Novel Flow Technologies and Their Application in Organic Synthesis

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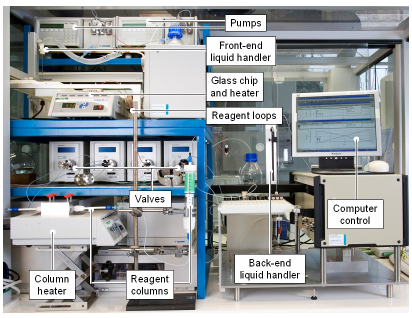
Introduction to Flow

Our group has pioneered the use of supported reagents for the synthesis of natural products and other biologically interesting molecules;[1] however, the discontinuous nature of the protocol coupled with slow reaction rates, high cost of the reagents limits the scalability and lead us to investigate other enabling techniques including microwave and flow systems.

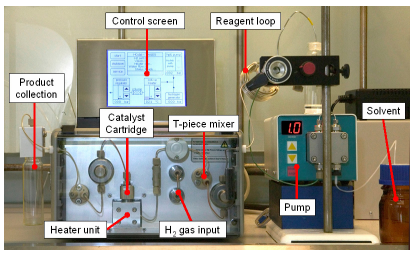
Flow-through processes enable precise mixing, rapid optimisation of reaction conditions, repeatability, generation and immediate use of potential hazardous intermediates and super heating of solvents. The reliability and facile scalability of these processes – either by using higher flow rates or by running the system for longer – bridges the often key gap between the medicinal chemist's couple of milligrams and the tens of grams required for property evaluation; thereby speeding the discovery process.

These combined advantages have driven multi-step flow processes to be developed; most notably the natural products Grossamide[2] and (±)-Oxomaritidine[3] have been synthesised without aqueous work-ups or chromatographic purification.

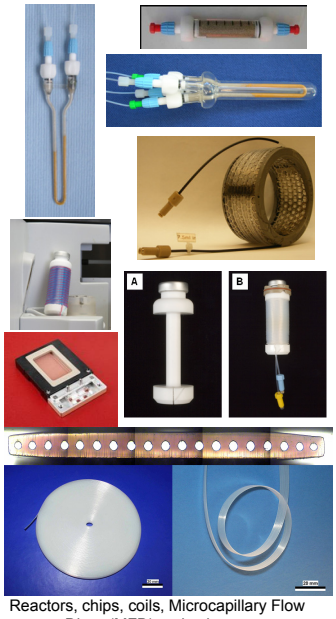
Tools of the Trade



Bespoke flow reactor



H-Cube hydrogenation system

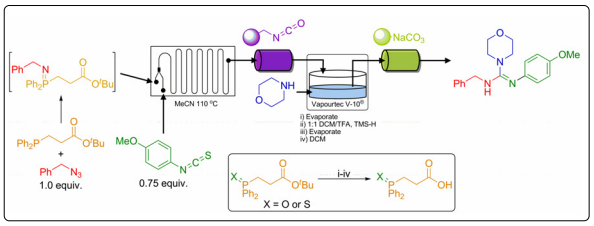


Reactors, chips, coils, Microcapillary Flow Discs (MFD) and columns

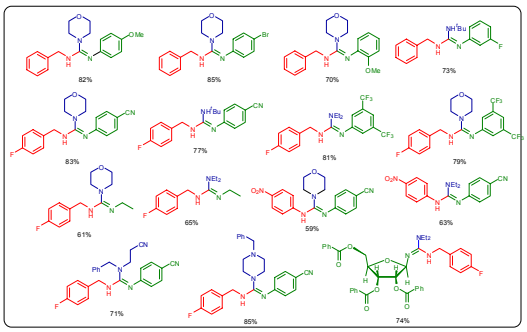
Tagged Reagents[5]

To overcome some of the disadvantages associated with solid supported reagents we have investigated the use of solution phase tagged reagents. The reaction is homogeneous – allowing improved reaction kinetics and monitoring of the reaction using classical methods – and the spent reagent can be selectively removed from the reaction mixture providing the pure product.

The aza-Wittig reaction is powerful method for introducing C-N double bonds; however it requires stoichiometric amounts of triphenylphosphine and azides, requires high temperatures to activate it and generates nitrogen gas. We synthesised a phosphine containing a *tert*-butyl ester as a masked carboxylic acid enabling selective removal of the spent reagent from the product.

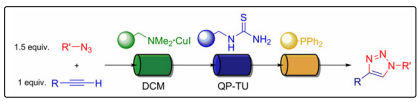


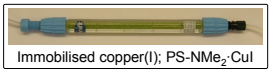
A pre-mixed solution of the azide and phosphine was reacted with the isothiocyanate on a glass chip heated to 110 °C at a combined 50 µL/min flow rate, thereby forming the carbodiimiide intermediate, the excess aza-Wittig reagent used was scavenged using an isocyanate resin before reacting with the amine stored in the collection vessel. The phosphorous derivatives were then unmasked using TFA and finally PS-$NaCO_3$ was used to sequester the tagged reagent, providing the desired guanidine as the free base.



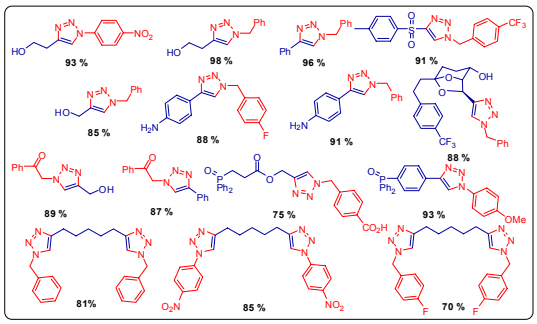
1,2,3-Triazole Formation[4]

The copper(I)-mediated coupling of azides with terminal alkynes – 'Click' chemistry – has attracted a great deal of interest in areas from cell biology to material science. Most examples of this chemistry are performed in aqueous/^{t}BuOH solution, which is not suitable for all substrates and requires either an aqueous work-up or crystallisation from the solution. By immobilising copper iodide onto a tertiary amine resin – acting as both the ligand and the base necessary for the mechanism – the reaction can occur in organic solution, thereby making it suitable for a flow through synthesis.





Immobilised copper(I); PS-NMe_2·CuI

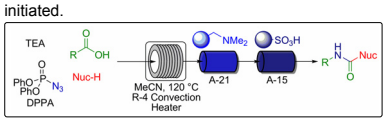


A reagent loop containing 0.1 M alkyne and 0.15 M azide in DCM solution was pumped at 30 µL/min through the column of immobilised CuI. This flow stream was directed through a column of Quadrapure™ TU (a thiourea resin) which sequestered any liberated copper. Finally, the stream flowed through a column of PS-PPh_2, which scavenged the excess azide used to drive the reaction to completion.

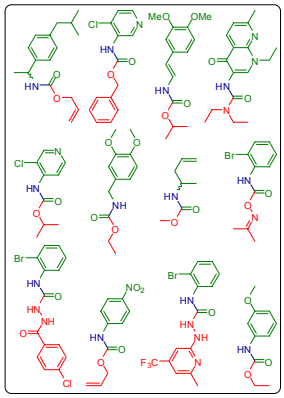
This process provides an efficient method for the rapid formation of triazoles in organic solvents without the need for work-up; importantly the desired compounds were obtained in high purity and no chromatography was required.

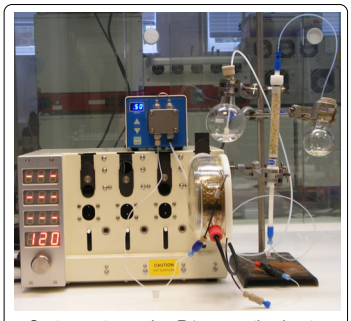
Curtius Rearrangement

The Curtius rearrangement of acyl azides to isocyanates is a powerful reaction, especially since it results in retention of stereochemistry and allows the synthesis of a variety of functional groups, most importantly protected amines. This reaction can be particularly difficult to execute on a larger scale since the reaction utilises toxic and explosive azides; furthermore, the reaction temperature must be carefully controlled due to the release of nitrogen and heat once the reaction has been initiated.



The carboxylic acid was converted to the acyl azide using DPPA as the azide source; the solution was passed through an R-4 convection heater coil at 120 °C, the reaction stream was then directed through columns of A-15 and A-21, removing the DPPA by-product and providing the pure products without further purification.





System set up using R4 convection heater.

References and Acknowledgments

References: (1) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc., Perkin Trans.* 1, 2000, 3815-4195. **(2)** I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley and G. K. Tranmer, *Synlett*, 2006, 427-430. **(3)** I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby and G. K. Tranmer, *Chem. Commun.*, 2006, 2566-2568. **(4)** C. D. Smith, I. R. Baxendale, Steve Lanners, J. J. Hayward, S. C. Smith and S. V. Ley, *Org. Biomol. Chem.*, 2007, **5**, 1559-1561. **(5)** C. D. Smith, I. R. Baxendale, G. K. Tranmer, M. Baumann, S. C. Smith, R. A. Lewthwaite and S. V. Ley, *Org. Biomol. Chem.*, 2007, 1562-1568. **Other examples in flow: (6)** M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Org. Lett.*, 2006, **8**, 5231-5234. **(7)** I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Chem. Commun.*, 2006, 4835-4837. **(8)** I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, and G. K. Tranmer, *Chem. Eur. J.*, 2006, 4407-4416. **(9)** C. J. Smith, F. J. Iglesias-Sigüenza, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2007, 2758-2761.

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