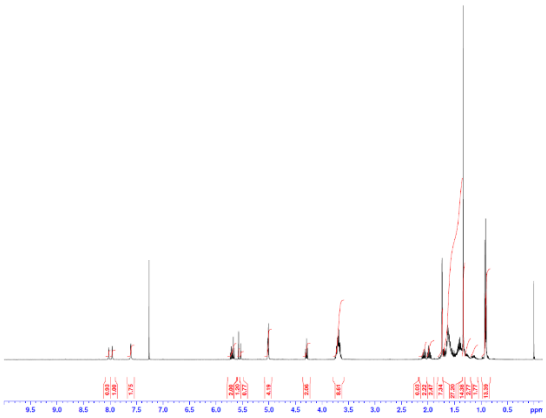

Figure S2 – Typical ^{1}H-NMR of crude product