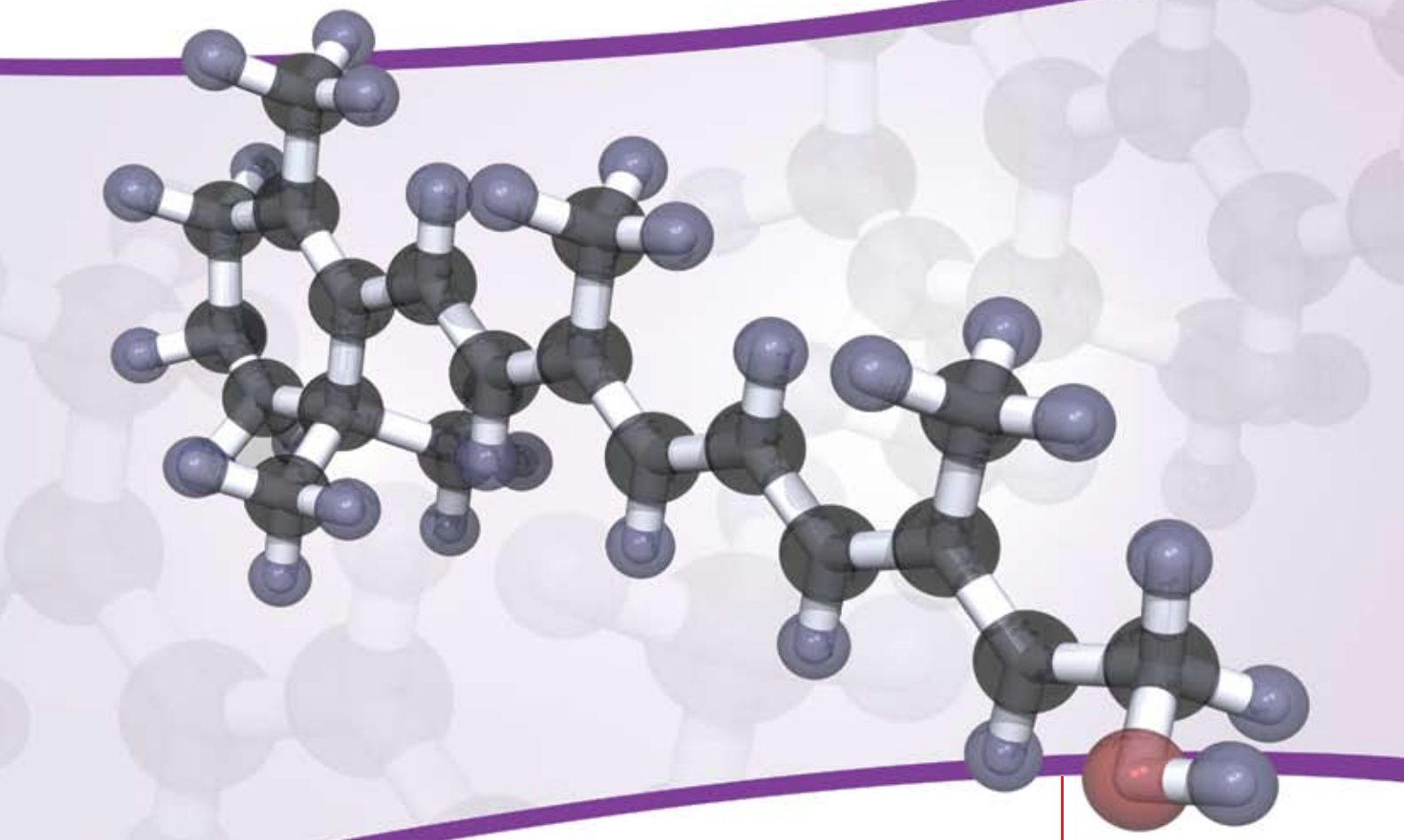
# ChemFiles

Vol. 9, No. 4

ALDRICH Chemistry

## Microreactor Technology



*Retinol — first product synthesized in industrial scales using Microreactor Technology at Sigma-Aldrich*

*Features include:*

Continuous Flow Synthesis in Microstructured Reactors

A Brief History of MRT at Sigma-Aldrich

The Sigma-Aldrich Microreactor Explorer Kit

Case Studies from Sigma-Aldrich Labs

Frequently Asked Questions



# Introduction

Matthias Junkers
Product Manager

Within the past two decades, Microreactor Technology (MRT) has evolved from a highly advanced toy for chemical engineers to a versatile tool for chemical synthesis. Since the time of the founders of synthetic chemistry, like Justus von Liebig or Friedrich Wöhler, the only way to conduct solution-phase synthesis was the conventional batch mode in stationary reactors with stirring or shaking as the only means to mix reactants.

Today, microstructured devices offer greatly enhanced mixing and heating capabilities compared to the batch process, leading to improved product profiles and higher yields. Thus, microreactors might be regarded as the chemist's round-bottomed flask of the 21st century (**Figure 1**). Microreactors are generally operated in a continuous flow mode. With a reactor volume of less than a milliliter, flow chemistry allows the scale-independent synthesis from g to kg amounts in a single day. The small reactor volume facilitates the safe and easy handling of hazardous or instable materials and highly exothermic reactions. Fast and easy parameter screening makes Microreactor Technology an ideal tool for process development.

Sigma-Aldrich is very proud to offer you a convenient all-in-one solution for the application of Microreactor Technology. Discover the numerous advantages of this innovative technology in detail in the present issue of ChemFiles. Then start right away to exploit MRT to accelerate and improve your own work with the Microreactor Explorer Kit (**19979**).

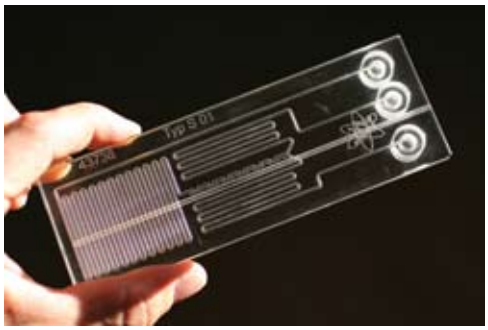


**Figure 1:** Microreactors — the chemist's round bottomed flask of the 21st century

If you have further questions, or would like to verify if Microreactor Technology could be the solution to your synthesis challenges "Please Bother Us." at *matthias.junkers@sial.com*, or contact your local Sigma-Aldrich office (see back cover). Useful information can also be found at *sigmaaldrich.com/mrt*. Alternatively, please join the Microreactor Technology Network group on *linkedin.com*, and connect directly to our product manager Matthias Junkers in order to discuss Microreactor Technology with other interested people and expert users.

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## About Our Cover

The cover structure depicts retinol (PN **95144**). This product was the first that Sigma-Aldrich transferred from an unreliable classical batch synthesis procedure to a highly stable continuous flow synthesis. By using a microreactor the yield was improved by 70%.




# ChemFiles

**Vol. 9 No. 4**



**Aldrich Chemical Co., Inc.**
**Sigma-Aldrich Corporation**
6000 N. Teutonia Ave.
Milwaukee, WI 53209, USA


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# Continuous Flow Synthesis in Microstructured Reactors — A New Way of Thinking Chemical Synthesis

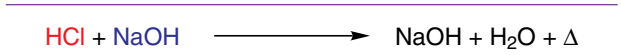
Organic chemists usually spend a substantial amount of time on the development of synthetic routes to new materials. The best pathways need to be chosen and reaction conditions must be optimized. Once a product is successful and demand for larger quantities is growing, the whole synthesis process needs to be revised again and readjusted for larger batch sizes.

This general procedure shows a typical problem in conventional batch synthesis: batch synthesis is a space-resolved process. The output of the reaction is determined by the size of the reaction vessel - the larger the vessel the higher the output of the reaction.

In sharp contrast to the batch mode, chemical synthesis becomes a time-resolved process in flow chemistry. Reagent streams are continuously pumped into a flow reactor where they are mixed and allowed to react. The product instantly leaves the reactor as a continuous stream. Therefore, only flow rate and operation time determine the synthesis scale. Identical reactors with an inner volume of less than a milliliter will produce kilogram quantities of material when operated for a whole day at fast flow rates, or small milligram batches if operated for a few minutes.

Rather than size, other parameters define the performance of a microreactor and will decide if it offers better features than a conventional batch reactor. First of all, the reactor material needs to be selected. Microreactors are readily available as metal, glass, or silicon builds. Each material offers specific advantages and disadvantages regarding price and compatibility with reagents or heat conductivity. The preferred material at Sigma-Aldrich is glass. Glass offers the highest compatibility with aggressive media and reagents. The production of glass microreactors is not too cost intensive, and blockages or other possible problems can be located visually through the material.

Independently from the reactor material, microreactors offer two major features that clearly make a difference vis-a-vis classical batch reactors. The neutralization of hydrochloric acid with sodium hydroxide (**Scheme 1**) can be taken as a simple exothermic model reaction to visualize the superior performance of microreactors compared to batch reactors.




**Scheme 1:** Exothermic model reaction

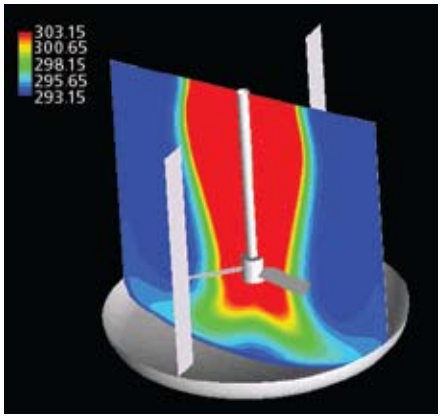



**Figure 2:** Heat distribution in a batch synthesis reactor

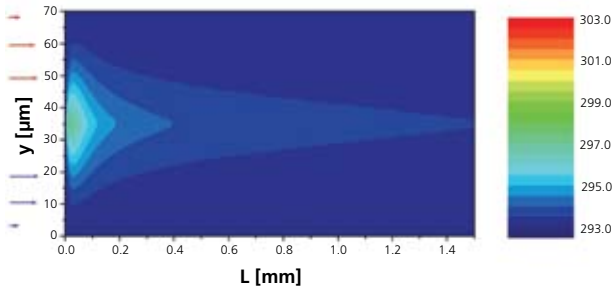



**Figure 3:** Heat distribution in a microreactor

## 1. Efficient Heat Transfer

Microreactors with their small surface to volume ratios are able to absorb heat created from a reaction much more efficiently than any batch reactor. **Figure 2** shows the initial heat distribution for the model reaction (**Scheme 1**) in a simulated 5 $m^3$ batch reactor stirred at 500 rpm.[1] The batch reactor is heated by the exothermic reaction. Cooling only takes place at the surface of the reactor. As a result, there is a strong temperature gradient from the surface of the reactor to its center. In a microreactor, the heat created by mixing the two reagents is also detectable but the temperature gradient is a lot smaller (**Figure 3**). Additionally, it only takes a few millimeters of path length for the reagent stream to cool down again to the temperature of the outside cooling medium.

The formation of hot spots or the accumulation of reaction heat may favour undesirable side reactions or fragmentation. Microreactors with their superior heat exchange efficiency present a perfect solution. Precise temperature control affords suppression of undesired by-products (**Figure 4**).

This becomes even more evident when looking at the scaling-up of a production routine. The surface to volume ratio is a function of reactor size. Bigger reactors have smaller surface to volume ratios (**Figure 5**). A synthesis procedure that works well in a small glass flask in R&D may pose huge problems when transferred directly to larger vessels in a kilo lab or pilot plant. Time consuming process development is necessary to fit the synthesis to the different parameters of a bigger reactor vessel. In flow chemistry a single microreactor can cover a broad range of production scales from mg to kg. For scaling-up, only the operation

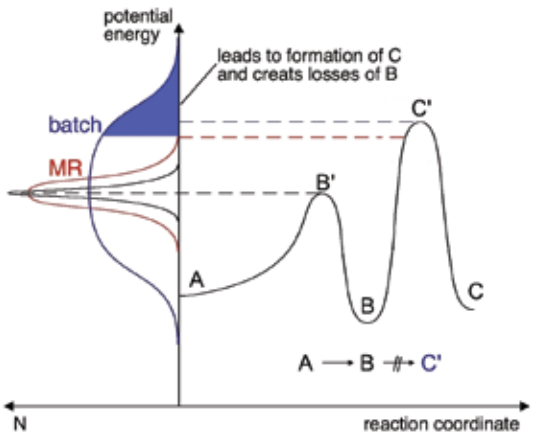



**Figure 4:** Precise temperature control in microreactors enhances product quality by suppression of side reactions[2]



time of the system is extended. No further process development is necessary.

Efficient heat transfer is also an important concern regarding safety. In batch reactors highly exothermic reactions require extended dosing times. There's always a risk that such a reaction might "run away" in a batch reactor. The small inner volume of a microreactor (typically less than a milliliter) combined with its strong heat exchange efficiency guarantees the safe and stable performance of highly exothermic reactions over hours. Even explosive reactants and intermediates can be handled safely in a microreactor.

## 2. Efficient Mixing

The core part of any microreactor is the mixing regime. Mixing quality is crucial for many reactions where the molar ratio between reactants needs to be controlled precisely in order to suppress side reactions. A sophisticated regime will mix reactants efficiently with a small path length of a few centimeters. The green color in **Figure 6** indicates the perfect 1:1 mixture for the same neutralization reaction as in the previous example (**Scheme 1**). The simulation clearly shows that mechanically stirred batch reactors cannot compete with microreactors with regard to mixing efficiency (**Figure 7**). Also simple T-joints in very basic flow chemistry systems will not give the same results as the engineered mixing regime of a microreactor.

**References:** (1) Schwalbe, T.; Autze, V.; Wille, G. *Chimia* **2002**, *56*, 63. (2) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440.

### Benefits from Microreactor Technology and Flow Chemistry

- Scale-independent synthesis
- Product profile improvement
- Accelerated process development
- Enhanced safety
- Constant product output quality
- Cleaner product profile
- Higher yields

| Reactor Type | Surface/Volume [$cm^2/cm^3$] |
|---|---|
| Flat microchannel width approx. 100 µm | 200 |
| 100 mL flask | 1 |
| 50 gallon reactor | 0.08 |
| 1 $m^3$ reactor | 0.06 |

**Figure 5:** Surface to volume ratio for different reactor sizes

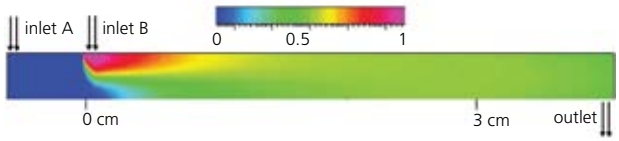



**Figure 6:** Mixing efficiency of a microreactor

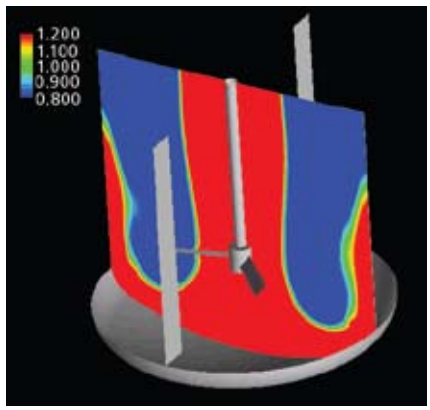



**Figure 7:** Mixing efficiency of a stirred batch reactor

## Recommended Literature

A couple of excellent reviews and highlight articles explain microreactor technology in detail. They give a comprehensive overview of which reaction types can profit from microfluidics, and describe which considerations should be made when planning a microreaction.


(1) "Green Chemistry Articles of Interest to the Pharmaceutical Industry": Andrews, I. et al. *Org. Process Res. Dev.* **2009**, *13*, 397.

(2) "Enabling Continuous-Flow Chemistry in Microstructured Devices for Pharmaceutical and Fine-Chemical Production": Kockmann, N.; Gottsponer, M.; Zimmermann, B.; Roberge, D.M. *Chem. Eur. J.* **2008**, *14*, 7470.

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(4) "Greener Approaches to Organic Synthesis Using Microreactor Technology": Mason, B.P.; Price, K.E.; Steinbacher, J.L.; Bogdan, A.R.; McQuade, D.T. *Chem. Rev.* **2007**, *107*, 2300.

(5) "Advanced organic synthesis using microreactor technology": Omer, B.A.; Brandt, J.C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733.

(6) "Mesoscale Flow Chemistry: A Plug-Flow Approach to Reaction Optimisation": Wheeler, R.C.; Benali, O.; Deal, M.; Farrant, E.; MacDonald, S.J.F.; Warrington, B.H. *Org. Process Res. Dev.* **2007**, *11*, 704.

(7) "Continuous Chemistry in Microreaction Systems for Practical Use": Müller, G; Gaupp, T.; Wahl, F; Wille, G. *Chimia* **2006**, *60*, 618.

(8) "Chemistry in Microstructured Reactors"; Jähnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 406.

(9) "Application of Microreactor Technology in Process Development": Zhang, X.; Stefanick, S.; Villani, F.J. *Org. Process Res. Dev.* **2004**, *8*, 455.

(10) "Chemical Synthesis in Microreactors": Schwalbe, T.; Autze, V.; Wille, G. *Chimia* **2002**, *56*, 63.


Further selected application examples can be found in the following publications.


(11) "Oxiranyl Anion Methodology Using Microflow Systems": Nagaki, A.; Takizawa, E.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2009**, *131*, 1654.

(12) "5-(Pyrrolidin-2-yl)tetrazole-Catalyzed Aldol and Mannich Reactions: Acceleration and Lower Catalyst Loading in a Continuous-Flow Reactor": Odedra, A.; Seeberger, P.H. *Angew. Chem. Int. Ed.* **2009**, *48*, 2699.

(13) "The Use of Copper Flow Reactor Technology for the Continuous Synthesis of 1,4-Disubstituted 1,2,3-Triazoles": Bogdan, A.R.; Sach, N.W. *Adv. Synth. Catal.* **2009**, *351*, 849.

(14) "MultiStep Synthesis using Modular Flow Reactors: Bestmann-Ohira Reagent for the Formation of Alkynes and Triazoles": Baxendale, I.R.; Ley, S.V.; Mansfield, A.C.; Smith, C.D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.

(15) "The Use of Diethylaminosulfur-Trifluoride (DAST) for the Fluorination in a Continuous Flow Reactor": Baumann, M.; Baxendale, I.R.; Ley, S.V. *Synlett* **2008**, *14*, 2111.

(16) "Rapid Multistep Synthesis of 1,2,4-Oxadiazoles in a Single Continuous Microreactor Sequence": Grant, D.; Dahl, R.; Cosford, N.D.P. *J. Org. Chem.* **2008**, *73*, 7219.

(17) "Multistep Continuous-Flow Microchemical Synthesis Involving Multiple Reactions and Separations": Sahoo, H.R.; Kralj, J.G.; Jensen, K.F. *Angew. Chem. Int. Ed.* **2007**, *46*, 5704.

(18) "Advantages of Synthesizing *trans*-1,2-Cyclohexanediol in a Continuous Flow Microreactor over a Standard Glass Apparatus": Hartung, A.; Keane, M.A.; Kraft, A. *J. Org. Chem.* **2007**, *72*, 10235.

(19) "A flow reactor process for the synthesis of peptides utilizing immobilized reagents, scavengers and catch and release protocols": Baxendale, I.R.; Ley, S.V.; Smith, C.D.; Tranmer, G.K. *Chem. Comm.* **2006**, 4835.

(20) "Microreactor Synthesis of β-Peptides": Flögel, O; Codée, J.D.C.; Seebach, D.; Seeberger, P.H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7000.

(21) "High Energetic Nitration Reactions in Microreactors": Panke, G.; Schwalbe, T.; Stirner, W.; Taghavi-Moghadam, S.; Wille, G. *Synthesis* **2003**, *18*, 2827.


As MRT becomes widely accepted, fine chemical and pharma companies frequently report utilization of at least one continuous flow step in API manufacturing campaigns and lab synthesis.


(22) *Eli Lilly*: Kopach, M.; Murray, M.; Braden, V.; Kobierski, M.; Williams, O. *Org. Process Res. Dev.* **2009**, *13*, 152.

(23) *Dow*: McConnell, J.; Hitt, J.; Daughs, E.; Rey, T. *Org. Process Res. Dev.* **2008**, *12*, 940.

(24) *Neurocrine Bioscience & Irix*: Gross, T.; Chou, S.; Bonneville, D.; Gross, R.; Wang, P.; Campopiano, O.; Quellette, M.; Zook, S.; Reddy, J.; Moree, W.; Jovic, F.; Chopade S. *Org. Process Res. Dev.* **2008**, *12*, 929.

(25) `*Organon*: Linden, J.v.d.; Hilberink, P.; Kronenburg, C.; Kempermann, G. *Org. Process Res. Dev.* **2008**, *12*, 911.




# A Brief History of MRT at Sigma-Aldrich — Our Mission

The purchase of an integrated flow chemistry system with a stainless steel microreactor in 2004 was Sigma-Aldrich's start into the exciting world of Microreactor Technology promoted by the early enthusiasts Fabian Wahl and Gernot Müller, today director of manufacturing and head of small-scale production (**Figure 8**). At its Buchs site in Switzerland, Sigma-Aldrich used the new technology to replace problematic batch synthesis processes. Soon limitations of the first microreactor system were discovered. For example, the steel reactor does not permit the use of corrosive reagents. The market was screened for alternative solutions, but no system was found that would meet all the requirements defined by Sigma-Aldrich:

- One single integrated MRT system for R&D scale evaluation of new synthesis procedures and immediate scale-up to kilogram quantities
- All reagent-touching materials should be metal free to ensure utmost compatibility with aggressive reagents
- Small and mobile system that can be moved easily between laboratories, set up fast when needed and put aside again when not needed
- Single fume-hood installation
- Handling as easy and simple as possible
- Small and robust monitoring unit that fits into laboratory environments and does not require training for complicated software
- Highly versatile system for all kinds of chemical transformations in liquid phase
- Offer only features a chemist really needs
- Enabling tool for accelerated process development

As a natural conclusion, the decision was made to develop such a system in-house. A team of experts was formed around the highly experienced senior scientist Gregor Wille (for a picture please refer to the case studies chapter), who established a knowledge network with manufacturers and other users. Consequently, the Sigma-Aldrich Microreactor Explorer Kit was realized. In close cooperation with Little Things Factory in Germany, the glass microreactor designed by Sigma-Aldrich was developed further over several generations (**Figure 9**). After it had proved its usability not only in test reactions, but also in "real life" for the production of Sigma-Aldrich catalog products and SAFC custom synthesis, Sigma-Aldrich started to offer the Microreactor Explorer Kit as product **19979** to customers worldwide in 2007 (**Figure 10**).

Today, microreactors are used at Sigma-Aldrich for the production of about 40 catalog products. A dedicated R&D research group continues to develop new flow chemistry synthesis routines. Another team in process development routinely uses the MRE kit to accelerate their work. Several custom synthesis projects have successfully been finished with Microreactor technology. Some selected examples will be explained in detail in the following chapters highlighting the specific benefits that were achieved with Microreactor Technology. At the next stage, Microreactor Technology know-how is spread to other Sigma-Aldrich subsidiaries all over the world with the MRE Kit **19979**.

The Sigma-Aldrich Microreactor Explorer kit covers production ranges from R&D scale to kilogram amounts of product. For larger production needs, several systems were evaluated at Sigma-Aldrich. Recently, an Alfa Laval Art® plate reactor was acquired to close the gap to larger production scales. Initial experience with this flow reactor shows that process knowledge gained with the Microreactor Explorer Kit **19979** can directly be transferred to the larger plate reactor.

Now our mission is to let customers benefit from Sigma-Aldrich's extensive MRT experience and equipment by exploring microreactor technology themselves with the MRE kit **19979**, and by faster completion of custom synthesis projects. If you're interested in receiving information or a quote on your custom synthesis project, please contact SAFC Pharma at *safcglobal@sial.com* or visit *safcglobal.com*.

### Microreactor Technology Facilities at Sigma-Aldrich

- Highly experienced and dedicated staff in R&D, process development and production
- Sigma-Aldrich Microreactor Explorer Kit **19979**
- CPC-CYTOS® based stainless steel microreactor
- Borosilicate glass reactors with different mixing regimes and different sizes manufactured by Little Things Factory
- Alfa Laval Art® plate reactor

**Figure 8:** Initiators of Sigma-Aldrich's journey to MRT, F. Wahl and G. Müller

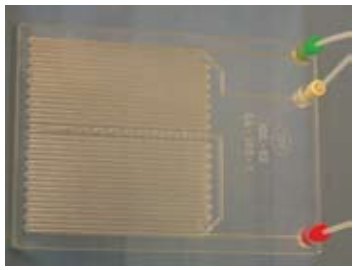


**Figure 9:** Two-layered XXL-version (15 mL) of Sigma-Aldrich's glass-microreactor manufactured by Little Things Factory

**Figure 10:** Sigma-Aldrich Microreactor Explorer Kit **19979** prototype.

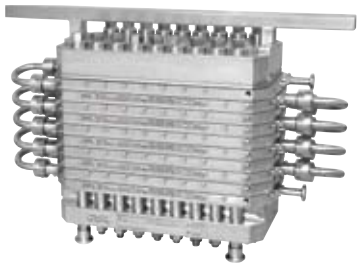


**Figure 11:** Alfa-Laval Art plate reactor for large scale synthesis (>1kg)

# The Sigma-Aldrich Microreactor Explorer Kit — Made by Chemists for Chemists

## All-in-One Solution

The Sigma-Aldrich Microreactor Explorer Kit was designed to give newcomers an opportunity to start discovering this innovative technology right away. Designed by chemists for chemists, it contains everything that is needed to perform flow chemistry experiments in a microstructured system right away: robust pumps for the transport of the reagent streams, a microreactor, an electronic monitoring unit including sensors for automated temperature and pressure supervision, sufficient tubing and fittings to connect all the different modules of the system, and last but not least spare replacements for consumptive parts. With its easy step-by-step manual, even non-experienced technicians or chemists will be able to set up and instantly use the system without effort. The Microreactor Explorer Kit **19979** gives chemists the opportunity to concentrate on what they can do best: chemistry!

In environments where microreactor and flow chemistry systems are already established, the Sigma-Aldrich Microreactor Explorer Kit can still be a valuable addition to the toolbox. With its highly attractive price, its portability and ease of use it can be applied to perform the initial process development for much more expensive and complicated systems. To this end it will help to employ all available flow chemistry tools as efficiently and cost-effectively as possible.

The Sigma-Aldrich Microreactor Explorer Kit **19979** is the most economical integrated solution for flow chemistry in microstructured reactors on the market. Why pay more?

## Robust, Multipurpose Microreactor Chip

The borosilicate glass microreactor chip manufactured by Little Things Factory in Germany following Sigma-Aldrich's design, offers the highest possible resistance to aggressive reagents (**Figure 13**). Even corrosive reactants like concentrated acids or acid halides can be used without harm. Glass offers the obvious advantage, where processes taking place in the microreactor are clearly visible. Blockages and impurities are easily detected and their removal can be followed visually. The Sigma-Aldrich glass microreactor with a total inner volume of 0.85 mL features two independent reagent stream inlets (indicated by the green and light yellow peek nuts on **Figure 13**, the red nut marks the output stream) with a small pre-heating unit of 0.08 mL each, a micromixer unit of 0.03 mL, and a fixed residence time unit (RTU) of 0.66 mL. Channel diameters are about 500 µm all through the reactor. This makes the reactor quite robust against blocking, because the channels will allow solid particles with diameters up to about 10% of the channel dimensions to flow freely through the system as long as the material does not accumulate at the channel walls. At the same time, channel dimensions are small enough to benefit from all advantages of microreactor technology (see previous chapter). A seperate channel allows insertion of the temperature sensor supplied with the kit directly into the glass chip. The temperature can be measured freely at any location between the beginning of the mixing zone to the end of the residence time unit.

## Easy Heating or Cooling

Heating and cooling of the glass microreactor is very straightforward. A chemist will simply do what he is used to doing with any conventional glass flask: immerse it in a heated or cooled bath. This method is simple, but highly efficient; and all common heating or cooling media can be used. The microreactor is usually submerged just below the fittings. If more precise temperature control is required then the reactor can be completely sumberged in a temperature regulated system.. However after large temperature changes the fittings should be retightened.

**Figure 12:** Microreactor Explorer Kit **19979** Set-Up Example

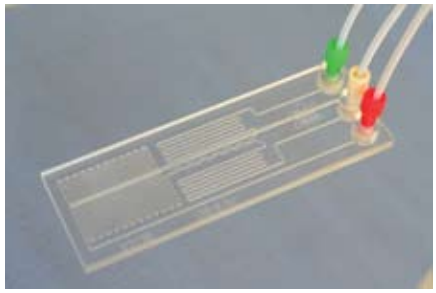


**Figure 13:** Borosilicate glass microreactor from Kit **19979**

**Figure 14:** Set-up example with heated bath (not included in kit)

## Variable Residence Time Unit

The residence time unit (RTU) on the glass microreactor is fixed to 0.66 mL. Reactions requiring a longer residence time variable, extension is possible with 25 mL of extra PTFE tubing supplied with the kit. The residence time $\tau$ is the flow chemistry equivalent of the reaction time in classical batch chemistry. It is defined by the combined volume of the microreactor and the residence time unit and the flow rate. The PTFE tubing can be cut down exactly to the length needed for a specific reaction. Smaller pieces can be combined again into longer residence time units with connectors. To control the reaction temperature the tubing can be coiled and submerged in a heated or cooled bath.

## Robust and Versatile Pumps

The Ismatec rotary piston pumps supplied with the Microreactor Explorer Kit **19979** are the best choice for continuous flow chemistry at an affordable price (**Figure 15**). They guarantee an undisturbed flow for hours, even at higher pressures. The ceramic pump heads align perfectly with the borosilicate glass reactor, which permits the prolonged use of aggressive and corrosive reagents. Flow rates can be chosen freely from 0.2 to 90 mL/min with adjustable stroke volumes. It should be noted though that backpressure in the system will limit the highest achievable flow rate depending on the viscosity of the solvent and the temperature. The system is specified to work up to 15 mL/min at its full temperature range from -70 to 150 °C with all common solvents. The Microreactor Explorer Kit **19979** requires only minimum maintenance or replacement of wearing parts that can be performed by any chemist or lab worker.

## Automated Pressure and Temperature Supervision

The Sigma-Aldrich Microreactor Explorer Kit **19979** is supplied with an easy to use monitoring unit based on a Siemens SPS element that is able to supervise two temperature and two pressure channels (**Figure 16**). Here the user can define upper and lower limits for each channel. If one of the sensor channels reports a violation of the threshold values the control unit will shut down the whole system. This allows unsupervised operation of the microreactor system. If for example a blockage of the microreactor occurs, then the pressure in the system will rise and the system is halted automatically in a safe state. This means that expensive parts like the pumps or the microreactor are protected from any serious damage and the risk of leakages of potentially harmful chemicals is also minimized. The user can remove the cause of possible problems upon return and restart the system. The electronic control unit is small (shoebox size) and robust and can be put into the fume hood together with the whole kit.

## Convenient Case

The transportation case allows convenient movement of the Microreactor Explorer Kit **19979** (15 kg) between laboratories and facilities. The whole system can be set up in less than an hour and if space is required in the laboratory for other tasks, the whole system can be stored away in its case.

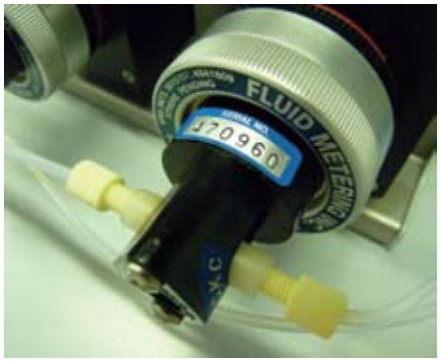



**Figure 15:** Rotary piston pump head

**Figure 16:** Pressure sensors

**Figure 17:** Transportation case

**Figure 18:** Microreactor clamp and support rod

## Included Accessories

The kit includes many useful accessories that will accelerate an instant start: a metal rod and holder help to lock the microreactor chip in the desired position; additional fittings and connectors; a tube cutter to facilitate working with the PTFE tubing, and three bottle caps to keep the reagent inlets and the product stream in place.

## Open Construction

All parts of kit **19979** are connected with standard fittings that are also used in chromatography equipment. This enables the easy incorporation of additional modules into the microreactor system. For example, a pressure valve can be attached to the output stream of the reactor in order to increase the boiling point of the solvent or to avoid phase separations in reactions with gas formation. The open construction of MRE Kit **19979** also makes it ideal for use in teaching. The function of all individual parts can be observed as opposed to the mystery of a black box.

## Requirements

The Microreactor Explorer Kit **19979** was developed as a highly versatile tool for chemical synthesis and all kinds of chemical transformations can be performed in this system with only a few requirements needing to be met. All starting materials and products have to be in solution or liquid form to avoid blocking the microreactor. Still, blockages do not need to be feared as the reactor can usually be liberated easily.

The formation of gases and volatile vapors during the reaction may diminish residence times unpredictably and should also be avoided. Flow pressure within the system via a pressure valve can help to suppress the formation of gas bubbles.

Finally, it should be noted that the faster a reaction runs the greater it benefits from microstructured reactors (preferrably less than 30 minutes). Slow reactions that take several hours or days to complete are not enhanced significantly by the special features of a microreactor.

## Comprehensive Manual

The Microreactor Explorer Kit **19979** is supplied with a comprehensive manual that will guide users easily through the system set-up. Many tips for the design of experiments are given (including e.g. an Excel® sheet on CD for the planning of a microreaction and the calculation of output, concentrations, etc.). The Microreactor Explorer Kit **19979** is so easy to set up and use that special, time-consuming training is not required to work with the kit.

## Optional Accessories

Some recommendations for optional accessories are given with the manual, e.g. valves required to perform reactions at elevated pressure in order to raise the boiling point of solvents.

## Multistep Synthesis

The Microreactor Explorer Kit **19979** can be used to perform continuous flow multistep reactions. Two kits with an additional 3rd glass microreactor contain all parts needed for a 3-stage assembly with full temperature and pressure supervision. Examples of multistep microreactions are presented in detail in the following chapter.

## MRE Kit 19979 at a Glance

### MRE Kit 19979 Components

- 0.85 mL borosilicate glass microreactor type S02 with clamp
- Two rotary piston pumps with adjustable ceramic pump heads
- Two thermo & two pressure sensors
- Electronic control unit
- 25 mL variable Residence Time Unit (PTFE tube, inner diameter 1/8 in.)
- Sufficient additional tubing, fittings and helpful tools
- Comprehensive manuals
- Convenient transportation case

### MRE Kit 19979 Features

- All reagent-touching materials metal-free
- Automated pressure & temperature supervision
- Temperature range: -70 to 150 °C
- Flow rates: 0.2 to 15 mL/min/pump at full temperature range (up to 90 mL depending on solvent viscosity and temperature)
- Max. inner pressure: 6.5 bar
- Suitable for production scales from g to kg amounts per day proven in industrial environment
- Compact system fitting into a single fume hood (space saving)
- The whole system weighs less than 15 kg and can be moved easily between different facilities in its convenient transportation case
- Easy handling, no special training required
- Open construction allowing easy system adaptions
- 120/240 Volt AC input
- CE compliant

### MRE Kit 19979 Benefits

- Reliable & secure scale-independent chemical synthesis (from R&D to kilo-lab)
- Accelerated process development (cost savings)
- Safe handling of highly exothermic reactions or hazardous materials
- Product profile improvement
- Side product suppression
- Protection of unstable products or intermediates
- Higher product yields with constant & better quality

| Microreactor Explorer Kit | |
|---|---|
| 19979-1KT | 1 kit |

# Case Studies from Sigma-Aldrich Labs

Every case study described in this chapter will highlight specific advantages of Microreactor Technology and Flow Chemistry and will show how this state-of-the-art technology was used to improve batch synthesis protocols significantly. The experiments have been conducted in the group of Sigma-Aldrich's senior expert on MRT, Gregor Wille, and in the process development group of senior scientist Patrick Kaiser (**Figure 19**). All synthesis protocols shown here are used today for the industrial production of chemicals intended for the Sigma-Aldrich catalogs or its SAFC business. Therefore, we have to apologize that in some cases not all process details (e.g. catalysts, reagents, structures) can be revealed.

## One-step synthesis procedures

### Retinol Synthesis

**Benefit from MRT & Flow Chemistry**: 70% improvement in yield by protecting the extremely sensitive product.

Retinol (Sigma **95144**) was the first product that was produced on industrial scale with Microreactor Technology at the Swiss Sigma-Aldrich facility in Buchs. The batch synthesis procedure that was used before the transfer into a flow chemistry process was unreliable and low yielding. The underlying chemical conversion - a simple basic ester hydrolysis - is not the cause of problems in this case (**Scheme 2**). The ester is cleaved quantitatively, but this process takes some time until it is completely finished. Portions of cleaved product that are formed right at the beginning of the process need to stay in the batch reactor under reaction conditions until all the remaining ester is cleaved. During this time the majority of the highly sensitive product degrades. Another observation was a serious unreliability of the batch process. Due to small and uncontrollable contributing factors, the yield of the reaction varied tremendously. By transferring the batch synthesis routine into a flow chemistry process in a microreactor the yield of the reaction was improved by 70%, now giving a constant output of 70% product each time the synthesis is performed. This improvement is a direct result of the flow process. In the continuous flow, every portion of product is streamed out of the reaction zone instantly after it has formed. The product outlet can lead directly into a protected storage vessel where the sensitive product is protected from degradation. The flow process facilitates quantitative conversion where as any yield lost is during work-up. It should be highlighted that the savings achieved with this single new synthesis procedure have already justified all investments into microreactor technology at Sigma-Aldrich.

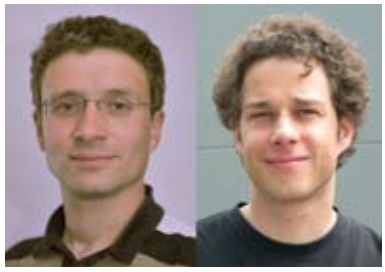
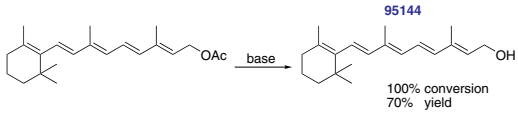
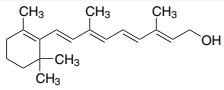


**Figure 19:** Senior MRT scientists Gregor Wille and Patrick Kaiser




**Scheme 2:** Retinol synthesis

**Retinol, ≥99.0% (HPLC)**




Axerophthol; Vitamin $A_1$; Vitamin A alcohol; all-*trans*-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol; Vitamin A
[68-26-8]
$C_{20}H_{30}O$
FW 286.45

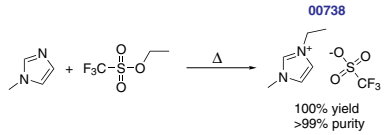
| | |
|---|---|
| 95144-250MG | 250 mg |
| 95144-1G | 1 g |

## Ionic liquids

**Benefit from MRT & Flow Chemistry**: Green production of a highly pure product with 100% yield thanks to precise control over reaction temperature.

The production of certain ionic liquids in high purity is a special challenge. The reaction between imidazole derivatives with sulfonates is extremely exothermic (**Scheme 3**). Conventional batch synthesis procedures fail to give purities higher than 96%. Even with very slow dosing times and careful cooling, batch reactors are heated up by the reaction. Our investigations show that brown impurities are formed if the temperature rises over 20 °C in any part of the batch reactor leading to an ugly colored product. Subsequent purification is troublesome and can only be achieved with huge efforts. Microreactors solve this dilemma with their superior heat exchange capabilities allowing synthesis with neat reagents with external cooling of -3 °C. Under these conditions the temperature inside the microreactor in the reaction zone is kept at a constant value of 8 °C. These are the perfect conditions to produce EMIm triflate **00738** with a purity exceeding 99%, and only traces of undesired materials (methylimidazole <50 mg/kg, water < 0.02%). Since neat reagents can be used without any solvent, the output of this procedure is very high. 1.5 kg of EMIm triflate **00738** is produced in just one hour. The synthesis procedure has been easily adapted to other substrates that can be found in the Sigma-Aldrich catalogs.

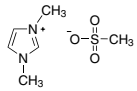
There is a lot of discussion questioning whether ionic liquids can generally be called 'green'. While this may be debatable production of ionic liquids in a microreactor is potentially as 'green' as chemical synthesis can be; as reagents are quantitatively converted into the final product, no solvents are needed for synthesis or purification and absolutely no waste is generated.




**Scheme 3:** Ionic liquids production

### 1,3-Dimethylimidazolium methanesulfonate, ≥99.0% (HPLC/T)

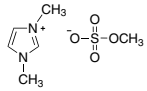
[521304-36-9]
$C_6H_{12}N_2O_3S$
FW 192.24



| | |
|---|---|
| 671738-5G | 5 g |
| 671738-50G | 50 g |

### 1,3-Dimethylimidazolium methyl sulfate, ≥98.0% (HPLC/T)

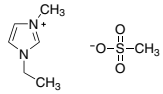
[97345-90-9]
$C_6H_{12}N_2O_4S$
FW 208.24



| | |
|---|---|
| 19409-5G | 5 g |
| 19409-25G | 25 g |

### 1-Ethyl-3-methylimidazolium methanesulfonate, ≥95%

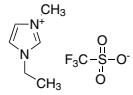
[145022-45-3]
$C_7H_{14}N_2O_3S$
FW 206.26



| | |
|---|---|
| 29164-100G-F | 100 g |
| 29164-1KG-F | 1 kg |

### 1-Ethyl-3-methylimidazolium trifluoromethanesulfonate, ≥99.0% (T)

[145022-44-2]
$C_7H_{11}F_3N_2O_3S$
FW 260.23



| | |
|---|---|
| 00738-5G-F | 5 g |
| 00738-50G-F | 50 g |



## Mono-Boc-Protection of Diamines

**Benefit from MRT & Flow Chemistry**: Green production of a highly pure product with 100% yield thanks to precise control over reaction temperature.

Mono-Boc-protected diamines are versatile building blocks for chemical synthesis. Their production is a lot more challenging than the simple reaction scheme might imply, because the Boc-anhydride reagent cannot differentiate between the two identical amino moieties in the substrate. The result is a crude mixture of unprotected, mono-protected and di-protected diamine (**Scheme 4**).

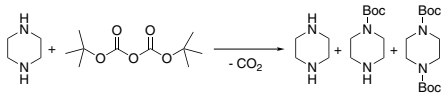
The preparation of mono-boc-protected piperazine **251356** is a very good example of how one can perform a very rapid process development for such a synthesis project with microreactor technology.

In a first series of 7 experiments, the reaction was tested with a couple of solvents at different temperatures. Apolar solvents like dichloromethane or toluene lead to the formation of solid particles and the blockage of the microreactor even at elevated temperatures. Methanol was able to keep all reagents and products in solution at room temperature, and was used for all further experiments.

In a second set of 6 experiments, the molar ratio between the boc-anhydride and the diamine was optimized. This task was accomplished a lot more easily with flow chemistry than with batch experiments. Batch reactions require individual set-up for every data point where as with flow chemistry one simply keeps the flow rate for one reagent stream constant. The flow rate in the other channel is changed step-wise and a product sample is taken after each change. Analysis of the data of this case showed that a maximum yield for the desired mono-protected piperazine **251356** was achieved with the addition of 0.8 equivalents of Boc-anhydride. Any less or more of the reagent then either the untouched piperazine or the di-protected product becomes predominant. The maximum yield of the reaction under optimal conditions in the microreactor is 45%. This does not seem very impressive however, it is significantly better than results achieved with batch reactors.

Industrial production, requires further considerations to be made in order to maximize the product output over time. In flow chemistry the output over time depends on concentration and flow rate. A series of three experiments allowed us to determine that 1.3 M of piperazine in methanol was the optimal concentration to avoid product precipitation blocking the system. Subsequent experiment series determined the optimal concentration of Boc-anhydride in the second channel (1.04 M, 0.8 eq), and the optimal flow rate (4mL/min), where the temperature was kept constant at 30 °C and the fixed residence time of 75 mL was used.

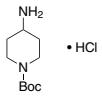
The best parameters found for the production of 600 g mono-Boc-protected piperazine **251356** were achieved in 8 hours with only 20 measurements. The procedure can typically be optimized for similar substrates in less than a day.




**Scheme 4:** Mono-Boc-protection of diamines

### 4-Amino-1-Boc-piperidine hydrochloride, ≥97.0% (N)

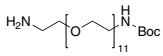
[179110-74-8]
$C_{10}H_{20}N_2O_2 \bullet HCl$
FW 236.74




| | |
|---|---|
| 75578-500MG-F | 500 mg |

### *O*-(2-Aminoethyl)-*O*′-[2-(Boc-amino)ethyl]decaethylene glycol, ≥90% (oligomer purity)

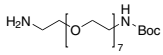
[890091-42-6]
$C_{29}H_{60}N_2O_{13}$
FW 644.79




| | |
|---|---|
| 77090-500MG-F | 500 mg |

### *O*-(2-Aminoethyl)-*O*′-[2-(Boc-amino)ethyl]hexaethylene glycol, ≥90% (oligomer purity)

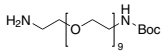
[206265-98-7]
$C_{21}H_{44}N_2O_9$
FW 468.58




| | |
|---|---|
| 70023-500MG-F | 500 mg |

### *O*-(2-Aminoethyl)-*O*′-[2-(Boc-amino)ethyl]octaethylene glycol, ≥90% (oligomer purity)

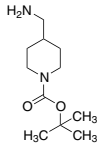
[890091-43-7]
$C_{25}H_{52}N_2O_{11}$
FW 556.69




| | |
|---|---|
| 79141-500MG-F | 500 mg |

### 1-Boc-4-(aminomethyl)piperidine

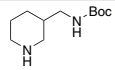
[144222-22-0]
$C_{11}H_{22}N_2O_2$
FW 214.30




| | |
|---|---|
| 641472-5G | 5 g |
| 641472-25G | 25 g |

### (±)-3-(Boc-aminomethyl)piperidine, ≥98.0% (TLC)

[142643-29-6]
$C_{11}H_{22}N_2O_2$
FW 214.30




| | |
|---|---|
| 55787-500MG-F | 500 mg |

### (*R*)-3-(Boc-amino)pyrrolidine, ≥98.0% (TLC)

[122536-77-0]
$C_9H_{18}N_2O_2$
FW 186.25


| | |
|---|---|
| 56308-1G-F | 1 g |
| 56308-5G-F | 5 g |

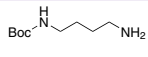
### (*S*)-3-(Boc-amino)pyrrolidine, ≥98.0% (TLC)

[122536-76-9]
$C_9H_{18}N_2O_2$
FW 186.25


| | |
|---|---|
| 52927-1G-F | 1 g |
| 52927-5G-F | 5 g |

### *N*-Boc-1,4-butanediamine, ≥97.0% (GC/NT)

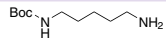
[68076-36-8]
$C_9H_{20}N_2O_2$
FW 188.27




| | |
|---|---|
| 15404-1ML | 1 mL |
| 15404-5ML | 5 mL |

### *N*-Boc-cadaverine, ≥97.0% (NT)

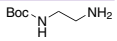
[51644-96-3]
$C_{10}H_{22}N_2O_2$
FW 202.29




| | |
|---|---|
| 15406-1ML | 1 mL |
| 15406-5ML | 5 mL |

### *N*-Boc-ethylenediamine, ≥98.0% (NT)

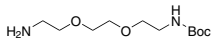
[57260-73-8]
$C_7H_{16}N_2O_2$
FW 160.21



| | |
|---|---|
| 15369-1G | 1 g |
| 15369-5G | 5 g |
| 15369-25G | 25 g |

### *N*-Boc- 2,2′-(ethylenedioxy)diethylamine, ≥95.0% (NT)

[153086-78-3]
$C_{11}H_{24}N_2O_4$
FW 248.32



| | |
|---|---|
| 89761-1G-F | 1 g |
| 89761-5G-F | 5 g |

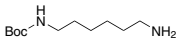
### 1-Boc-hexahydro-1,4-diazepine, 98%

[112275-50-0]
$C_{10}H_{20}N_2O_2$
FW 200.28

| | |
|---|---|
| 511382-5G | 5 g |

### *N*-Boc-1,6-hexanediamine, ≥98.0% (GC)

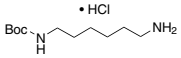
[51857-17-1]
$C_{11}H_{24}N_2O_2$
FW 216.32



| | |
|---|---|
| 79229-1G | 1 g |
| 79229-5G | 5 g |

### *N*-Boc-1,6-hexanediamine hydrochloride, 97%

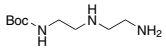
[65915-94-8]
$C_{11}H_{24}N_2O_2 \bullet HCl$
FW 252.78



| | |
|---|---|
| 437018-1G | 1 g |
| 437018-5G | 5 g |

### *N*[1]-Boc-2,2′-iminodiethylamine, ≥97.0% (NT)

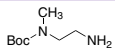
[193206-49-4]
$C_9H_{21}N_3O_2$
FW 203.28



| | |
|---|---|
| 17752-1ML | 1 mL |
| 17752-5ML | 5 mL |

### *N*-Boc-*N*-methylethylenediamine, ≥97.0% (GC)

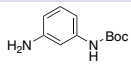
[121492-06-6]
$C_8H_{18}N_2O_2$
FW 174.24



| | |
|---|---|
| 15567-1ML | 1 mL |
| 15567-5ML | 5 mL |

### *N*-Boc-*m*-phenylenediamine, ≥98.0% (HPLC)

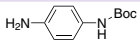
[68621-88-5]
$C_{11}H_{16}N_2O_2$
FW 208.26



| | |
|---|---|
| 53175-5G | 5 g |

### *N*-Boc-*p*-phenylenediamine, ≥97.0% (NT)

[71026-66-9]
$C_{11}H_{16}N_2O_2$
FW 208.26



| | |
|---|---|
| 15485-5G | 5 g |
| 15485-25G | 25 g |

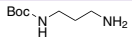
### 1-Boc-piperazine, ≥98.0% (GC)

[57260-71-6]
$C_9H_{18}N_2O_2$
FW 186.25

| | |
|---|---|
| 15502-5G | 5 g |
| 15502-25G | 25 g |

### *N*-Boc-1,3-propanediamine, ≥97.0% (GC/NT)

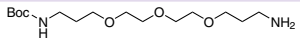
[75178-96-0]
$C_8H_{18}N_2O_2$
FW 174.24



| | |
|---|---|
| 15408-1ML | 1 mL |
| 15408-5ML | 5 mL |

### *N*-Boc-4,7,10-trioxa-1,13-tridecanediamine, ≥97.0% (NT)

$C_{15}H_{32}N_2O_5$
FW 320.42



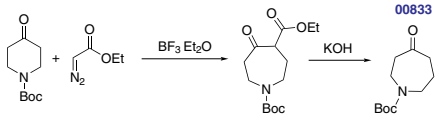
| | |
|---|---|
| 93113-1G-F | 1 g |

## Ring Expansion

**Benefit from MRT & Flow Chemistry**: safe & scale-independent handling of diazo reagents.

Potentially hazardous reagents like diazo compounds can be handled safely in microreactors because actual reaction volumes are very small. In a procedure developed at Johnson&Johnson ethyl diazoacetate is used in the presence of $BF_3 \bullet Et_2O$ to expand the six-membered ring of *N*-Boc-4-piperidone.[1] Thorough calorimetric investigations showed that this reaction can only be performed safely at small scales (test runs with 70 mg) in batch reactors. Scale-up to kilogram quantities cannot be recommended due to the risk of overheating and excessive nitrogen formation, leading to dangerous over-pressurization of the reaction vessel. The existing small-scale batch protocol was transferred into a flow process without the need of any further process development achieving a throughput of 91 g per hour at 89% yield.

Inspired by the Johnson&Johnson research this procedure was developed further and is used today by Sigma-Aldrich for the catalog production of *N*-Boc-hexahydro-1*H*-azepin-4-one (**00833**). The microreaction is followed by base induced decarboxylation performed in a conventional batch reactor (**Scheme 5**).




**Scheme 5:** Michael addition with subsequent Dieckmann condensation and decarboxylation leads to ring expansion

### *N*-Boc-hexahydro-1*H*-azepin-4-one, ≥95.0% (HPLC)

[188975-88-4]
$C_{11}H_{19}NO_3$
FW 213.27

| | |
|---|---|
| 00833-1G | 1 g |
| 00833-5G | 5 g |

**Reference:** (1) Zhang, X.; Stefanick, S.; Villani, F.J. *Org. Process Res. Dev.* **2004**, *8*, 455.



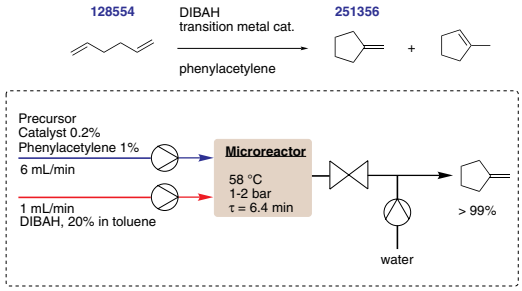
# Multistep Synthesis Procedures

## Ring Closure — Synthesis of Methylenecyclopentane

**Benefit from MRT & Flow Chemistry**: complete suppression of side-reactions.

The cyclization of 1,5-hexadiene to *exo*-methylenecyclopentane (**251356**) poses multiple challenges: the batch reaction affords an inseperable mixture of the *endo*- and *exo*-cyclization product (**Scheme 6**), the desired kinetically favoured product isomerizes under reaction conditions in presence of the catalyst; separation of the two isomers is difficult since both have virtually the same boiling point, and last but not least, the transition metal catalyst used for this transformation requires a minimum working temperature of 55 °C, as at this temperature the starting material evaporates.

Microreactor Technology proved to solve all these problems. Insertion of a pressure valve into the product channel allows the reaction to be performed at an elevated pressure of 2 bar. This raises the boiling point of the reactant sufficiently to meet the perfect working temperature of the catalyst at 58 °C without gas formation. Isomerisation of the desired product is completely suppressed by immediate transport of freshly formed product out of the reaction zone and an instant quench of the product stream. A simple T-piece suffices to mix the product stream with an excess of water and induce the fast quenching of the reaction. This procedure affords a highly pure product (>99%, 700g / 8 h) without the need of a time-consuming workup.




**Scheme 6:** Production of exomethylenecyclopentane in a microreactor

## Staudinger Hydration

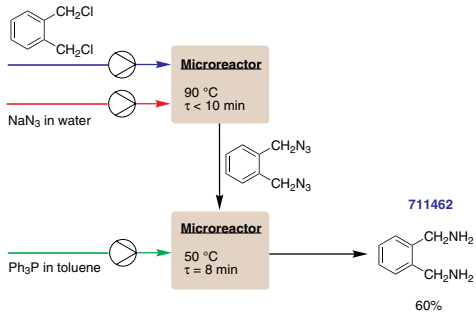
**Benefit from MRT & Flow Chemistry**: Efficient phase transfer catalysis; safe & scale-independent handling of explosive intermediates in small hold-up volumes with instant conversion.

Organic azides are high-energy compounds, an substrates with multiple azide moieties and low carbon content have to be considered as potential explosives, the azide intermediate shown in **Scheme 7** has a potential of 3.8 kJ/g at 114 °C (measured by DSC).

A two-stage microreactor continuous flow system allows the handling organic azides safely in small hold-up volumes with immediate conversion in the 2nd microreactor. In the 1st microreactor the azide intermediate is formed by nucleophilic substitution.[1] The azide intermediate is submitted to Staudinger hydration with triphenylphosphine in a subsequent 2nd microreactor. Notably, it is possible to work with biphasic systems in microreactors. A phase transfer catalyst moderates the initial reaction with efficient mixing by the microreactor.

Production capacity of o-Xylylenediamine **711462** in two subsequent glass microreactors exceeds 1 kg per day with an overall yield of 60%. Work-up and isolation of the potentially hazardous intermediate is completely avoided between reaction steps, saving time, money and offering scale-independent safety levels.

**Reference:** (1) Kopach, M.; Murray, M.; Braden, T.; Kobierski, M.; Williams, O. *Org. Process Res. Dev.* **2009**, *13*, 152-160.




**Scheme 7:** Two-stage microreactor assembly for the safe production and immediate conversion of organic azides

### 1,5-Hexadiene, 97%

[592-42-7]
$C_6H_{10}$
FW 82.14

| | |
|---|---|
| 128554-25G | 25 g |
| 128554-100G | 100 g |

### Methylenecyclopentane, 97%

[1528-30-9]
$C_6H_{10}$
FW 82.14

| | |
|---|---|
| 251356-1G | 1 g |
| 251356-10G | 10 g |

### 2-(Aminomethyl)-2-methyl-1,3-propanediamine trihydrochloride, ≥95.0% (NT)

$C_5H_{15}N_3 \cdot 3HCl$
FW 226.58

| | |
|---|---|
| 690023-1G | 1 g |

### *tert*-Butyl 12-amino-4,7,10-trioxadodecanoate, ≥80% (T)

[252881-74-6]
$C_{13}H_{27}NO_5$
FW 277.36

| | |
|---|---|
| 83060-1G-F | 1 g |
| 83060-5G-F | 5 g |

### *o*-Xylylenediamine dihydrochloride, ≥98%

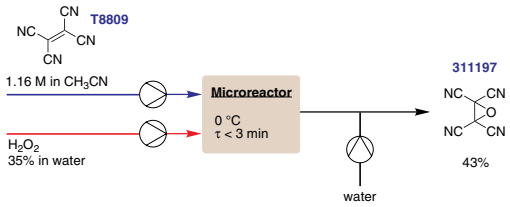
[21294-14-4]
$C_8H_{12}N_2 \cdot 2HCl$
FW 209.12

| | |
|---|---|
| 711462-5G | 5 g |

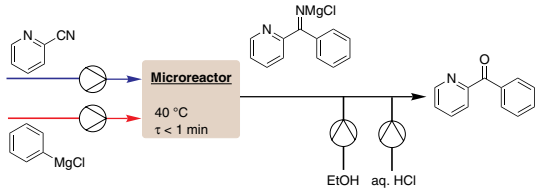
## Epoxidation

**Benefit from MRT & Flow Chemistry**: 87% improvement in yield, better product quality, with safe & scale-independent handling of hazardous reagents and intermediates.

The batch synthesis of tetracyanoethylene oxide (**311197**) requires extended dosing times due to the exothermic nature of the reaction, however the product decomposes under reaction conditions and demands fast work-up. As already shown in previous examples, microreactor technology offers an ideal solution to this type of challenge (**Scheme 8**). Efficient heat transfer capabilities of microreactors allow very short contact times ($\tau < 3$ min), where instant quenching of the product stream with water is easy to accomplish using a simple T-joint. Transfer of the synthesis from a batch to a flow process raised the product quality instantly from a yellow solid in only 23% yield, to a white powder in 43% yield without any optimization of the process. A considerable additional benefit is that the flow process can be scaled up without any further process development simply by prolonging the operation time. Scaling up the batch process would mean intensive additional work on the safety issues concerning the handling of accumulated large amounts of potentially hazardous oxygen compounds.




**Scheme 8:** Epoxidation




**Scheme 9:** Grignard microreaction with two subsequent quench modules

## Grignard Reaction

**Benefit from MRT & Flow Chemistry**: cost savings combined with accelerated & economic process development for large scale synthesis.

Microreactors also have some simple pragmatic advantages over traditional batch vessels: they take up less space on the factory floor and yet can still be used to make large quantities of product. 2-Benzoyl pyridine is an important building block, with an annual demand of about 15 tons. It is synthesized through a Grignard reaction (**Scheme 9**), and in a microreactor, this takes less than a minute. The Grignard microreaction is followed by two online quench modules. Precise reaction control leads to a highly pure product making a distillation step unnecessary that is needed for purification of the lower quality batch product.

The flow process was first developed with the Sigma-Aldrich Microreactor Explorer Kit **19979** using a 2 mL glass microreactor, which is able to produce up to 1 kg of 2-benzoyl pyridine per day. In a pilot study for the transfer of microreactor technology into large scale production we could show that process economic parameters evaluated with the Sigma-Aldrich Microreactor Explorer Kit **19979** ccould be directly transferred to production in a stainless steel Alfa Laval Art® plate reactor. Thus the rapid flow rates that can be achieved with this reactor allows the continuous production of 200 to 300 of kg 2-benzoyl pyridine per day. All of this from a reactor that requires only 30 x 50 cm of bench space!

### 3,4-Epoxy-1-cyclohexene, ≥96.0%

[6705-51-7]
$C_6H_8O$
FW 96.13

| | |
|---|---|
| 669911-1G | 1 g |
| 669911-5G | 5 g |

### Tetracyanoethylene, 98%

[670-54-2]
$C_6N_4$
FW 128.09

| | |
|---|---|
| T8809-5G | 5 g |
| T8809-25G | 25 g |

### Tetracyanoethylene oxide

[3189-43-3]
$C_6N_4O$
FW 144.09

| | |
|---|---|
| 311197-100MG | 100 mg |

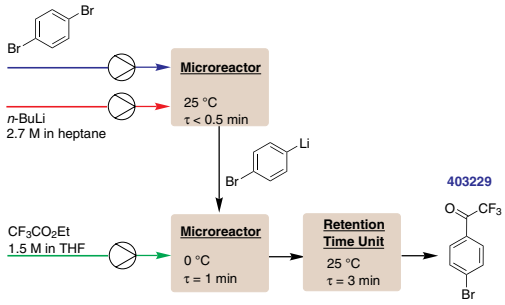
## Synthesis with Aryllithium Intermediates

**Benefit from MRT & Flow Chemistry**: cost savings & scale-independent metal organic chemistry at room temperature.

Organo lithiums formed by the metal halogen exchange reaction of butyllithium with organic halides, are extremely powerful intermediates for the synthesis of a plethora of products. Performed as a batch synthesis, the lithium bromine exchange reaction requires thorough dry ice cooling and extended dosing times. If the exothermic reaction is allowed to heat the batch reactor greater than -60 °C, undesired side reactions like the Wurtz coupling or double lithiation become predominant. This makes scaling up this process very difficult and expensive. Exceedingly cost-intensive cryogenic vessels are needed which are not even available at all in many kilo-lab facilities. Conversion of the process into microfluidics makes it more reliable and scale-independent (**Scheme 10**).[1-4]

A two-stage set-up with two sequential microreactors is required (**Figure 20**). In the first microreactor the bromine lithium exchange takes place and the aryllithium intermediate formed is fed directly into a second microreactor where it its coupled to the desired electrophile, e.g. $CF_3CO_2Et$ as illustrated in **Scheme 10**. Interestingly, particular cooling is no longer necessary for this reaction sequence as a microfluidic process, as simple wet ice cooling completely suffices. The fast transport of the lithium intermediate from its formation in the first microreactor to the follow-up reaction in the second microreactor effectively protects it from undesired side reactions. Depending on the substrates it is even recommended to carry out one of the reactions at room temperature, to avoid clogging of the micro channels. The procedure described here affords up to 1 kg product in about 8 hours of operation time of the microreactor system.

**References:** (1) Nagaki, A.; Takizawa, E.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2009**, *131*, 1654. (2) Nagaki, A.;Tomida, Y.; Usutani, H.; Kim, H.; Takabayashi, N.; Nokami, T.; Okamoto, H.; Yoshida, J.-I. *Chem. Asian J.* **2007**, *2*, 1513. (3) Gross, T.; Chou, S.; Bonneville, D.; Gross, R.; Wang, P.; Campopiano, O.; Quellette, M.; Zook, S.; Reddy, J.; Moree, W.; Jovic, F.; Chopade, S. *Org. Process Res. Dev.* **2008**, *12*, 929-939. (4) Schwalbe, T.; Autze, V.; Hohmann, M.; Stirner, W. *Org. Process Res. Dev.* **2004**, *8*, 440.




**Scheme 10:** Direct conversion of Lithium-organic intermediates in a 2-stage MRT system

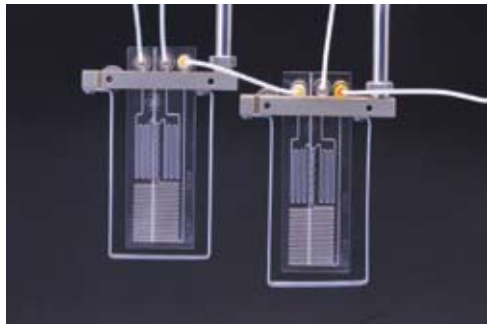


**Figure 20:** Two-stage assembly of two Sigma-Aldrich glass microreactors

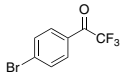
### 3′-Bromo-2,2,2-trifluoroacetophenone, ≥97%

[655-26-5]
$C_8H_4BrF_3O$
FW 253.02


| | |
|---|---|
| 689238-1G | 1 g |
| 689238-5G | 5 g |

### 4′-Bromo-2,2,2-trifluoroacetophenone, ≥98%

[16184-89-7]
$C_8H_4BrF_3O$
FW 253.02




| | |
|---|---|
| 403229-1G | 1 g |
| 403229-5G | 5 g |

### 1,3-Dibromobenzene, 97%

[108-36-1]
$C_6H_4Br_2$
FW 235.90


| | |
|---|---|
| 194395-5G | 5 g |
| 194395-25G | 25 g |

### 1,4-Dibromobenzene, 98%

[106-37-6]
$C_6H_4Br_2$
FW 235.90

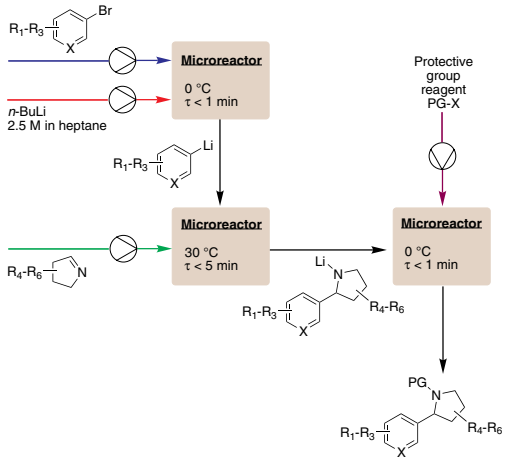

| | |
|---|---|
| D39029-5G | 5 g |
| D39029-100G | 100 g |
| D39029-500G | 500 g |
| D39029-2KG | 2 kg |

## Three-Stage Lithium-Organic Synthesis

**Benefit from MRT & Flow Chemistry**: cost & time savings, highly reliable synthesis protocol guaranteeing constant quality.

**Scheme 11** shows an extension of the concept described in the previous example. For a custom API synthesis project the general reaction sequence from **Scheme 10** was prolonged by an additional 3rd microreactor. In the 1st microreactor a substituted heterocyclic bromide is submitted to the metal halide exchange. The 2nd microreactor couples the aryllithium intermediate to a substituted cyclic imine. A protective group reagent intercepts the resulting lithiated amine in the 3rd microreactor leading directly to the final product. Traditional work-up between reaction steps is completely avoided by placing all reactions into one flow sequence.

Parallel investigation of the same reaction sequence performed as a batch process showed severe variation of yields and product profiles. In contrast the product was synthesized in the microreactors constant quality with an overall yield of 55%, independent from production scale variations. The flow synthesis procedure benefits from all advantages described for the previous example and allows production of 3kg of API within 24 hours. The whole custom synthesis project was finished in less than three months, proving the feasibility of flow chemistry for industrial scale multi-step synthesis of APIs.




**Scheme 11:** 3-stage microreactor API synthesis campaign

## Butyllithium Solutions

### *sec*-Butyllithium solution

[598-30-1]
$C_4H_9Li$
FW 64.06

**▸ 1.4 M in cyclohexane**

| | |
|---|---|
| 195596-50ML | 50 mL |
| 195596-100ML | 100 mL |
| 195596-800ML | 800 mL |

### *tert*-Butyllithium solution

[594-19-4]
$C_4H_9Li$
FW 64.06

**▸ 1.6-3.2 M in heptane**

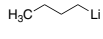
| | |
|---|---|
| 94439-100ML-F | 100 mL |

**▸ 1.7 M in pentane**

| | |
|---|---|
| 186198-50ML | 50 mL |
| 186198-100ML | 100 mL |
| 186198-800ML | 800 mL |
| 186198-8L | 8 L |
| 186198-18L | 18 L |

### Butyllithium solution

[109-72-8]
$C_4H_9Li$
FW 64.06



**▸ 2.0 M in cyclohexane**

| | |
|---|---|
| 302120-100ML | 100 mL |
| 302120-800ML | 800 mL |

**▸ ~2.7 M in heptane**

| | |
|---|---|
| 20159-100ML-F | 100 mL |
| 20159-500ML-F | 500 mL |

**▸ 10.0 M in hexanes**

| | |
|---|---|
| 230715-100ML | 100 mL |
| 230715-800ML | 800 mL |

**▸ 2.5 M in hexanes**

| | |
|---|---|
| 230707-50ML | 50 mL |
| 230707-100ML | 100 mL |
| 230707-800ML | 800 mL |
| 230707-8L | 8 L |
| 230707-18L | 18 L |

**▸ 1.6 M in hexanes**

| | |
|---|---|
| 186171-50ML | 50 mL |
| 186171-100ML | 100 mL |
| 186171-800ML | 800 mL |
| 186171-1L | 1 L |
| 186171-8L | 8 L |
| 186171-18L | 18 L |

**▸ 2.0 M in pentane**

| | |
|---|---|
| 302104-100ML | 100 mL |
| 302104-800ML | 800 mL |
| 302104-1L | 1 L |



# Frequently Asked Questions

**Why do you prefer rotary piston pumps to syringe pumps, peristaltic pumps, or HPLC pumps?**

The rotary piston pumps provided with kit **19979** represent a very robust system with appropriate specifications for continuous flow chemistry. Adjustable stroke volumes allow a broad range of flow rates between 0.2 and 15 mL/min (depending on solvent viscosity and temperature even up to 90 mL/min are possible) and guarantee an undisturbed flow over hours, even at higher pressures. The pressure behaviour is constantly linear. The ceramic pump heads permit the prolonged use of highly corrosive reagents, with only minimum maintenance required, allowing any lab worker can perform necessary calibration procedures, and replace consumptive parts.

**Can reactions be carried out on the micro-reaction system that are usually carried out under reflux?**

Reactions in the microreactor should be carried out at least 5 °C below the boiling temperature of the solvent. The formation of gas or bubbles will diminish retention times unpredictably. By applying a pressure valve (not included in the kit) at the product outlet, it is possible to run reactions at elevated pressures of up to 6.5 bar. This makes working at higher temperatures possible.

**Can reactions, during which volatile vapors and gases are produced, be carried out?**

The formation of gas or bubbles will diminish retention times unpredictably and should be avoided. Performing the reaction under elevated pressure by applying a pressure valve can help to suppress gas bubble formation.

**Can hydrolysis-sensitive reactants be used?**

Since the microreactor already is a self-contained system no additional measures have to be taken to exclude humidity. The reactor should simply be flushed with dry solvent prior to the reaction. The reactants can be easily supplied from sealed vessels.

**The glass reactor has only two inputs (reactant connections). Can three or more reaction components be used in the micro-reaction system simultaneously?**

In most cases it is possible to distribute all components needed for a specific reaction to only two different solutions. If this is not applicable several microreactors can be operated in a line, i.e. a first microreactor is used to mix the first two solutions, with the output is pumped directly into a second microreactor, where it can be mixed with a third solution.

**To what extent can particle-dependent reactions be performed in a glass reactor?**

Generally the microreactor is only suitable for liquid-phase chemistry and formation or feeding of solid particles should be avoided. Nevertheless it can be observed that particles with a maximum diameter of about 100 μm pass the reactor without blocking the channels.

**What do I do if the reactor gets blocked? How can the system be unblocked?**

For cleaning purposes the reactor can be treated without harm with pressurized air, surfactants or diluted acids and bases. The glass chip allows detection of the major precipitation visually. In most cases it is actually a lot easier to clean the microreactor with a simple solvent flow than in a classical glass flask.

**What is the temperature range at which reactions can be carried out?**

-70 to +150 °C

**What is the maximum permissible pressure in the system?**

The system is specified to work safely up to 6.5 bar.

**What flow rates can be achieved?**

The pumps are able to deliver up to 90 mL/min. Depending on solvent viscosity and temperature, the back pressure in the system might rise to critical values at high flow rates. The system is specified to work from 0.2 to 15 mL/min per pump at the full temperature range with all typical solvents.

**Which materials are used for the parts of the system that have contact with the reactants?**

PTFE, borosilicate glass, ceramics. This metal-free construction enables safe handling of aggressive compounds (e.g. acids, acid halides, nitration reagents etc.).

**What is the volume of the included glass reactor?**

The following values can vary somewhat based on production tolerances (+/-10 %):

Pre-heating section (pre-heating volumes):
0.08 mL per channel
Mixing section (mixing volume): 0.03 mL
Retention section (retention volume): 0.66 mL
Total volume:
0.85 mL

**What is the loss in pressure in the system with water at a specified temperature and specified flow rate?**

The pressure may deviate, but at room temperature the pressure loss in the glass reactor at a total flow of 10 mL water is 0.7 bar. At a total flow of 20 mL water, the pressure loss increases to about 1.7 bar.

**What is the specific heat conductance of the glass reactor?**

The glass reactor is made of borosilicate glass (Borofloat 33 Duran®). This material has a specific heat conductance of l (90 °C) = 1.2 W/m/K. On request glass reactors that have one side made of silicon may also be produced. The specific heat conductance l of silicon is approx. 146 W/m/K, which is significantly better than that of stainless steel (Fe/Cr18/Ni 8) with l (23°C) = 16.3 W/m/K.

**What is the residence time τ? How do I calculate it?**

The residence time τ is the flow chemistry equivalent of the reaction time in traditional batch synthesis. τ depends on the total volumes of the microreactor, the subsequent residence time unit, and the total flow rate of the system: τ = (MR Volume + RTU volume) / (Flow rate pump 1 + Flow rate pump 2)

**How can I calculate the output of a flow reaction?**

Output [g/h] = Feed rate [mL/min] x Concentration [mmol/L] x MW [g/mol] x Reaction yield [%] x $6x10^{-4}$

Please note that this equation does not depend on the reactor volume! Even the smallest microreactors can produce a high output at high concentrations and flow rates.

# SAFC® Launches New Vendor Audit Services

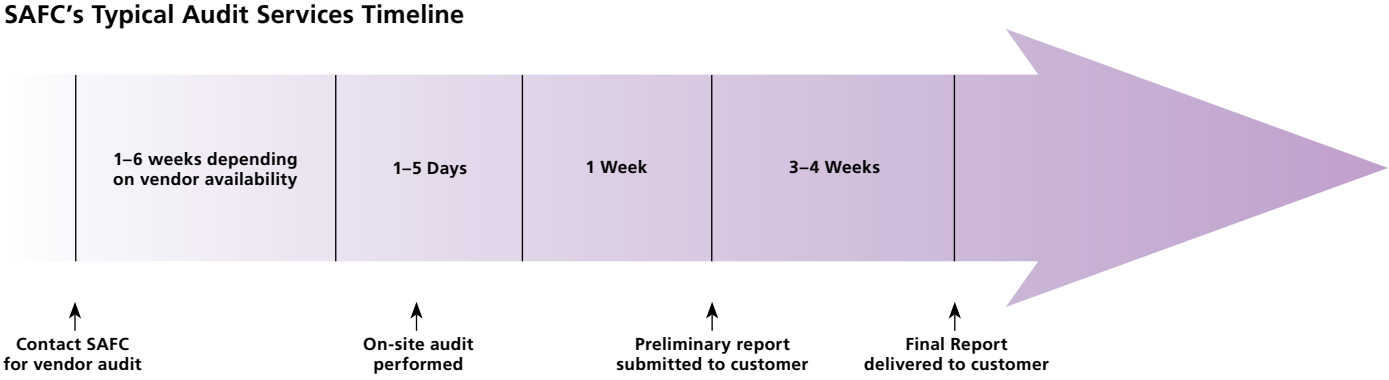
On March 19, 2009, SAFC® announced details of its new Vendor Audit Services, designed to extend audit reach for customers that need to secure global supply chain integrity through enhanced traceability and quality confirmation for critical raw materials and key intermediates. SAFC's Vendor Audit Services are an extension of in-house auditing programs, and provide pharmaceutical and biotechnology firms with a team of highly trained auditors that have extensive regulatory compliance expertise and are on the ground in local regions, including China.

**Standard audits available include:**

- ISO 9001:2008 (previously ISO 9001:2000)
- ISO 13485:2003
- 21 CFR 211
- 21 CFR 820
- ICH Q7A
- GAMP 5
- GLP
- 21CFR58

SAFC can also perform audits to customer specifications upon request.

**SAFC's Typical Audit Services Timeline**

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Sigma-Aldrich
3050 Spruce Street
St. Louis, MO 63103 USA
*sigma-aldrich.com*

**Argentina**
SIGMA-ALDRICH DE ARGENTINA S.A.
Free Tel: 0810 888 7446
Tel: (+54) 11 4556 1472
Fax: (+54) 11 4552 1698

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SIGMA-ALDRICH PTY LTD.
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Free Fax: 1800 800 096
Tel: (+61) 2 9841 0555
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Tel: (+43) 1 605 81 10
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Free Tel: 0800 14747
Free Fax: 0800 14745
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Fax: (+32) 3 899 13 11

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Fax: (+1) 905 829 9292

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SIGMA-ALDRICH spol. s r. o.
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Fax: (+420) 246 003 291

**Denmark**
SIGMA-ALDRICH DENMARK A/S
Tel: (+45) 43 56 59 00
Fax: (+45) 43 56 59 05

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SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800 51 55 000
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Tel: (+49) 89 6513 0
Fax: (+49) 89 6513 1160

**Greece**
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Ingyenes fax szám: 06 80 344 344
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Fax: (+36) 1 235 9050

**India**
SIGMA-ALDRICH CHEMICALS
PRIVATE LIMITED
Telephone
Bangalore: (+91) 80 6621 9400
New Delhi: (+91) 11 4358 8000
Mumbai: (+91) 22 2570 2364
Hyderabad: (+91) 40 4015 5488
Kolkata: (+91) 33 4013 8003
Fax
Bangalore: (+91) 80 6621 9650
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Free Fax: 1800 600 222
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Fax: (+ 353) 402 20375

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Numero Verde: 800 827018
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Fax: (+39) 02 3801 0737

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SIGMA-ALDRICH JAPAN K.K.
Tel: (+81) 3 5796 7300
Fax: (+81) 3 5796 7315

**Korea**
SIGMA-ALDRICH KOREA
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Free Fax: (+82) 80 023 8111
Tel: (+82) 31 329 9000
Fax: (+82) 31 329 9090

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Tel: (+60) 3 5635 3321
Fax: (+60) 3 5635 4116

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Free Fax: 01 800 712 9920
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Fax: (+52) 722 276 1601

**The Netherlands**
SIGMA-ALDRICH CHEMIE BV
Free Tel: 0800 022 9088
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Fax: (+31) 78 620 5421

**New Zealand**
SIGMA-ALDRICH NEW ZEALAND LTD.
Free Tel: 0800 936 666
Free Fax: 0800 937 777
Tel: (+61) 2 9841 0555
Fax: (+61) 2 9841 0500

**Norway**
SIGMA-ALDRICH NORWAY AS
Tel: (+47) 23 17 60 00
Fax: (+47) 23 17 60 10

**Poland**
SIGMA-ALDRICH Sp. z o.o.
Tel: (+48) 61 829 01 00
Fax: (+48) 61 829 01 20

**Portugal**
SIGMA-ALDRICH QUÍMICA, S.A.
Free Tel: 800 202 180
Free Fax: 800 202 178
Tel: (+351) 21 924 2555
Fax: (+351) 21 924 2610

**Russia**
SIGMA-ALDRICH RUS, LLC
Tel: (+7) 495 621 5579
Fax: (+7) 495 621 5923

**Singapore**
SIGMA-ALDRICH PTE. LTD.
Tel: (+65) 6779 1200
Fax: (+65) 6779 1822

**Slovakia**
SIGMA-ALDRICH spol. s r. o.
Tel: (+421) 255 571 562
Fax: (+421) 255 571 564

**South Africa**
SIGMA-ALDRICH (PTY) LTD.
Free Tel: 0800 1100 75
Free Fax: 0800 1100 79
Tel: (+27) 11 979 1188
Fax: (+27) 11 979 1119

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SIGMA-ALDRICH QUÍMICA, S.A.
Free Tel: 900 101 376
Free Fax: 900 102 028
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Fax: (+34) 91 661 96 42

**Sweden**
SIGMA-ALDRICH SWEDEN AB
Tel: (+46) 8 742 4200
Fax: (+46) 8 742 4243

**Switzerland**
SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800 80 00 80
Free Fax: 0800 80 00 81
Tel: (+41) 81 755 2828
Fax: (+41) 81 755 2815

**United Kingdom**
SIGMA-ALDRICH COMPANY LTD.
Free Tel: 0800 717 181
Free Fax: 0800 378 785
Tel: (+44) 1747 833 000
Fax: (+44) 1747 833 313

**United States**
SIGMA-ALDRICH
Toll-Free: 800 325 3010
Toll-Free Fax: 800 325 5052
Tel: (+1) 314 771 5765
Fax: (+1) 314 771 5757

**Vietnam**
SIGMA-ALDRICH PTE LTD. VN R.O.
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