Introduction to Flow

Our group has pioneered the use of supported reagents for the synthesis of natural products and other biologically interesting molecules; 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 tons of grams required for property evaluation.

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

Vapourtec R2+ and R4 flow system

In order to perform the Curtius rearrangement 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 equaling 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 (11; 3.5 equiv. each) at ambient temperature. Removal of the solvent using a Büchi V10 solvent evaporator enabled direct isolation of a wide range of products in both high yield (> 75 %) and excellent purity (> 90 %) as determined by LC-MS and 'H-NMR'.

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

References and Acknowledgements


Acknowledgements: Many thanks to Prof. Steven V. Ley, Dr. Ian R. Baexendale, Christopher D. Smith and the ITC team for their help and guidance. MB would also like to thank the Cambridge European Trust and the Ralph Raphael studentship for funding. We would also like to thank Syrris, Thales and Vapourtec for the use of their equipment and EPSRC, GSK, Insight Faraday, Novartis, Pfizer and Syngenta for their continued support of our laboratory.