Welcome to the **Flow Synthesis Online** newsletter.

This publication is released bi-monthly and will showcase new applications, events, and equipment in the Flow Synthesis world.

This issue's theme is growth. We have product announcements about being able to more, details of a new annual Flow Chemistry event, plus more interesting new publications than ever.
And some Vapourtec news too.

Product News

R Series Now supports 2 High Temperature Reactors

Up to now the Vapourtec R4 reactor heater module has featured 4 reactor positions, but only 1 of these could support the high temperature coil reactor module (capable of up to 250°C). All new systems (built from April 2010 onwards) will be capable of supporting the HT reactor in 2 of the 4 positions.

Click here for more details

Gilson 215 Liquid Handler Now Supported

Last year Vapourtec announced the facility to load reagents into the R Series system from an autosampler (liquid handler) for each reaction.
Now support for the Gilson 215 Liquid handler (right) has been added.

Existing users can get a free upgrade for their **Flow Commander™** software to add this feature

Click here to read about autosampler support

Bigger Sample Injection Loop Loading Ports

One feedback request that a few users sent us was for bigger ports so that the sample loops could be loaded faster.

So for R Series systems ordered from April 2010, the ports have been upgraded to 1mm.

Sample loops can be loaded either manually or using a liquid handler (see article above).

Vapourtec News

We're Moving !

After three consecutive years of revenues doubling, Vapourtec can no longer fit in the current location, and will shortly be moving to larger, more suitable premises on the award winning Park Farm Business Centre near Bury St Edmonds.

The new building will have a dedicated clean manufacturing area, purpose built lab facilities, and product demonstration and training area.

The move should be completed by the end of Q2.

Click here to read more

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Is it your first time ?

If this is the first issue of the newsletter that you've received, you might like to take a look at what you've missed in some previous issues.

click here to see newsletter archive

Events

Attendees of the following events will be able to see the latest Vapourtec Flow Chemistry equipment in action, and no doubt talk to other users.

RSC/SCI Symposium on Continuous Processing and Flow Chemistry. 3-4 November

This is a new event, and is surely set to become a major annual fixture on the Flow Chemistry calendar.
Check the link below to see the excellent lineup of speakers for the event.

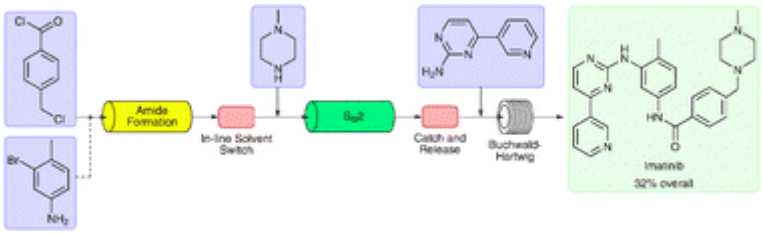
Click here for details of this event

UKASF Meeting 16-17 November 2010

The U.K. Automated Synthesis Forum will hold their annual meeting at the Merck Sharpe Dohme site in Newhouse, Scotland.

Publications

A flow-based synthesis of Imatinib: the API of Gleevec



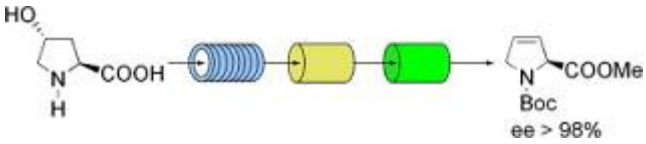
Mark D. Hopkin, Ian R. Baxendale and Steven V. Ley

Innovative Technology Centre, Department of Chemistry, University of Cambridge, U.K

A concise, flow-based synthesis of Imatinib, a compound used for the treatment of chronic myeloid leukaemia, is described whereby all steps are conducted in tubular flow coils or cartridges packed with reagents or scavengers to effect clean product formation. An in-line solvent switching procedure was developed enabling the procedure to be performed with limited manual handling of intermediates.

Click here to go straight to the publication

A highly efficient flow reactor process for the synthesis of *N*-Boc-3,4-dehydro-l-proline methyl ester



Lucia Tamborini, Paola Contia, Andrea Pintoa and Carlo De Michelia

Dipartimento di Scienze Farmaceutiche 'Pietro Pratesi', Università degli Studi di Milano, Italy

The multi-step preparation of *N*-Boc-3,4-dehydro-l-proline methyl ester using a modular flow reactor is reported. The use of immobilised reagents and scavengers in pre-packed glass tubes allows us to obtain the pure product in 87% overall yield, 97% purity, and >98% enantiomeric excess without any additional purification step. Our flow-based protocol enables the rapid multi-gram synthesis (about 9 g/12 h) of the desired product.

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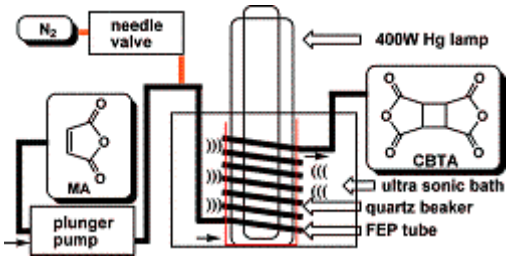
Photodimerization of Maleic Anhydride in a Microreactor Without Clogging



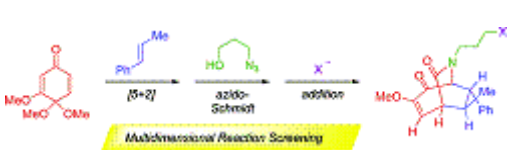
Tomoaki Horie, Motoshige Sumino, Takumi Tanak, Yoshihisa Matsushita, Teijiro Ichimura and Jun-ichi Yoshida

The Research Association of Micro Chemical Process Technology (MCPT), Kyoto, Japan

Photodimerization of maleic anhydride (MA) gives insoluble precipitated products that can be a trigger to clog a conventional microreactor. To avoid this problem, we devised a microreactor that uses liquid/gas slug flow and ultrasonication.
The slug flow microreactor could be operated for more than 16 h continuously without clogging. Compared to using a batch reactor, this method achieves better product quality, improved conversion, and reduced waste.

Click here to go straight to the publication

Reaction Discovery Using Microfluidic-Based Multidimensional Screening of Polycyclic Iminium Ethers



Jennifer L. Treece†, John R. Goodell‡, David Vander Velde†, John A. Porco, Jr.‡ and Jeffrey Aube*†

† Department of Medicinal Chemistry, and KU Center for Chemical Methodology and Library Development (KU-CMLD), The University of Kansas, USA
‡ Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, USA

Polycyclic iminium ethers are ambident electrophilic intermediates that react with a range of nucleophiles in a highly condition-dependent manner to afford densely functionalized lactams. In an effort to expand the scope of reactivity and assist in the generation of new chemotypes from these intermediates, several iminium ethers were subjected to reaction screening using an automated microfluidics reaction platform. Application of this approach led to the discovery of

several interesting reaction pathways involving the iminium ether intermediates that will be described.

Click here to go straight to the publication

Phase-Transfer Catalysis in Segmented Flow in a Microchannel: Fluidic Control of Selectivity and Productivity

Jovan Jovanovi, Evgeny V. Rebrov, T. A. (Xander) Nijhuis, Volker Hessel and Jaap C. Schouten

Laboratory of Chemical Reactor Engineering, Department of Chemical Engineering and Chemistry, and Institute for Complex Molecular Systems, Eindhoven University of Technology, The Netherlands

Precise control over the interfacial area of aqueous and organic slugs in segmented flow in a microchannel reactor provides an attractive means to optimize the yield and productivity of a phase-transfer-catalyzed reaction. Herein, we report the selective alkylation of phenylacetonitrile to the monoalkylated product in a microchannel of 250-μm internal diameter operated in a continuous and solvent-free manner in the slug-flow regime. The conversion of phenylacetonitrile increased from 40% to 99% as a result of a 97% larger slug surface-to-volume ratio when the volumetric aqueous-to-organic phase flow ratio was raised from 1.0 to 6.1 at the same residence time. The larger surface-to-volume ratio significantly promoted catalyst phase transfer but decreased selectivity because of the simultaneous increase of the rate of the consecutive reaction to the dialkylated product. There exists an optimum flow ratio with a maximum productivity. Conversion and selectivity in the microchannel reactor were both found to be significantly larger than in a stirred reactor.

Click here to go straight to the publication

A Flow Process Using Microreactors for the Preparation of a Quinolone Derivative as a Potent $5HT_{1B}$ Antagonist

Zizheng Qian, Ian R. Baxendale, Steven V. Ley

Innovative Technology Centre, Department of Chemistry, University of Cambridge, UK

This article describes the continuous flow synthesis of 6-methoxy-8-(4-methyl-1,4-diazepan-1-yl)-N-(4-morpholinophen-yl)-4-oxo-1,4-dihydroquinoline-2-carboxamide, a potent $5HT_{1B}$ antagonist developed by AstraZeneca.

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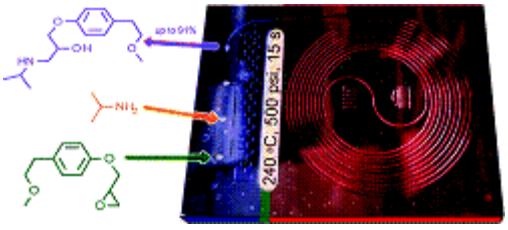
Aminolysis of Epoxides in a Microreactor System: A Continuous Flow Approach to ß-Amino Alcohols



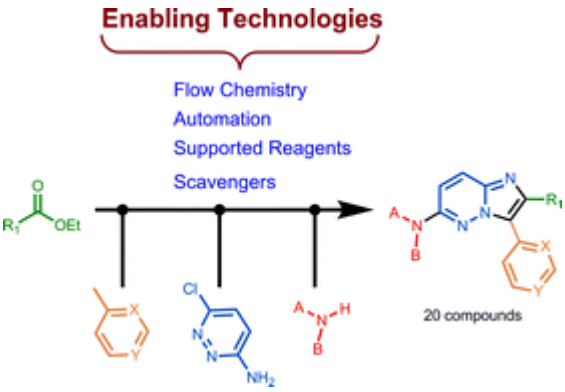
Matthew W. Bedore, Nikolay Zaborenko, Klavs F. Jensen and Timothy F. Jamison

Departments of Chemistry and Chemical Engineering, MIT

The use of a continuous flow microreactor for β-amino alcohol formation by epoxide aminolysis is evaluated. Comparison to microwave batch reactions reveals that conditions obtainable in the microreactor can match or improve yields in many cases. By increasing the pressure of the system, maximum temperatures can also exceed those accessible using a microwave unit. The use of a microreactor for epoxide aminolysis reactions in the synthesis of two pharmaceutical relevant compounds is described.

Click here to go straight to the publication

The application of flow microreactors to the preparation of a family of casein kinase I inhibitors



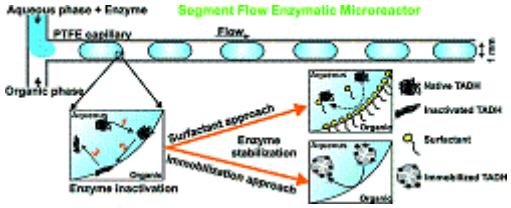
Francesco Venturoni, Nikzad Nikbin, Steven V. Ley and Ian R. Baxendale

Innovative Technology Centre, Department of Chemistry, University of Cambridge, UK

In this article we demonstrate how a combination of enabling technologies such as flow synthesis, solid-supported reagents and scavenging resins utilised under fully automated software control can assist in typical medicinal chemistry programmes. In particular automated continuous flow methods have greatly assisted in the optimisation of reaction conditions and facilitated scale up operations involving hazardous chemical materials. Overall a collection of twenty diverse analogues of a casein kinase I inhibitor has been synthesised by changing three principle binding vectors.

Click here to go straight to the publication

Enzyme Catalysis in an Aqueous/Organic Segment Flow Microreactor: Ways to Stabilize Enzyme Activity



Rohan Karande†, Andreas Schmid*†‡ and Katja Buehler†

† Laboratory of Chemical Biotechnology, Department of Biochemical and Chemical Engineering, Dortmund, Germany
‡ ISAS-Institute for Analytical Science, Dortmund, Germany

Multiphase flow microreactors benefit from rapid mixing and high mass transfer rates, yet their application in enzymatic catalysis is limited due to the fast inactivation of enzymes used as

biocatalysts. Enzyme inactivation during segment flow is due to the large interfacial area between aqueous and organic phases. The Peclet number of the system points to strong convective forces within the segments, and this results in rapid deactivation of the enzyme depending on segment length and flow rate. Addition of surfactant to the aqueous phase or enzyme immobilization prevents the biocatalyst from direct contact with the interface and thus stabilizes the enzyme activity. Almost 100% enzyme activity can be recovered compared to 45% without any enzyme or medium modification. Drop tensiometry measurements point to a mixed enzyme−surfactant interfacial adsorption, and above a certain concentration, the surfactant forms a protective layer between the interface and the biocatalyst in the aqueous compartments. Theoretical models were used to compare adsorption kinetics of the protein to the interface in the segment flow microreactor and in the drop tensiometry measurements. This study is the basis for the development of segment flow microreactors as a tool to perform productive enzymatic catalysis.

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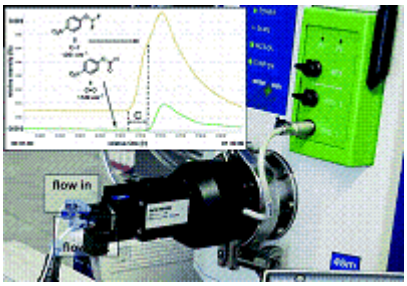

ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing

Catherine F. Carter†, Heiko Lange†, Steven V. Ley*†, Ian R. Baxendale†, Brian Wittkamp‡, Jon G. Goode§ and Nigel L. Gaunt§

†Innovative Technology Centre, Department of Chemistry, University of Cambridge, U.K.
‡Mettler-Toledo AutoChem, USA
§Mettler-Toledo AutoChem UK

A newly developed ReactIR flow cell is reported as a convenient and versatile inline analytical tool for continuous flow chemical processing. The flow cell, operated with ATR technology, is attached directly into a reaction flow stream using standard OmniFit (HPLC) connections and can be used in combination with both meso- and microscale flow chemistry equipment. The iC IR analysis software (version 4.0) enables the monitoring of reagent consumption and product formation, aiding the rapid optimisation of procedures. Short-lived reactive intermediates can also be observed in situ, giving further mechanistic insight into complex transformations.

Click here to go straight to the publication

Any 3rd Party publications referred to may require a subscription to download.

About Vapourtec Ltd

Vapourtec develop and manufacture the R Series Flow Chemistry Platform, the leading choice of industrial and academic users worldwide. To find out more about the R Series, or about Flow Chemistry generally, go to

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