Application Note 39:

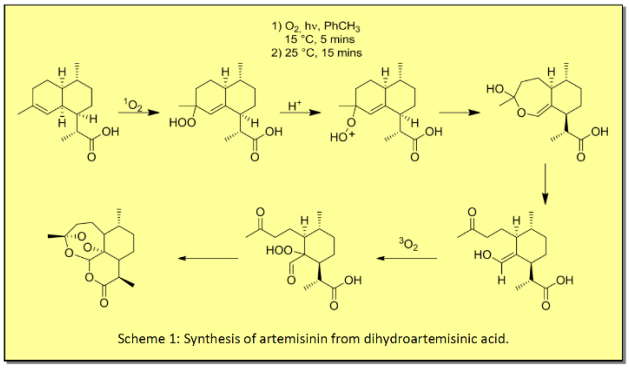
Anti-Malarial Photochemistry

Submitted by:

Dr. Kerry Gilmore of the Max Planck Institute for Colloids and Interfaces, Biomolecular Systems Department.
Email: kerry.gilmore@mpikg.mpg.de

Abstract

This application note illustrates the use of the new Vapourtec UV-150 reactor which allows access to continuous photochemistry in an easy-to-use, safe and efficient manner.



Scheme 1: Synthesis of artemisinin from dihydroartemisinic acid.

For more details, please contact:
Vapourtec Application Support
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Background

Continuous flow chemistry offers easy access to scaling reactions from milligrams to kilograms, and many successful examples have been well documented. The Vapourtec UV-150 photochemical reactor extends these advantages by giving the chemist easy access to continuous photochemical reactions. Photochemistry is a valuable but underused synthetic tool and offers potentially shorter, 'greener' and more efficient synthetic routes as well as access to new chemical space.[1]

The main advantages of continuous photochemistry over conventional batch applications are:[2]

- consistent light penetration,
- controlled exposure times,
- precise temperature control,
- higher photonic efficiencies,
- removal of photochemical products from the irradiated area and
- easy scalability.

These features typically result in higher conversions or yields, increased productivities or space-time yields, improved selectivity, enhanced energy efficiencies and reduction of solvent volumes and consequently waste.

When considering continuous photochemistry it is useful to view the light source as a reagent (but not one that can be added all at once). The lamp emits a flux (or stream) of photons which facilitate the reaction. The number of moles of photons the reaction sees will have a direct relationship with the productivity of the reaction.

A distinction in performing continuous flow chemistry via a photochemical method is needed. The throughput (number of moles of reactant per unit time) has to be considered over the traditional 'residence time' calculation. The flow rate and concentration will therefore have a direct effect on the conversion and yield of any photochemical reaction.

Considering the lamp as a fixed flux of photons (photons/min) the flow rate and concentration of the reagent will therefore have a direct effect on the stoichiometry of the reaction and therefore the conversion and yield of any photochemical reaction.

This application note demonstrates the use of the UV-150 photochemical reactor and E-Series system in the continuous synthesis of Artemisinin via the photooxidation of dihydroartemisinic acid. The chemistry has been previously demonstrated delivering oxygen via a mass flow controller in a 'home-made' system; this application shows that the easy-Photochem system can deliver not only the substrate but also oxygen in a safe, efficient continuous manner with the UV-150 effectively generating the singlet oxygen required for the reaction. This self-contained unit, coupled to an additional room temperature reactor is shown to synthesize the anti-malarial medicine artemisinin in comparable yields to previously published methods.

Method (Optimization).

The aim of this work was to demonstrate the utilization of the E-series to deliver oxygen gas to the UV-150 reactor, where it could react with an excited dye to generate singlet oxygen. This reactive intermediate was trapped by an alkene in an ene reaction to yield a series of peroxides. The reaction was optimized based on filter, flow rates, and power of lamp.

Setup

The flow reactor was set up using the **E-Series** pump module as shown in Fig 1.

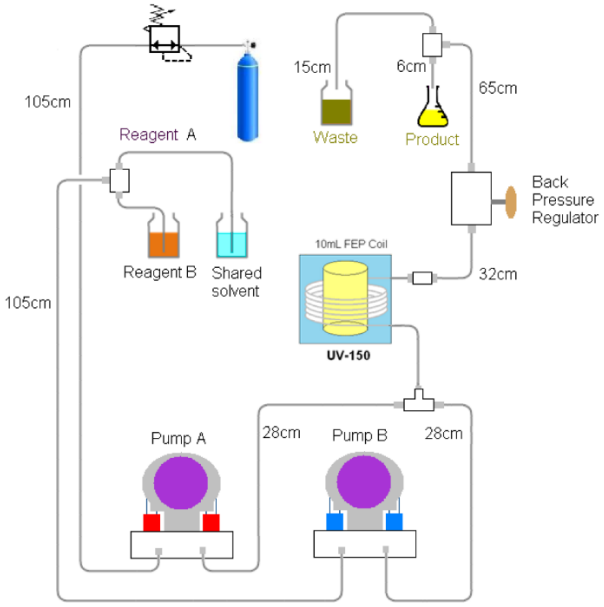


Fig 1: E-Series Setup.

Pump Tubing

It is to be noted that the V-3 pump used by the E-Series is based on the peristaltic principle, and so features a high performance fluoropolymer tube at its core. More than one pump tube type is available to ensure compatibility with the broadest possible range of solvents, so selection of the correct tube for a given application is critical.

A table showing recommended tube type compatibility with a wide selection of solvents, acids and bases is available both within the E-Series user manual and also built into the User Interface software.

In this case

- blue tube was used for the toluene solution
- red tube was used for oxygen gas

Reagents

All reagents and solvents were used as purchased;

Reagent A

Oxygen gas (ALPHAGAZTM 99.995 %).

Reagent B

0.5 M Dihydroartemisinic acid (8.46 mmol, Honseabio, China) in toluene (anhydrous, Aldrich) anthracene-9,10-dicarbonitrile (0.042 mmol, Aldrich).

System Parameters

System solvent:	Anhydrous toluene (Tol)
Reagent A:	Oxygen gas
Reagent B:	0.5 M Dihydroartemisinic acid (8.46 mmol) in toluene with and anthracene-9,10-dicarbonitrile (0.042 mmol).
Flow rate A:	1 mL/min
Flow rate B:	1 mL/min
Reactor volume:	10 mL UV-150 reactor.
Lamp Power:	variable (50-100%)
Filter:	variable (1, 2, 3, 6)
Reactor temperature:	variable (-5 to 15°C)
Back pressure regulator:	6 bar

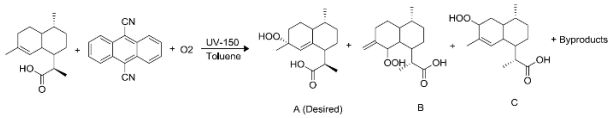
Then the optimization reactions followed the sequence of event listed below:

1) *Priming the pumps with toluene (Tol):* Valve B was set to 'Solvent' and the pumps were `primed with Toluene. This is done by selecting the prime function from the touchpad control and is fully automated.
2) *Priming the pumps with reagents*: The selection valve for line 2 was set to 'Reagent', the prime function selected and the line connecting the valves to stock bottle 2 was filled with **Reagent B.** The selection valve was set back to 'Solvent' and Toluene pumped through the lines using the 'prime' function.
3) *Setting the oxygen flow rate*: Pump **A** was directly attached to a 10 L oxygen tank, with the pressure of the regulator set to 8 bar. The full system was allowed to reach pressure by running Toluene and oxygen through the entire system prior to beginning the reaction.
4) *Reaction optimization*: A selective range of conditions were run using the easy-Scholar™ software . Residence times of ~5 minutes were run using a variety of available filters (1, 2, 4, 6) in the 10 ml UV-150 reactor at a variety of temperatures (-5 to 15 °C). A 2 mL aliquot of solution B (0.5 M dihydroartemisinic acid) was used in each experiment.
5) *Work-Up and Analysis*: The collection stream was directed into a flask where XX g (mmol) benzoic acid was added. The solution was then dried via rotary evaporation and ^{1}H NMR ($CDCl_3$) was taken, using benzoic acid as an internal standard.

To learn more about the Vapourtec system visit www.vapourtec.com

Results and Discussion

Wavelength Filtering



Scheme 2: Ene reaction with singlet oxygen and dihydroartemisinic acid.

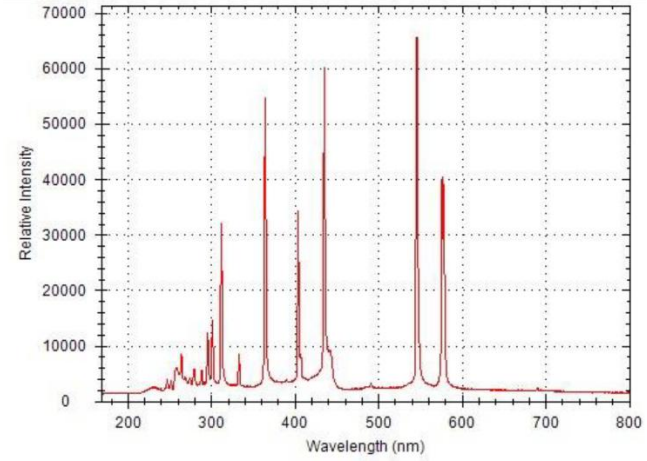
A strong dependence on the formation of peroxide products (Scheme 2) was observed with respect to the filter utilized in the UV-150 reactor. The initial screening was run at ~0 °C with the lamp at 50 % power, resulting in ~59-95 % conversions. While the formation of peroxides B (6-10 %) and C (1-2 %), remained relatively constant, the yield of the desired peroxide A varied greatly with different filters: Filter 1 (60 %), Filter 2 (38 % - 41 % recovered SM), Filter 3 (65 %), Filter 6 (70 %). These yields correspond with the degree of selectivity for irradiation around the □-max of the dye (420 nm). Doubling the flow rate to 2.0 mL/min with filter 6 resulted in a large decrease in both conversion (59%) and yield of the desired peroxide (44 %). Increasing the lamp power using filter 6 (flow rates 1.0 mL/min) to 75 % (~10 °C) and 100 % (~15 °C) resulted in increased conversions and higher overall yield of the desired intermediate (75 %).

The following optimized conditions were utilized for the full reaction, described in the next section:

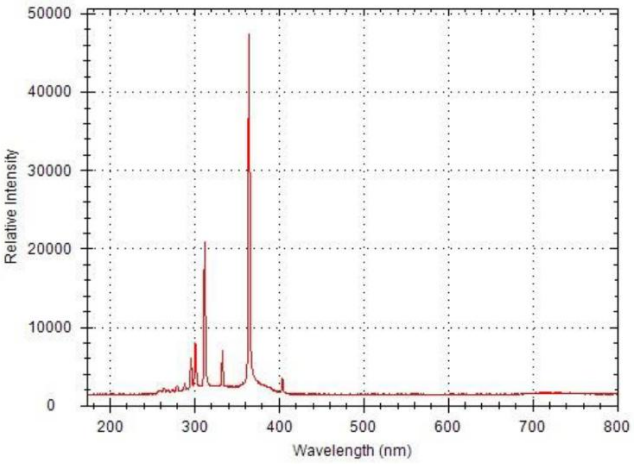
Lamp Power:	100 %
Filter:	6
Flow Rate O2:	1.0 mL/min
Flow Rate Solution:	1.0 mL/min
Temperature:	~15 °C

The table below clearly shows the wavelengths filtering of the different filters relative to 420 nm

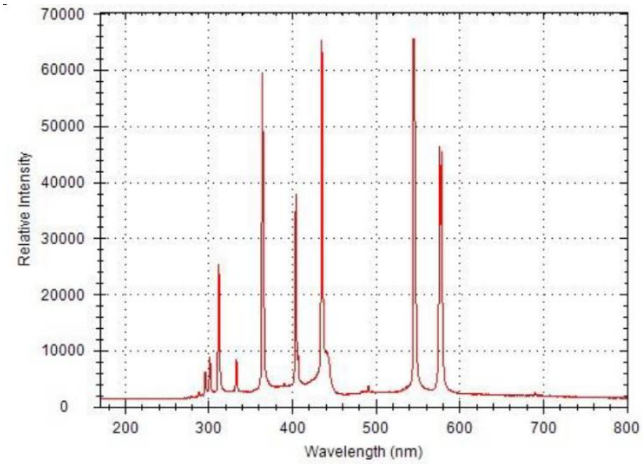
Transmission Spectra Type 1 Filter - Silver



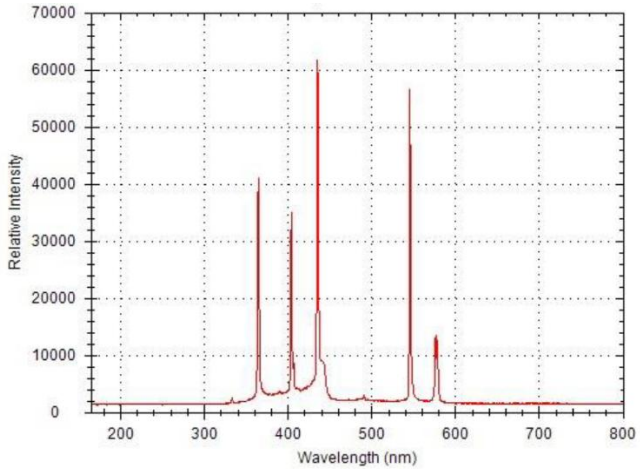
Transmission Spectra Type 2 Filter – Gold



Transmission Spectra Type 3 Filter - Red



Transmission Spectra Type 6 Filter – Silver



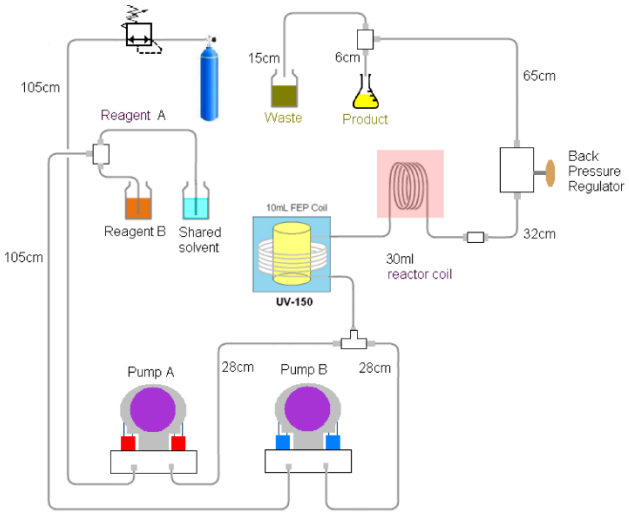


Figure 2: E-Series setup

Method (Full Synthesis)

With the conditions optimized for the formation of our target compound, the intention was then to demonstrate that the E-Series was able to convert dihydroartemisinic acid into artemisinin via photooxidation and a subsequent Hock cleavage/triplet oxygen oxidation.

Applying these optimized reaction conditions described above, a 17 mL aliquot of Reagent B solution (described below) was processed.

Setup

The equipment was exactly as used in the optimization with the addition of a 30 mL PFA reactor between the UV-150 reactor and the BPR. The UV-150 reactor was run at 15 °C while the second reactor was used at room temperature (25 °C).

Reagent A

Oxygen gas (ALPHAGAZTM 99.995%).).

Reagent B

0.5 M Dihydroartemisinic acid (8.46 mmol, Honseabio, China) in toluene with trifluoroacetic acid (4.23 mmol, Alfa Aesar) and anthracene-9,10-dicarbonitrile (0.042 mmol) (Aldrich).

System Parameters

System solvent:	Anhydrous Toluene (Tol)
Reagent A:	Oxygen gas
Reagent B:	0.5 M Dihydroartemisinic acid (8.46 mmol) in toluene with trifluoroacetic acid (4.23 mmol) and anthracene-9,10-dicarbonitrile (0.042 mmol)
Flow rate A:	1.00 mL/min
Flow rate B:	1.00 mL/min
Reactor volume:	10 mL UV-150 reactor, 30 mL PFA reactor.

Lamp Power:	100 %
Reactor temperature:	~15 °C, room temperature (25 °C)
Back pressure regulator:	6 bar set BPR

Then the full synthesis of artemisinin followed the sequence of event listed below;

1) Priming the pumps with toluene (Tol): Valve B was set to 'Solvent' and the pump was `primed with Tol. This is done by selecting the prime function from the touchpad control.
2) Priming the pumps with reagents: The selection valve for line 2 was set to 'Reagent', the prime function selected and the line connecting the valves to stock bottle 2 was filled with Solution B. The selection valve was set back to 'Solvent' and Tol pumped through the lines using the 'prime' function.
3) Continuous running: The chosen conditions were run using the Manual Control interface. A residence time ~20 minutes was run using filter 6 in a 10 mL UV-150 reactor at ~15 °C) with flow rates of 1.0 mL/min for both oxygen and reagent. A 17 mL aliquot of solution B (0.5 M dihydroartemisinic acic) was processed and the entire reaction stream was collected.
4) Work-Up and Analysis: Following collection, the reaction was washed twice with 20 mL saturated $NaHCO_3$ and dried to a yellow solid using rotary evaporation. The solid was dissolved in a warm ethanol/toluene (80/20) solution and allowed to cool to room temperature. Following the addition seed crystals of artemisinin (20 mg), the solution was cooled to 0 °C. The resulting white crystalline solid was filtered, washed with cold ethanol, and dried to yield 836 mg of pure artemisinin.

Results (Full Synthesis)

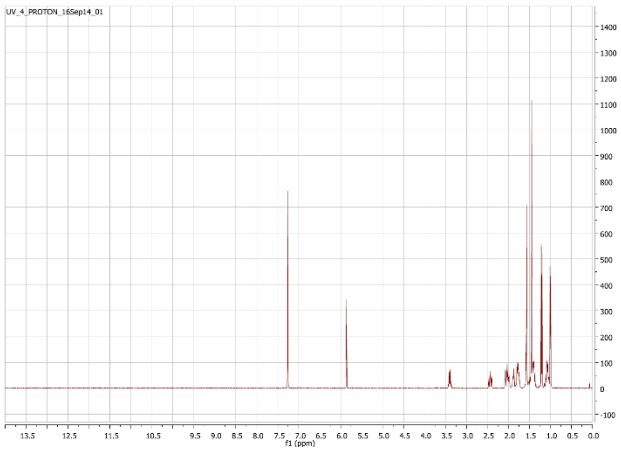
17 ml (2 g) of **Reagent B** (8.46 mmol) was processed and collected over ~35 mins as shown above. After crystallization a white solid was isolated. Yield = 838 mg, 35 % (isolated yield based on 1H NMR). This is similar to yields previously reported (ACIE 2012, 51, 1706.)

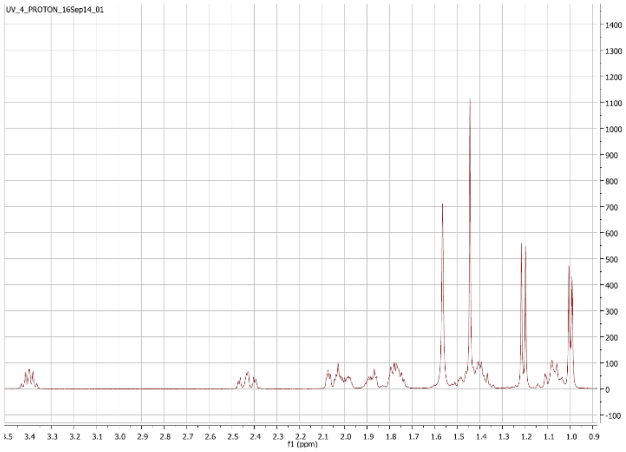
This demonstrates a throughput of 1.6 g/hr. Extrapolation of this experiment, indicates a potential yield of 38 g/24hrs under continuous reaction conditions.

NMR Analysis

VT301-P Scale-Up Experiment

^{1}H NMR





Expanded 4.5-0.9 ppm,

Conclusion

The work described in this report demonstrates that the Vapourtec E-Series is able to deliver oxygen gas in a safe, efficient and continuous manner. The UV-150 reactor was able to effectively generate singlet oxygen in the presence of a dye.

This self-contained unit, coupled with an additional room temperature reactor, was utilized to synthesize the anti-malarial medicine artemisinin, in comparable yields and output to previously published “home-made” reactors. The yields could be greatly enhanced using selective wavelength filters.

Acknowledgements

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kerry.gilmore@mpikg.mpg.de

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