Microscale High-Throughput Synthesis in Continuous Flow

Victoire Laude[1], Manuel Nuño[1], Ricardo Labes[2], Claudio Battilocchio[3], Duncan Guthrie[1]

1 - Vapourtec Ltd, Park Farm Business Centre, Bury St Edmunds, UK. 2 - Syngenta, Jealott's Hill International Research Centre, Bracknell, UK. 3 - Syngenta Crop Protection, Schaffhauserstrasse, Stein, CH-4332, Switzerland

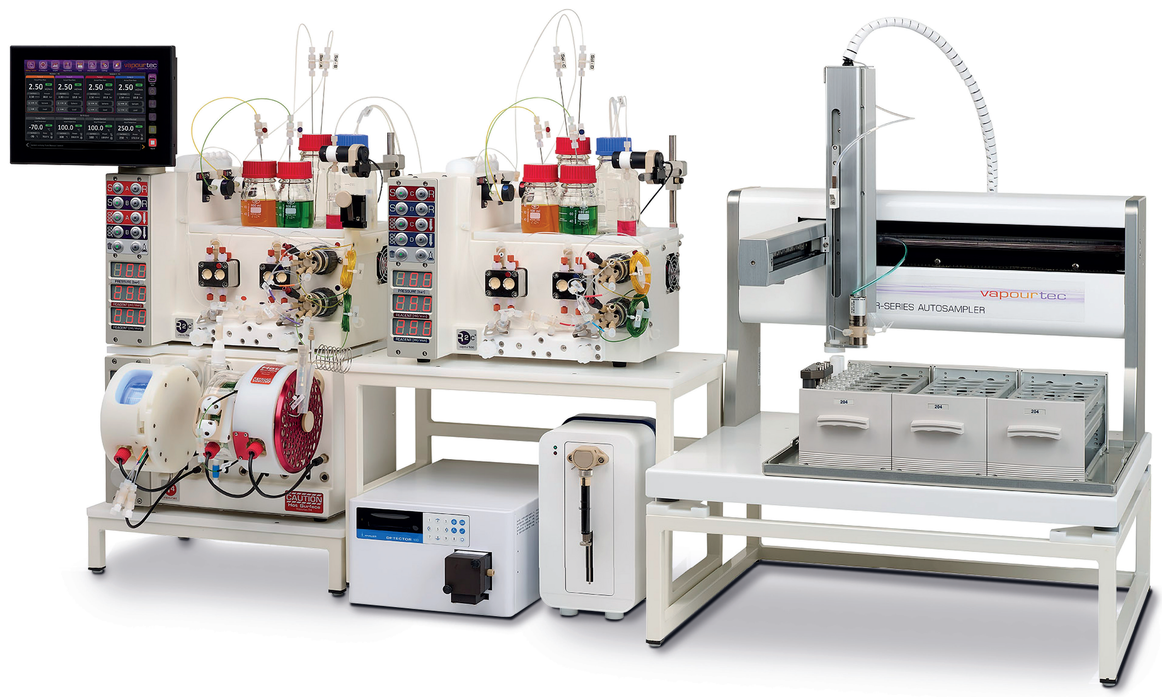
Introduction

Flow chemistry is a well-established method in research and development labs across academia and industry for screening of reagents and optimization of processes. It allows safer and faster reactions, but also better control over the reaction conditions, key for reproducibility.

Library synthesis in continuous flow provides ease of integration with advanced analytical equipment and Machine Learning, as well as performing reactions difficult to do in batch.

There are limitations that have previously limited the implementation of High-Throughput Synthesis in flow:

- **Dilution of the leading and trailing edges of reaction plugs.**
- **Dilution effects meaning sub 1 ml reaction plugs need small volume reactors that are prone to blocking combined with exceedingly low flowrates.**
- **Reaction plugs must exit the reactor before the next reaction enters limiting throughput.**



Minimum cycle time is typically 10-15 minutes

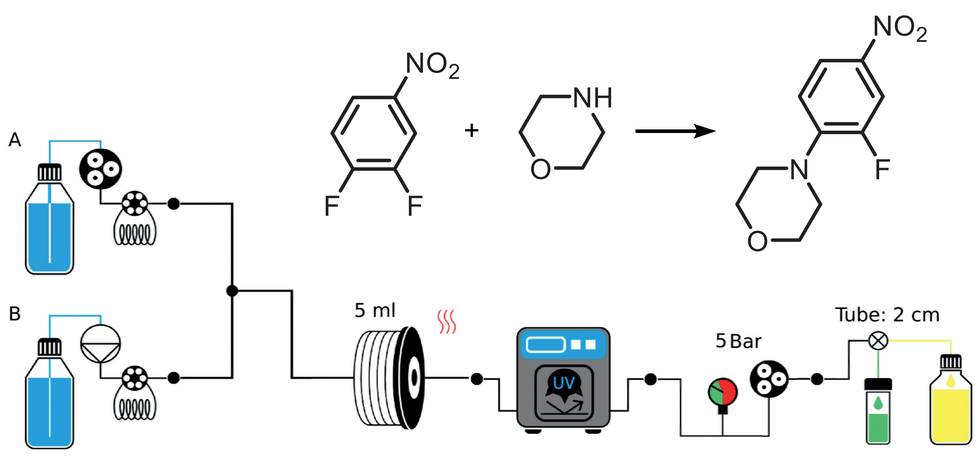
Vapourtec and Syngenta have been working on developing a solution based on Vapourtec's R-Series platform that will allow to run reactions with only 100- 250 µl of reagent and eliminating dispersion, with increased throughput, one reaction starts every 2-3 minutes.

Experimental setup

A Vapourtec RS-400 platform was used for this work.
The Vapourtec R-Series Software was used to run the reactions.
Collection was triggered by UV/Vis detection.

Robustness of this protocol was evaluated at different temperatures and pressures using a tracer.

Finally, reagents were prepared in DMF as reported by literature to perform a S_NAr at microscale.



Flow schematic used in this work

Results & Discussions

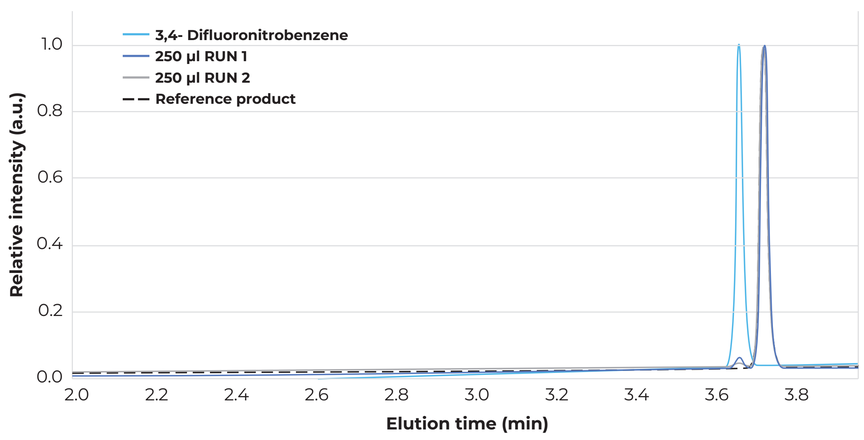
This approach to high throughput experimentation has proven reliable at pressures up to 20 bar and temperatures between -10 to 150 °C.

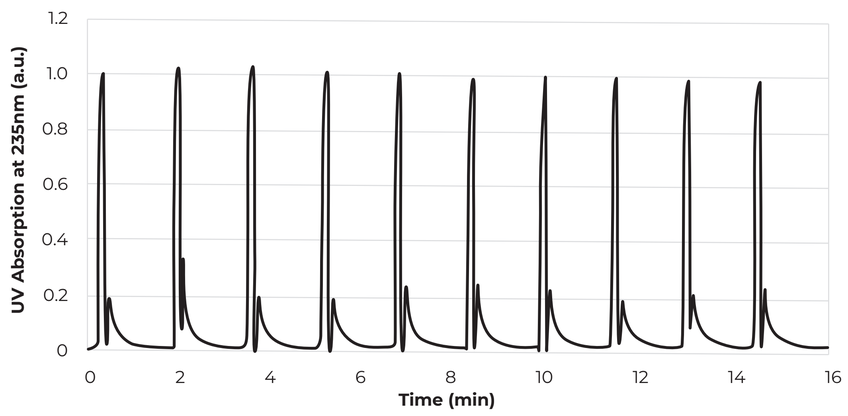
As dispersion is eliminated, reactions can start every 2-3 minutes without disturbing the reaction in front of the queue. This increases the throughput to over 20 samples per hour.

A S_NAr between morpholine and 3,4-difluoronitrobenzene was performed at 250 µl scale. The reaction conditions were taken from Application Note 2:

- **100 °C**
- **8 minutes residence time**
- **8 bar BPR**

Under these conditions, full conversion of the starting material was achieved, as previously reported.





UV absorption of 10 x 100 µl injections in 15 minutes.
Each plug had a 10 minute residence time inside the reactor.

Conclusion

We have successfully developed a protocol that allows the R-Series flow chemistry platform to perform high throughput synthesis in continuous flow, which will enable users to convert their lab into a high throughput platform:

- **Reagent usage has been reduced to from 500 to 100 µl of limiting reagent.**
- **Reaction plugs have constant concentration, there are no dilution effects**
- **The whole reaction plug can be reacted without significant wastage caused by dilution**
- **Users can now start reactions every 2 to 3 minutes**
- **This approach is compatible with both integration with a UPLC or automated collection for offline analysis**

References
[1] Vapourtec Ltd. Application Note 2 – Optimisation of Step 1 in the Synthesis of Linezolid using a 'Dual-CoreTM' Tubing Reactor. (2006).
[2] A Slug Flow Platform with Multiple Process Analytics Facilitates Flexible Reaction Optimization – F. Wagner et al. 2024 - Advanced Science

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T +44 (0) 1284 728659 **E** info@vapourtec.com **www.vapourtec.com**

Park Farm Business Centre, Fornham St Genevieve, Bury St Edmunds, Suffolk, IP28 6TS, UK