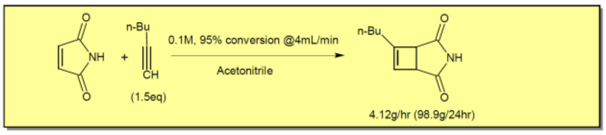
Application Note 36:
[2+2] Photocycloaddition of Maleimide and 1-Hexyne

Produced by Vapourtec

Abstract

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



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Background

Continuous flow chemistry offers easy access to scaling reactions from milligrams to kilograms, and many successful examples have been 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 and more efficient synthetic routes as well as access to new chemical space.

The main advantages of continuous photochemistry over conventional batch techniques are:

- Consistent light penetration
- Controlled exposure times
- Precise temperature control
- Removal of photochemical products from the irradiated area
- Easy scalability

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

The [2+2} photocycloaddition of Maleimide and 1-Hexyne is a well established continuous photochemical reaction[1]. Due to the precise control of the irradiation time this transformation has been shown to be superior to the equivalent batch conditions when performing this problematic photochemical reaction on a larger scale.

This reaction was carried out with the UV-150 photochemical reactor to bench-mark the UV-150 against current proven technologies.

When considering continuous photochemistry it is useful to consider 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. 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.

Method (Optimization)

The aim of this work was to demonstrate the [2+2] photocycloaddition of maleimide and 1-hexyne under continuous photochemical irradiation.

Setup

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

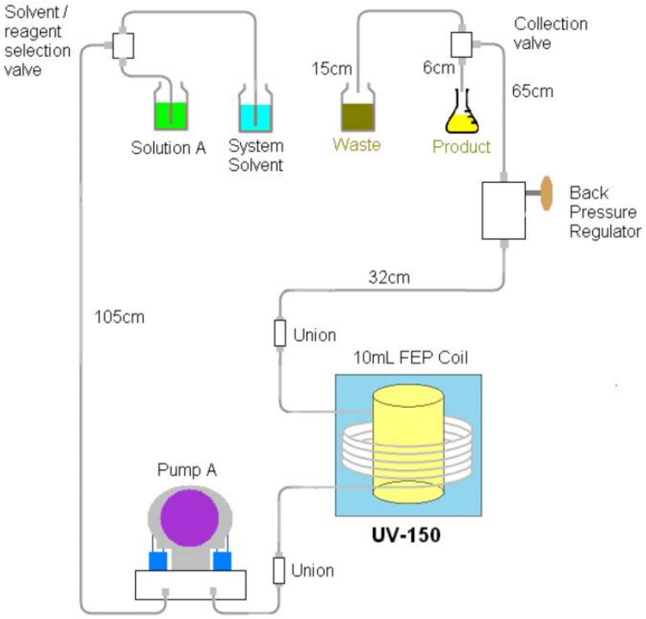


Fig 1: E-Series Setup

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

It is to be noted that the V-3 pump used by the E-Series is an advanced peristaltic pump, 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 the **BLUE** tube was used for the acetonitrile solution

Reagents

All reagents and solvents were used as purchased from Aldrich;

Reagent A

0.1 M Maleimide (1.0 eq), 1-Hexyne (1.5 eq) in Acetonitrile

System Parameters

System solvent:	Acetonitrile
Reagent A:	0.1 M Maleimide (1.0 eq), 1-Hexyne (1.5 eq) in Acetonitrile
UV Light Source:	Medium pressure pure H g lamp set to 120 W, quartz filter only
Flow rate A:	variable (1 - 8 mL/min)
Stiochiometry A:B	fixed 1.5 eq B)
Reactor volume:	10 mL FEP reactor.
Reactor temperature:	30 °C, Cooled using the Vapourtec cooling module
Back pressure regulator:	4 bar set with the variable BPR

The optimization reactions followed the sequence of event listed below;

1) *Priming the pumps with acetonitrile (MeCN):* Both selection valves were set to 'Solvent' and the pumps were `primed with THF. 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 1 was set to 'Reagent', the prime function selected and the line connecting the valves to stock bottle 1 was filled with **Solution A**. The selection valve was set back to 'Solvent' and THF pumped through the lines using the 'prime' function.
3) *Reaction optimisation:* A selective range of conditions were run using the Easy-Scholar™ software. Flow rates were varied between 1 – 10 mL/min at a fixed stoichiometry (1.5 eq 1-Hexyne) in a 10 ml FEP reactor at 30 °C. The reactor was cooled using the Vapourtec cooling module.
4) *Work-Up and Analysis:* Using the Vapourtec dispersion model to determine the region of steady state a sample of the reaction was collected via the E-Series collection gantry. The sample was evaporated to dryness in-vacuo and analysed by ^{1}H NMR (DMSO-d6)

Results and Discussion

Our initial reactions were carried out at 0.1 M concentrations at flow rates of between 1 mL/min and 8 mL/min. The effect of increasing the flow rate through the reactor at a constant 120W reduced the conversion to the product relative to the maleimide (determined by NMR analysis).

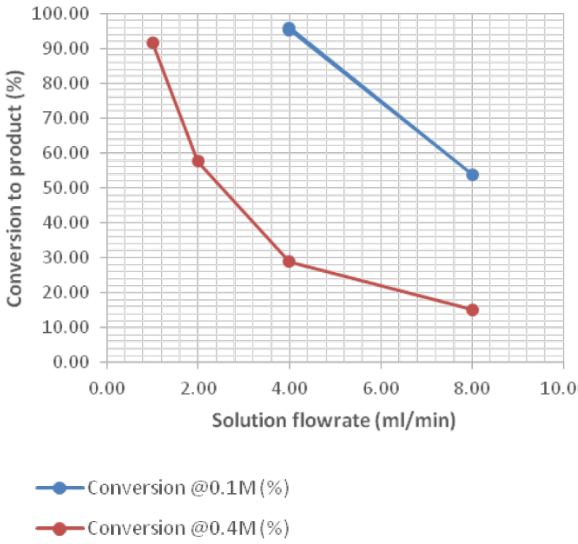
At the 0.1 M concentration a flow rate of 4 ml/min gave a conversion of 95%, flow rates below this showed no starting material remaining by NMR. Duplicate reactions over two days showed exact reproducibility.

This was expected as decreasing the throughput of the reagent allowed the reaction mixture to absorb more photons.

Reactions were then carried out at a 0.4 M concentration at 1.0 ml/min, 2.0 ml/min, 4.0 ml/min and 8.0 ml/min. Again by increasing the flow rate and therefore throughput of the reaction mixture the conversion to the product was observed to reduce.

The optimized flow rates for the reaction carried out at 0.1 M and 0.4 M concentrations showed that the same throughput of the Maleimide (mmole / min) was required further illustrating the significance of treating the lamp source as a reagent with a constant addition of photons

0.1 M, 95% conversion @ 4 mL/min = 0.4 M, 92% conversion @ 1 mL/min

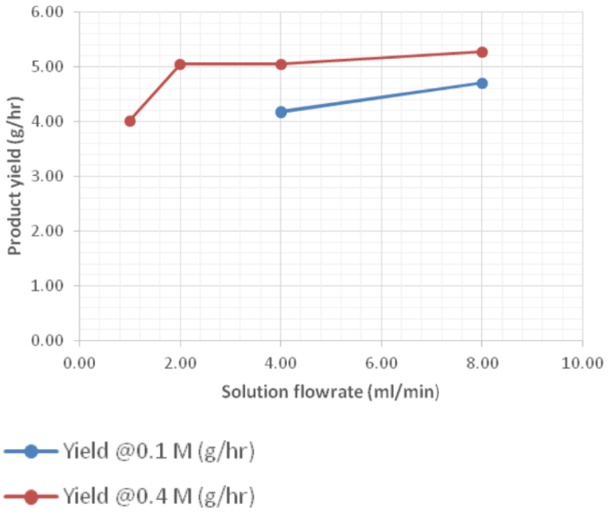


Conversion to Product under different conditions of concentration and flow

The graph below shows that under the condition where starting material is not entirely consumed the product yield (calculated from the conversion by NMR) is independent of flow rate. This result is as expected and is due to the constant lamp output (photons / min). It is also interesting to note:

0.1 M concentration at 4.0 ml/min showing a throughput of 4.1 g/hr.

0.4 M concentration at 1.0 ml/min showing a throughput of 4.0 g/hr.



Product yield (calculated conversion by NMR) under different conditions of concentration and flow

It should be noted that all the optimization reactions were carried using a quartz filter and the reaction irradiated with the medium pressure mercury discharge at 120W. When the effect of the reaction temperature was explored the conversion to the product decreased.

When the reaction temperature was increased from 30 °C to 60 °C the conversion decreased from 95% to 86% with a 0.1 M solution at 4 mL/min.

Based on a 100% conversion at 0.1 M with a flow rate of 4 mL/min our results give a throughput of 4.32 g/hr. The results agree well with the published results1 from Kevin Booker- Milburn Group's results for the large bore triple wound Vycore reactor (reactor 3) in terms of throughput / 100 watts of lamp power.

Booker-Milburn (large bore, 3 windings, Vycore, 400 watt): 102 g/24 hr/100 watts (280 mL internal volume)

Vapourtec (lamp power at 120 watt): 100 g/24 hr/100 watts (10 ml internal volume)

The Vapourtec FEP reactor has a much smaller internal volume compared with the Booker-Milburn FEP reactor. A smaller reactor volume allows smaller amounts of material to be committed to optimize reaction conditions; this can be significant when substrate is limited.

Scale-up Reaction

To test the scale up potential of the photochemical reactor a larger quantity of the reaction mixture was processed over an extended period of time.

Solution A (0.1 M, 12 mM, 120 ml) was processed at 4 mL/min under the same conditions (120W lamp power) over 30 mins. The reaction mixture was evaporated to dryness in-vacuo and the resultant residue purified by column chromatography (SiO_2, 20% EtOac/Heptane) to give a pale yellow oil Yield = 1.66 g, 77%

Wavelength Filtering

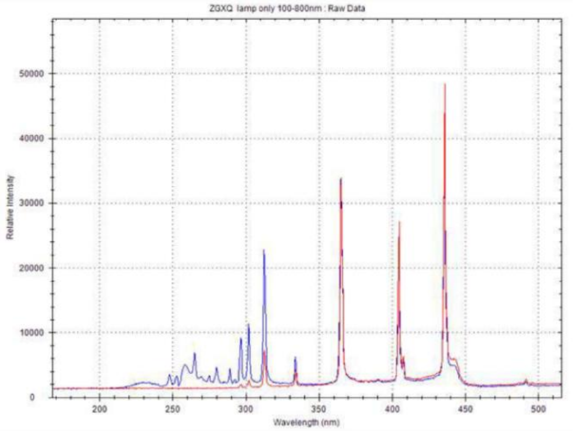
When undertaking photochemical reactions it is highly advantageous to measure the wavelengths and spectral intensity that the reagents are exposed to. It is also valuable to measure the degree of absorption by reactants at different wavelengths. The UV-150 is provided with the ability to attach a fibre-optic probe and spectrometer to 'look through' the reactor towards the lamp. In this way we can measure the relative spectral intensity of exposure of the reactants in real time and understand the effects of using a range of bandpass and longpass filters.

To investigate the effect of using wavelength filtering two experiments were looked at using a single experimental condition and replacing the quartz filter with a pyrex filter.

0.1 M Solution A, 4 mL/min at 60 °C using a Quartz filter - 87%

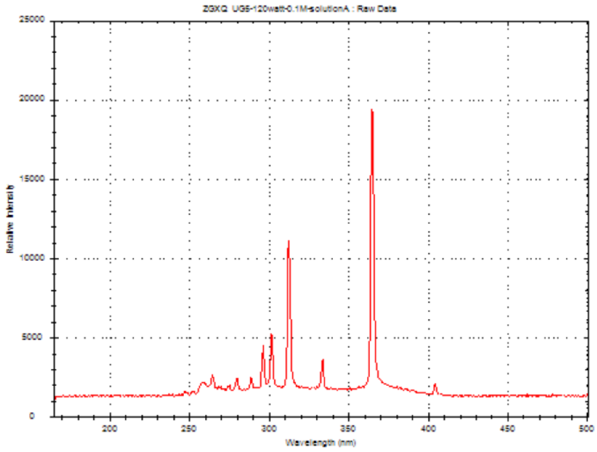
0.1 M solution A, 4 mL/min at 60 °C using a Pyrex filter - 24%

The following spectra show the wavelengths and relative intensities of the lamp with both quartz and pyrex filters in place. Comparing the two spectra (Blue is Quartz) it is clear that the pyrex filter dramatically reduces the intensity of the lamp output and removes all wavelengths below 290 nm.

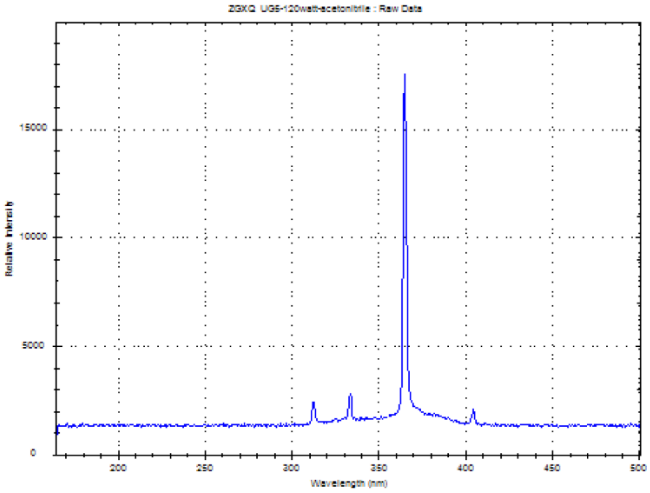


Using the spectrometer to view the reactor we were able to identify the specific wavelength absorption of our system solvent (acetonitrile) passing through the reactor and then the wavelength absorption of the reaction mixture as it passed through the reactor.

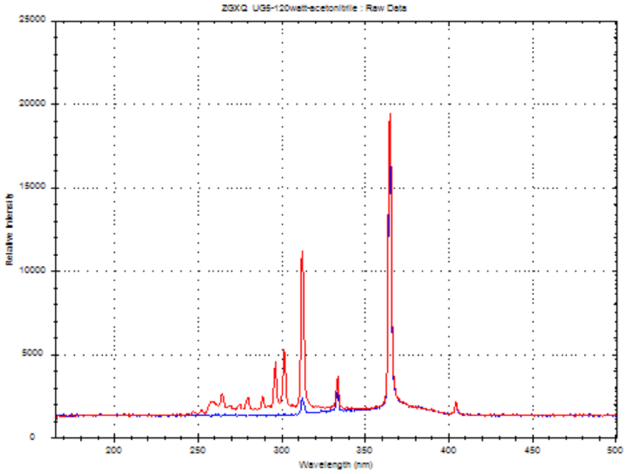
Spectra with a pyrex filter and FEP reactor + Acetonitrile at 4 ml/min



Spectra with a pyrex filter and FEP reactor + Solution A at 4 ml/min



Above two spectra overlaid



The spectra clearly show the wavelengths absorbed by the components in the reaction. They also show that the wavelengths of interest is in the region between 250 – 330 nm. This range of wavelengths was earlier shown to be is significantly attenuated by the pyrex filter. Armed with this information it is clear why the conversion is reduced when using a pyrex filter compared with the quartz filter.

Using this approach to further understand any photochemical reaction and having a range of band-pass and long-pass filters to select a desired range of wavelengths is a valuable tool.

Conclusion

The precise control of the irradiation time, temperature control and wavelength filtering has been shown to be crucial in the [2+2] photocycloaddition of maleimide and 1-hexyne. The same reaction conditions carried out in a batch reaction would be very difficult to achieve.

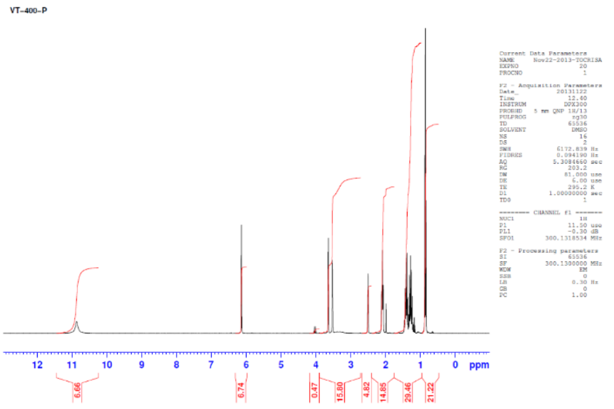
The UV-150 reactor coupled with the Vapourtec flow chemistry platform has been shown to perform reaction of this type with equivalent throughputs measured when compared to existing continuous photochemical technologies.

The unique and easy-to-use design of the UV-150 gives access to continuous photochemistry not readily available to most chemists. With a safe and convenient tool the UV-150 now gives chemists the ability to start to think photo-retrosynthetically, develop new synthetic routes and opens up novel chemical space and molecules.

Reference

1) Benjamin D. A. Hook, Wolfgang Dohle, Paul R. Hirst, Mark Pickworth, Malcolm B. Berry and Kevin Booker-Milburn, J. Org. Chem., 2005, 70, 7558-7564

NMR Analysis



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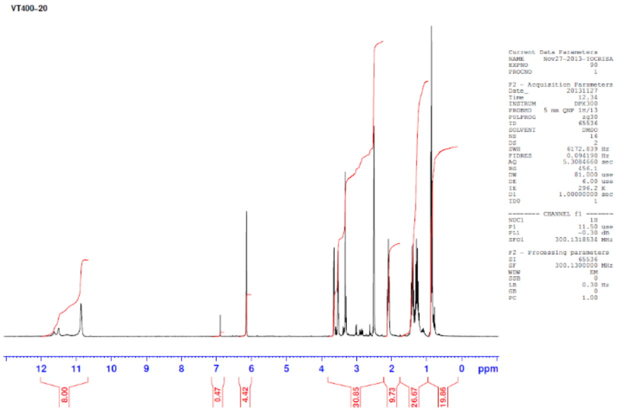

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^{1}H NMR, 300 MHz, DMSO-d6 VT400-P. Product supplied by University of Bristol.