Application Note 66:
230% increase in throughput of a photocycloaddition demonstrated by Vapourtec High Power LED

Produced by Vapourtec

Abstract

This application note demonstrates a 230 % increase in throughput on the direct [2+2] cycloaddition of maleic anhydride with ethene to form a cyclobutane motif by using the new Vapourtec's 365 nm High Power LED.

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

Background

The [2+2] photocycloaddition is undisputedly the most important and most frequently used photochemical reaction, and has been the focus of a review by Bach et al [1].

It can be particularly useful for the synthesis of highly functionalized cyclobutanes of interest in drug discovery and natural products synthesis [2],[3].

Recent publications [4] reported one of the simplest examples [5], the photocyclization of ethene to maleic anhydride as Figure 1 summarizes. Noting the practical difficulties associated with this chemistry in batch photochemical reactors, not least of which is maintaining a suitably high concentration of ethene, the scarcity of photochemical reactors capable of working at pressure and the very modest batch throughput, we hereby seek to show the advantages of the Vapourtec UV-150 photochemical flow reactor, and the steps that can be taken to avoid some common pitfalls of photochemical reactions using the example outlined by Naber [4].

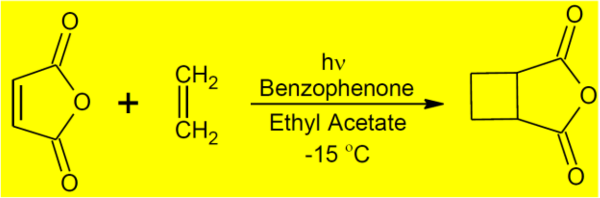


Figure 1 – [2+2] photocycloaddition of ethene to maleic anhydride

Based on Naber's work, we took the optimized conditions as a platform to compare the effect of increasing photon flux on conversion to the desired product.

Benzophenone was used as photosensitizer, which would ensure photons of wavelength over 300 nm would excite benzophenone and then transfer that energy to maleic anhydride.

Setup

All reactions were performed using a Vapourtec easy-Photochem, with a UV-150 reactor. Two different 365 nm UV sources were used:

- A Generation 2 UV LED with an input power of 62 W.
- A High Power LED with an input power of 150 W.

Figure 2 – Picture of the 365 nm High Power LED

Taking advantage of the V-3 pumps' versatility:

- **Pump A** delivered maleic anhydride solution
- **Pump B** delivered ethene gas to the reactor
- **Pump C** was set as active backpressure regulator.

The reagent and ethene were mixed in a tee-piece and passed into a Vapourtec UV-150 photochemical flow reactor as Figure 3 shows.

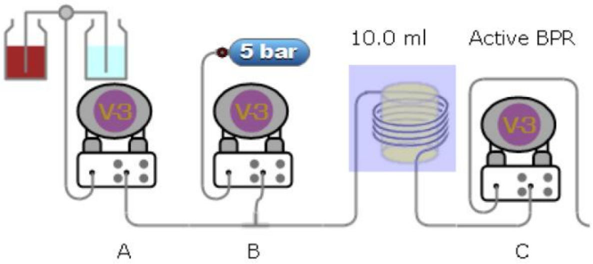


Figure 3 – Schematic of the E-Series used during this application note

To prevent any possibility of backfilling the ethene line, a check valve was placed between ethene gas cylinder and the tee-piece.

Cooling to -15 °C was achieved using a Vapourtec cooling module filled with pelleted dry ice. In this case, dry compressed air was used as cooling gas.

System pressure was maintained at 6 bar throughout the experiments. Product was collected using the collection valve and dried in vacuum before analysis.

Conversion and yields were calculated from 1H-NMR analysis, correlating the intensity of the product by maleic anhydride.

Reagents

Ethene gas was purchased from BOC.

Maleic anhydride, benzophenone and anhydrous ethyl acetate were purchased from Sigma Aldrich.

System Parameters

System solvent: Ethyl acetate
Solution A: 1.0 M and 0.5 M solutions of maleic anhydride were prepared, including 40 mol% of Benzophenone
Flow rate A: 0.250 and 0.500 ml/min
Solution B: Ethene gas, neat
Inlet pressure on pump B: A BOC ethene gas cylinder was equipped with a low-pressure regulator outputting 5 bar (after passing through a check valve)
Flow rate B: 6.2, 12.4, and 24.8 scc/min
Reactor volume: 10 ml
Reactor temperature: -15 °C
Back pressure regulator: V-3 pump C set as BPR at 6 bar.

Procedure

Both solvent and reagent bottles were degassed for 30 minutes with N_2 prior to use, and they were kept under inert atmosphere.

To ensure ethene and ethyl acetate solution reach equilibration within the reactor, both pump A and B were pumping at the reaction conditions for 40 minutes prior switching to reagents.

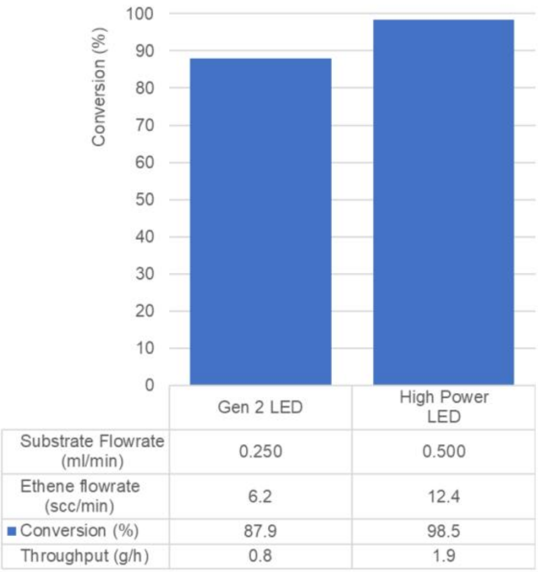
Crude product was dried in vacuo and analyzed by ^{1}H-NMR (400 MHz Bruker NMR, samples were diluted with $CDCl_3$).

Results and Discussion

As the quantum yield of this reaction is less than 1, we anticipated that increasing the substrate concentration while increasing the photo flux by the same multiple should provide the same yield in the scale up reaction.

To test this hypothesis, the same solution of maleic anhydride (0.5 M) was passed at two different flowrates, 0.250 and 0.500 ml/min, effectively doubling the moles of substrate per minute.

Ethene flowrate was modified accordingly to ensure a 2 fold excess present in all the reactions. Figure 4 compiles the reaction conditions and shows the conversion and throughput when using Gen 2 LED and the High Power LED.



	Gen 2 LED	High Power LED
Substrate Flowrate (ml/min)	0.250	0.500
Ethene flowrate (scc/min)	6.2	12.4
■ Conversion (%)	87.9	98.5
Throughput (g/h)	0.8	1.9

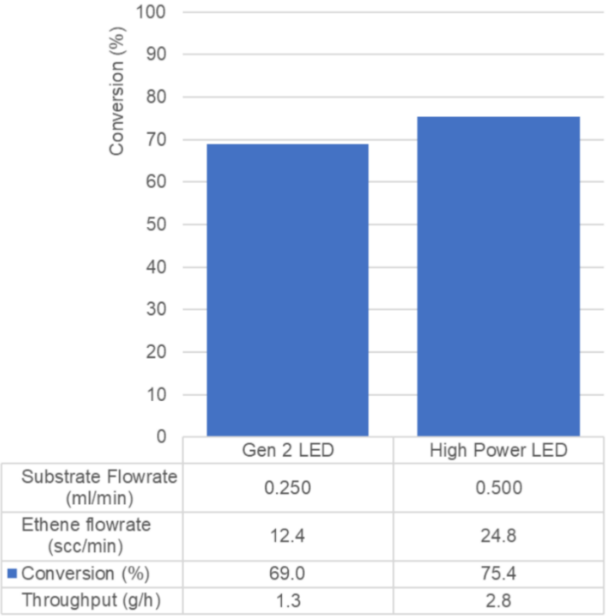
Figure 4 – Conversion rates of [2+2] photocycloaddition at two different UV intensities starting with a 0.5 M solution of maleic anhydride

By using the high-power LED, throughput was increased in line with our expectations however conversion also increased to 98.5%, almost complete conversion. To fully assess the relative performance increase of the HP LED it was clear that we needed push the conditions further.

The next step was to push the reaction conditions to a photon deficit state for the HP LED, allowing us to understand the limitations of the system.

Therefore a 1 M solution of maleic anhydride was used in the same conditions as before.

Figure 5 compiles the reaction conditions as well as the results.



	Gen 2 LED	High Power LED
Substrate Flowrate (ml/min)	0.250	0.500
Ethene flowrate (scc/min)	12.4	24.8
■ Conversion (%)	69.0	75.4
Throughput (g/h)	1.3	2.8

Figure 5 – Conversion rates of [2+2] photocycloaddition at two different UV intensities starting with a 1 M solution of maleic anhydride

Although conversion dropped to 70 %, a 2.8 g/h throughput was achieved when the high-power LED was used.

Conclusion

Using the UV-150 flow photochemical reactor we have investigated a [2+2] photocycloaddition of relevance in the pharmaceutical industry.

We have successfully developed a new High Power UV LED that allowed an increase the throughput of the reaction by 230 %.

Supporting information

NMR

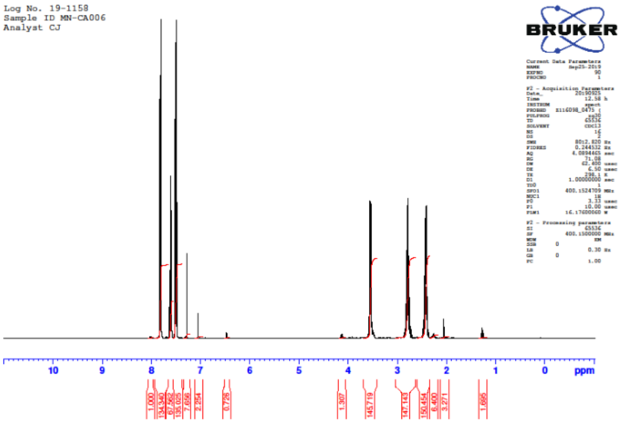


Figure 6 – ^{1}H-NMR of [2+2] photocycloaddition carried out at 0.5 M and using the High Power LED. δ 2.35-2.41 (m, 2H), 2.70-2.78 (m, 2H), 3.49-3.53 (m, 2H) ppm, which matches previously reported data for this compound [6]. Signals in the 7-8 ppm region are benzophenone

References

[1] S. Poplata, A. Tröster, Y.-Q. Zou, and T. Bach, "Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions," *Chem. Rev.*, vol. 116, no. 17, pp. 9748–9815, Sep. 2016.

[2] A. Sergeiko, V. V Poroikov, L. O. Hanus, and V. M. Dembitsky, "Cyclobutane-containing alkaloids: origin, synthesis, and biological activities," *Open Med. Chem.* J., vol. 2, pp. 26–37, Apr. 2008.

[3] Vapourtec, "Application Note 59 – Automated photochemical library synthesis." [Online]. Available: https://www.vapourtec.com/flow-chemistry-resource-centre/application-note-59-automated-photochemical-library-synthesis/

[4] E. B. Corcoran, F. Lévesque, J. P. McMullen, and J. R. Naber, “Studies Toward the Scaling of Gas-Liquid Photocycloadditions,” *ChemPhotoChem*, vol. 2, no. 10, pp. 931–937, Oct. 2018.

[5] S. Faure et al., “Stereoselective Chemoenzymatic Synthesis of the Four Stereoisomers of l-2-(2-Carboxycyclobutyl)glycine and Pharmacological Characterization at Human Excitatory Amino Acid Transporter Subtypes 1, 2, and 3,” *J. Med. Chem.*, vol. 49, no. 22, pp. 6532–6538, Nov. 2006.

[6] E. J. Toone and J. B. Jones, “Enzymes in organic synthesis 49. Resolutions of racemic monocyclic esters with pig liver esterase.,” *Tetrahedron: Asymmetry*, vol. 2, no. 3, pp. 207–222, Jan. 1991.