



Ozonolysis Combined with Hydrogenation for the Simple Synthesis of Aldehydes in Tandem Continuous Flow

INTRODUCTION

While ozonolysis itself is a useful reaction in organic chemistry it is not performed regularly because of its hazardous nature. Under common laboratory conditions, the ozonide can decompose explosively during the quenching process because of its highly exothermic nature. Stringent safety regulations need to be obeyed to avoid this. In order to increase adoption of this useful technique, ThalesNano developed the O-Cube™ ozonolysis reactor which is designed to make ozonolysis safer by quenching the potentially explosive ozonides continuously on a small scale. The small scale nature of flow means that the temperature of both reaction steps is precisely controlled, significantly lowering the risk of a runaway reaction. The other downside to ozonolysis is that many quenching reagents, such as PPh_3 or NaBH_4 require extensive work up, while alternatives such as DMS give off an unpleasant odour. In order to enhance the performance of the O-Cube™ reactor further and simplify the workup procedure after ozonolysis, we have developed the combination of two flow systems where the intermediate of the ozonolysis reaction is converted to final product via hydrogenation in the H-Cube® continuous flow system (Figure 1). The setup also contains a ReactIR™ flow-cell, so the reactions can be monitored in real-time and optimized rapidly in order to reach a high selectivity through precise residence time control.



Figure 1. Tandem Continuous Flow Reactor and Analysis Setup

GENERAL PROCEDURE

After setting up the corresponding reaction parameters (see Table 1), the O-Cube™ reactor was started in Auto Mode. In the meantime parameters on the H-Cube® system were also set and the catalyst in the CatCart® column was preactivated by passing solvent through the system in the presence of hydrogen.

The ozonide solution from the O-Cube™ instrument was collected into a cooled (-30 °C) small sample vial. The solution was purged with nitrogen in order to drive out any excess of ozone prior to pumping into the H-Cube® instrument. The product (aldehyde) was collected at the outlet of the device.

In order to decrease the time spent for optimization of the reaction we have used a FT-IR inline monitoring by integrating the flow cell of the ReactIR™ (product of Mettler Toledo Autochem Inc.) and making measurements in the near IR range (650-4000 cm⁻¹) every 30 secs.

Before running each reaction, reference spectra of the solvent, the starting material and product were recorded, and the peaks of the solvent were subtracted from the starting material and product spectra. In the case of the products and starting materials we needed to find a specific wave number where the ReactIR™ system was able to continuously monitor the intensity of each compound (Figure 2) over time. The optimal reaction conditions were identified when the maximum intensity of the product could be recorded and where the peak of the starting material disappeared (Figure 3). The product mixture collected under the optimal conditions was evaporated to yield the product. The optimal conditions for each reaction and results can be seen in Table 1.



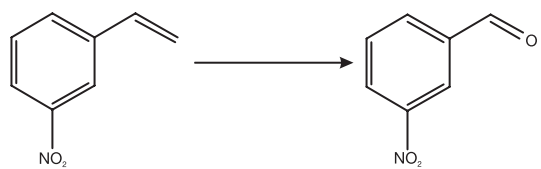
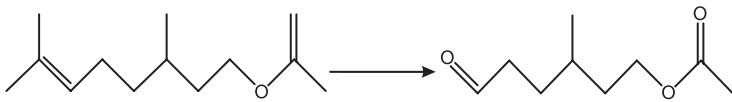
Reaction	Reaction conditions	Result
	c = 0.02 M in DCM O-Cube™: -30 °C, 1 mL/min, 50% O ₃ excess H-Cube®: RT, 30 bar, 1mL/min, 10% Pd/C	Isolated yield: 85% Purity*: >95%
	c = 0.04 M in EtOAc O-Cube™: -28 °C, 1 mL/min, 50% O ₃ excess H-Cube®: RT, 30 bar, 1mL/min, 10% Pd/C	Conversion**: quantitative Isolated yield: 80% Purity*: 90%
	c = 0.06 M in DCM O-Cube™: -9 °C, 0.7 mL/min, 50% O ₃ excess H-Cube®: RT, 30 bar, 0.7 mL/min, 10% Pd/C	Conversion**: quantitative Isolated yield: 77% Purity*: 100%
	c = 0.07 M in EtOH O-Cube™: -28 °C, 0.7 mL/min, 30% O ₃ excess H-Cube®: RT, 30 bar, 0.7 mL/min, 10% Pd/C	Isolated yield: 50% Purity*: 100%

Table 1: Reaction conditions and results, *: by ¹H-NMR, **: by TLC

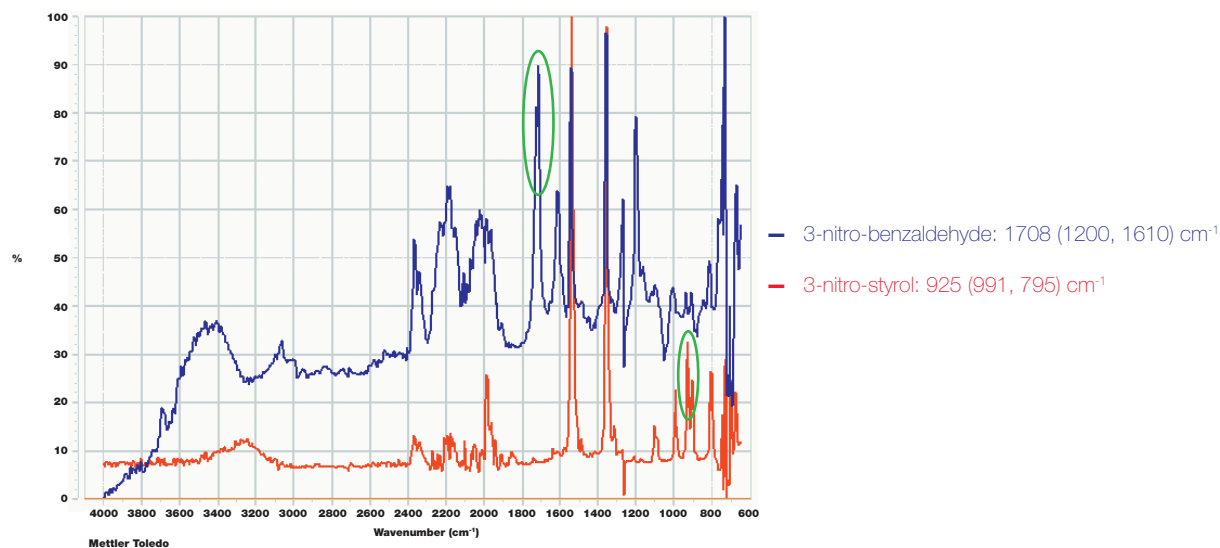


Figure 2: In-line FT-IR monitoring of ozonolysis of 3-nitro-styrol

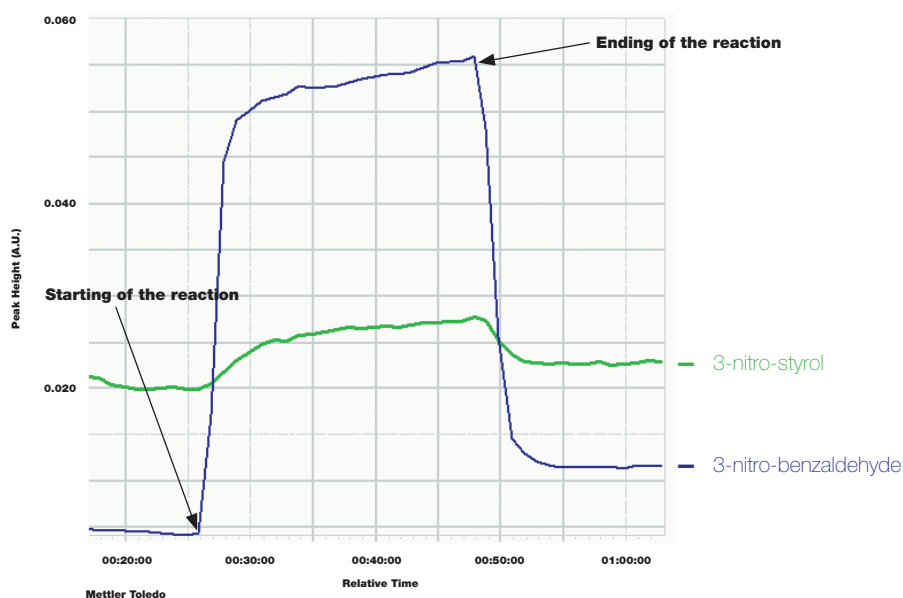


Figure 3. Reaction monitoring

CONCLUSION

We were able to perform two hazardous reactions, ozonolysis and hydrogenation, in a safe manner. We have demonstrated that the combination of two continuous flow instruments led to a significant speeding up of the work up process. To obtain the product only evaporation of solvent needed to be performed. No extensive work up procedure was necessary. The optimization time was reduced dramatically by employing the ReactIR™ system to monitor the reactions in real time. In light of these results it can be stated that we have worked out a green and effective process for the synthesis of aldehydes via ozonolysis and hydrogenation.

LEGAL INFORMATION

H-Cube and CatCart are registered trademarks, and O-Cube is a trademark of ThalesNano Inc., ReactIR is a trademark of Mettler-Toledo Autochem Inc..

REFERENCES

- [1] Irfan, M.; Glasnov, T. N.; Kappe, C.O.; Continuous flow ozonolysis in a laboratory scale reactor; *Org. Lett.*; **2011**; 13 (5); 984-7
- [2] Carter, C.F.; Lange, H.; Baxendale, I.R.; Ley, S.V.; Goode, J.; Gaunt, N.; Wittkamp, B.; ReactIR™ Flow Cell – A New Analytical Tool for Continuous Flow Chemistry Processing; *Org. Proc. Res. Dev.*; **2010**; 14; 393-404



O-Cube™ Ozonolysis Reinvented

The O-Cube™ is a ground breaking flow reactor designed to make ozonolysis and other low temperature reactions easier and safer to perform. The O-Cube™ makes ozonolysis safe enough to be performed in any lab environment by any level of chemist, so companies need not avoid or work around this important process any longer.

Specifications of O-Cube™

Flow rate range:	0.1 – 3 mL/min
Temperature range:	Ambient to -25 °C (lower temperature is possible with additional setup)
Pressure range:	1 bar (max. 6 bar)
O ₂ /O ₃ production range:	5 – 20 mL/min
Ozone production:	7 - 15% wt
Dimensions:	Width: 364 mm (14.33") Height: 471 mm (18.54") Depth: 495.5 mm (19.51")
Weight:	54 kg (119 lbs)
Voltage:	115 VAC - 230 VAC
Frequency:	50 - 60 Hz
Power consumption:	Max. 600 VA



H-Cube® Continuous Flow Hydrogenation Reactor

A revolutionary bench-top standalone hydrogenation reactor, uniquely combining continuous-flow microchemistry with endogenous on-demand hydrogen generation and a disposable catalyst cartridge system. It allows fast and cost-efficient hydrogenation with superior yield when compared to conventional methods.

Specifications of H-Cube®

Flow rate range:	0.1 - 3 mL/min
Temperature range:	Ambient to 100 °C
Pressure range:	1 bar to 100 bar
H ₂ production:	30 cm ³ /min in Full Hydrogen Mode 7 gas/liquid % in Controlled Mode
Dimensions:	Width: 26 cm (10.2") Height: 29 cm (11.4") Depth: 44 cm (17.3")
Weight:	12 kg (27 lbs)
Voltage:	100 VAC - 240 VAC
Frequency:	47 - 63 Hz

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