A Modular Flow Reactor for Performing Curtius Rearrangements as a Continuous Flow Process

Marcus Baumann and Steven V. Ley

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom

mb588@cam.ac.uk; http://leyitc.ch.cam.ac.uk/

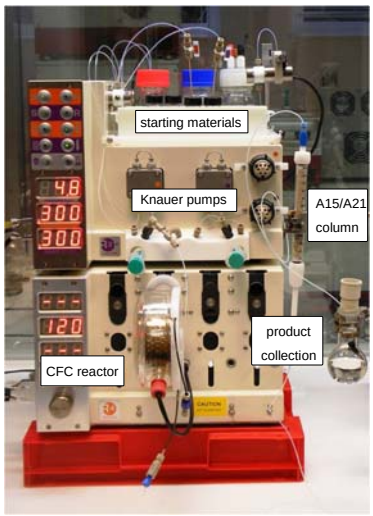
Introduction to Flow

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 and high cost of the reagents limits the scalability and lead us to investigate other enabling techniques such as microwave and flow chemistries.

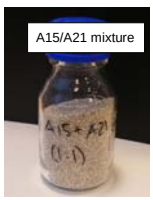
Flow-through processes enable precise mixing, rapid optimisation of reaction conditions and repeatability as well as the generation and immediate use of potential hazardous intermediates and superheating of solvents. The reliability and facile scalability of these processes – either by using higher flow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

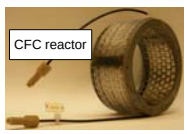
These combined advantages have driven the development of multi-step flow processes; most notably the natural products Grossamide[2] and (±)-Oxomaritidine[3] have been synthesised without aqueous work-ups or chromatographic purification.

Vapourtec R2+ and R4 flow system

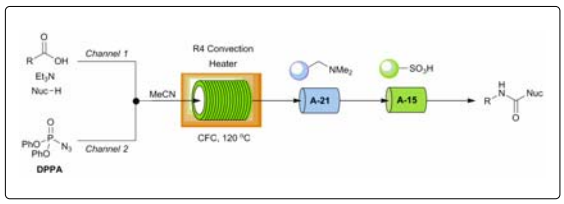


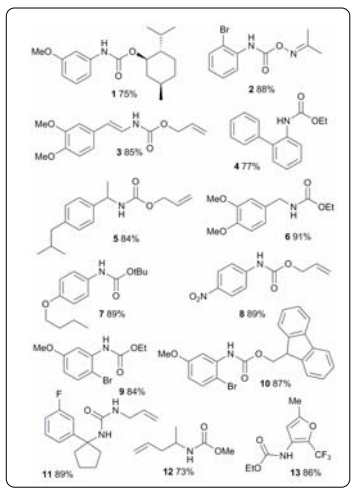
In order to perform the Curtius rearrangements in a convenient fashion the commercially available flow synthesis platform from Vapourtec has been used.





General procedure

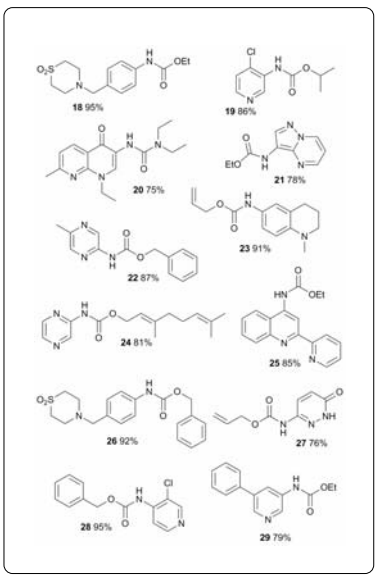




In a general procedure a mixture of triethylamine (2 equiv.), the appropriate nucleophile (1-3 equiv.) and the carboxylic acid (1.1 equiv.) were loaded into channel 1 and DPPA (1 equiv.) into channel 2 (both samples being prepared as solutions in acetonitrile at between 50 and 66.7 mM concentrations). A total flow rate of 0.2-0.5 mL/min equating to a reactor residence time of 20-50 min at a temperature of 120 °C was used to ensure complete conversion. The resulting flow stream was then purified by passage through a glass column packed with a mixture of A-21 and A-15 (1:1; 3.5 equiv. each) at ambient temperature. Removal of the solvent using a Biotage V10 solvent evaporator12 enabled direct isolation of a wide range of products in both high yield (> 75 %) and excellent purity (> 90 % as determined by LC-MS and ^{1}H-NMR).

This procedure was successfully applied to the efficient synthesis of a small collection of carbamates as shown in the adjacent figure.

Novel heterocyclic carbamates



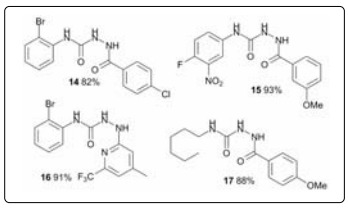
To extend the originally described protocol further and enable the use of additional heterocyclic carboxylic acid building blocks it was necessary to adapt the purification procedure.

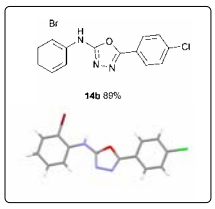
Certain products could be selectively sequestered from the reaction mixture directly onto the A-15 resin (5 equiv.) as they exited the CFC reactor *via* a 'catch and release' protocol. A rapid washing sequence ensured only the ionically bound product remained within the column.

A relay selection valve then enabled a secondary stream containing a solution of excess ammonia in methanol to be eluted through the A-15 trapping column liberating the desired product. In certain cases a small plug of silica gel was also used to remove a dark coloured unknown impurity from the reaction mixture leading to significantly improved purities (10-15% increase).

Evaporation of the solvent along with carried through triethylamine then enabled isolation of the product, again in high yields and excellent purities .

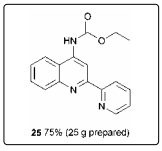
Semicarbazides as oxadiazole precursors





In order to further extend our flow procedure we turned our attention to the synthesis of semicarbazides. These compounds, although synthetically very useful, are notoriously difficult to handle because of there insolubility. Hence, we made use of this by generating and purifying the isocyanate intermediate following the standard procedure. The reaction stream was then collected in a flask containing the acyl hydrazine nucleophile which reacted immediately leaving the product as white precipitate. Filtration and washing furnished the desired compound in very good yields.

Furthermore, the conversion of such semicarbazides to oxadiazoles (**14b**) has been demonstrated following microwave assisted cyclodehydration using tosyl chloride and PS-BEMP.



Another study dealt with the preparation of carbamates *via* the Curtius rearrangement on larger scale. Therefore, carbamate **25** was selected and synthesised using the 'catch and release' protocol in five consecutive batches yielding 25 g of the desired compound.

References and Acknowledgements

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)** M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith and J. P. Tierney, *Org. Biomol. Chem.*, 2008, 1577-1586. **Other examples in flow: (5)** M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Org. Lett.*, 2006, **8**, 5231-5234. **(6)** I. R. Baxendale, S. V. Ley, C. D. Smith and G. K. Tranmer, *Chem. Commun.*, 2006, 4835-4837. **(7)** C. J. Smith, F. J. Iglesias-Sigüenza, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2007, 2758-2761. **(8)** M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin, C. D. Smith and J. P. Tierney, *Org. Biomol. Chem.*, 2008, 1577-1586. **(9)** M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin and C. D. Smith, *Org. Biomol. Chem.*, 2008, 1587-1593.

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