Fully Automated Synthesis of Secondary Sulfonamides in a Binary Flow-Through Reactor System§

[a]Charlotte Griffiths-Jones, [b]Duncan Guthrie, [a]Mark Hopkin, [a]Emma Vickerstaffe, [c]Steven V. Ley, [a]Mark Ladlow*

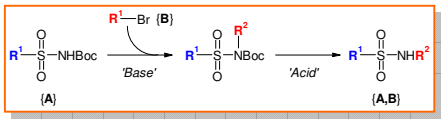
[a]Technology Development UK, GSK Cambridge Technology Centre, Cambridge, UK; [b]Vapourtec Ltd, Place Farm, Ingham, Suffolk, UK; [c]University Chemical Laboratory, Lensfield Road, Cambridge, UK.

Introduction

PACT Mesoflow Chemistry

Polymer-Assisted Continuous flow-Through (PACT) synthesis utilises supported reagents packed into *reactor columns* that are located in a continuous flow reaction stream. These may be linked to create a continuous multi-step flow process in which individual substrates are periodically introduced into the flow stream prior to elution through a series of functionalised supports to effect both sequential synthetic transformations and in-line purification. Moreover, flow-through synthesis is typically performed under pressure, thereby affording straightforward access to superheated reaction conditions, comparable to those achieved in a microwave reactor.

Central to our efforts in this emerging area has been the development of a new, multi-channel flow reactor, the Vapourtec R-4. The R-4 can be used in manual mode for simple flow chemistry experimentation, however, here we exemplify a more sophisticated implementation of this device as a central component within a fully automated flow synthesis platform that is able to perform unattended combinatorial library synthesis.



Scheme 1.

Monoalkylsulfonamides are an important drug-like chemotype. However, their preparation by the treatment of sulfonyl chlorides with primary amines often leads to the formation of bis-sulfonylated contaminants. Alternatively, *N*-alkylation of Boc-protected sulfonamides {**A**} with alkyl halides {**B**} followed by Boc deprotection under acidic conditions affords monoalkylsulfonamides {**A**,**B**} directly in good yields and high purities (Scheme 1). In this way, monoalkylsulfonamide arrays may be prepared by a fully automated 2-step PACT synthesis.

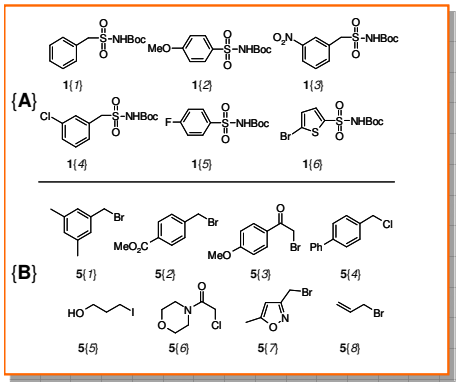


Figure 1. *Sets of starting materials* {**A**} *and* {**B**}.

Flow-through Synthesis

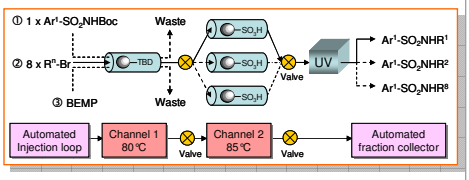


Figure 2. *Automated flow-through synthesis process.*

Synthesis:

1. A Boc-sulfonamide {**A**} is 'captured' in an activated zwitterionic form by elution through a column containing the strong polymer-supported base PS-TBD at 80ºC.
2. The column is then sequentially eluted with calibrated, sub-stoichiometric amounts of 8 different alkyl halides {**B**} that react in turn to 'release' the corresponding monoalkylated sulfonamide reaction products {**A,B**} into the outflow stream.
3. The outflow is directed through a second, in-line reactor column containing an acidic resin (Amberlyst H-15) at 85ºC, which quantitatively removes the Boc protecting group.
4. The eluted monoalkylsulfonamide reaction products {**A,B**} are detected by UV and collected.
5. The 'release' cycle is repeated until the PS-TBD column is exhausted.

Regeneration:

1. The PS-TBD column is fluidically isolated from the Amberlyst H-15 column.
2. The PS-TBD column is regenerated by elution with a solution of the P_1-phosphazene base BEMP.
3. The PS-TBD column is washed with system solvent (MeCN).

This process was repeated twice more using a new Amberlyst H-15 PACT reactor each time. In this case, 8 library compounds were prepared in each cycle.

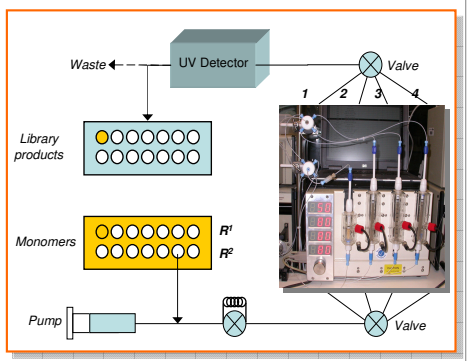


Figure 3. *Schematic showing automated PACT flow-through synthesiser configuration and the central Vapourtec R-4 multi-channel flow reactor.*

Results

Each stage of the process is programmed to run automatically on a synthesiser that combines an automated sample injection/collection module with the Vapourtec R-4 flow reactor (Figure 3). The system is controlled through a common user interface.

In this way, 24 individual compounds can be synthesised in a single automated run. The H-15 PACT reactors are then replaced prior to performing additional array syntheses.

The same PS-TBD reactor column can typically be re-used in excess of 30 times and the on-column residence time for each synthetic step was approximately 20 min.

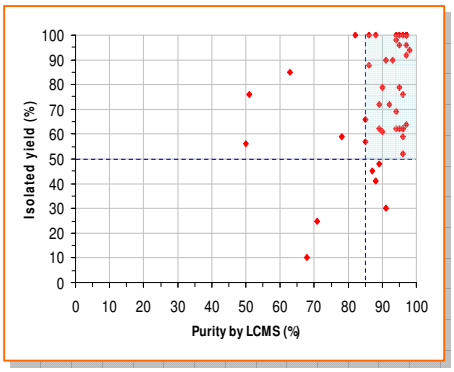


Figure 4. *Yield vs. purity (unpurified) plot for 48-member monoalkylsulfonamide array.*

Conclusions

- A 2-step PACT synthesis based upon a 'catch-and-release' strategy has been developed leading to a 48-member monoalkylsulfonamide compound array {**A**,**B**}.
- The flow-through PACT synthesis combines iterative cycles of substrate capture, alkylative release, column regeneration, and column selection protocols in a fully automated process.
- All compounds were prepared on a 33 µmol scale corresponding to ~15 mg product.
- 88% Of the targeted compounds were isolated directly from the synthesiser in excellent purities (>85%) without the need for further chromatographic purification (Fig. 4).
- This work was facilitated by the development of the Vapourtec R-4, a new and flexible tool for exploring flow-through chemistry applications in the research laboratory.

Acknowledgements

We are grateful to GlaxoSmithKline for financial support, and Gary Davies is thanked for technical assistance.

§Griffiths-Jones, C. M.; Hopkin, M. D.; Jönsson, D.; Tapolczay, D. J.; Vickerstaffe, E.; Ley, S. V.; Ladlow, M. *J. Combi. Chem.* **2007**, 10.1021/cc060152b.

vapourtec