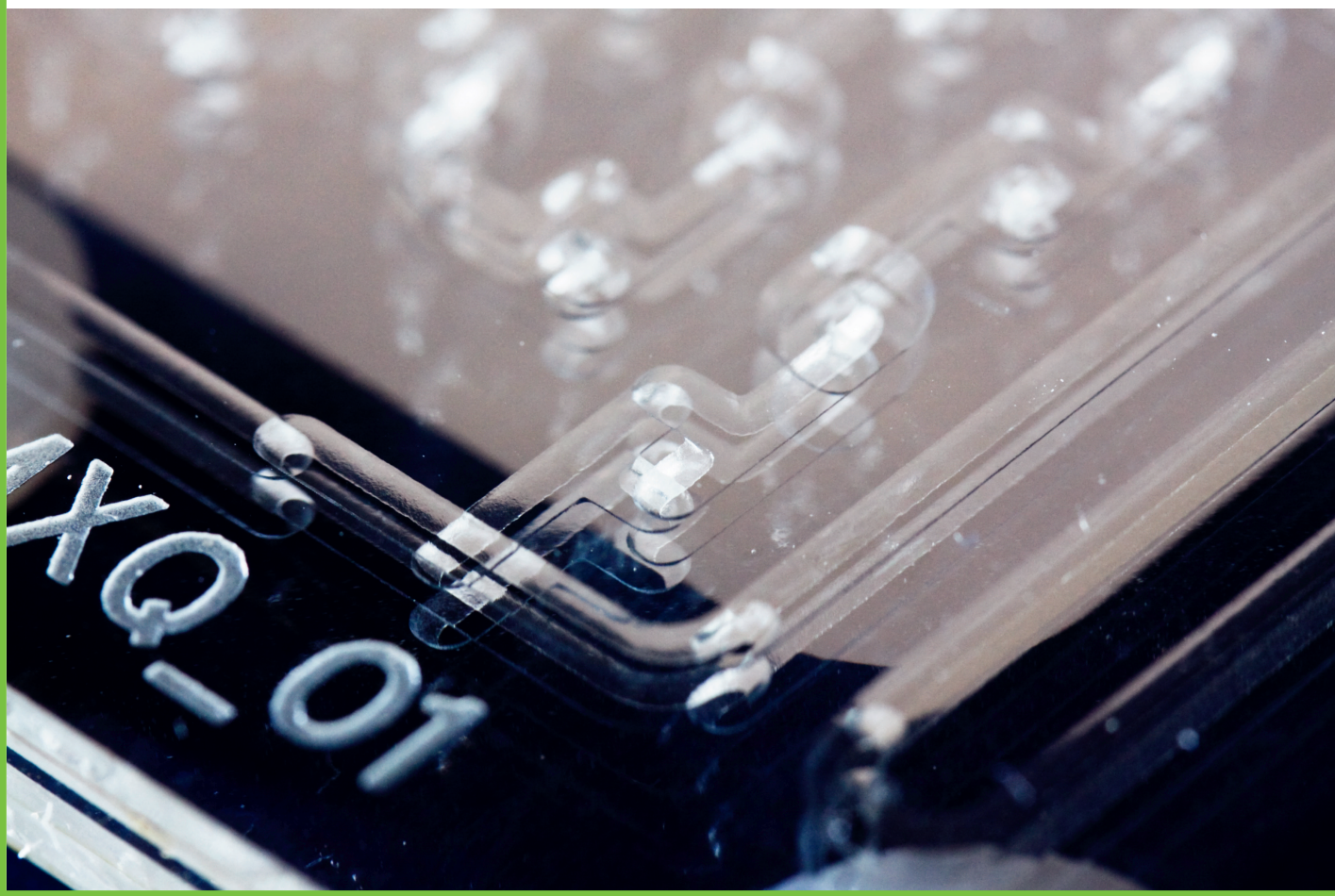
ACCESS2FLOW

Application note

Fast scale up of microreactor technology from lab scale to production

No. 1

The Paal-Knorr synthesis



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Future Chemistry

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Summary

Access2Flow, with its members FutureChemistry, Flowid and Micronit Microfluidics, has shown the fast scalability and applicability of microreactors in a case study for flow chemistry. For the case study, the Paal-Knorr reaction was used as a model reaction. This reaction is moderately exothermic, posing a problem for conventional industrial scale manufacturing, while flow chemistry is known to be advantageous for such processes due to high heat transfer capabilities.

The Paal-Knorr reaction was translated from conventional batch processing into continuous flow chemistry without any major issues. The kinetic parameters reaction time and reagent ratio were controlled by flow rates. These reaction parameters, together with temperature, were then screened fully automated to find optimal conditions.

After optimization and data interpretation, small preparative runs in a larger microreactor were performed. While maintaining a sufficiently large surface to volume ratio, the lateral dimensions of the reactors were enlarged to 1-2 mm, while maintaining mixing over the full length of the reactor by integrating mixers. The small preparative runs resulted in correct validations and confirmed conversions of 100% at optimal settings.

Finally, the optimized and validated reaction parameters were applied to larger microreactors connected in parallel. A production rate of 55 g per hour could be reached with this device, giving an overall scaling factor from optimization device to preperative lab scale of 1250. Further parallelization of the reactors will increase the production rate up to kgs per hour.

Major benefits of the flow chemistry route vs. conventional batch chemistry in this particular case are the safe and easy operation of an exothermic reaction, fast development time of approximately 200 man hours and low reagent consumption during optimization.

Introduction

Access2Flow, with its members FutureChemistry, Flowid and Micronit Microfluidics, has shown the fast scalability and applicability of microreactors in a case study for flow chemistry.

Processes based on more conventional techniques such as batch processes are scaled up by increasing the physical size of the equipment used. By doing so, several process determining parameters like heat- and mass transport are changed, resulting in new, time consuming and costly process optimization for each scale up step.

Microreactor technology comprises continuously mixing and performing chemistry in equipment with small internal dimensions. These small dimensions are the base for more efficient, economic and safer chemistry. Furthermore, the technology is ideal for reaction screening: it is possible to test several reaction parameters in a fast and efficient way. By slightly scaling up the internal dimensions and then numbering out the reactors, the reaction is planned to be scaled up in this study. It is expected that the newer route through flow chemistry enables a fast trajectory of product development and scale up.

This document informs about the project, results and equipment used.

Project description

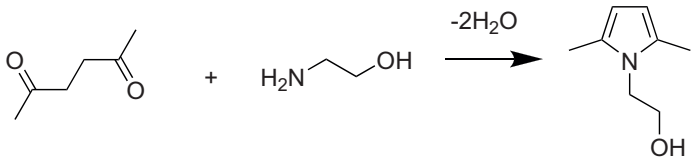

Figure 1 - Reaction scheme Paal Knorr synthesis

For this project the Paal-Knorr reaction (Figure 1) is chosen as model reaction. It is an elegant ring closing elimination reaction, forming the relatively complex pyrrole from simple primary amines and γ-diketones. Although the procedure requires only one easy addition step, on industrial scale the procedures requires great care due to the exothermic properties. Therefore, continuous flow is an excellent alternative for this fast reaction.

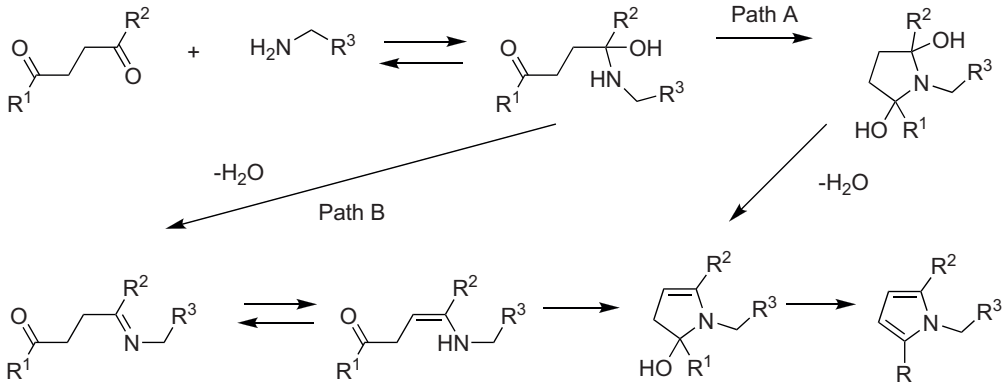

Figure 2 - General reaction mechanism Paal Knorr synthesis

While the reaction was already discussed in 1914, the exact mechanism is not certain. Figure 2 shows the two most probable pathways (path A and B), differing only in the order of the first elimination step and ring closure. Because all steps in Path A are exothermic, while the enamine ring closure step in path B is endothermic, path A is the most probable mechanism. Studies have shown that the reaction rate is decreased by larger R^1 and R^2 groups. In this case, the methyl groups, being the smallest possible side groups for a γ-diketone, do not sterically hinder the reaction and the rate can be expected to be high.

The project is divided into three successive phases:

1. Convert batch chemistry to flow chemistry on µL-scale;
2. Scaling up the internal dimensions of the reactor to mL-scale;
3. Numbering out mL-scale reactors towards the capacity desired.

Phase 1 – Converting batch to flow chemistry on µL-scale

In this phase, a procedure for continuous flow equipment was prepared. Not only was the actual procedure translated from conventional batchwise to flow chemistry, but also a full parametric optimization was performed, achieving optimal conditions for the continuous flow equipment. When a reaction is to be optimized, one can choose from several different optimization criteria, such as reactant conversion, product yield, space-time yield, production rate to total cost ratio, etc. For the sake of clarity and simplicity, in this study conversion was chosen, thus formulating the following aim:

Reduce reaction time as much as possible, while maintaining 100% conversion.

The optimization was performed on the following parameters: reaction time, diketone / amine ratio and temperature. A multidimensional optimization method was used, after which a mathematical model was created. However, before the actual optimization, first the parameters were screened independently to establish the ranges having the greatest impact on the reaction.

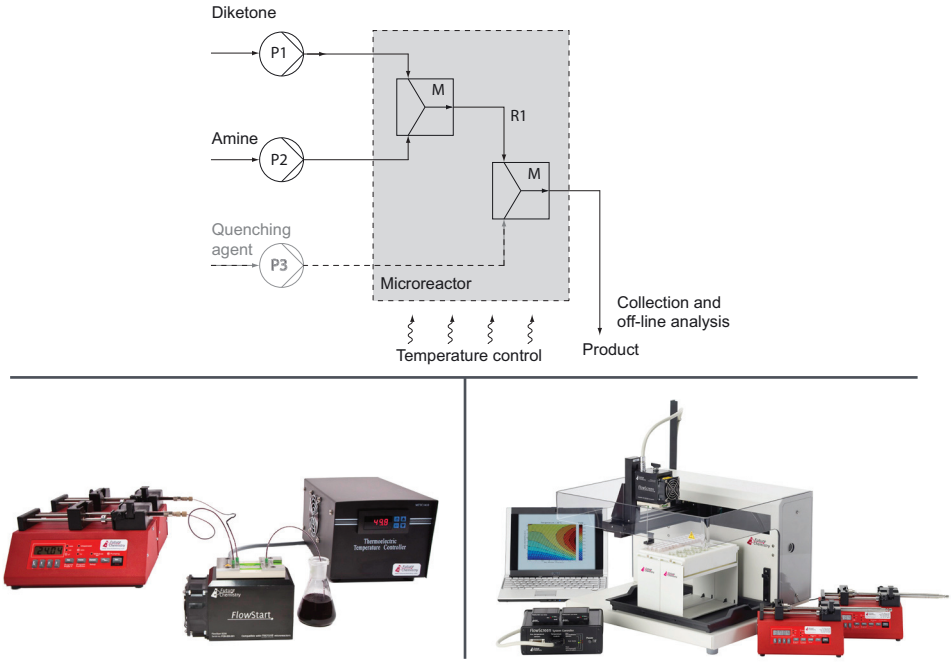

Figure 3 - Continuous flow setup for Paal-Knorr optimization: Schematic representation (top), FutureChemistry FlowStart for first flow experimentation (bottom left) and FutureChemistry FlowScreen for automated optimization (bottom right)

Because reaction time in a continuous flow system is determined by flow rate in the system and the volume of the reactor, the latter must be exactly known. Furthermore, because off-line analysis was used, stopping the reaction using quenching agents was necessary. It was found that acetone was an adequate quenching agent, inhibiting the primary amine from further reacting by imine formation.

The conceptual total flow setup and equipment as used in all experiments is shown in Figure 3. The quenching agent, marked in grey, was used only in the optimization. Equipment details are given in Table 1.

Table 1: Details equipment for optimization

Reactor volumes	0.13 and 7.03 µL (dependent on reaction time)
Channel width	120 µm
Channel height:	60 µm
Channel length:	26 or 1325 µm (dependent on reaction time)
Reactor material	Borosilicate glass
Pumps	Syringe pumps with stainless steel syringes

In conventional batch procedures, the diketone and the amine are simply mixed without any solvent. This is an adequate method for small (laboratory) scale, but not possible for industrial manufacturing due to the exothermicity. The reaction could easily be carried out in a continuous flow system by using continuous feeds of both reagents, but it was found that some fouling occurred by product crystallization. Therefore, 1:1 mixtures of the reagents dissolved in methanol were used. While this is an adequate solution to prevent blocking, minimal solvent consumption should be achieved. However, optimization towards this parameter was not performed in this study.

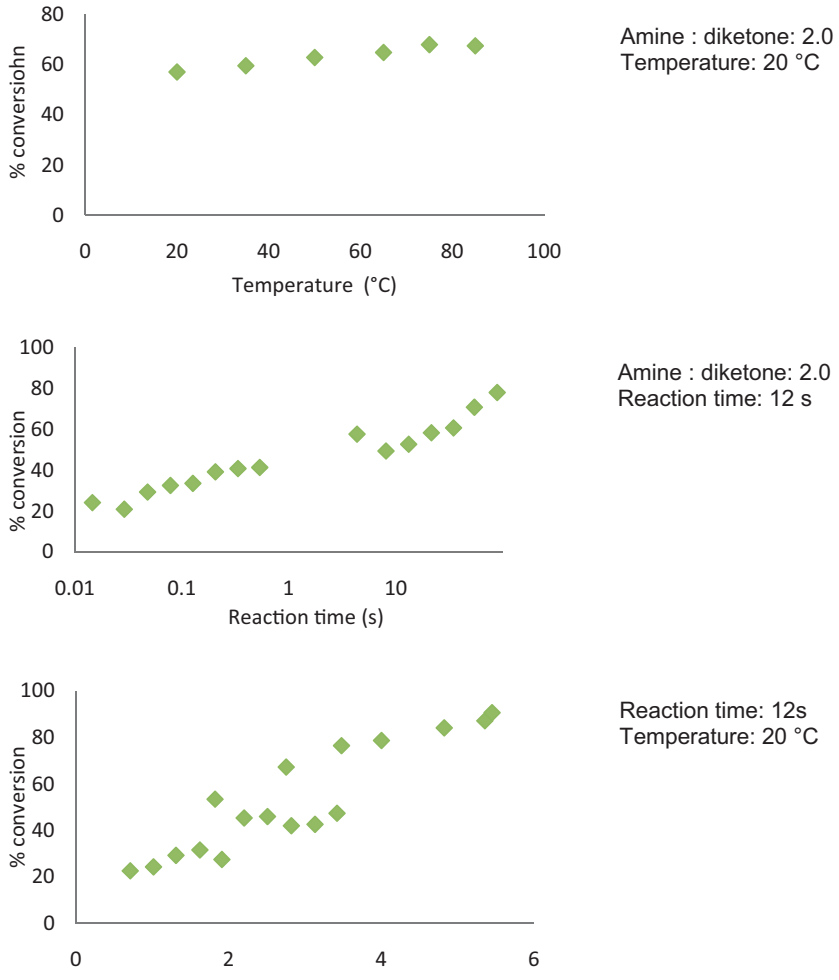

Figure 4 - Singlevariate reaction screening

The three parameters were first screened independently using conventional singlevariate experiments. In Figure 4 the results are shown. Reaction time and amine:diketone ratio both have a major influence on the reaction as can be expected. Thus, these two parameters were included into the multidimensional screening study using roughly the same ranges. Although temperature seems to have barely significant influence on the reaction, which is in itself remarkable, it still was included into the multidimensional screening because of possible dependent effects between two different parameters.

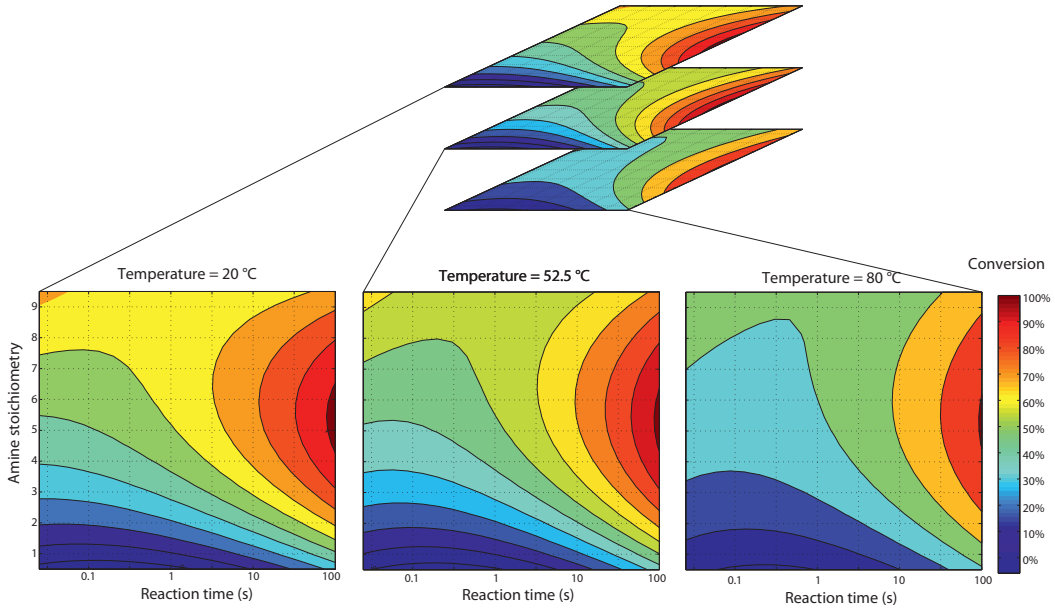

Figure 5 - Contour plots of multivariate optimization

The results from the multivariate optimization run are shown in Figure 5, visualized by three contour plots representing slices in the three-dimensional space (as shown above the contour plots).

Again, it is clear that temperature only has a minor influence on the reaction results. An optimum was found at the following settings:

Reaction time	**100 s**
Amine : Diketone ratio	**5**
Temperature	**20 °C**

Although the optimum is on the edge of the experimental domain, it complies with the original aim of the study: 100% conversion at the lowest possible reaction time.

Experimental

For the microreactor set up, FutureChemistry's FlowScreen was used, equipped with microreactors from Micronit Microfluidics (details in Table 1).

The first syringe was loaded with solution A containing 2,5-hexadione (45% v/v) and 2-bromotoluene (5% v/v, internal standard) dissolved in methanol. The second syringe was loaded with solution B containing ethanolamine (40% v/v) and dimethoxyethane (10% v/v, internal standard) dissolved in methanol. The third syringe was loaded with acetone as a quenching agent. The syringes were then connected to the microreactor system and the optimization program was run. The flow rates were varied using a preset program to control reaction time and reagent ratio, while the temperature was controlled with the built-in temperature controller. Of each reaction mixture, 25 µL was collected into 1 mL portions of collection liquid containing 2-bromonaphthalene (0.6% v/v) as an external standard in methanol. Due to the varying flow rates, sampling times differ for every experiment. All reaction conditions were randomized. The samples were analyzed with GC-FID. Flow rates were calculated from calibrated responses of the internal standards against the external standard. Conversion was calculated from calibrated responses of the diketone substrate against the internal standard 2-bromotoluene.

Phase 2 – Scaling up to mL-scale

Figure 6 - Micronit mL scale microreactor

Now that optimal conditions for flow chemistry were established, the reaction was scaled up to mL-scale using large scale Micronit Micoreactors (Figure 6, details of the setup are shown in Table 2). While maintaining a sufficiently large surface to volume ratio, the lateral dimensions of such reactors are enlarged to 1-2 mm. Mixing due to diffusion is not sufficient anymore at these scales, and therefore continuous mixing is established by the integration of split-and-recombine mixers over the total length of the channel.

Table 2: Details equipment for mL-scale

Reactor volumes	2.4 mL
Reactor material	Borosilicate glass
Pumps	Uniqsis FlowSyn integrated pumps

In order to obtain confidence for scalability, two validation points were performed with the mL-scale system. The first point obviously represents the optimal conditions found in the previous step. The second is an arbitrary point resulting in 50% conversion within the optimization study. Parameters and results of these points are summarized in Table 3.

Table 3: Validation points

	Optimized point	**Validation point**
Reaction time	100 s	10 s
Amine : Diketone ratio	5.0	2.5
Temperature	20 °C	20 °C
Conversion predicted	100%	54%
Conversion observed	100%	57%

The results clearly indicate that scaling up to mL scale is very well possible. After validation was achieved, a production run was performed, using the same optimal conditions as in the optimization experiments. Details of settings and results of the production run are shown in Table 4.

Table 4: Production run single meso-scale microreactor

Total feed [mL/min]	1.43
Amine : Diketone ratio	5.0
Run time [min]	72 min
Isolated yield	98%

Experimental

For the milliliter scale microreactor set up, FutureChemistry's FlowSyn was used, equipped with a milliliter microreactor from Micronit Microfluidics (details in Table 2).

The first bottle was loaded with solution A containing 2,5-hexadione (45% v/v) and 2-bromotoluene (5% v/v, internal standard) dissolved in methanol. The second bottle was loaded with solution B containing ethanolamine (50% v/v) dissolved in methanol. The bottles were then connected to the inlet ports of the FlowSyn, while the microreactor was connected to the outlet tubing of the FlowSyn. The flow rates were manually set and the experiments were run, while the outflow was collected into a bottle containing acetone as a quenching agent. The samples were analyzed with GC-FID. Conversion was calculated from calibrated responses of the diketone substrate against the internal standard 2-bromotoluene. Isolation was performed as follows: the reaction mixture was partially concentrated on a rotary evaporator. The remaining mixture was extracted with diethyl ether (three portions of 100 mL) and washed firstly with 150 mL 1M hydrochloric acid and secondly with 50 mL brine. After drying on magnesium sulfate and filtration, the organic layer was concentrated on a rotary evaporator. A yellow oil was obtained, which crystallized shortly after the solvent was evaporated.

Phase 3 – Numbering out towards desired capacity

Figure 7 - Micronit parallel multi-layered reactor module

For these experiments 4 meso-scale reactors were integrated into one Micronit parallel multi-layered reactor module (15 x 15 x 5 cm, Figure 7), with a total internal volume of 9 mL (see Table 5 for details). This multi-layered reactor is custom engineered, and consists of two sections, each section containing two reactors that are placed in parallel. The sections can operate independently, in series or in parallel. For this experiment the sections were placed in series.

Table 5: Details equipment for mL-scale

Reactor volumes	9 mL
Reactor material	Borosilicate glass
Pumps	Bronkhorst Liquid Dosing System

All reaction parameters as determined in phase 1 are taken over for the phase 3 experiments, approximately quadrupling the liquid feed rates, as shown in Table 6.

Table 6: Production run parallel multi-layered reactor module

Total feed [mL/min]	5.4
Amine : Diketone molecular ratio	5.0
Run time [min]	60 min
Conversion	100%
Isolated yield	55.8 g / 96% (Figure 8)

Results show that scaling out this reaction using parallel microreactors give the same results, indicating again excellent scalability of the Paal-Knorr reaction in flow chemistry.

Figure 8 - Solid product after isolation - total yield 55.8 g; 96%

Experimental

For the parallel multi-layered reactor module set up, two Bronkhorst Liquid Dosing Systems were used, equipped with a reactor module from Micronit Microfluidics (details in Table 5).

The first bottle was loaded with solution A containing 2,5-hexadione (50% v/v) dissolved in methanol. The second bottle was loaded with solution B containing ethanolamine (50% v/v) dissolved in methanol. The bottles were then connected to the inlet ports of the pumps, while the microreactor was connected to the outlet tubing of the pumps. The flow rates were manually set and the production run was performed, while the outflow was collected into a bottle containing acetone as a quenching agent. Isolation was performed as in Phase 2.

Conclusions

This application note shows that Access2Flow has the capability of translating batch chemistry to flow chemistry and holds the technological and engineering expertise to quickly scale up the capacity of a process. For example, for the project as described in this application note, roughly 200 man hours were required.

Furthermore, the 3-phase methodology of Access2Flow has proven to be successful. Process parameters determined on small microreactor chips in phase 1 still hold when the internal dimension of the reactor are increased in phase 2, while maintaining the reaction results. Phase 3 demonstrated the scalability of microreactors by numbering out towards production capacities.

Organizational benefits

Access2Flow is able to implement microreactor technology within your organization. By increasing the controllability of a reaction; exothermic, fast, hazardous or sub-optimal reactions can be performed, increasing the chemical scope for route scouting and product development. In this case, it was actually proven that an exothermic reaction could be readily scaled out.

The small volumes in the first Phase ensure low reactant consumption, a key issue when only small amounts of testing substances are available.

Furthermore, the complete process of feasibility through optimization up to outscaling to production level proceded without any complications, showing the time efficiency of scaling out flow chemistry in comparison to scaling up conventional batch chemistry.

If you are interested in this technology, Access2Flow is able to provide you with the expertise and technology needed within each phase: from early stage exploration to advanced process implementation.

Contact

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