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Continuous Process Engineering with Microreactors: A Complementary Method in Fribourg

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Abstract: Microreactors are discussed as a complementary tool for chemical development. Two reactions were studied: the formation of an ionic liquid, the 3-butyl-1-methylimidazolium bromide is presented, and the synthesis of cinnamaldehyde.

Keywords: Batch process · Chemical development and production · Continuous process · Ionic liquids · Microreactor

1. Introduction

Still today, chemists are perceived like chefs in a kitchen wearing white coats, elaborating recipes by mixing and heating up ingredients of different types in simple pans. This picture is not that far from the truth. Synthetic organic chemists work most often in a simple chemical glass reactor by mixing reagents. When it comes to produce greater quantities (about a kilogram), development chemists, who have most often also a strong background in organic chemistry, use the similar recipe with larger but rather similar reactors. While increasing the quantity, they seek to optimize the synthesis batch after batch. Even at a production scale of hundreds of kilograms the procedure is based on the same technique.

The industrial process is reviewed, optimized and redesigned only when the quantities needed become sufficiently important. At this point, it can be of economic interest to conduct the process in a continuous way. Many large productions (petrochemistry, distillation, or quite simply waste-water treatment) work in a continuous mode. The choice of conducting a reaction in a continuous mode may also stem from ecological and safety considerations.

There are plenty of good reasons to stick with batch reactions from the research laboratory up to a tonne scale production. However, in many cases it is worthwhile to consider a continuous mode already in the research lab or at least in the development phase.

Many authors such as Ehrfeld[1] or Roberge *et al.*[2] explain microreactor technology. Microreactors allow chemical reactions to be run with a volume of some microliters (µl). The amounts required to optimize a chemical reaction are thus minimal. The use of parallelism leads to an increase of the productivity without changing process variables. Reactions are no longer 'scaled-up' but 'numbered-up'.

Many studies, for example Schwalbe *et al.*,[3] propose microreactor use even for chemical production. The microreactor, rather than a conventional vessel, allows better control of the reaction, an increase in safety and a better portability. The reaction trajectory can be more accurately followed thanks to a precise temperature control. This is due to an extremely high thermal heat-transfer coefficient in relation to the volume. Safety is directly related to the volume of solvent in the microreactor. The reduced size makes it possible to easily move the microreactor between different laboratories. The modularity of the installation and the laboratory is, *de facto*, improved.

It is also easier to integrate on-line analysis, see Koch and Marquardt,[4] such as UV/VIS spectroscopy, infrared spectroscopy (FT-IR). Micro-analytical systems such as gas chromatography (GC) or high-pressure liquid chromatography (HPLC) with or without the mass spectrometry (MS) can be interfaced with microreactors. Standard sensors (temperature, pH, conductivity…) are directly integrated in the microreactor.

Thurow *et al.*[5] describes many automation possibilities for microreactors. This can be a cost reducing factor.

However, even if microreactors seem to have only advantages, it is necessary to verify this in practice. It is also important to remember that many solid reactions and reactions with suspensions are not possible.

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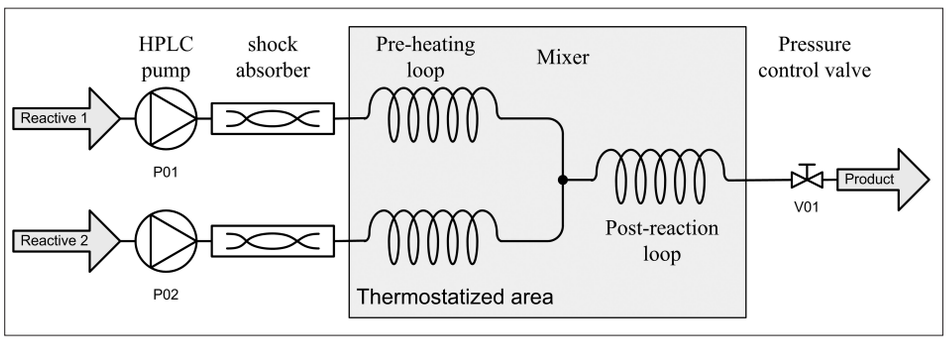


Fig. 1. Scheme of a basic microreactor installation

2. The Choice of an Appropriate Microreactor

In 2006, we began with a semester work studying flow dynamics in a simple HPLC tube. Many reactions require two or three reactives to create a product. The simplest construction utilizes two pumps, a mixer, and a loop for the post-reaction. By adding a regulation valve at the end of the tube, the global pressure can be controlled. The system must be temperature controlled. Fig. 1 presents the installation scheme.

Our study continued with the diploma work by Alonso[6] with the synthesis of an ionic liquid. This synthesis was optimized with the classical methodology by Vanoli *et al.*[7] We used HPLC pumps offering a flow between 0.1 ml/min and 9 ml/min, HPLC tubes (STAINLESS) with an internal diameter of 0.5 mm and three kinds of mixers (a simple T, two micromixers SSIMM and Caterpillar from the institute of Mikrotechnik at Mainz (IMM, Germany). The whole of the microreactor was placed in an open temperature-controlled bath. Two HPLC tubes in spiral form of 50 cm allow the liquids to be preheated. At the end of the micromixer, an HPCL tube in spiral of 2.5 m is used to offer a post-reaction time equivalent to 2 min for a flow rate of 1 ml/min (Fig. 2).

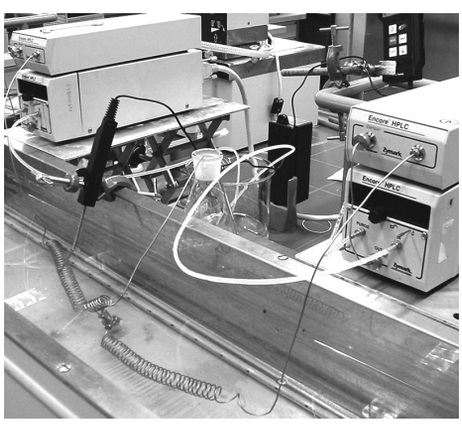


Fig. 2. Simple microreactor based on a HPLC system

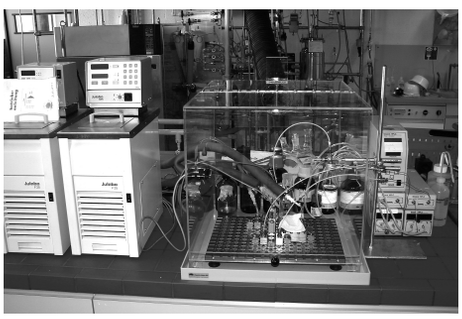


Fig. 3. Modular microreactor platform using the Ehrfeld system

This year, we started a project named 'Microréacteur' funded by the Centre de compétences REALTECH of the HES-SO (n° 16625). In parallel, the school bought from Ehrfeld a platform with microelements making it possible to build a modular microreactor (Fig. 3).

3. Synthesis of an Ionic Liquid

The term 'ionic liquid' is used for salts showing a point of fusion lower than 100 °C. Here we describe the synthesis of 3-butyl-1-methylimidazolium bromide or [BMIM]Br which is a commonly known ionic liquid. This product is obtained by reacting (Scheme 1) 1-methylimidazol and the 1-bromopropane.

Traditionally, the reaction is carried out in semi-batch mode with a 2 l reactor (reaction calorimeter from Mettler-Toledo). The bromopropane is placed in the reactor (60 °C) and 1-methylimidazol is added drop by drop. The reaction is strongly exothermic (an enthalpy of –282 kJ/kg and a $\Delta T_{adiabatic}$ = 332 K). The post-reaction varies between 3 and 6 h.

A series of tests (Fig. 4) shows the relation between the flow rate and the conver-

Scheme 1. Synthesis of the ionic liquid [BMIM]Br

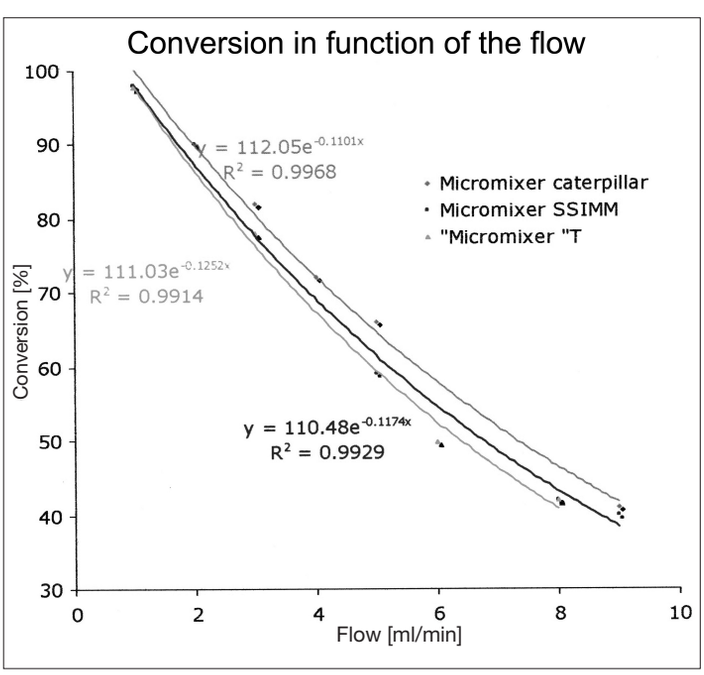
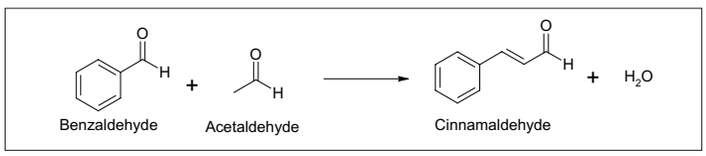


Fig. 4. Ionic liquid synthesis, conversion in function of the flow rate

sion (determined by NMR). It is also interesting to note that for this synthesis, the type of micromixer has only a small influence on the final conversion. After optimization of the reaction variables we obtained a conversion equal to 100% with a post-reaction time of approximately 2 min and an outgoing flow of 2.7 ml/min.



Scheme 2. Cinnamaldehyde synthesis

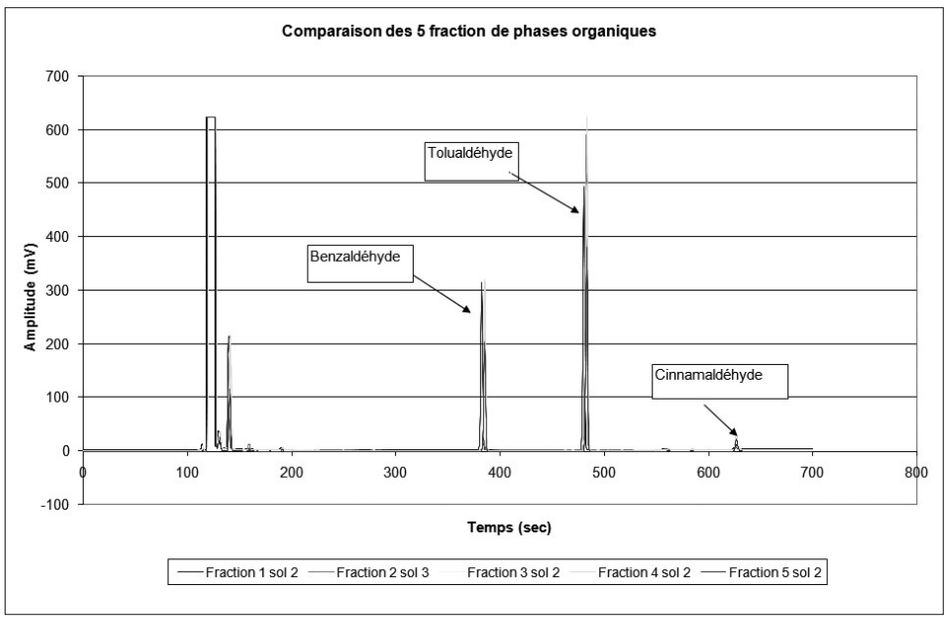


Fig. 6. Cinnamaldehyde synthesis with microreactor

4. Cinnamaldehyde Formation

Cinnamaldehyde formation (cinnamon flavor, Scheme 2) was studied, and optimized in classical reaction mode at our school within a project aiming at the development of chemometric methods for chemical process improvement. Depending on the reaction conditions, the yield of the desired product is lowered by the formation of crotonaldehyde.

Synthesizing cinnamaldehyde in a continuous reactor requires some modifications of the reagents. It is obvious that solid KOH can no longer be a reagent. At the moment the target molecule can be obtained in a microreactor (Fig. 6). However with the chosen process variables the yield is still below the one obtained in the semi-batch mode.

5. Future Challenges: Development Facilities and Online Analysis

The cinnamaldehyde synthesis will be optimized in the microreactor and in the home-build continuous reactor (micromixer and temperature-controlled HPLC tubes). These results will be compared in order to gain an insight into the importance of microfluidics for chemical transformations.

In collaboration with the HES-SO Valais (Prof. Dr. Simon Crelier), a new methodology for the continuous renaturation of proteins is currently under investigation. Catalytic reaction (hydrogenation) will also be looked at.

It remains also an objective to increase the online analytical capabilities of the reactor by coupling it with an FT-IR spectrometer having a continuous flow cell.

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