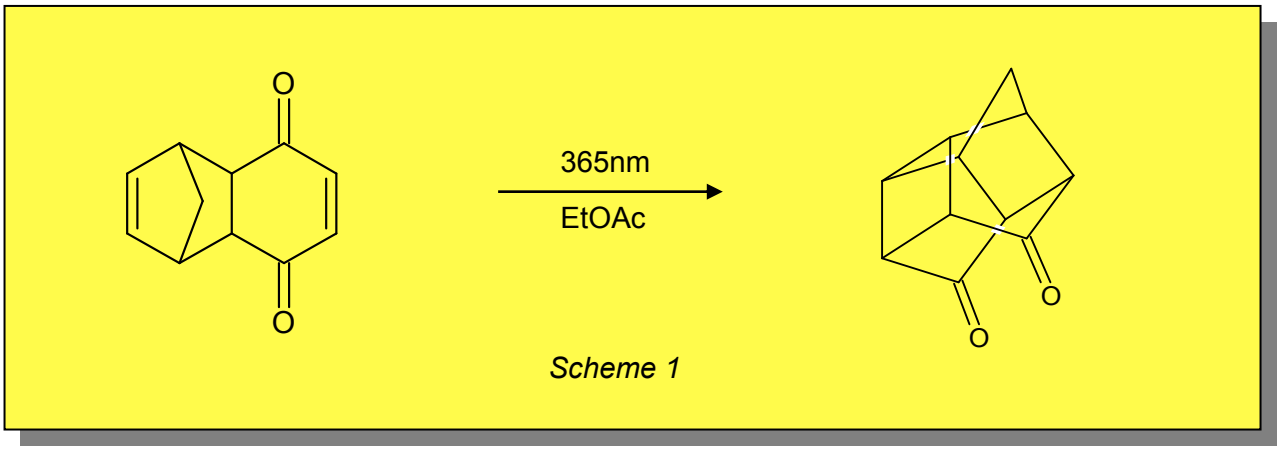
Application Note 44: Direct [2+2] photocycloaddition using LED light source

Abstract

This application note demonstrates the potential throughput capabilities of the UV-150, using an uncatalysed, intramolecular photochemical [2+2] cycloaddition. Further, it showcases the efficiency of the Vapourtec LED gen 2 light source, showing that a single, relatively small reactor together with low power LED can achieve a noteworthy throughput.



Scheme 1

Background

Photochemistry is a relatively underused technique in organic synthesis. This application note aims to demonstrate the simplicity, effectiveness and capability of photochemistry under continuous flow conditions. The chosen transformation is an uncatalysed intramolecular reaction. The reaction is optimized with the aim to produce the highest throughput possible. This photochemical reaction is undertaken using a Vapourtec UV-150 photochemical reactor having a single 1mm bore fluoropolymer reactor of 10ml volume. A Vapourtec E-Series (easy-MedChem) system is used to pump solvents, and control the reactor.

LED technology is constantly improving. Many reactions use UV wavelengths, which are traditionally obtained via mercury lamps, with or without filtering to exclude unwanted wavelengths. However, LEDs provide advantages over mercury lamps including safety, efficiency, reduction in heat production and increased selectivity in the wavelengths output. Vapourtec have tested and compared different light sources previously in application note 41. The light source used in this application note is Vapourtec's 60 Watt Gen-2 LED at 365nm wavelength.

The reagent used for this reaction is 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione, which undergoes an intramolecular cycloaddition at a wavelength of 365nm to form a cage compound, pentacyclo(5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$)undecane-8,11-dione, as shown in scheme 1. The reaction scheme is straightforward with few factors to consider. Therefore this reaction is ideal for demonstrating throughput possibilities without additional variables as might be the case should other reagents or catalysts be employed.

Method

Setup

The flow reactor was set up using the Vapourtec E-series as shown in figure 1.

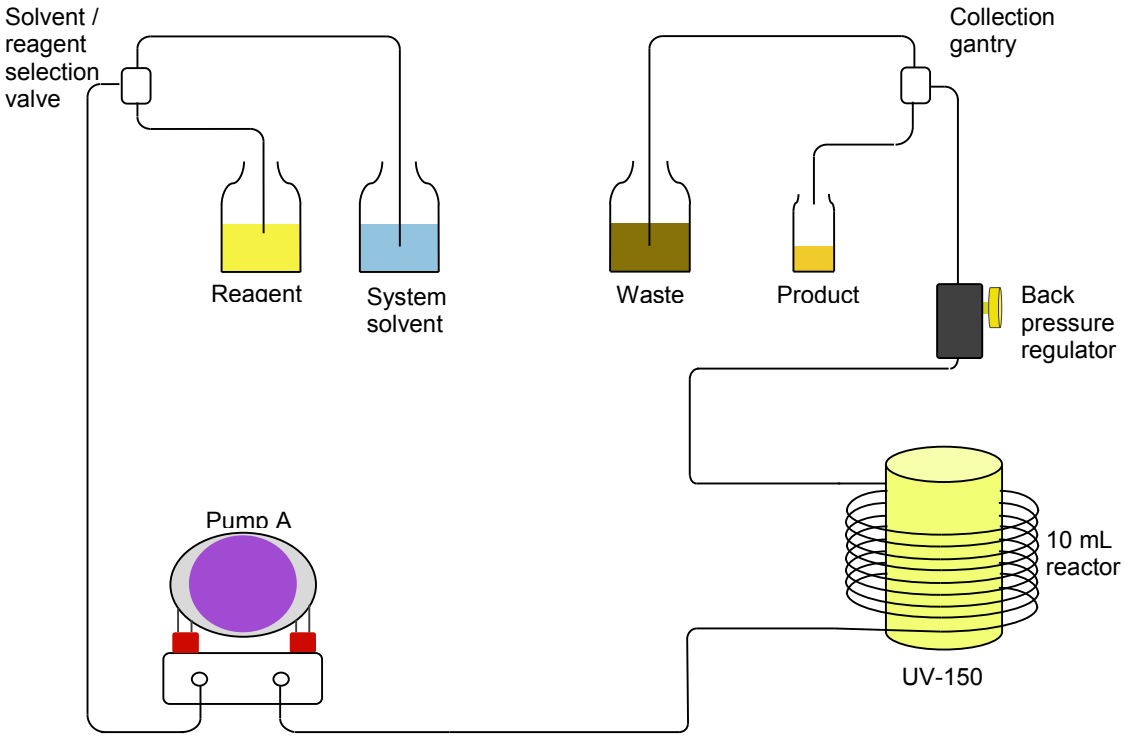


Figure 1

The UV-150 was fitted with a 10 mL reactor, a connecting tube in series and a manually adjustable back pressure regulator. The elution outflow was collected via the waste/collection switching valve.

Pump Tubing

The E-Series is fitted with two or three high performance V-3 peristaltic pumps and features a fluoroelastomer tube as its core. The pumps feature more than one different tube type to ensure the largest range of chemical compatibility. Therefore the correct selection of tubing is crucial for any given reaction.

A table showing recommended tube type compatibility with a wide selection of solvents, acids and bases is available within the E-Series manual and also built into the user interface software.
It is important to note, each V-3 pump can achieve a maximum of 10 mL/min.
The solvent used was ethyl acetate; therefore the blue tubing was selected for this study.

Reagents

All reagents and solvents used were purchased from Sigma-Aldrich.

Reagent A – 5ml solution of (0.1-0.8M) 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione in ethyl acetate.

System Parameters

System solvent:	Ethyl acetate
Solution A:	0.1 – 0.8M 1,4,4a,8a-tetrahydro-endo-1,4-methanonaphthalene-5,8-dione in ethyl acetate
UV Light Sources:	LED generation 2 (365nm)
Flow rate A:	1 – 10 mL/min
Reactor volume:	10 mL reactor
Reactor temperature:	0 – 60°C
Back pressure regulator:	Atmospheric pressure

The reaction process followed the sequence of steps listed below:

1. Prepping the system
   The system was prepped by running the system solvent through the pump and reactor and ensuring everything all connections are correct and reagents prepared.

2. Product pumping and collection
   Each reaction was run automatically using the FlowWizard software on the E-Series (FlowWizard is standard on easy-MedChem variant). After prepping the system, the parameters were set for the reaction and was completed, with FlowWizard accurately collecting the desired amount of product from the steady state using the automatic valve mounted on the collection gantry.

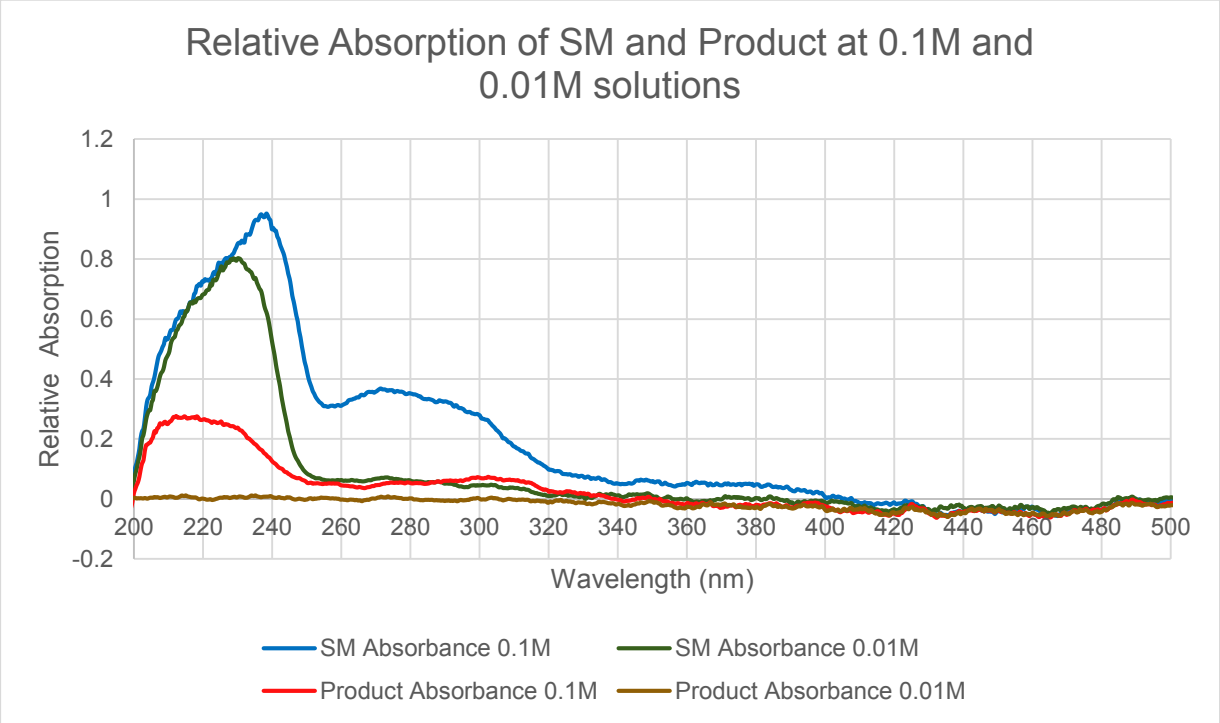
3. Analysis
   A small amount of the resulting product was analysed by HPLC and NMR. The conversion was determined from NMR spectra.

Results and Discussion

The reaction is a single compound, direct intramolecular 2+2 cycloaddition without the use of a catalyst, which leaves very few variables to consider when examining the conversion and throughput. Additionally, the benefit of using an enclosed, temperature controlled UV-150 reactor with an LED light source keeps many reaction environment variables constant, including the output power, same exposure (i.e. same light transfer/leakage) and the same reactor. Therefore the only variables to test for the highest possible throughput in flow were temperature, concentration and residence/exposure time.

Absorbance of the starting material and product

From analysis, it was found that the starting material absorbed 365nm wavelength much more strongly than the product. The difference in absorption also accounted for the difference between HPLC and NMR spectra when determining conversions. Therefore the relative absorption of the starting material and product were compared (see graph 1).



Graph 1

It was found that the starting material absorbs light much more strongly than the product. A 0.1M solution of the product absorbed about 1/3 the amount of a 0.01M solution of the starting material. This is ideal for a photochemical reaction, ensuring that the product does not absorb photons in preference to the starting material. However, the absorption pattern at other wavelengths were also similarly biased towards the starting material, causing the HPLC spectra to be inaccurate for determining the exact conversion.

All the following results are based on conversion from NMR spectra.

Concentration (M)	Residence time (s)	Temperature (°C)	Conversion (%)	Throughput(g/h)
0.2	240	30	100.0	7.0
0.2	90	30	95.6	13.3
0.2	90	0	94.5	13.2
0.2	90	15	95.8	13.4
0.2	90	60	94.0	13.1
0.1	45	30	90.4	12.6
0.4	180	30	99.0	13.8
0.8	360	30	99.5	13.9

Table 1

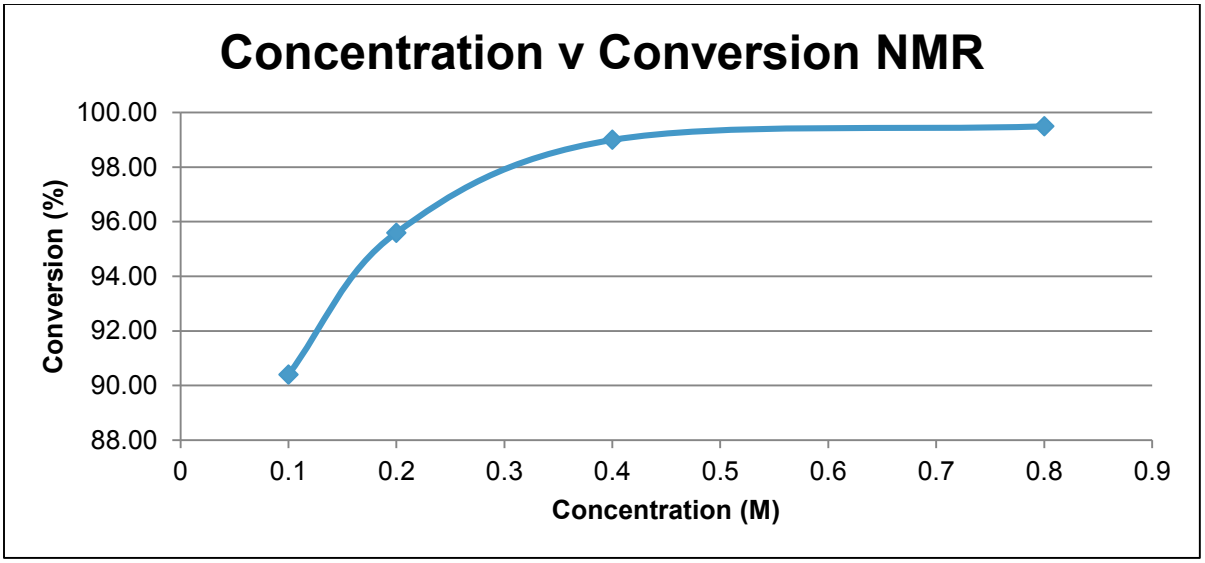
Effect of temperature

From the results, increasing or decreasing the temperature does not significantly affect the conversion or throughput of the reaction. There was no observed change to the product appearance or any change/additional peaks seen in the HPLC or NMR spectra. This indicates that the reaction is temperature independent and that there are no further interactions occurring at temperatures in the tested range (0 to 60°C). There was found to be no benefit in throughput or conversion of altering the temperature from room temperature.

Effect of concentration and residence time

Concentration and exposure time were found to play a big part in the resulting throughput of the reaction. As seen from the results, given enough time, the reaction will go to complete conversion. Increasing the flowrate to reduce the residence time was seen to decreases the conversion. This is clearly because the time available is reduced for the starting material to absorb a photon and undergo a 2+2 cycloaddition. This may result in a slightly higher throughput, but with incomplete conversion. Incomplete conversion is not ideal due to a potential waste of starting material and the requirement for subsequent work up.

When investigating the concentration, the residence time was changed in proportion to the concentration of the staring material. This was to ensure the identical theoretical molar ratio of photons to starting material was maintained. As shown from the results, increasing the concentration gave an increased conversion, and correspondingly higher throughput. The trend is shown in graph 2, this indicates (possibly unsurprisingly) that the absorption of available photons was more efficient at higher concentrations. We have previously shown in Graph 1 that the product does not absorb photons strongly. The higher concentration of product has a minimal effect on the reaction performance over the range of concentrations studied.



Graph 2

This pattern is likely a mixture from several factors. Since the starting material absorbs much more strongly than the product, a higher concentration means more photons can be absorbed with no interference from the product and a higher probability that a cycloaddition occurs. Further, since the residence time was increased also, and with no competing absorption, there is more time for all the starting material to react.

As a result, to obtain the highest throughput would be to use a high concentration and longer residence time rather than shortening the residence time with a lower concentration comparatively.

Conclusion

This application note set out to demonstrate the throughput capabilities of photochemistry with an uncatalysed intramolecular cycloaddition using only a single 10 mL reactor and only a small 60 Watt LED array. A relatively high throughput of ~14 g/hour was achieved. The application note sets some ground work for further reactor advances. It is not unreasonable to envisage the next step-up in Vapourtec photochemical reactor having a modest 1000 Watt LED array and achieving 250 g/hour (3 kg / day or 15 kg / week) throughput. Opening the door to greener possibilities for large scale and alternative synthetic steps.