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Flow chemistry using milli- and microstructured reactors—From conventional to novel process windows

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ABSTRACT

The terminology Novel Process Window unites different methods to improve existing processes by applying unconventional and harsh process conditions like: process routes at much elevated pressure, much elevated temperature, or processing in a thermal runaway regime to achieve a significant impact on process performance. This paper is a review of parts of IMM's works in particular the applicability of above mentioned Novel Process Windows on selected chemical reactions. First, general characteristics of microreactors are discussed like excellent mass and heat transfer and improved mixing quality. Different types of reactions are presented in which the use of microstructured devices led to an increased process performance by applying Novel Process Windows. These examples were chosen to demonstrate how chemical reactions can benefit from the use of milli- and microstructured devices and how existing protocols can be changed toward process conditions hitherto not applicable in standard laboratory equipment. The used milli- and microstructured reactors can also offer advantages in other areas, for example, high-throughput screening of catalysts and better control of size distribution in a particle synthesis process by improved mixing, etc. The chemical industry is under continuous improvement. So, a lot of research is being done to synthesize high value chemicals, to optimize existing processes in view of process safety and energy consumption and to search for new routes to produce such chemicals. Leitmotifs of such undertakings are often sustainable development[1] and Green Chemistry[2].

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1. Introduction

Common industrial processes are mostly carried out in batch vessels (e.g., CSTR's):[3] The reactants are loaded into the reactor and chemical reaction is taking place. After completion, the reactor is emptied and loaded again. This is a well developed procedure and works well for most chemical reactions. However, if one considers fast and exothermic reactions these processes are strongly limited by their inertia and the disadvantage of a low surface to volume ratio. Especially for industrial scale-up this leads to severe limits.

The increase in size leads to a decrease in mixing quality, heat transfer, and in some cases to safety risks, if one considers the large hold up of reactive substances.[4] In addition, processes are run below this kinetic potential and leaving much room for process intensification.[5–13] These technical limitations are strongly influencing the preparation protocols, for example, fast and exothermic reactions are deliberately slowed down to control the heat of reaction and to avoid side reactions possibly triggered by increased reaction temperature. The use of microstructured equipment like microstructured heat exchangers and mixing devices can considerably help to overcome these limitations. For engineering- and process-related reviews on micro process technology see Refs. 14–30 a view on this subject from the perspective of chemists is given in Refs. 31–40.

There are diverse companies that already have developed continuous processes using microreactors on a production scale that can meet the needs of the market as well or even better as the 'old school' batch process (see examples in Ref. 41). The industrial uses of microstructured reactors have shown their ability to improve chemical processes for a variety of processes such as fine chemistry, polymerizations, and even for material manufacture.[42]

The following sections will give a review on recent research done at the Institut für Mikrotechnik Mainz GmbH in the field of flow chemistry, that is, chemical syntheses not traditionally performed batch wise in flasks, but using continuous flow through milli- and microstructured reactors with a particular emphasis

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on the exploration of Novel Process Windows not accessible with conventional equipment.

1.1. Definition of microreactors and their advantages

The word ‘micro’ in the expression microreactor implies the association of little and tiny reactors—in terms of outer dimensions with corresponding low productivity. But for microreactors, as meant in this paper, the word ‘micro’ refers mostly to their inner dimensions; thus ‘microstructured reactor’ being the more adequate term. These structures are typically below a millimeter in size, and more specifically in the region of 10 and 100 mm.[36] The specific surface area increases in a range between 10,000 and 50,000 $m^2\ m^{-3}$ which is an order of magnitude higher than for traditional reactors.

The heat transfer efficiency also correlates to the provided specific surface area and thus a superb heat transfer can be achieved in such devices—envisage the fine-lamella type radiator of a car. This characteristic is one big advantage for highly exothermic reactions for which the heat of reaction needs to be removed at the point where it is produced, resulting in a much more defined temperature profile over the whole reaction pathway. Thus nearly isothermal reaction conditions can be achieved.

Besides the superb heat conductivity, mixing can also be enhanced. Due to the short diffusion pathways mixing time can significantly be shortened down to several milliseconds. Thus the influence on mass/diffusion transport limitations can be minimized.

Additionally the well defined flow profile inside the microchannels is an important feature. In most cases the flow is laminar and thus back mixing is suppressed which helps to avoid side reactions. Also, regular flow patterns for multiphase flow can be generated in such channel dimensions. In segmented flow, each segment behaves like a single reactor and due to internal circulations an enhancement in mass transfer is achieved.[43–45]

Based on the small reaction volume inside each channel, process parameters such as pressure and temperature can be controlled more easily than in large-volume batch reactors. This characteristic opens new ways to change existing protocols—limited by the nature of common technology. Also processing at higher concentrations or even solvent-free is possible. This in turn can lead to a reduction in process costs and in a more environmentally friendly process.[46–49] The usage of this technology will lead to new chemical protocols using hitherto impossible reaction conditions; the so-called Novel Process Windows. Flow chemistry for a large diversity in chemical reactions has been reported. Almost all name reactions and other well established chemical transformations were tested. Recent examples, among many others, are the Moffat–Swern oxidation,[50] copper-free Sonogashira coupling,[51] hydrosylilation of various alcohol-derived thiocarbonyl derivatives,[52] mannosylation of diisopropylidene galactose,[53] dedicated fluorinations with diethyl-amino-sulfur trifluoride (DAST)[54] including one-pot multistep synthesis such as the 4-diamino-1*H*-isochromen-1-ones synthesis[55] and cascade multistep synthesis such as to the natural products rimonabant and efaproxiral[56] and the seven-step sequence of (±)-oxomaritidine synthesis in automated flow reactor.[57]

1.2. Definition of Novel Process Windows

The terminology Novel Process Window unites different methods to improve existing processes by applying unconventional process conditions like: process routes at much elevated pressure, much elevated temperature, and processing in a thermal runaway regime to achieve a significant impact on process performance.[4] This methodology can be subdivided to a list of the following major topics.

- Routes at much elevated temperature.
- Routes at much elevated pressure.
- Routes at increased concentration or even solvent-free.
- Routes in the explosive or thermal runaway regime.
- Process integration or simplification.
- New chemical transformations.

This is further broken down in Figure 1.

This description will be the guideline for the following sections in which different types of reactions are presented in which the use of microstructured devices led to an increased process performance by applying Novel Process Windows. Main characteristics

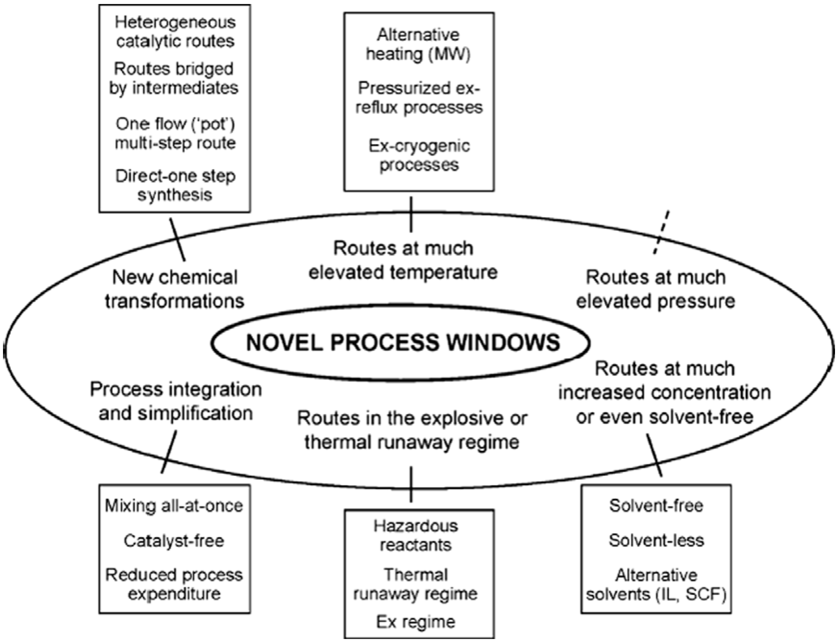


Figure 1. Novel Process Windows[4] (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).

of this new flow chemical transformations are higher selectivity (yield), higher conversion and much reduced reaction times, safe handling of hazardous materials, and facile operation und high temperature and high pressure.

2. Application of milli- and microstructured reactors in Conventional Process Windows

As outlined in Section 1, milli- and microstructured reactors can open Novel Process Windows which is the major focus of this paper. Nevertheless, these components offer also advantages in other areas being related to more conventional processing. As illustration two examples are given below, which relate to gathering of information (screening) and functions (materials) rather than only to the generation of chemicals. In the first example, a micromixer enables a high-throughput screening of catalysts. In this context, it is also worth mentioning that these reactors can also be used in a broader sense to gain rapid information, for example, through parameter screening for reaction optimization. In the second example, the good mixing performance of a micromixer is used to achieve a better control over the size distribution in a particle synthesis process.

2.1. High-throughput screening of homogeneous catalysts

The high-throughput screening of homogeneously catalyzed reactions in biphasic systems (g/L and L/L) using a micromixer was demonstrated by de Bellefon et al.[58] Exemplarily, the isomerization reaction of 1-hexene-3-ol to ethylpropylketone (Scheme 1) is described in the following paragraph.

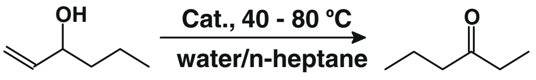
1-Hexene-3-ol is dissolved in *n*-hexane while the catalyst is dissolved in water. The screening of different catalysts was performed using an interdigital micromixer of IMM (SSIMM) connected to a tube reactor. The catalyst solution was injected in pulses and because of the rapid mixing in this special micromixer (10^{-2} s) it was possible—in combination with gas chromatography—to screen different types of catalyst with very small amounts of 1–2 μmol of catalyst. In this case, 18 tests were performed (each of them was repeated twice to test the reproducibility) within a total screening time of 1 h. This procedure is very useful when only small amount of catalysts are available and fast information about their catalytic performance is needed.

2.2. Improvement of dye properties

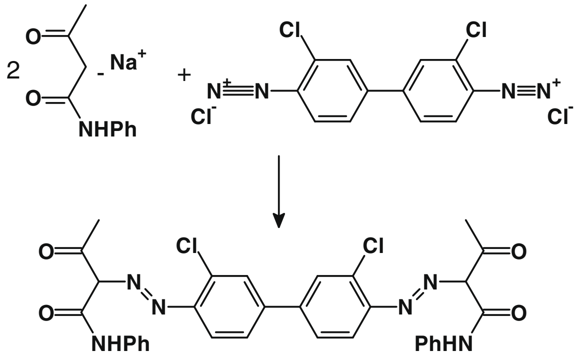
The properties of pigments are affected by the mean particle size as well as the particle size distribution. Both parameters are influence by mixing during synthesis. So it is in general possible to improve dye properties by optimization of the mixing process.

In industrial processes, for example, azo pigments are synthesized in large batch stirred tank reactors and the coupling component is added to a stirred solution or suspension of the diazo component or the other way around. Depending on the performance of these batches the quality can change from batch to batch and relatively broad particle size distributions can be obtained.

For the synthesis of the dye Yellow 12 it has been demonstrated that a semi-continuous processing using a micromixer led to an improvement of dye properties compared to the batch processing (Scheme 2).[59] Additionally, the possibility to handle solid products in microstructured components has been shown. As central element a slit interdigital micromixer of IMM (SSIMM with 60 μm mixing slit width and 25 μm wide feed channels) was used. The applied total flow rate was varied between 10 and 50 mL/min.



Scheme 1. Isomerization reaction of 1-hexene-3-ol to the desired ethylpropylketone.



Scheme 2. Azo coupling resulting in Yellow 12.

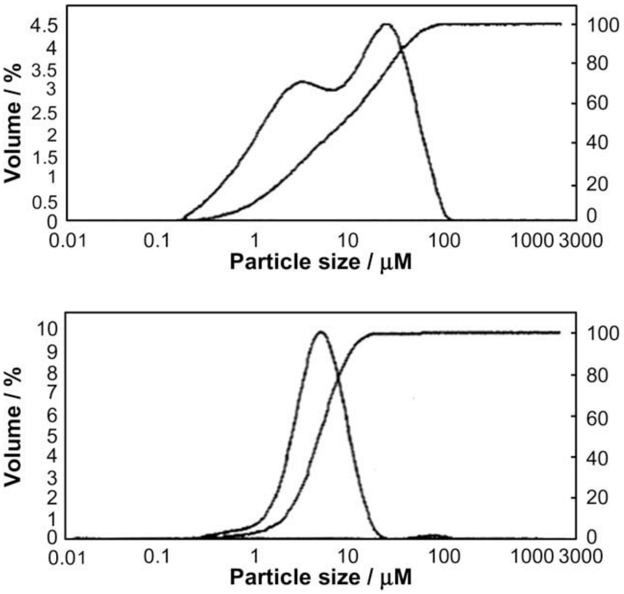


Figure 2. Particle size distribution for Yellow 12; batch procedure (top), micro mixer based process at a flow rate of 30 mL/h (bottom[59]) (by courtesy of ACS).

Due to the very fast mixing of the diazo and the coupling compound a significant smaller median diameter of the particles as well as a narrow particle size distribution was obtained compared to the batch procedure (see Fig. 2).

Compared to the Yellow 12 standard an increase of glossiness by 73% and an increase in transparency by 66% in connection with an unchanged tinctorial power were achieved. Overall, the micromixer based process resulted in an improvement of the azo pigment process, no blockage at the mixing unit was observed and higher flow rates had a positive effect on mixing efficiency and thus on pigment quality.

3. Novel Process Windows

3.1. Routes at much elevated temperature and routes at much elevated pressure

3.1.1. Introduction

In the late 1800 van't Hoff stated that increases of 10 °C in the reaction temperature will double the reaction rate.[60] This 'rule of thumb' and is strictly only valid in ambient temperature ranges. But with this approximation it is obvious that one can shorten reaction times and thereby improving process performance by increasing the reaction temperature by orders of magnitude. However, this is under the assumption that side reactions can be neglected and the main reaction pathway is not negatively affected. In laboratory equipment, for example, glass flask, autoclaves, etc. the reaction temperature is mostly maintained by using, for example, a water bath, oil bath, electrical heating, liquid nitrogen and dry ice mixtures in various alcohols. Microstructured reactors now offer improved heat transfer capabilities and therewith better temperature control during the chemical process. Also they allow fast heating-up and cooling-down steps. In many cases it is sufficient to simply embed microstructured reactors in temperature controlled baths using the same fluids as mentioned above. For more demanding applications concerning thermal management it is easily possible to implement a defined cooling/heating circuit into the device through which the service fluid is continuously pumped through.

Microstructured reactors therewith enable novel process windows at much elevated temperature. When reaction temperatures above the boiling point of a solvent used are targeted, it is necessary to increase the system pressure to avoid boiling and to keep the reaction mixture in a liquid state. The mechanical stability of microstructured devices—depending on channel dimensions and material—allows one to run processes in a high pressure regime without loss in safety. For these kinds of processes the novel process window 'elevated temperature' is interconnected to the novel process window 'elevated pressure'. Nevertheless, it is also thinkable, for example, that in some cases the increase in pressure can be used to shift the reaction equilibrium to the side of the product or that this is even of kinetic implication through the activation volume of the reaction intermediate and that therewith the operation under higher pressure is a novel process window on its own. Since the examples from IMM's work offer only examples of the interconnected type, there is no separate section for the 'higher pressure' novel process window.

Furthermore, milli- and microstructured reactors offer also the flexibility in design for an additional degree of freedom allowing the implementation or the usage of alternative heating (e.g., microwave heating)/cooling devices.

3.1.2. Grignard reaction to synthesize phenyl boronic acid

The Grignard reaction is a common route to yield a new carbon–carbon bond. The feasibility to perform a Grignard reaction using microstructured devices was demonstrated for the example of the phenyl boronic acid synthesis[48] giving at the same time a good example for structured reactors enabling to run a former cryogenic process at ambient temperature due to the better mixing capabilities and therewith eliminating a slow-down of reaction kinetics through use of low temperature for maintaining selectivity (keeping kinetic and not mixing-masked regime). The reactants—phenylmagnesium bromide and boronic acid trimethyl ester, each being dissolved in tetrahydrofuran were contacted in a micromixer and then transferred into a tubular reactor embedded in a thermostat bath to control the reaction temperature. The formed phenyl boronic acid dimethoxy ester (Intermediate 2 in Scheme 3) was then hydrolyzed to yield the final product (Product 1 in Scheme 3).

Since the phenylmagnesium bromide (Reactant 1 in Scheme 3) is a highly reactive nucleophile and will react with electrophiles, such as protic solvents, acids, amines, alcohols, and nitriles potentially present in the reaction mixture, various side reactions can occur.

The hydrolysis of Reactant 1 results in the formation of Byproduct 1 and Byproduct 2, additionally phenol (Byproduct 2), chlorobenzene (Byproduct 3), and biphenyl (Byproduct 4) are formed by a more complex reaction pathway not mentioned in Scheme 3. An excess of phenylmagnesium bromide can react with Intermediate 2 to Intermediate 3 which can further be hydrolyzed to Product 2. The reaction of an additional phenylmagnesium bromide with Product 2 will result in Intermediate 4 and finally in Product 4 after hydrolysation. If Product 2 is directly hydrolyzed, Product 3 will be obtained. A large amount of Product 3 will lead to a more complex purification and therefore has to be avoided.

The industrial process is conducted at −50 to −40 °C yielding in 65% of Product 1 to prevent mixing masking. Using micro process technology as outlined above—it was possible to increase the yield to 89% which is nearly 25% higher than the industrial process and about 18% higher than the laboratory batch experiment at a temperature of 20 °C, that is, it has been feasible to replace the cryogenic processing which is linked to a high technical expenditure. Furthermore, side reactions and the formation of consecutive products could be suppressed below a value of 1%; resulting in a higher purity of Product 1 ($\sim$99%) compared to 82% for the conventional process.

3.1.3. Kolbe–Schmitt synthesis under high-p,T-process conditions

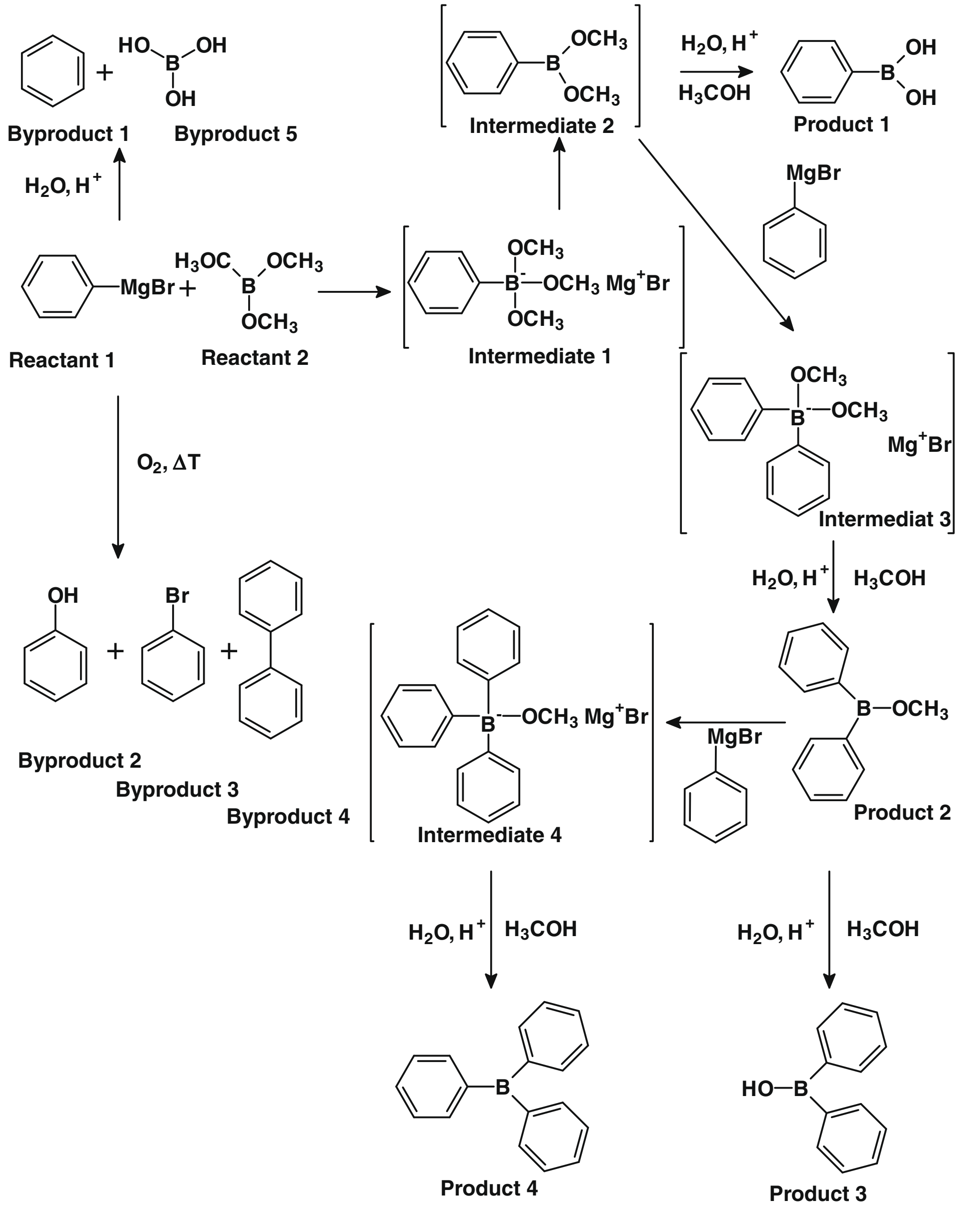
The Kolbe–Schmitt synthesis was developed by A. W. Hermann Kolbe in 1860 to produce salicylic acid (Scheme 4) and was further improved by Rudolf Schmitt in 1885.[61,62]

In 1874 Friedrich von Heyden, a former assistant of Rudolf Schmitt, founded the 'Chemische Fabrick von Heyden'. This was the birth of the modern pharmaceutical industry since salicylic acids and its derivatives are used to synthesize pharmaceutical products. The industrial salicylic acid production is based on reacting from sodium phenoxide in a stream of carbon dioxide at 150–160 °C and 5 bar over pressure.[63] This reaction is mostly conducted in batch stirred tank reactors, for example, in a 6 m^3 reactor and a reaction time of 25 h, where the long reaction time is caused by the exothermicity of the carboxylation step. The Kolbe–Schmitt synthesis is a general method for the introduction of carboxylic moieties into a phenolic core and not limited to the above discussed starting material phenol itself.

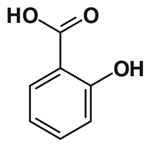
Hessel et al.[46] investigated the application of micro process technology to the synthesis of 2,4-dihydroxy benzoic acid starting from resorcinol via Kolbe–Schmitt synthesis. Thanks to the high reactivity of the electron-rich phenolic ring, a mild version of the above mentioned Kolbe–Schmitt reaction can be applied. In standard laboratory protocols, the reaction is performed using $KHCO_3$ and water as solvent under boiling/reflux condition. The microreactor enabled in contrast operation at temperatures as high as 220 °C and above by operating at pressures up to 40 bar. While benchmark lab experimentation using a batch process under reflux conditions under atmospheric pressure delivers a yield of 50% after two hours, the microreactor process delivered yields close to 40% at full conversion within only 56 s. This represents a 130-fold decrease in reaction time compared to the conventional processing and illustrates nicely the process improvement reached by the novel process window opened by working at higher temperature and pressure. This example also indicate the limitations of the approach: at even higher temperatures decomposition of the product lead to a decrease of process performance.

3.1.4. Kolbe–Schmitt synthesis using microwave heating

In the framework of a DBU promoted project 'PIKOS' within the DBU research cluster 'Novel Process Windows' the intensification of the Kolbe–Schmitt synthesis of 2,4-dihydroxy benzoic acid is further investigated above the approach outlined in Section 3.1.3 (Scheme 5). The synthesis hereby represents an example reaction to gain information that is also beneficial for other Kolbe–Schmitt syntheses. Within this project, different aspects like microwave heating, reactive ionic liquids, and also electrical heating in



Scheme 3. Synthesis of phenyl boronic acid, some side products and consecutive reaction products.



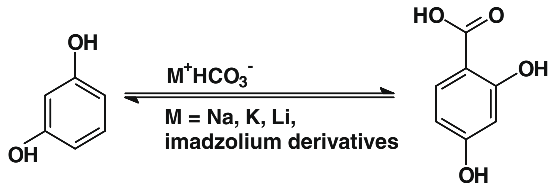
Scheme 4. Salicylic acid.

compact microstructured devices are investigated to achieve process intensification.

In the following the microwave heating is discussed. The other topics like the use of ionic liquids as reactive solvents will be discussed in the subsequent sections.

Based on results given in Ref. 46 and repeated experiments an approximate benchmark of conventional (i.e., in this case the micro process technology approach outlined in Section 3.1.3) versus microwave heated Kolbe–Schmitt synthesis is given. The microwave performance was tested with a comparable set-up of the former used for conventional heated experiments. Therefore, a simple glass capillary reactor with a total internal volume of 25 mL (OD × ID × length: 6 mm × 3 mm × 3600 mm) was embedded in a microwave and connected to pumping equipment, pressure sensor, temperature sensor, microstructured heat exchanger (downstream of the microwave), and fine metering valves to maintain the system pressure at a constant level.

For all experiments performed the results obtained from microwave heating were higher than comparable conventional heated experiments. An explanation is given by the faster heating of the fluid in the capillary using microwave, than by oil bath heating and thus a longer path of the capillary can be used at



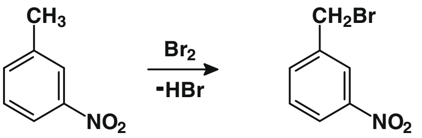
Scheme 5. Reaction scheme for the synthesis of 2,4-dihydroxy benzoic acid starting from 1,3-dihydroxy benzene.

set-temperature (and a shorter one for preheating, respectively). The highest yield obtained for microwave heated synthesis was 52% at 160 °C, 8 bar, 1 L/h (conventional heated synthesis: 47%, 140 °C, 40 bar, 84 mL/h). The reaction time could be reduced from 390 s (conventional) to 90 s (microwave).

3.1.5. Bromination of 3-nitrotoluene

The bromination of a range of organic compounds using elemental bromine in microreactor set-ups has been investigated (see review in Ref. 65). The bromination of 3-nitrotoluene to 3-nitro benzylbromide which represents a high temperature side-chain bromination performed under harsh reaction conditions is thereby a further example where a microreactor set-up enabled continuous processing under elevated pressure and temperature. In contrast to the Kolbe–Schmitt example (see Section 3.1.3) the high pressure is here necessary to prevent evaporation of the reactant bromine and not for that of the solvent. In the course of the reaction, however, gaseous hydrogen bromide is formed which naturally led even when starting with a single liquid phase from bromine and nitrotoluene finally to a gas/liquid system (Scheme 6). Nevertheless, this can led to process performance improvement (e.g., in the sense of higher space-time yields).

In a series of experiments both reactants—bromine and 3-nitrotoluene—were contacted inside a microreactor set-up consisting of a micromixer followed by a Hastelloy capillary (with a total inner volume of 8.4 cm^3) immersed in a thermostated bath and so heated up to reaction temperatures between 170 and 230 °C.[49,65] Molar ratios bromine/nitrotoluene from 0.25 up to 2.00 were investigated. Figure 3 shows exemplarily the results for two experiments (molar ratio: 2; total flow rate 3.3 cm^3/min; temperature: 200 °C; theoretical residence time: 2.5 min neglecting gaseous hydrogen bromide but only in the few seconds range when taking into account gaseous hydrogen bromide under atmospheric pressure) differing in the applied pressure. The comparison shows that the conversion of nitrotoluene significantly increases from 42% to 95% when going from atmospheric pressure to 15 bar overpressure. This is probably due to an elongation of the residence time and also due to the bromine being dissolved in the nitrotoluene and not (completely) evaporated because of the pressure applied. With regard to the nitrotoluene conversion an increase of space-time-yield by a factor of over 2 has been achieved. More details are given in the cited references above. Such operation certainly, needs refinement with regard to the improvement of yield achieved for the target product. The main point is that the reported scouting studies showed that bromination reactions using elemental bromine are quite easily feasible even up to temperatures of 230 °C and pressures in the range of 15 bar with a microreactor set-up and open therefore the window to explore extreme process conditions (Fig. 4).



Scheme 6. Bromination of 3-nitrotoluene to the corresponding benzylbromide.

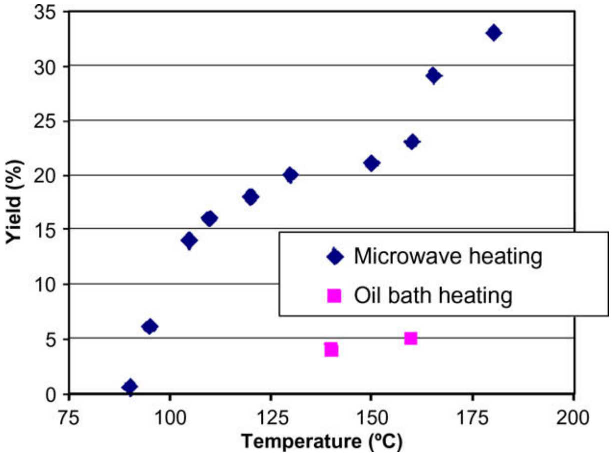


Figure 3. Comparison on obtained yield, conventional versus microwave heated Kolbe–Schmitt synthesis at 18 s reaction time[64] (by courtesy of ACS).

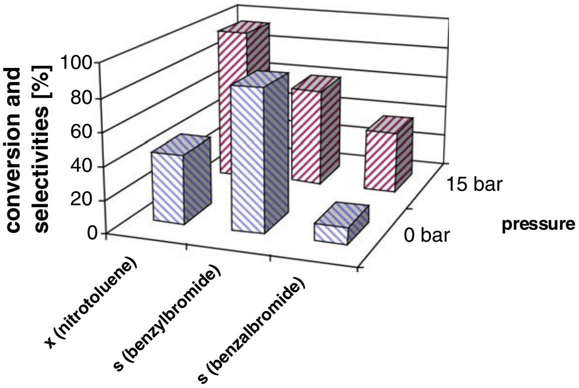


Figure 4. Comparison of conversion of nitrotoluene and of selectivity with regard to the corresponding target product benzylbromide and the side product benzalbromide (3-nitro benzalbromide; (1-dibromomethyl)-3-nitrobenzene) derivate for the bromination of nitrotoluene at atmospheric pressure and 15 bar overpressure (more details see text).

3.1.6. 2-Mercaptoethanol synthesis under high pressure and temperature conditions

In the context of the German public funded BMBF-project µ.pro.Chem dealing under the motif 'Microprocess Engineering for Process Intensification in Chemical Production', the BASF process example of synthesizing 2-mercaptoethanol (MCE) has been investigated using structured components exploring a new high pressure and high temperature regime.[66] MCE synthesis is highly exothermal (adiabatic temperature rise of 700 K) and starts from the highly flammable and extremely toxic materials ethylene oxide and hydrogen sulfide. A specifically adapted microstructured heat exchanger has been realised by IMM to allow processing up to 160 bar and 250 °C. The new process conditions enabled thereby led to increase in space-time-yield of the synthesis by about two orders of magnitude while reaching selectivites up to 95% due to the near isothermic conditions in the microreactor. The process was transferred from lab to pilot scale associated with an increase of throughput by a factor of 180, from below 20 mL/h to about 3 L/h. Figure 5 shows the microstructured pilot reactor used.

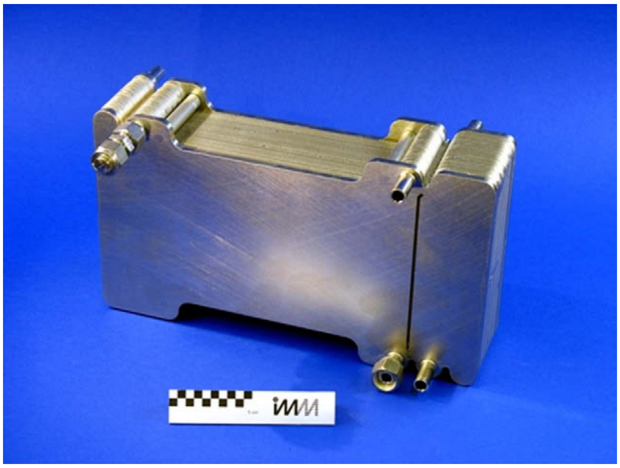


Figure 5. Microstructured pilot reactor for the MCE synthesis for operation up to 160 bar and 250 °C.

3.1.7. Biphasic Suzuki coupling

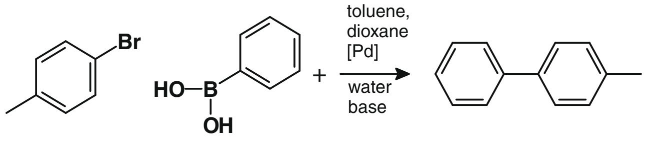
The Pd catalyzed biphasic Suzuki coupling is a very efficient method for the introduction of new carbon–carbon bonds. Since this reaction is biphasic it is essential to supply sufficient interfacial area to avoid mass transport limitations. The conventional Pd catalyzed coupling reaction is carried out in a batch stirred tank reactor. Usually the substrates and the catalyst are dissolved in the organic phase and the auxiliary inorganic base is dissolved in the aqueous phase. The cross coupling of phenylboronic acid and 4-bromotoluene was conducted in a mini tubular reactor filled with metal foam for dispersion renewal and palladium-tri-(*o*-tolyl)-phosphine as catalyst (Scheme 7).[67]

An increase in reaction temperature to 150 °C made it necessary to apply a system pressure of 7–14 bar to keep the reaction mixture in a liquid stage. An optimum on conversion was found for a reaction temperature of 140 °C and a reaction time of 10.5 min. For this parameter set a conversion of 90% with a yield of 89% was obtained; resulting in a space-time-yield of 125 kg/m^3 h, a TON of 424 and a TOF 121 h^{-1}. To cope with industrial pharmaceutical productions TON's larger 100 and TOF's larger 10 h^{-1} are necessary.

3.2. Routes at much increased concentration or even solvent-free

3.2.1. Introduction

The use of solvents in chemical synthesis is in most cases necessary to dissolve reactants simply to fill the reaction volumes (flasks') to a level suited for operation (e.g., impeller agitation) and to promote reaction pathways in a suited environment. For example, in the case of a nucleophilic substitution the usage of a protic solvent favors SN_1 whereas aprotic solvents promote the SN_2 reaction mechanism. For an exothermic reaction the heat of reaction can be 'smeared' by the usage of an additional solvent with a high heat capacity. Another example which benefits from an additional solvent is the method of reactive extraction. In this case, the formed product is removed from the reaction mixture by an immiscible solvent and thus the equilibrium is shifted to the product side. But beside these benefits there are good reasons to decrease the amount of solvent. First and foremost, there are ecological arguments. To isolate the pure substance it is necessary to strip off the added solvent, which is energy intensive and in cases without recycle, the generated waste may be enormous and deteriorates the eco-efficiency of the process. In some cases it might also be possible to substitute conventional solvents, for example, by ionic liquids or supercritical fluids to achieve process intensification. Ionic liquids and supercritical fluids provide a completely different reaction environment with much higher operation temperatures. Supercritical fluids in addition provide much faster diffusivities for the reactants and thus can speed-up reactions by orders of magnitude.



Scheme 7. Cross-coupling of phenylboronic acid and 4-bromotoluene.

3.2.2. Kolbe–Schmitt synthesis using reactive solvents

In the framework of the above mentioned DBU promoted project 'PIKOS' (see Section 3.1.4) also a new process route using the ionic liquids [1-ethyl-3-methyl-imidazolium hydrogen carbonate (EMIM-HC), 1-butyl-3-methylimidazolium hydrogen carbonate (BMIM-HC), and also 1,3-dimethylimidazolium hydrogen carbonate (DMIM-HC)] as solvent and at the same time as carboxylating agent for the production of 2,4-dihydroxy benzoic acid starting from resorcinol was explored.[68]

For this purpose, the premixed reactant mixture was pressurized with N_2 to avoid degassing and was then fed into the coil shaped capillary microreactor (OD × ID × length 1.59 mm × 0.9 mm × 1000 mm) via a HPLC pump with the reactor being embedded in an oil bath to maintain the reaction temperature. The reaction mixture was cooled down in a microstructured heat exchanger and a back pressure regulator was used to apply a constant system pressure. For monitoring the reaction temperature, thermocouples were introduced at several points and the temperature profile was recorded. The molar ratio HCO_3^-/resorcinol was set to be 3 in all cases to avoid limitations in reactant availability. The reaction time was varied to investigate the temperature sensitivity of product formation and decomposition. To point out the positive influence of such alternative reactive solvents a benchmark was undertaken between the aqueous $KHCO_3$ processing and the ionic liquid processing (see Fig. 6).

Due to the thermal instability of EMIM-HC at 250 °C, there are only data at 220 °C available to compare to the data obtained for $KHCO_3$ as carboxylating agent. In most cases, the usage of EMIM-

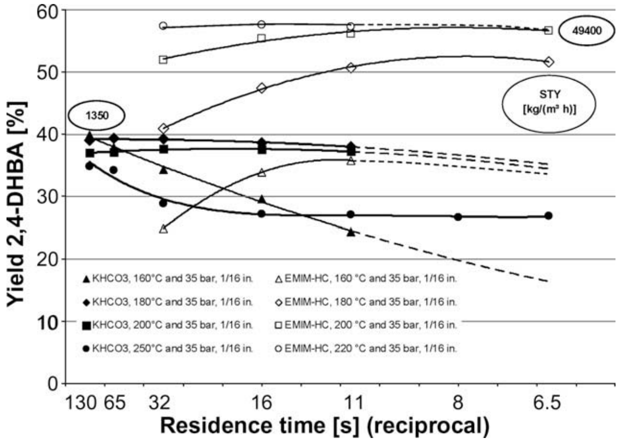


Figure 6. Comparison of yield obtained in aqueous $KHCO_3$ solution and in EMIM-HC[68] (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).

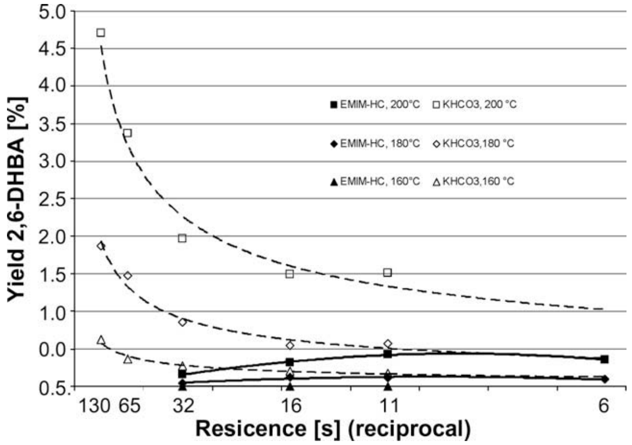


Figure 7. Comparison of byproduct formation using EMIM-HC and $KHCO_3$ as carboxylating agent[68] (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).

HC resulted in higher yields of 2,4-dihydroxy benzoic acid. Only for a reaction temperature of 160 °C and reaction times longer than 16 s, the performance of the $KHCO_3$ reaction mixture is better compared to the one with EMIM-HC. Using EMIM-HC, the maximum yield obtained at a reaction temperature of 220 °C and a reaction time of 32 s was 57% (compared to 50% in conventional batch process[69]). A slightly lower yield was obtained by decreasing the reaction time and the reaction temperature down to 6.5 s and 200 °C. However, even for this case, the obtained yield was 13% higher compared to the best result for the $KHCO_3$ based synthesis. However, the calculation of the corresponding space-time-yield of 49,400 kg/(m^3 h) which is 100-fold higher compared to the respective $KHCO_3$ based processing, emphasizes the benefit gained.

Similar results were obtained by using BMIM-HC as carboxylating agent. In these experiments, the calculated space-time-yield for a reaction time of 4 s, a reaction temperature of 200 °C, and an obtained yield of 56% of 2,4-dihydroxy benzoic acid was 69,900 kg/(m^3 h). This increase of space-time-yield is mainly due to the lower reaction time needed. However, in general the performance of BMIM-HC was not as good as of EMIM-HC.

The use of DMIM-HC at comparable reaction times was only possible at reaction temperatures between 120 and 160 °C due to its thermal instability. Although due to these temperature restrictions the maximum achievable yields were lower as those for EMIM-HC and BMIM-HC, the obtained yield at 160 °C, was the highest in case of DMIM-HC. This was assumed to be a polarity and solubility effect since the smaller the alkyl side chain, the higher the yield of 2,4-dihydroxy benzoic acid under comparable reaction conditions.

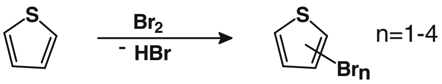
Besides the increased yields, the obtained selectivity in all three cases is higher than the selectivity obtained using the $KHCO_3$ solution (see Fig. 7).

In the case of the $KHCO_3$ based Kolbe–Schmitt synthesis, the amount of 2,6-dihydroxy benzoic acid decreases with a decrease in reaction time. Using reactive ionic liquids the opposite behavior is observed. However, the amount of 2,6-dihydroxy benzoic acid is in the range of a maximum ~0.5%, resulting in selectivities of 99 and ~100%.

3.2.3. Solvent-free bromination of thiophene

The bromination of thiophene represents a good example for exploring process routes avoiding the use of a solvent.

The selective bromination of thiophene poses a challenge since the thiophene ring is an electron-rich environment and multi-substituted reaction products will be obtained. The feasibility to perform selective bromination using microstructured devices was demonstrated for the example of 2,5-dibromothiophene,[70] which is an intermediate for the production of LED materials (Scheme 8).



Scheme 8. Bromination of thiophene.

The main focus was to develop a solvent- and catalyst-free continuous process to produce the above mentioned intermediate 2,5-dibromothiophene with high selectivity. A literature survey revealed that conventional chemical protocols relied so far on the use of solvents. In the microreactor experimentations, the thiophene and the elemental bromine were directly contacted without any dilution by a solvent inside a micromixer. The completion of the reaction was performed in an additional capillary embedded in a thermostat bath. The stoichiometric ratio was changed from 1 to 5 and also the effect of reaction temperature ranging from 0 to 60 °C on the degree of substitution was investigated to find the optimum parameter set for a selective substitution to 2,5-dibromothiophene. The total flow rate was kept constant at 93.4 mL/h, corresponding to a reaction time of less than a second. First experiments were performed using a glass triangular interdigital micromixer to visualize the reaction progress by discoloration of the reaction mixture. Inside this type of mixer, very small lamellae are generated and the diffusion length can be kept very short. Due to the formation of gaseous hydrogen bromide during the reaction, some channels were blocked by gas bubbles and no stable flow pattern was achieved inside the micromixer. Therefore, a change of mixing device was necessary. Further experiments were performed using a so-called caterpillar micromixer. This device has an alternating ramp structure on the floor and ceiling of the channel and induces circulatory motion giving rise to chaotic mixing. Due to its large internal diameter the mixer is not sensitive to clogging and other effects that can block microchannels. Results of these experiments are shown in Figure 8.

As expected, an excess of bromine favors the formation of threefold and fourfold bromination products. Additionally, the increase of reaction temperature showed a negative effect on the selectivity of 2,5-dibromothiophene which was the target product in these investigations.

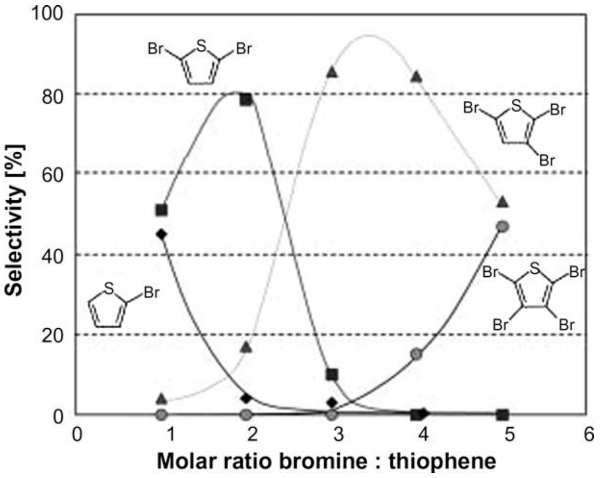


Figure 8. Product distribution for different bromine/thiophene molar ratios[71] (by courtesy of Chemistry Today).

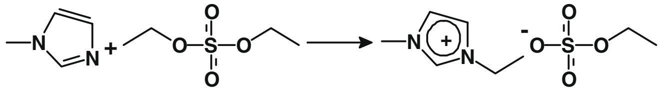
Nevertheless, the formation of 2,5-dibromothiophene at high selectivity was achieved when using a bromine to thiophene molar ratio of 2 and a reaction temperature close to room temperature. Under these conditions, a selectivity of 86% 2,5-dibromothiophene and a corresponding yield of 88% (literature 50% yield; self made batch processing: 77% yield) was obtained. Furthermore, a significant reduction of reaction time down to less than 1 s compared to 2 h in batch processing could be realized, resulting in high space-time-yields compared to a batch reference experiment.

It is furthermore worth mentioning (supporting the discussion in Section 2), that the microreactor set-up has enabled a fast performance of this parametric study and has supported therewith a fast identification of optimal process conditions.

3.2.4. Solvent-free synthesis of ionic liquids

In the framework of the EU IMPULSE project, the highly exothermic ($\Delta H_R = 100$ kJ/mol) synthesis of ethylmethylimidazole ethyl sulfate (commercially termed ECOENG212) by an alkylation reaction was investigated as a model reaction for the continuous and solventless production of ionic liquids.[47,71,72] Solventless, because the removal of solvent in the context of ionic liquids as work-up step requires significant efforts (Scheme 9).

Conventionally, this alkylation reaction is conducted in a semi-batch stirred tank reactor where the velocity of the dosage of the alkylation agent to the methylimidazole in the vessel is adapted to the heat transfer capability of the reactor in order to control temperature. Since heat transfer capability of the stirred tank reactor is not high, dosage time and therewith the process time is prolonged much above the process time required based on the kinetics. Even though, one negative characteristic owned to too high local temperatures is coloration of the product. Since this coloration is temperature dependent, hot spot formation has to be avoided strictly; otherwise the product color will change from colorless to yellow. The used diethyl sulfate is a strong carcinogenic substance, and therefore it is also essential for the product quality, that the amount of unreacted alkylation agent is as small as possible, that is, a high conversion degree above 99% has to be reached. A small lab-scale batch reaction performed in a 50 mL glass flask illustrates the strong exothermicity of the reaction and the hot spot formation due to insufficient heat removal capacity of the used batch reactor. The reaction temperature was set to be 50 °C and the diethyl sulfate was added in four equal portions, resulting in large temperature rise after each dosing step (see Fig. 9), up to 130 °C, for example, unacceptable high increases in temperature in this model reaction. The task therefore was to develop a continuous process using a microstructured reactor with higher heat transfer capability for a better temperature control during processing.



Scheme 9. Synthesis of ECOENG212 by the alkylation of methylimidazole by diethyl sulfate.

First lab-scale experiments were performed using a set-up consisting of a micromixer connected to a 1/8 inch tubular reactor which demonstrated the feasibility of a microreactor processing approach. Special focus has been given to the axial temperature during continuous processing. The axial temperature profile (see Fig. 10) showed a smaller temperature increase as seen in the batch processing (Fig. 9) but still at an unacceptable level at the beginning of the tubular reactor. It was derived there from that it is necessary to improve the heat transfer capability of the set-up in the first section further for a much better temperature control.

To this end an increase of heat exchange area was realized by changing the capillary diameter. The reduction from 1/8 inch down to 1/16 inch capillaries resulted in a much smoother temperature increase under the same reaction conditions (see Fig. 10).

The data obtained during these experiments was used to develop a production scale reactor concept perfectly suited to the needs

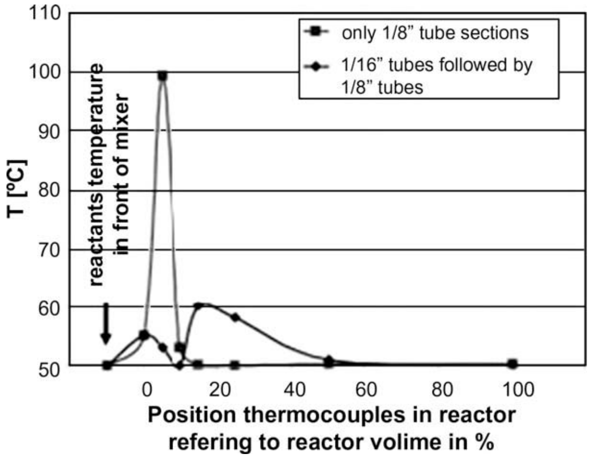


Figure 10. Comparison of temperature profile in different capillary diameters for the production of ECOENG212[71] (by courtesy of Chemistry Today).

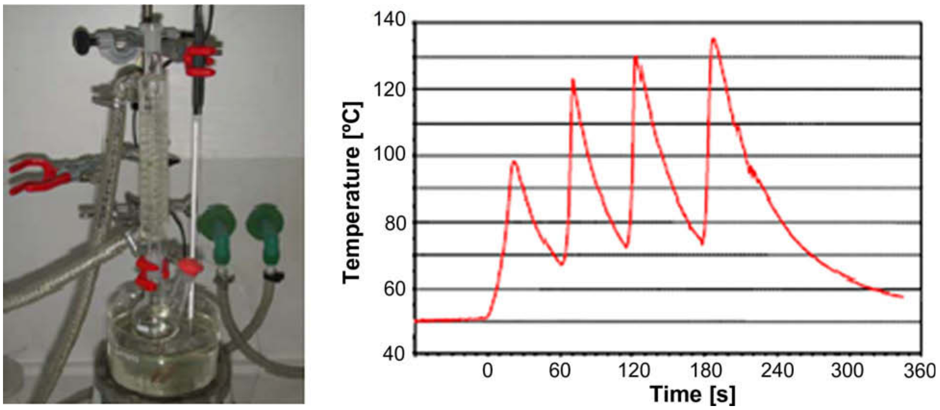


Figure 9. Small scale batch of ECOENG212, temperature profile at a four-step dosing procedure.[73]

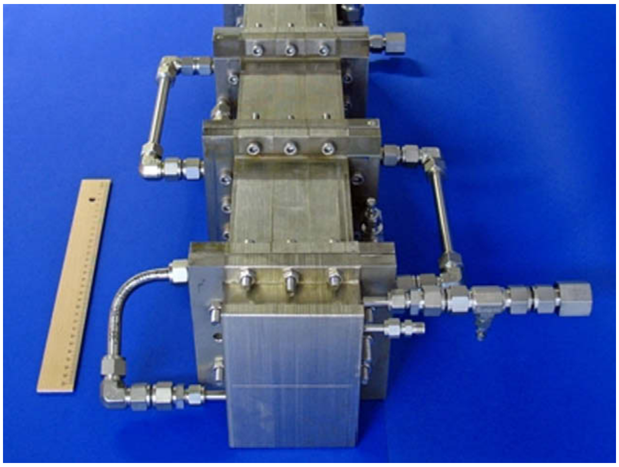


Figure 11. Modular microreactor: central part of the production scale reactor set-up for ionic liquid synthesis.

of the reaction. As intermediate step before the realization of a production scale reactor, a set-up consisting of a micromixer followed by a microstructured heat exchanger and then by a tube section has been realized. In comparison to initial lab set-up a part of the tube section has been replaced by the microstructured plate heat exchanger in order to improve further heat management and also to have a better basis for later scale-up of the set-up. Finally, a production scale (about 100 kg/d) reactor has been realized consisting of a micromixer, followed by a large modular microstructured reactor (see Fig. 11) and a multi-tubular reactor, that is, the general design approach has been kept and just transfer to larger scale. This cascaded reactor set-up is a good example of the multi-scale design principle used throughout the EU IMPULSE project.

At the final stage of the project, this production scale reactor was successfully tested in a two-day campaign under reactive conditions.

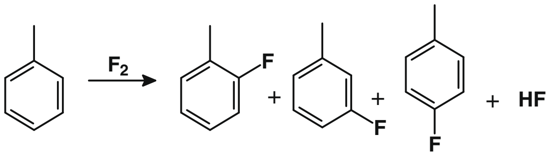
3.3. Routes in the explosive or thermal runaway regime

3.3.1. Introduction

Process intensification often goes hand in hand with unconventional reaction conditions. The improvement of process performance or even the production of substances that cannot be produced under moderate conditions might render necessary to work in the explosive or in the thermal runaway regime. Conventionally the reaction mixture is then diluted or the heat production is controlled by step-wise dosing to keep the reaction under control. Thus intrinsic fast reactions are slowed down for safety reasons (see Section 3.3.4). Micro process technology, on the contrary, enables full exploitation of harsh and explosive conditions. It was demonstrated that the usage of microstructured devices allows controlling the process at conditions under which normal equipment would fail.[74] The possibility to use microstructured reactors in the explosive regime is critically discussed by Klais et al.[72]

- Under explosive reaction conditions it is possible that an explosion is enters the microreactor from the outside. In this special case it is possible that the reactor might be destroyed.
- But under the same conditions an explosion cannot be generated from within the microreactor.

A second containment is advised; covering all critical parts of the plant set-up. If one considers the size of microstructured reactors, this second containment is much simpler than for conventional chemical reactors. Such simple enframed set-up suffices for processing in the explosive regime at minimum risk.



Scheme 10. Fluorination of toluene.

3.3.2. Fluorination of toluene using elemental fluorine

The fluorination of toluene by elemental fluorine was first described in 1968. According to the reaction mechanism (electrophilic or radical), different product mixtures can be obtained. While a radical substitution will result in unselective side chain and/or ring fluorination and even give undefined polymerization; the electrophilic substitution will lead to *ortho*-, *meta*- and *para*-substitution products. Radical substitution resulted in undefined product mixtures and often in an explosion caused by the uncontrolled heat release of the reaction. Thus a lot of efforts have been focused on the development of tools that allow for the safe and controlled formation of a specific substitution product. The direct fluorination using a falling film microreactor, a micro bubble column, and a laboratory bubble column was demonstrated for the example of the direct fluorination of toluene using elemental fluorine.[75] These three reactor types were compared to each other and an approximate benchmark to the industrial Schiemann process is given.

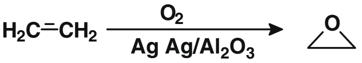
Using the falling film microreactor and a fluorine content of 10 vol %, a product mixture of 5:1:3 of the *ortho*-, *meta*- and *para*-product was obtained. Thus, by smart temperature control the favoured electrophilic substitution could be achieved. Different parameter sets, for example, solvents; fluorine concentration, residence time, and reaction temperature, were varied to find the optimum process condition to perform the direct fluorination of toluene in microstructured devices (Scheme 10).

An increase of the fluorine content from 10 vol % to 50 vol % increased conversion up to 76% and yield raised up to 28% of the *para*-product (*ortho* to *para*: 1:4). The reaction temperature was varied between −40 and −15 °C; with the temperature increase resulting in an increase in conversion, however, accompanied by a decrease in selectivity. The reaction performance could also be affected by the used solvent. For this purpose, the influence of a protic polar solvent (methanol) and an aprotic polar (acetonitrile) solvent on the reaction was tested. The yields obtained for the aprotic polar solvent where higher than the ones for the polar protic one. The usage of the falling film microreactor and the micro bubble column resulted in significantly higher space-time-yields when referred to the channel volume (10,000–100,000 $\text{mol}_{\text{mono-F}}/\text{m}^3$ h) compared to the laboratory bubble column (below 100 $\text{mol}_{\text{mono-F}}/\text{m}^3$ h). For the falling film microreactor operation with 10% fluorine, yields up to 20% of the monofluorinated *ortho*- and *para*-products were obtained. This value approaches the yield obtained in the industrial Schiemann process.

3.3.3. Oxidation of ethylene to ethylene oxide

The oxidation of ethylene with oxygen to ethylene oxide is conventionally performed in the explosive regime and thus the benefits of microstructured components can be used to gain benefits in process safety (Scheme 11).[72,74]

The epoxidation reaction is a highly exothermic process with a reaction enthalpy of −105 kJ/mol, whereas the total oxidation is a



Scheme 11. Oxidation of ethylene to ethylene oxide.

much more dangerous reaction pathway given by a reaction enthalpy of −1327 kJ/mol.[36] Therefore very large hot spots can occur shifting the reaction toward the undesired total oxidation. Kestbaum et al. used a multiplate stacked microstructured reactor made out of polycrystaline silver foil in which they achieved a conversion of 12% and a selectivity of 49%.[36,76] Since they used pure oxygen for their oxidation reaction, their experiments proved that processing in the explosive regime is possible using microstructured devices in accordance with the theoretical considerations by Klais et al.[72,74] By change toward polycrystalline silver, the selectivity was increased up to 65% without the use of industrial promoters (like 1,2-dichloroethane) and with a combination of promoters and catalyst (like Ag/Al_2O_3) they were able to shift the selectivity toward industrial relevant parameters (80%). Since the overall costs of the process are dominated by the costs of ethylene it is essential to increase the selectivity to achieve process intensification. Processing in the explosive regime also let to quite high space-time-yields of 0.14–0.78 tons h^{-1} m^{-3} which are in the order of the conventional process (0.13–0.26 tons h^{-1} m^{-3}).

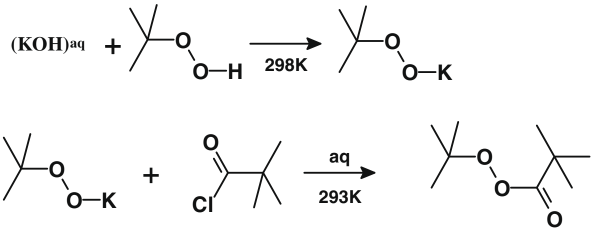
3.3.4. Synthesis of the ionic liquid ECOENG212

The synthesis of ECOENG212 in a microreactor system is described in general in Section 3.2.4. Apart from discussing it under the perspective of the novel process window aspect 'solvent-free' (as done there), it can be considered also from the perspective of operating under thermal runaway conditions. As outlined in Section 3.2.4 the improved heat transfer capability of the microreactor allowed decreasing processing time down from the hour into the few minutes range, that is, an operation window not feasible in larger scale in a batch process without ending in a thermal runaway regime.

3.3.5. Synthesis of *tert*-butyl peroxy pivalate

The synthesis of organic peroxides is challenging in different ways (corrosive reactants, thermal sensitive substances, biphasic reaction steps, etc.) and can largely benefit from using milli- or microstructured devices.

Currently, the exothermic two-step synthesis of *tert*-butyl peroxy pivalate using structured reactors is investigated as example also for other peroxide syntheses (Scheme 12).[77] The synthesis is conventionally conducted in batch or semi-batch processes whereby the reaction temperature is limited by the so-called Self Acceleration Decomposition Temperature (SADT) of the used reactants and the formed product. The SADT is defined as the lowest temperature at which a packaging size will undergo a self accelerating decomposition reaction. The SADT is inversely proportional to packaging size—thus it is one limiting parameter for the peroxide production due to the high hold up in production.



Scheme 12. Synthesis of *tert*-butyl peroxy pivalate.

The dosage of the reactants is adapted to the heat transfer in the used reactor to avoid a thermal runaway; resulting in nonessential long reaction times.[78,79] Additionally, the large hold up in batch stirred tank reactors is a safety risk, for example, when one considers process deviations as, for example, malfunction of the cooling system and thus an uncontrolled exponential increase of temperature inside the reactor. The inertia of such large reaction vessel makes it nearly impossible to remove the produced heat in case of a thermal runaway in a very short time and therewith to cool down the system to an ambient and safe reaction temperature. Thus a lot of effort is put into maintaining the process temperature at a certain level to avoid a thermal runaway or even an explosion.

The investigations using milli- and microstructured components now aim at processing above the limiting SADT which is expected to open a novel process window for the peroxide production. This specific novel process window is introduced as 'Hyper-SADT' concept and defined as running the process at or above the limiting SADT without losses in process safety based on a small reaction volume enabled by using micro process technology and resulting in shorter process times and higher space time yields. The high flexibility and the short response time in microstructured devices make it feasible to keep the thermal exposure as long as needed to speed up the reaction and as short as possible to avoid thermal decompositions and side reactions accelerated by the increased reaction temperature.

The validity of this concept was demonstrated by first promising experiments (31 s, 67%, 70 °C vs ~100 min, ~84%, 10–20 °C in batch[80]). These experiments are conducted in a micromixer-tube set-up targeting at a dispersed flow with its benefit of a high interfacial area.

3.4. Process integration and simplification

3.4.1. Introduction

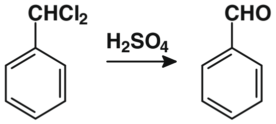
Advanced process integration, that is, the combination of reaction and separation, in microstructured membrane reactors, is more relevant to fuel processing applications with micro process technology and thus no attention is given here in the fine-chemical context of the paper. Process simplification in microstructured devices is possible in different ways. Above mentioned examples point out most of the benefits obtained on reaction stage.

3.4.2. Synthesis of the ionic liquid ECOENG212

The highly exothermic reaction described in Section 3.2.4 gained a large advantage when transferred into a continuous process. The high heat transfer efficiency in the specially designed modular microstructured reactor finally allowed for mixing the pure reactants without any dilution step and with the hot spot formation inside the reactor controlled in a way that it was not affecting product quality (see Sections 3.3.4 and 3.2.4).

3.4.3. Hydrolysis of benzal chloride to benzaldehyde catalyzed by sulfuric acid

The acid catalyzed hydrolysis of benzal chloride to benzaldehyde in a mixer tube microreactor set-up was investigated (Scheme 13).[81]



Scheme 13. Hydrolysis of benzal chloride.

This exothermic reaction is conventionally controlled by stepwise dosing to maintain the temperature at an ambient level. The direct contacting of the reactants in conventional equipment would lead to large super-heating and even to boiling or even to an explosion if the heat of the reaction is not removed sufficiently fast out of the system. In a micromixer-tube set-up consisting of a slit interdigital micromixer made of glass, a 6 m long tube with an inner volume of 7 mL, and a water bath the direct contacting can be conducted in a safe manner achieving high selectivity. A comparison of the micro mixer tube set-up with a conventional T-junction as mixing device gave a significant increase of yield for the micro mixer (69%) when compared to the T-junction (33%). In both cases conversion is almost complete. Since the conventional hydrolysis is conducted at 0 °C and a yield of 65% for control of reaction temperature and to avoid a thermal run away the micro process was safely carried out at 60 °C reaction temperature, rendering cooling unnecessary.

3.4.4. Brominations using elemental bromine

The usage of microstructured devices for the bromination of toluene, 3-nitrotoluene (see Section 3.1.5), and thiophene (see Section 3.2.3) did not only resulted in better selectivities and higher space-time-yields compared to the conventional processes, but also in simpler process control. Processing in microstructured devices allowed using elementary bromine without loss in selectivity and it allowed performing the process at higher temperatures which diminished the energy consumption for cooling down the reaction mixture.

4. Conclusion and outlook

In this review we presented different types of reactions in which the use of microstructured devices led to an increased process performance by applying Novel Process Windows. These examples were chosen to demonstrate how chemical reactions can benefit from the use of milli- and microstructured devices and how existing protocols can be changed toward process conditions hitherto not applicable in standard laboratory equipment.

The application of Novel Process Windows—process conditions beyond usual conditions—to suited chemical reactions can help to improve process performance and can open new ways for chemical transformations, for example, direct one-step synthesis instead of a multistep one, combined two-step routes bridged by unstable intermediates, etc. Yoshida et al. developed the concept of Flash Chemistry—a complementary concept to the Novel Process Window concept—which is based on the assumption that most of the intrinsic steps of a chemical reaction are fast or can be made fast by using highly reactive intermediates.[82] Those very fast reactions will need equipment that can process down to these very short time frames and is thus well suited for micro process technology.

IMM has shown several flow chemistry routes to Novel Process Window, most prominent the first reported direct synthesis (fluorination), a detailed and by orders of magnitude intensified superheated reaction study (Kolbe–Schmitt reaction), and the safe handling of a solvent-free reaction with massive heat production up to production scale (ECOENG212).

Micro process technology has entered laboratories and thus a redesign of existing processes has started. However, thinking about the applicability of microstructured devices to industrial processes and thus to a significant higher product output than in microstructured lab-scale plants, one will come to the question of scale-up. There are two main ways to increase the product output: the first one is internal numbering up, which is done by, for example, increasing the number of reaction plates of a microreactor and the second one is external numbering up which is done by parallelization of a number of smaller microstructured devices to meet the required product output. Each of them has pro's and con's and the decision which one is the best one, has to be based on the special needs of the reaction itself.

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