A warm welcome to the Vapourtec Winter 2014 e-newsletter.

A Merry Christmas and a very happy 2015 from all of the team at Vapourtec!

Contents

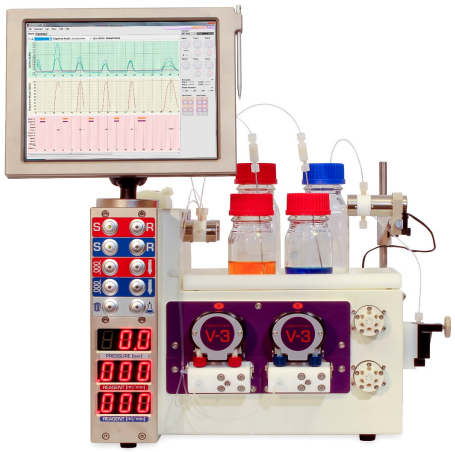
Product News

Introducing the new R2-S Suspension / light slurry pump module

Vapourtec have announced a new addition to the range of pump modules available for the R-Series™ system. In addition to the standard, acid resistant and high pressure there is now a special suspension / slurry capable version.

The new module has all the same control and data logging functionality as the standard pump with some additional pumping capabilities...

MORE DETAILS



Latest News

A continuous flow of published breakthroughs for Vapourtec

Vapourtec have recently reached the impressive milestone of having been cited in 150 peer review publications.

By way of a comparison Vapourtec's two closest competitors in flow chemistry technology have been mentioned in 51 and 40 publications respectively.
READ MORE

Vapourtec sees flow chemistry growth in India

Vapourtec is establishing a burgeoning market for its flow chemistry systems across India with the continued development of a distribution partnership with Mumbai-based Pi-Process Intensification. Pi-Process Intensification have been acting as distributors for Vapourtec's R-Series systems for the past three years and will now also be distributing their E-Series system. Dr Reddy's Labs is one of a number of key customers.
READ MORE

Flow v Batch Photochemistry - a like-for-like comparison

There are a number of key advantages of a continuous flow approach to photochemistry over a traditional batch method including consistent light penetration, controlled exposure times, precise temperature control and easy scalability as well as the removal of photochemical products from the irradiated area.
READ MORE

Events

Events where you can see Vapourtec systems in action:

15th – 16th December 2014
RSC Macrocyclic and Supramolecular Chemistry Meeting
Norwich, UK
Click here for more details

22nd – 23rd January 2015
Flow Chemistry India 2015
Mumbai, India
Click here for more details

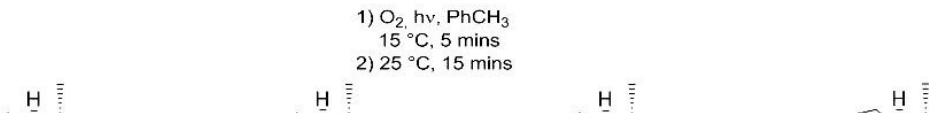
17th – 18th February 2015
Flow Chemistry Conference Europe
Berlin, Germany
Click here for more details

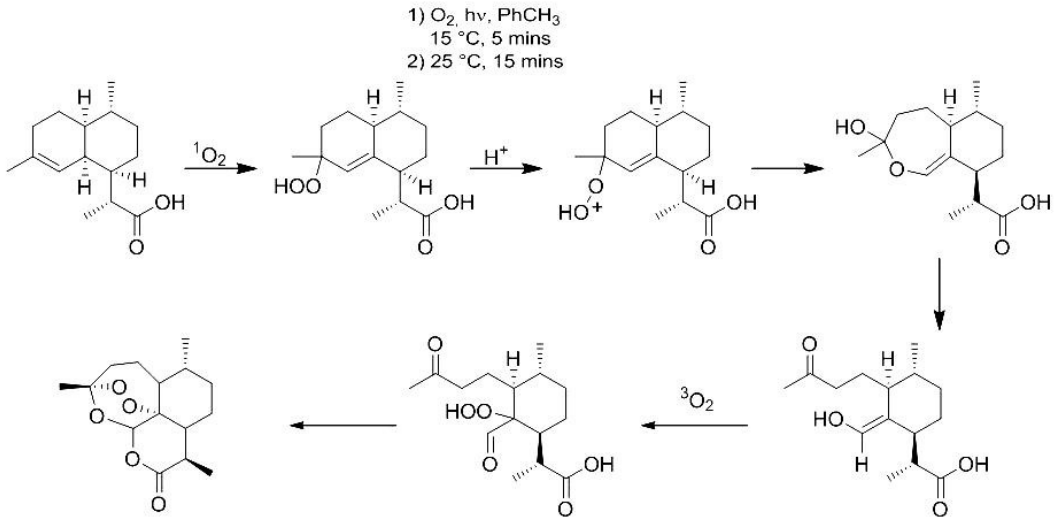
22nd – 26th March 2015
ACS Spring Meeting
Denver, USA
Click here for more details

1st April 2015
Reagentless Synthesis
SCI, London, UK
Click here for more details

Applications

Synthesis of Artemisinin via the Photooxidation of Dihydroartemisinic Acid

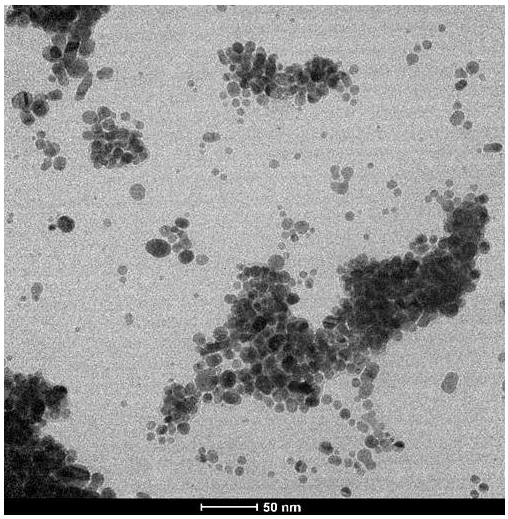




Scheme 1: Synthesis of artemisinin from dihydroartemisinic acid

Application Note 39: This Application Note shows the versatility of the Vapourtec easy-PhotoChem system. Artemisinin is synthesized directly from dihydroartemisinic acid via the continuous photooxidation route first published by Seeberger et al in 2012. In this example the easy-PhotoChem system is used to, pump liquid reagents, meter oxygen and provide the light source for the photooxidation. Artemisinin was produced at an impressive rate of 1.6 grams / hour.

Preparation of Silver Nanoparticles under Continuous Flow Conditions



Application Note 40: This Application Note describes the controlled formation of silver nanoparticles in tubular reactors using the Vapourtec E-Series. Control of particle size is shown over the size range 10 to 60 nm. Two classes of nanoparticle are reported.

Click here to go to the Application Notes page on the Vapourtec website

Publications

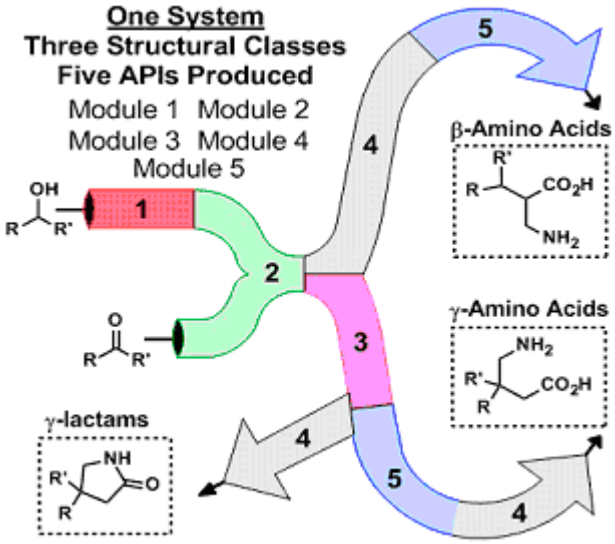
Chemical Assembly Systems: Layered Control for Divergent, Continuous, Multistep Syntheses of Active Pharmaceutical Ingredients

Dr. Diego Ghislieri,

Dr. Kerry Gilmore, Prof.

Dr. Peter H. Seeberger*

Department of Biomolecular Systems, Max-Planck Institute for Colloids and Interfaces, Universität Berlin, Germany



While continuous chemical processes have attracted both academic and industrial interest, virtually all active pharmaceutical ingredients (APIs) are still produced by using multiple distinct batch processes. To date, methods for the divergent multistep continuous production of customizable small molecules are not available. A chemical assembly system was developed, in which flow-reaction modules are linked together in an interchangeable fashion to give access to a wide breadth of chemical space. Control at three different levels—choice of starting material, reagent, or order of reaction modules—enables the synthesis of five APIs that represent three different structural classes (γ-amino acids, γ-lactams, β-amino acids), including the blockbuster drugs Lyrica and Gabapentin, in good overall yields (49–75 %).

Click here to go straight to the publication

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions

Nerea Alonso[2,3],

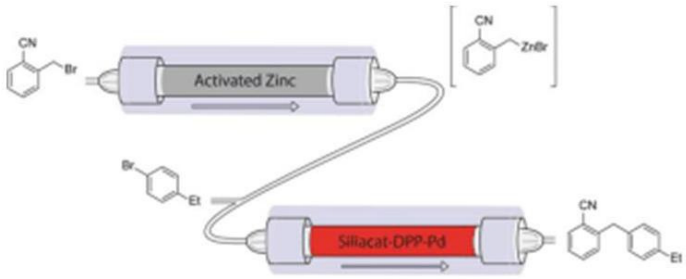
L. Zane Miller[1],

Juan de M. Muñoz[2],

Jesus Alcázar[2,*]

D. Tyler McQuade[1,*]

[1]Department of Chemistry and Biochemistry, Florida State University, USA
[2]Janssen Research and Development, Janssen-Cilag, Toledo, Spain
[3]Facultad de Química, Universidad de Castilla-La Mancha, Spain



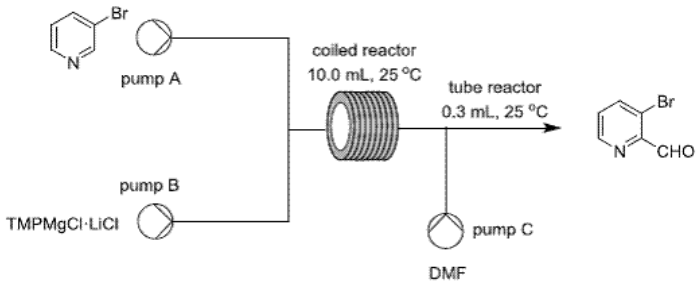
The Negishi cross-coupling is a powerful CC bond forming reaction. The method is less commonly used relative to other cross-coupling methods in part due to lack of availability of organozinc species. While organozinc species can be prepared, problems with reproducibility and handling of these sensitive species can complicate these reactions. Herein, we describe the continuous formation, using an activated packed-bed of metallic zinc, and subsequent use of organozinc halides. We demonstrate that a single column of zinc can provide excellent yields of organozinc halides and that they can be used downstream in subsequent Negishi cross-couplings. The preparation of the zinc column and the scope of the reaction are discussed.

Click here to go straight to the publication

Continuous Flow Magnesiation of Functionalized Heterocycles and Acrylates with TMPMgCl·LiCl.

Dr. Trine P. Petersen,
Matthias R. Becker,
Prof. Dr. Paul Knochel*

Ludwig-Maximilians-Universität München,
Department Chemie,
München, Germany
*Corresponding author



A flow procedure for the metalation of functionalized heterocycles (pyridines, pyrimidines,

thiophenes, and thiazoles) and various acrylates using the strong, non-nucleophilic base TMPMgCl·LiCl is reported. The flow conditions allow the magnesiations to be performed under more convenient conditions than the comparable batch reactions, which often require cryogenic temperatures and long reaction times. Moreover, the flow reactions are directly scalable without further optimization. Metalation under flow conditions also allows magnesiations that did not produce the desired products under batch conditions, such as the magnesiation of sensitive acrylic derivatives. The magnesiated species are subsequently quenched with various electrophiles, thereby introducing a broad range of functionalities.

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Continuous Synthesis of Artemisinin-Derived Medicines

Kerry Gilmore,[a]

Daniel Kopetzki,[a]

Ju Weon Lee,[b]

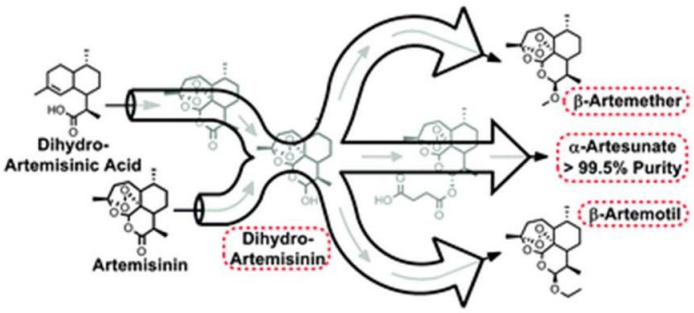
Zoltan Horvath,[b]

D. Tyler McQuade,[a]

Andreas Seidel-Morgenstern,[b,c]

Peter H. Seeberger[a,d]

[a] Max-Planck-Institute of Colloids and Interfaces, Department of Biomolecular Systems, Germany
[b] Max-Planck-Institute for Dynamics of Complex Technical Systems, Germany
[c] Otto-von-Guericke-University, Chair for Chemical Process Technology, Germany
[d] Freie Universität Berlin, Institute of Chemistry and Biochemistry, Berlin, Germany

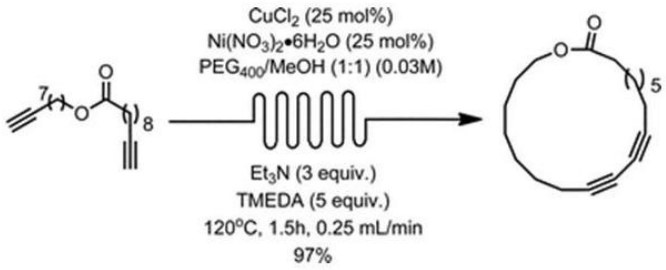


Described is a continuous, divergent synthesis system which is coupled to continuous purification and is capable of producing four anti-malarial APIs. The system is comprised of three linked reaction modules for photooxidation/cyclization, reduction, and derivatization. A fourth module couples the crude reaction stream with continuous purification to yield pure API.

Click here to go straight to the publication

Continuous flow macrocyclization at high concentrations: synthesis of macrocyclic lipids

Anne-Catherine Bédard,
Sophie Régnier,
Shawn K. Collins



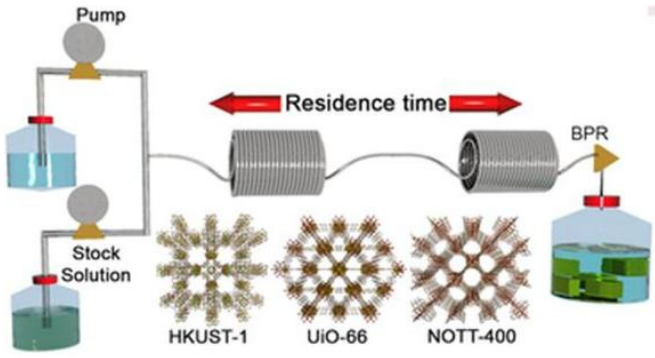
Département de Chimie, Centre for Green Chemistry and Catalysis, Université de Montréal, Montréal, Canada

A phase separation/continuous flow macrocyclization protocol eliminates the need for high-dilution conditions and can be used to prepare gram quantities of biologically relevant macrocyclic lipid structures. The method presents several green advantages towards macrocycle synthesis: (1) the prevention of unwanted oligomers and waste, (2) a reduction in the large quantities of toxic, volatile organic solvents and (3) the use of PEG as an environmentally benign reaction media. Macrocycles could be synthesized in high yields (up to 99%) in short reaction times (1.5 h) and on gram scales without the need to alter the reaction conditions.

Click here to go straight to the publication

Versatile, High Quality and Scalable Continuous Flow Production of Metal-Organic Frameworks

Marta Rubio-Martinez,
Michael P. Batten,
Anastasios Polyzos,
Keri-Constanti Carey,
James I. Mardel,
Kok-Seng Lim
Matthew R. Hill



CSIRO Materials Science and Engineering, Australia

Further deployment of Metal-Organic Frameworks in applied settings requires their ready preparation at scale. Expansion of typical batch processes can lead to unsuccessful or low

quality synthesis for some systems. Here we report how continuous flow chemistry can be adapted as a versatile route to a range of MOFs, by emulating conditions of lab-scale batch synthesis. This delivers ready synthesis of three different MOFs, with surface areas that closely match theoretical maxima, with production rates of 60 g/h at extremely high space-time yields.

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First Example of a Continuous-Flow Carbonylation Reaction Using Aryl Formates as CO Precursors

Nerea Alonso[1, 3],

Juan de Muñoz[1],

Brecht Egle[2],

Johannes L. Vrijdag[2],

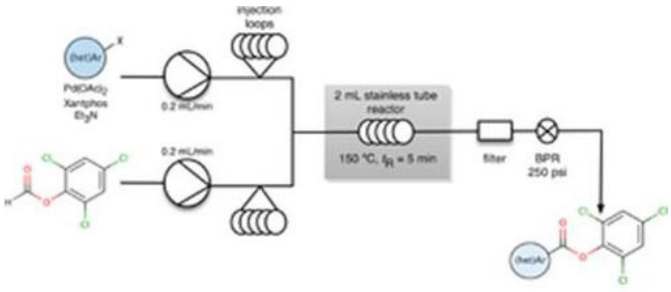
Wim M. De Borggraeve[2] ,

Antonio de la Hoz[3],

Angel Díaz-Ortiz[3],

Jesús Alcázar[1]

[1]Janssen Research and Development, Janssen-Cilag Department of Medicinal Chemistry S.A., Toledo, Spain
[2]Molecular Design and Synthesis University of Leuven, Department of Chemistry, Heverlee Belgium
[3]Universidad de Castilla-La Mancha Facultad de Ciencias y Tecnologías Químicas Real,



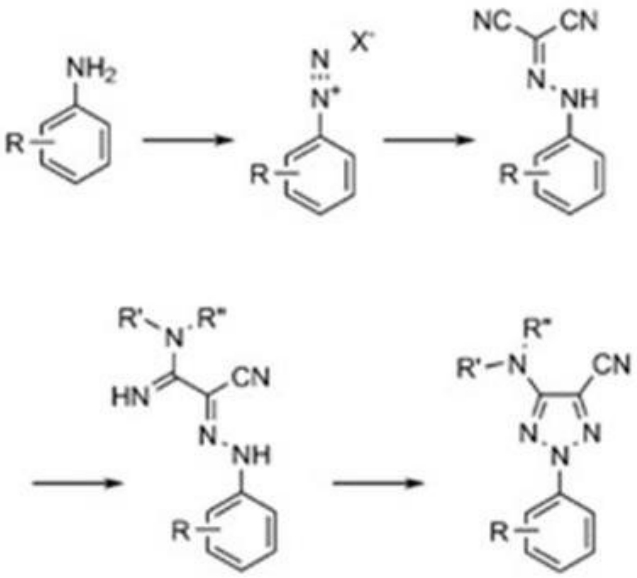
The first continuous flow carbonylation reaction using aryl formates as CO precursor is reported. The reaction is practical, scalable and high yielding. The use of a flow protocol safely allows expanding the scope to activated chlorides, nitrogen heterocycles and to the selective introduction of an ester group in dihalo-derivatives. Further selective reduction of the ester formed to an aldehyde in flow is also described.

Click here to go straight to the publication

Multistep Flow Synthesis of 5-Amino-2-aryl-2H-[1,2,3]-triazole-4-carbonitriles

Dr. Jérôme Jacq,

Dr. Patrick Pasau*



UCB Biopharma, Avenue de l'Industrie, 1420 Braine l'Alleud (Belgium)

1,2,3-Triazole has become one of the most important heterocycles in contemporary medicinal chemistry. The development of the copper-catalyzed Huisgen cycloaddition has allowed the efficient synthesis of 1-substituted 1,2,3-triazoles. However, only a few methods are available for the selective preparation of 2-substituted 1,2,3-triazole isomers. In this context, we decided to develop an efficient flow synthesis for the preparation of various 2-aryl-1,2,3-triazoles. Our strategy involves a three-step synthesis under continuous-flow conditions that starts from the diazotization of anilines and subsequent reaction with malononitrile, followed by nucleophilic addition of amines, and finally employs a catalytic copper(II) cyclization. Potential safety hazards associated with the formation of reactive diazonium species have been addressed by inline quenching. The use of flow equipment allows reliable scale up processes with precise control of the reaction conditions. Synthesis of 2-substituted 1,2,3-triazoles has been achieved in good yields with excellent selectivities, thus providing a wide range of 1,2,3-triazoles.

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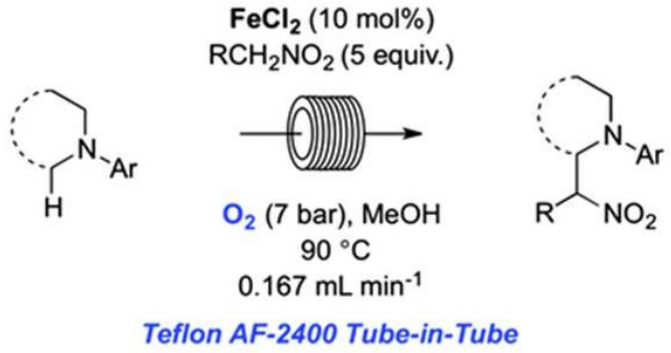
The direct α-C(sp^3)–H functionalisation of N-aryl tetrahydroisoquinolines via an iron-catalysed aerobic nitro-Mannich reaction and continuous flow processing.

Martin Brzozowski,

Jose A. Forni,

G. Paul Savage

Anastasios Polyzos*



CSIRO Manufacturing Flagship, Bayview Avenue, Clayton, Australia

An efficient nitro-Mannich type direct α-C(sp^3)–H functionalisation of *N*-aryl-1,2,3,4-tetrahydroisoquinolines catalysed by simple iron salts in combination with O_2 as the terminal oxidant is described. The use of a Teflon AF-2400 membrane Tube-in-Tube reactor under continuous flow conditions allowed for considerable process intensification to be achieved relative to previous batch methods.

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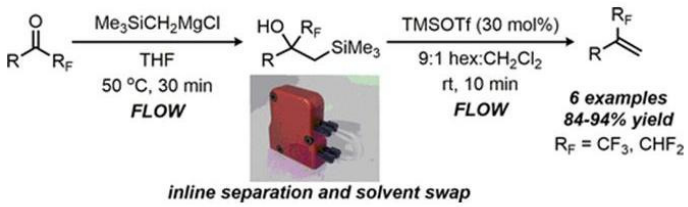
A Continuous-Flow Approach to 3,3,3-Trifluoromethylpropenes: Bringing Together Grignard Addition, Peterson Elimination, Inline Extraction, and Solvent Switching

Trevor A. Hamlin†,

Gillian M. L. Lazarus†,

Christopher B. Kelly †,

Nicholas E. Leadbeater *†‡



† Department of Chemistry, University of Connecticut, United States
‡ Department of Community Medicine & Health Care, University of Connecticut Health Center, United States

A continuous-flow approach to the synthesis of 3,3,3-trifluoromethylpropenes involving Grignard addition of (trimethylsilyl)methylmagnesium chloride to a trifluoromethyl ketone followed by dehydrative desilylation of the α-trifluoromethyl-β-hydroxysilyl alcohol using trimethylsilyl trifluoromethanesulfonate is reported. An inline aqueous/organic extraction and a concomitant solvent switch were key to the success of the methodology. Transition from batch to continuous flow conditions allows for higher yields, shorter reaction times, and facile scale out.

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Continuous-Flow Oxidative Cyanation of Primary and Secondary Amines Using Singlet Oxygen

Dmitry B. Ushakov,

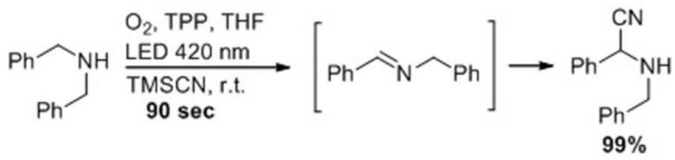
Kerry Gilmore,

Daniel Kopetzki, D.

Tyler McQuade,

Peter H. Seeberger

[1]Department für Biomolekulare Systeme, Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Potsdam, Germany
[2]Institut für Chemie und Biochemie, Freie Universität Berlin, Berlin, Germany
[3]Department of Chemistry and Biochemistry, Florida State University, Tallahassee, USA



Primary and secondary amines can be rapidly and quantitatively oxidized to the corresponding imines by singlet oxygen. This reactive form of oxygen was produced using a variable-temperature continuous-flow LED-photoreactor with a catalytic amount of tetraphenylporphyrin as the sensitizer. α-Aminonitriles were obtained in good to excellent yields when trimethylsilyl cyanide served as an in situ imine trap. At 25 °C, primary amines were found to undergo oxidative coupling prior to cyanide addition and yielded secondary α-aminonitriles. Primary α-aminonitriles were synthesized from the corresponding primary amines for the first time, by an oxidative Strecker reaction at –50 °C. This atom-economic and protecting-group-free pathway provides a route to racemic amino acids, which was exemplified by the synthesis of *tert*-leucine hydrochloride from neopentylamine.

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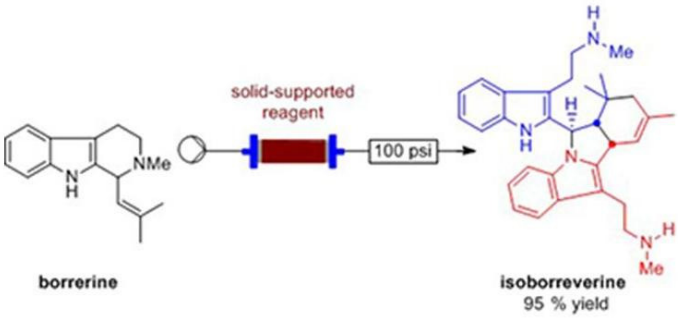
Facilitating Biomimetic Syntheses of Borrerine Derived Alkaloids by Means of Flow-Chemical Methods.

Sonja B. Kamptmann [A]
Steven V. Ley [A B]



[A] Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK.
[B] Corresponding author.

Flow chemistry is widely used nowadays in synthetic chemistry and has increasingly been applied to complex natural product synthesis. However, to date flow chemistry has not found a place in the area of biomimetic synthesis. Here we show the syntheses of borrerine derived alkaloids, indicating that we can use biomimetic principles in flow to prepare complex architectures in a single step.

Click here to go straight to the publication

Is it your first time?

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Thanks for reading.

See you again in 2015!
