Flow Synthesis Online - May 2012

Welcome to the first summer issue.
There's plenty of interesting stuff this month.

- An exciting new Vapourtec collaboration in India
- A case study of a fully automated discovery platform for hit to lead optimisation
- New publications

We've also added a new feature where we announce news concerning groups around the world involved in flow chemistry. Send us your news, and we'll give it a mention.

Contents

You have received this email because you have in the past expressed an interest in Vapourtec Flow Chemistry products. If you'd prefer not to receive this newsletter any more, use the unsubscribe link at the end of the email.

Announcements

Vapourtec and Pi-Inc

In May 2012, Vapourtec appointed Pi as their representatives in India.

Pi is a group of Chemical Engineers and Scientists specialized in Process Intensification for the API and Fine-Chemical Industries with 20 to 35 years of industrial and research experience.

Click here for more details

Max Planck Strengthens Flow Chemistry Program

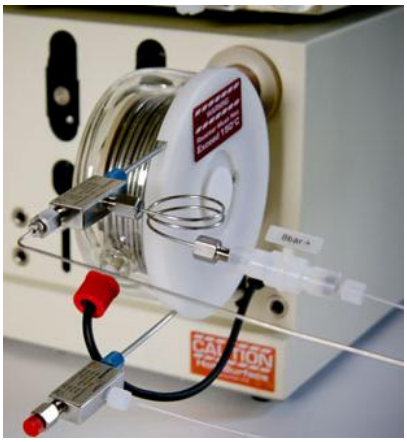
In May 2012, Prof. Dr. Tyler McQuade (right) joined the Department for Biomolecular Systems, Max-Planck Institute for Colloids and Interfaces(MPI), Potsdam, Germany on leave of absence from Florida State University (FSU). McQuade will head the Microreactors subgroup working closely with Prof. Dr. Peter Seeberger to push the boundaries of flow chemistry. One major objective in the first quarter of this collaboration will be to streamline

workflow and define a clear set of targets. Purchasing two more Vapourtec R Series systems was the first step in this effort.

Dr. McQuade indicates that "The Vapourtec R Series systems drive much of our flow efforts at FSU and here at the MPI. The robust pumping system is essential in our thrust to scale-up the recently reported Artemisinin routeand the temperature controlled column and reactors are essential for accelerating our new and ongoing projects. Unlike other systems I have experienced, the R2/R4 just keeps going and going."

Applications

Continuous Flow Hydrogenation



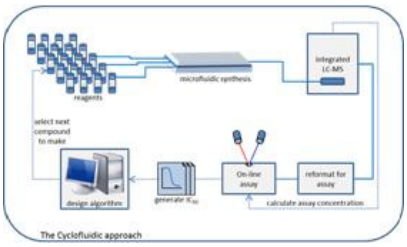
The first publication shown in the list below features the recently launched Vapourtec gas/liquid tube-in-tube reactor.

Because the reactor allows gas to be fed into a heated reactor as it is consumed (rather than relying on it being "pre-dissolved"), the constraints imposed by poor hydrogen solubility become less of a limitation, and the study shows steady state hydrogenation with 3M substrate concentration.

The reactor is available now and can be used with any Vapourtec R Series system.

More details here

Case Study - Cyclofluidic



In a typical hit to lead project, an iterative cycle (each comprising of designing the molecule, chemical synthesis, analysis and biological assay) is carried out to build a structure activity relationship. Each of these iterations can take from one to a number of weeks with the quality of the final output dependent on the number of iterations that can be performed in the available time.

So three years ago Cyclofluidic Ltd was formed to create an automated iterative system which could synthesise candidate molecules, test against a biological assay and then, via a suitable algorithm, decide what molecule to synthesise next to get closer to the optimum.

And they've done it. And it has a typical iteration period of 90 minutes.

Click here to find out more

Events - Where to see Vapourtec

A Celebration of Organic Chemistry

Where : AstraZeneca, Alderley Edge, UK
When : 24-25 Sep 2012

More details

Fourth Symposium on Continuous Flow Reactor Technology for Industrial Applications

Where : Lisbon, Portugal
When : 26-27 Sep 2012

More Details

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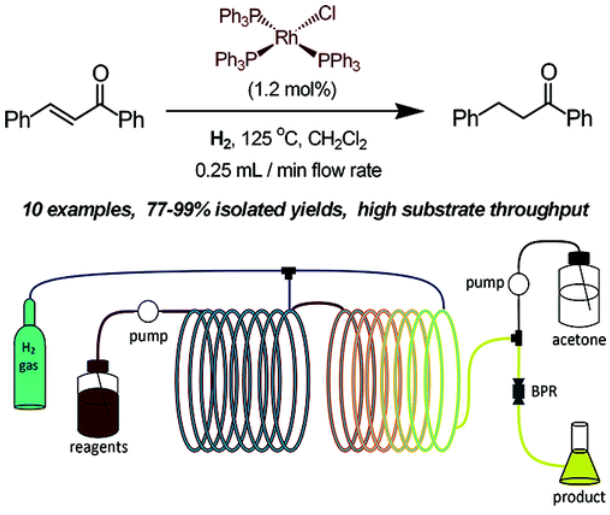
Publications

Continuous Flow Hydrogenation Using an On-Demand Gas Delivery Reactor

Michael A. Mercadante, Christopher B. Kelly, Christopher (Xiang) Lee, Nicholas E. Leadbeater*
Department of Chemistry, University of Connecticut, USA



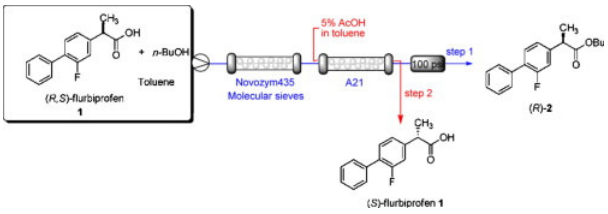
A continuous-flow approach to the hydrogenation of alkenes utilizing Wilkinson's catalyst is reported. The approach relies on a newly developed coil design in which it is possible to load gas and heat the reaction mixture simultaneously. The hydrogenation of various

substrates has been performed successfully on small scale and can be scaled up substantially.

Click here to go straight to the publication

An efficient method for the lipase-catalysed resolution and in-line purification of racemic flurbiprofen in a continuous-flow reactor

Lucia Tamborini[1], Diego Romano[2], Andrea Pinto[1], Arianna Bertolani[12], Francesco Molinari[2], Paola Conti[1]
[1] Dipartimento di Scienze Farmaceutiche 'Pietro Pratesi', Universitá degli Studi di Milano, Italy
[2] Dipartimento di Scienze e Tecnologie Alimentari e Microbiologiche, Universitá degli Studi di Milano, Italy



The lipase-catalysed kinetic resolution of flurbiprofen was performed in a flow-chemistry reactor allowing for a significant reduction of the reaction time compared to the classical batch method. The process was implemented by adding an in-line purification step of the exiting solution, consisting in a catch and release protocol, which allows easy separation and recovery of both (S)-flurbiprofen and (R)-flurbiprofen butyl ester with an enantiomeric excess =90% and a chemical purity >98%.

Click here to go straight to the publication

Soluble Polymer-Supported Flow Synthesis: A Green Process for the Preparation of Heterocycles

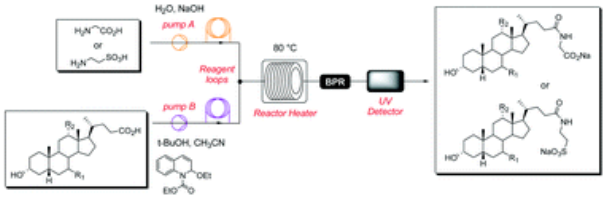
Nicolò Prosa, Raphaël Turgis, Riccardo Piccardi, Marie-Christine Scherrmann
Institut de Chimie Moléculaire et des Matériaux d'Orsay, Université Paris-Sud, France

PEG-supported aqueous flow synthesis coupled with ultrafiltration as the separation technique has been investigated for the first time. This strategy was applied to the preparation of new 3,4-dihydropyrimidin-2(1H)-ones, tetrazoles and tetrahydro-1,3-oxazines from the same PEG-linked aldehyde as case studies. Dihydropyrimidinones were prepared by a copper(II)-catalysed Biginelli reaction whereas a new tetrazole-containing compound was obtained by Baylis–Hillman reaction followed by reduction and 1,3-dipolar cycloaddition. Finally, various new tetrahydro-1,3-oxazines were prepared by a four-step synthesis, that is, Baylis–Hillman reaction, Michael addition of amines, cyclization with formaldehyde and hydrolysis of the linkage to PEG. The use of water during the synthesis and most of the purification steps, as well as the benefits of the flow process in terms of improved safety and heat transfer agree with the principles of green chemistry.

Click here to go straight to the publication

Continuous flow synthesis and scale-up of glycine- and taurine-conjugated bile salts

Francesco Venturoni , Antimo Gioiello , Roccaldo Sardella , Benedetto Natalini and Roberto Pellicciari
Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Italy



A multi-gram scale protocol for the N-acyl amidation of bile acids with glycine and taurine has been successfully developed under continuous flow processing conditions. Selecting ursodeoxycholic acid (UDCA) as the model compound and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) as the condensing agent, a modular mesoreactor assisted flow set-up was employed to significantly speed up the optimization of the reaction conditions and the flow scale-up synthesis. The results in terms of yield, in line purification, analysis, and implemented flow set-up for the reaction optimization and large scale production are reported and discussed.

Click here to go straight to the publication

Reviews

Micro reactor and flow chemistry for industrial applications in drug discovery and development

Baraldi, Patricia T. [1]
Hessel, Volker [2]
[1]*Laboratory of Organic Synthesis, Vita Nova Institute, Brazil*
[2]*Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, The Netherlands*

In this review, case studies focused on syntheses of active pharmaceutical ingredients, intermediates and lead compounds are reported employing micro reactors and continuous flow technology in areas such as medicinal chemistry, chemical development and manufacturing. The advantages of flow technology are currently very clear as opposed to conventional batch methods. Most strikingly and relevant for pharmaceutical's time-to-market needs, flow processing has the important advantage of the ease with which reaction conditions can be scaled. As this technology is new and has major full-process scale implications, we also wanted to point out that this cannot be applied and released to all chemistries yet, thereby also critically mirroring disadvantages and advantages of the step-change technology. However, the positive impact has been dominating and thus pharmaceutical and fine-chemical industries have increased their awareness and interest in flow chemistry applications. Beyond pharmaceutical syntheses, this review aims to conclude with the special needs of pharmacy on flow and micro reactor chemistry, which is not the same as for the fine-chemical industry. Here,

the needs of Brazil are considered, as the mirroring of micro reactor and flow chemistry was done from a European – academic and business – perspective. The hope is to stimulate and promote flow developments in emerging developing nations.

Click here to do straight to the publication

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