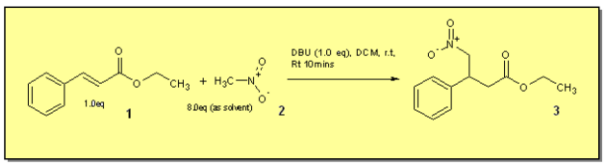
Application Note 21:

Michael Addition of Nitromethane to a Cinnamate Ester

Produced by Vapourtec

Abstract

This example illustrates the use of the Vapourtec R-Series flow chemistry platform to safely process an extremely energetic, reactive intermediate.



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

Background

The use of nitromethane in the pharmaceutical laboratory is often limited due to its reactive exothermic nature when deprotonated. This example illustrates how limiting the tube reactor size limits the hazardous nature of this reaction.

Setup (Initial Reaction Optimization)

The flow reactor was configured using a combination of the R2 Plus pump module and R4 reactor module.

A 5 ml PFA tubing reactor was used, with a 100 psi back pressure regulator (BPR) fitted in-line between the reactor outflow and the collection valve.

The system used two 2 ml sample loops, into which each of the reagents was loaded before the reaction.

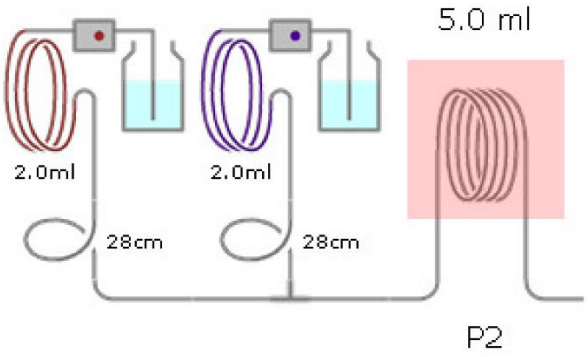


Figure 1 (Diagram exported from flow control software)

Reagent stock solutions A (2.3 M substrate 1 in nitromethane) and B (neat DBU) were prepared respectively.

The collection valve 'Collect' output was directed into 20 ml glass vials containing water (5 ml) to

quench the reaction product. The product was extracted from the subsequent partition, the organics washed with water, dried and evaporated to dryness *in-vacuo*.

Summary

System solvent: DCM
Reagent A: 2.3 M substrate 1 (46.5 mmol) in $MeNO_2$ (20 mL)
Reagent B: Neat DBU
Flow rate A: variable (125-500 µL/min)
Flow rate B: variable (125-500 µL/min)
Ratio A:B: 1:1 for all experiments
Reactor volume: 5 mL PFA
Reactor temperature: Rt - 60 °C
Residence time: Various
Back pressure regulator: 100 psi

Method

1. The system was flushed with DCM at 2.5 mL/min per pump and checked for leaks before pumping any reagents.
2. Priming the pumps with DCM: Both selection valves were set to 'Solvent' and the pumps were primed with DCM at 1.0 mL/min per pump.
3. Loading the sample loops with reagents: The selection valve for each sample loop was set to 'Load', the pumps set to 1 mL/min and the desired solution manually injected via the rheodyne valve input. Solution A in loop A and solution B into loop B.
4. Reaction optimization: A range of conditions were run manually. Residence times of 5, 10 and 20 minutes (flow rates of 500, 250 and 125 µL/min per channel) were run at three temperatures (25, 40 and 60 °C) in a 5 ml reactor.

It should be noted that a series of batch optimization reactions had been carried out at an earlier time investigating co-solvents, equivalents of $MeNO_2$ and a screen of organic bases and concentration.

Optimal conversion was observed at 25 °C (Rt) with a residence time of 10 mins.

Setup (Scale up)

The configuration was altered from the screening reactions. The sample loops were by-passed with the reagents introduced directly through the pumps.

The same stock solution originally prepared was used.

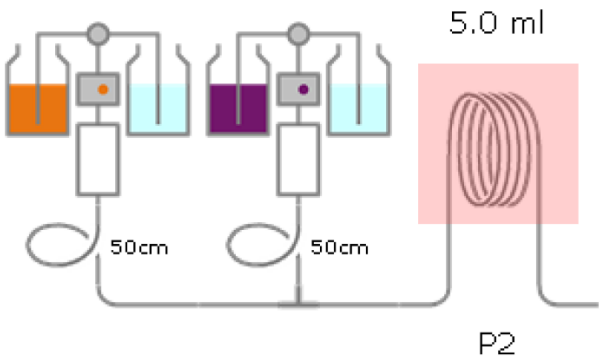


Figure 2. Configuration of Vapourtec R-series for scale up.

Summary:

System solvent: DCM

Reagent A: 2.3 M substrate 1 (46.5 mmol) in $MeNO_2$ (20 mL)

Reagent B: Neat DBU

Flow rate A: 250 µL/min

Flow rate B: 250 µL/min

Ratio A:B: 1:1

Reactor volume: 5 mL PFA

Reactor temperature: 25 °C

Back pressure regulator: 100 psi

Residence time: 10 minutes

Reaction time: 70 minutes (47 mmol of substrate 1)

Method (Scaleup)

1. The system was flushed with DCM at 1.0 mL/min per pump (with the BPR in place to give full operating pressure) and checked for leaks before pumping any acids.
2. *Priming the pumps with DCM*: Both selection valves were set to 'Solvent' and the pumps were primed with DCM at 1.0 mL/min per pump.
3. *Priming the pumps with reagents*: The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line connecting the valves to stock bottle 1 was filled with solution A. The selection valve was set back to 'Solvent' and DCM pumped through the lines for 2 minutes. The same process was repeated with line 2, solution B to fill the second reagent line.
4. The reaction was run according to the conditions above, using flow control software. Flow control software dispersion model was used to collect the steady state output.

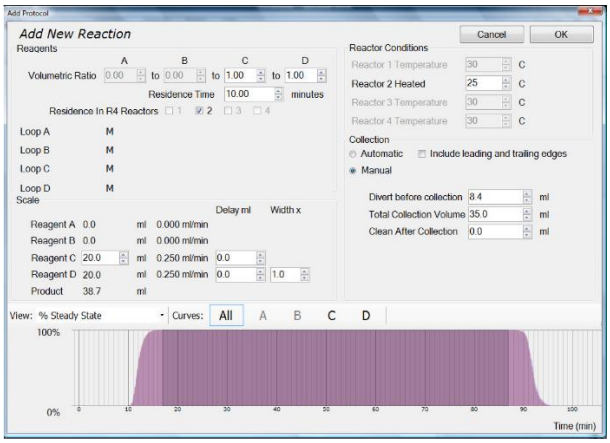


Figure 3. Reaction conditions and dispersion profile for scale up.

20 ml of solution A were processed and collected over 70 mins. After workup and purification by flash chromatography 8.82g (80%) of the desired product was isolated.

Conclusion

This study demonstrates the capability of the Vapourtec R-Series system to allow difficult to scale in batch reactions to be developed and optimized quickly. This application shows conditions that allow a safe and controlled scale up in flow.

Acknowledgements

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www.flowchemistrysolutions.co.uk