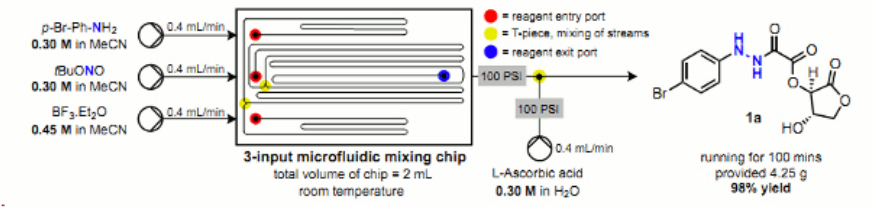
Publication 18: Continuous Production of Oxamic Acid Derivatives in the Mild, Metal-free reduction of Diazonium Salts to Hydrazines



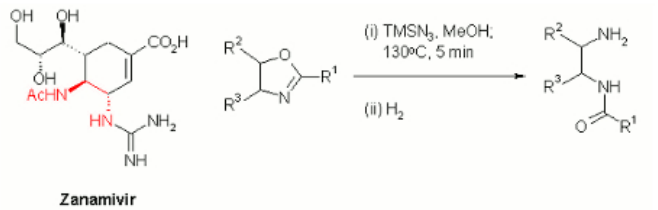
The use of ascorbic acid for the mild, metal-free reduction of *in situ* formed diazonium salts is presented.

The oxamic acid derivatives thus formed have the potential to act as latent hydrazines.

The ability to perform this chemistry under continuous flow-through conditions reduces considerably the risk of explosion when dealing with both diazonium salts and hydrazines on scale.

D. L. Browne, I. R. Baxendale, S. V. Ley, Tetrahedron, 2011, 10296

Publication 17: Synthesis of Mono-acyl 1,4-Diamines from Hydrazoic Acid under Continuous Flow-through Conditions



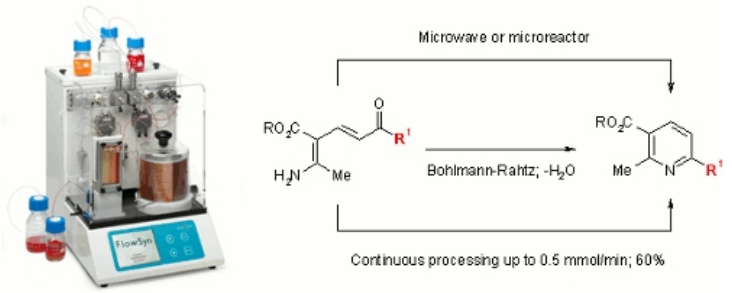
A fast and efficient high temperature protocol for the ring opening of 2-oxazolines to generate *mono*-acyl 1,4-diamines under continuous flow-through conditions has been reported by Kappe's group in Graz.

Their approach involves the *in situ* generation of hydrazoic acid by methanolysis of trimethylsilylazide and concomitant reaction with an appropriate 2-oxazoline.

Ring opening of 2-oxazolines under acidic conditions is an important route to the *mono*-acyl 1,4-diamine moiety found in neuraminidase inhibitors such as GSK's Zanamivir. The ability to perform this reaction in a continuous manner without the potential of accumulating explosive hydrazoic acid in the head space of a batch reactor affords an inherently safer process for large scale synthesis.

(i) B. Gutmann, D. Obermayer, J-P. Roduit, D. M. Roberge, C. O. Kappe, Journal of Flow Chemistry, 2012, (2), 8. (ii) B. Gutmann, J.-P. Roduit, D. Roberge, C. O. Kappe, Chem. Eur. J., 2011, (17), 13146.

Publication 8: Bohlmann-Rahtz Cyclodehydration Reaction



In a study to exemplify the use of continuous flow processing to scale up microwave batch reactions, Bagley's group in Cardiff examined the Bohlmann-Rahtz pyridine synthesis. They found that both glass microreactors and stainless steel coil reactors were equally effective, the latter giving a higher throughput.

Discrepancies observed between optimised conditions in batch and flow-through microwave reactors and conductively heated continuous flow reactors were attributed to a lack of certainty in accurately measuring the temperature at the point of reaction in the microwave devices.

M. C. Bagley, V. Fusillo, R. L. Jenkins, M. C. Lubinu and C. Mason, Org. Biomol. Chem., 2010, 8, 2245-2251.