Application Note 52:

Angiotensin Inhibitors

Produced by Vapourtec

Abstract

This application note describes:

- Greater than 95 % yield from a biphasic reaction
- 14.5 g/h at 50 °C
- Useful synthetic strategy accelerated using intense mixing

For more details, please contact:
Vapourtec Application Support
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Background

Synthesis of amides from amines and acid chlorides is a very important transformation for fine chemical and pharmaceutical products and as such is subject to much research and development[1] The direct synthesis requires two equivalents of amine; the first amine reacts with the acid chloride and liberates HCl, which forms an unreactive amine salt with the second amine. To avoid the need for this excess, another base can be added to ensure the amine remains the free base, however this additional base can also react directly with the acid chloride.

The Schotten-Baumann method of amide synthesis was developed to overcome this issue, and makes use of a biphasic system, typically between DCM and H_2O. The amine and acid chloride remain in the DCM, and the NaOH remains in the aqueous layer, but the newly formed HCl is able to pass from the DCM to the H_2O where it can be neutralized. This makes the Schotten-Baumann conditions a useful synthetic strategy for amide synthesis or protection, which has been used in a wide range of commercial syntheses.[2,3]

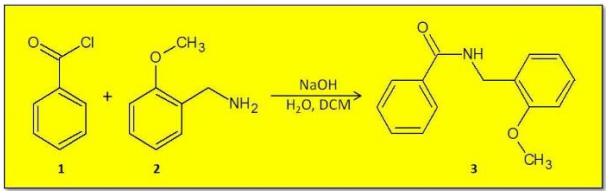

Figure 1: Amide synthesis using Schotten-Baumann biphasic conditions

Setup

All reactions were performed using a Vapourtec R-Series. Reagent bottle A contained a 0.5 M solution of benzoyl chloride in dichloromethane. Reagent bottle B contained a 0.5 M solution of 2-methoxybenzylamine in dichloromethane. Reagent bottle C contained a 1.0 M solution of

sodium hydroxide. Reaction took place in two Vapourtec 20 ml Reactors for Rapid Mixing, connected in series and maintained at 50 °C. All reagent flow rates were 2.5 ml/min and the system pressure was fixed at 5 bar.

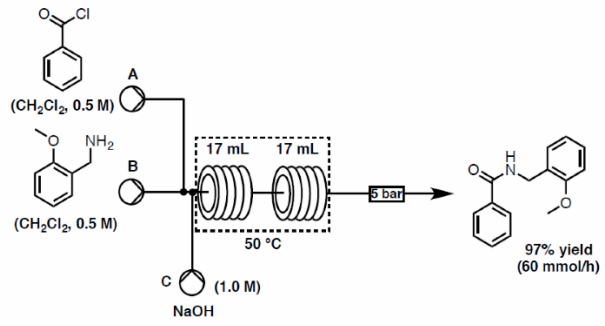

Figure 2: Schematic for an amide synthesis under Schotten-Baumann conditions using two 20 ml reactors for rapid mixing.

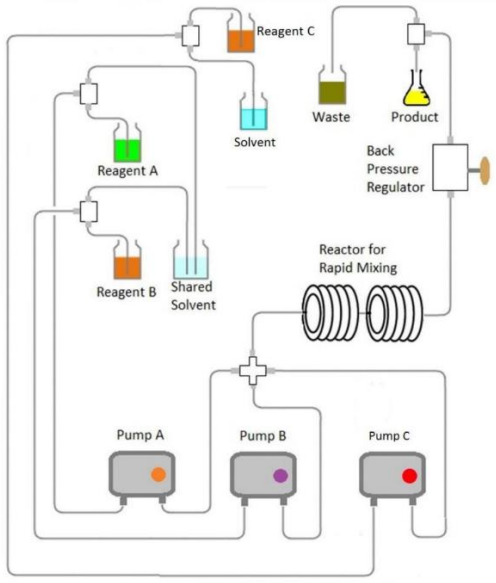

Figure 3: Vapourtec R-Series configured for an amide synthesis under Schotten-Baumann conditions using two 20 ml reactors for rapid mixing.

Continuous Flow Amide Formation

Schotten-Baumann conditions rely on the neutralization of HCl as it is generated, so the rapid transfer of the acid to the aqueous phase is important for fast removal of the HCl, and overall reaction rate. There is great opportunity within continuous flow to generate very intense mixing environments, however some reactors have one brief period of mixing, typically at a tee-piece mixer or similar, and then a continuous, non-mixed environment to give the required residence time. For reactions under biphasic conditions, the two phases simply separate after the mixing point.

The Vapourtec reactors for rapid mixing contain static mixers along the full length of the reactor, producing an intense mixing environment throughout. This ensures that any biphasic reaction remains mixed the entire time it is exposed to the reaction environment.

Amide 3 (a known intermediate in the synthesis of angiotensin inhibitors[4]) was chosen as a target for the synthesis under Schotten-Baumann conditions, and the reaction was performed inside two 20 ml Vapourtec Reactors for Rapid Mixing at 50 °C and 5 bar, and a residence time of 5 minutes. Under these conditions, and with the enhanced mixing afforded by the rapid mixing reactor, it was possible to achieve a yield of 97 % of 3, at a throughput of 14.5 g/hour.

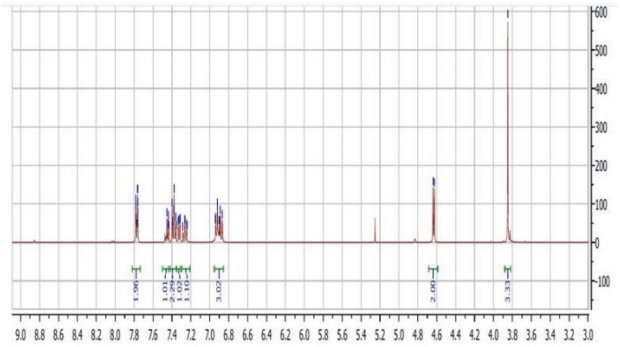

Figure 2: ^{1}H NMR (400 MHz, $CDCL_3$) of amide 3 obtained from the reactor output before workup

Conclusion

Using a Vapourtec reactor for rapid mixing, it has been possible to achieve a 97 % yield of an amide using Schotten-Baumann conditions. The intense

mixing characteristics of these reactors ensure vigorous mixing throughout the length of the reactor, accelerating the reaction and permitting a throughput of 60 mmol (14.5 g) per hour.

Acknowledgements

Vapourtec wish to thank Dr Claudio Battilocchio and Prof. Steven Ley at the University of Cambridge for conducting the experimental work and providing additional information for this application note.

References

1. V. R. Pattabiraman, J. W. Bode, *Nature*, 2011, **480**, 471-479
2. A. Isidro-Llobet, M. Alvarez, F. Albericio, *Chem. Rev*., 2009, **109**, 2455-2504
3. R. Angelaud, M. Reynold, C. Venkatramani, S. Savage, H. Trafelet, T. Landmesser, P. Demel, M. Levis, O. Ruha, B. Rueckert, H. Jaeggi, *Org. Proc. Res. Dev*., 2016, **20**, 1509-1519
4. M. Seki, M. Nagahama, *J. Org. Chem*., 2011, **76**, 10198-10206