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Fast Scale-Up Using Microreactors: Pyrrole Synthesis from Micro to Production Scale

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Supporting Information

ABSTRACT: A flow chemistry method for the synthesis of pyrroles was developed. The method was optimized in 0.13 to 7 μL microreactors in continuous flow, reaching yields of nearly 100%. Subsequently, the method was scaled up in continuous flow using a 9.6-mL internal volume, glass, microstructured flow reactor, leading to production of a pyrrole derivative at a rate of 55.8 g per hour .

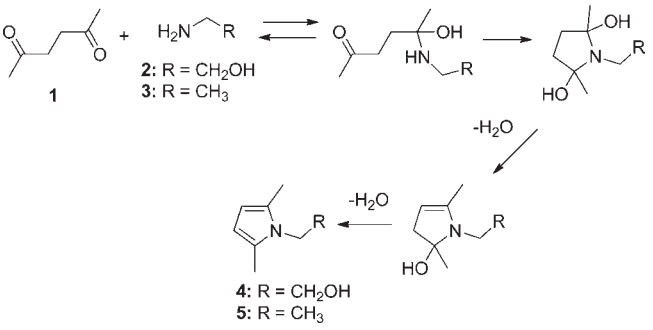
INTRODUCTION

In the fine chemical and pharmaceutical industry, conventional chemical production processes are commonly scaled up by increasing the physical size of the reactors, generally resulting in time-consuming and costly process optimization per scale-up step. Microreactor flow technology allows optimal control over reaction conditions due to the small internal dimensions, leading to inherent reliability and reproducibility, better efficiency, and economic and safer chemistry.[1−5] The optimal control is achieved in particular by the small lateral dimensions of microreactor channels, thus avoiding heat flow and mass limitations of batch reactors. Furthermore, the continuous flow technology is ideal for reaction screening, since it allows testing of reaction parameters in a fast and efficient way. In the recent past, we have developed a plug-and-play microreactor platform[6] that can be routinely used for optimization of a diverse array of reactions including enzymatic conversions,[7] palladium-catalyzed processes,[8] oxidation reactions,[9] formation of organic azides,[10] and deprotection steps.[11] The use of folding split-and-recombine mixing units have proved to be effective and scalable.[12] Therefore, we envisioned that by slightly increasing the channel cross-sectional area from 0.40 to 1.25 mm^2, followed by numbering out by placing four reactors in a two-by-two serial/parallel setup, optimized reactions could be readily scaled up as well. Thus, such a continuous flow route should offer a fast and therefore valuable trajectory for product development and production.

The Paal−Knorr cyclocondensation of 1,4-diketones with amines and other nitrogen derivatives is a well-established and valuable procedure for the preparation of pyrroles and related heterocycles.[13−15] In Scheme 1, the mechanism for the Paal−Knorr cyclocondensation as demonstrated by Amarnath et al.[16,17] is shown. Amarnath has shown that the first addition step is a pre-equilibrium, while the subsequent cyclization is the rate-determining step, after which the two subsequent dehydration steps readily follow.

The Paal−Knorr process is an industrially relevant synthesis, since it directly yields relatively complex pyrroles from readily available amines and diketones. A drawback of this reaction is the exothermic behavior,[15] especially pronounced when carried out at high concentrations. Although the procedure requires only one addition step, on an industrial scale great care is required due to its exothermic nature. It was previously shown that continuous flow offers an excellent alternative for this fast reaction in order to cope with this drawback.[18] However, no details on finding optimal conditions have been published. Therefore, we now present a facile approach to optimize and perform pyrrole synthesis in high yields using flow chemistry, readily maintaining good control over the reaction even at high concentrations, due to high heat transfer capabilities. We designed a continuous flow process for two amine substrates and focused on retrieving chemical data from flow chemistry experiments, which were subsequently used to design a continuous flow process with optimal parameters for scale-up.

Scheme 1. Proposed mechanisms for the Paal−Knorr cyclocondensation



RESULTS AND DISCUSSION

In the development of a scalable continuous flow process three successive phases were followed: (1) design of the continuous flow process, (2) reaction optimization by parameter screening, (3) outscaling to preparative-scale synthesis.

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Phase 1. A procedure for continuous flow equipment (Figure 1) was designed, which allows executing the initially batchwise procedure in a continuous flow manner. Two stock solutions in methanol were applied, the first one containing the diketone substrate 2,5-hexanedione (**1**), and the second, either of the two amine substrates, ethanolamine (**2**) or ethylamine (**3**) in methanol. This approach was adequate for keeping the product and all reaction intermediates in solution, while flow rates of the two substrate solutions could be used to control both residence time in the microreactor, as well as relative stoichiometries of the substrates. To the first solution, 2-bromotoluene was added as an internal standard to follow conversion of the substrate and yield by quantitative GC-FID analysis. As a third flow acetone was used as an appropriate quenching agent, inhibiting the primary amine from further reacting through imine formation. The quenching agent was required for optimization experiments in order to carefully determine the reaction time in combination with off-line analysis. Single variate experiments were designed to roughly screen conversions of both reactions varied by temperature, amine stoichiometry and reaction time. The regions for these parameters were based on limited data available in literature: the work of Amarnath gives an indication on what conditions should to be used, although they apply to different substrates. Three series, varying only one parameter at a time, were performed with fixed values at 12 s, an amine stoichimetry of 2.0, and a temperature of 20 °C. Conversions from 20 to 100% were observed (Figure 2). Reaction time was investigated in a logarithmic fashion in order to cover a wide range, and a regular kinetic profile was recorded from the reaction time data. Stoichiometry data indicated no surprising effects, while temperature showed only minor influence on the converstion. On the basis of the data of these experiments, it may be concluded that the activation energy of the rate-determining step is low.

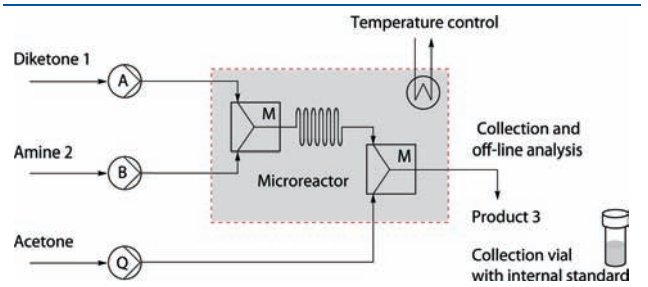

Figure 1. Continuous flow design.

Phase 2. While these univariate runs provided useful data on the reactions, potential dependency of parameters was not taken into account. Therefore, full parametric optimizations were performed, aiming at optimal conditions for the continuous flow equipment focusing on maximal reduction of the reaction time, while maintaining 100% conversion. All parameter ranges were kept identical, except for ethylamine stoichiometry, as in the univariate series it was found that the conversion was saturated around a value 10. Using D-optimal algorithms, an experimental design was made. In the stoichiometry and reaction time dimensions, four levels were used, while in temperature three levels sufficed due to the expected low influence on the reaction. For a full overview of all data points, please refer to the Supporting Information. After the runs were fully performed, the samples were analyzed, and the resulting data were fit to mathematical models. The results from the multivariate optimizations are visualized in Figure 3 by two sets of three contour plots representing slices in the three-dimensional polynomial curve fitted to the data. For the ethanolamine substrate, optimal settings were found at an amine:diketone ratio = 5, reaction time = 100 s, and T = 20 °C, for ethylamine these values were amine:diketone ratio = 10, reaction time = 100 s, and T = 20 °C. In both cases the reaction model showed a broad and therefore robust area at which high yields were obtained. The model describes a decrease of yield at higher amine:diketone ratios. This observation can be most probably attributed to a lower substrate concentration; while the ratio of amine to substrate is increased by controlling flow rates, the absolute concentration of the diketone is decreased. Even though the pre-equilibrium is not rate determining in the final rate of product formation, it is first order to substrate concentration, therefore impacting the final rate of formation, in particular at short reaction times.

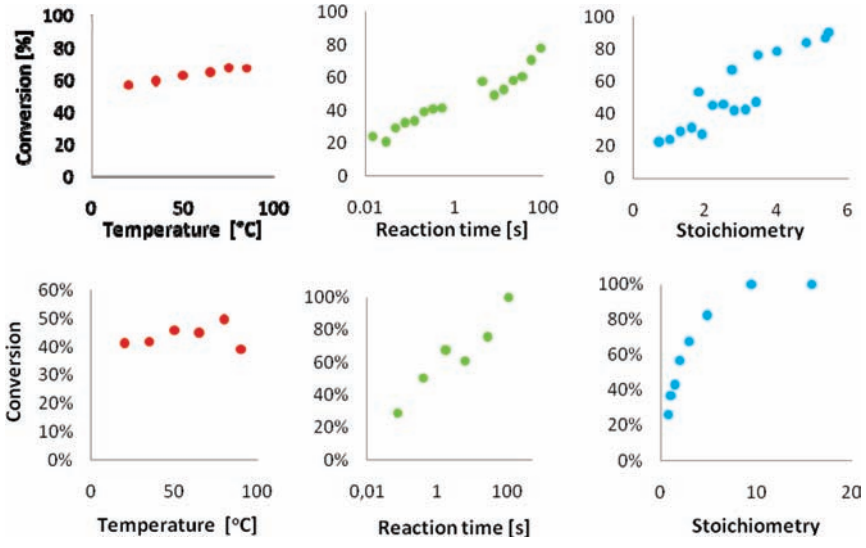

Figure 2. Substrate conversion: univariate screening for substrates, ethanolamine **2** (top) and ethylamine **3** (bottom). Fixed parameters for both substrates: reaction time 12 s, stoichiometry 2.0, temperature 20 °C.

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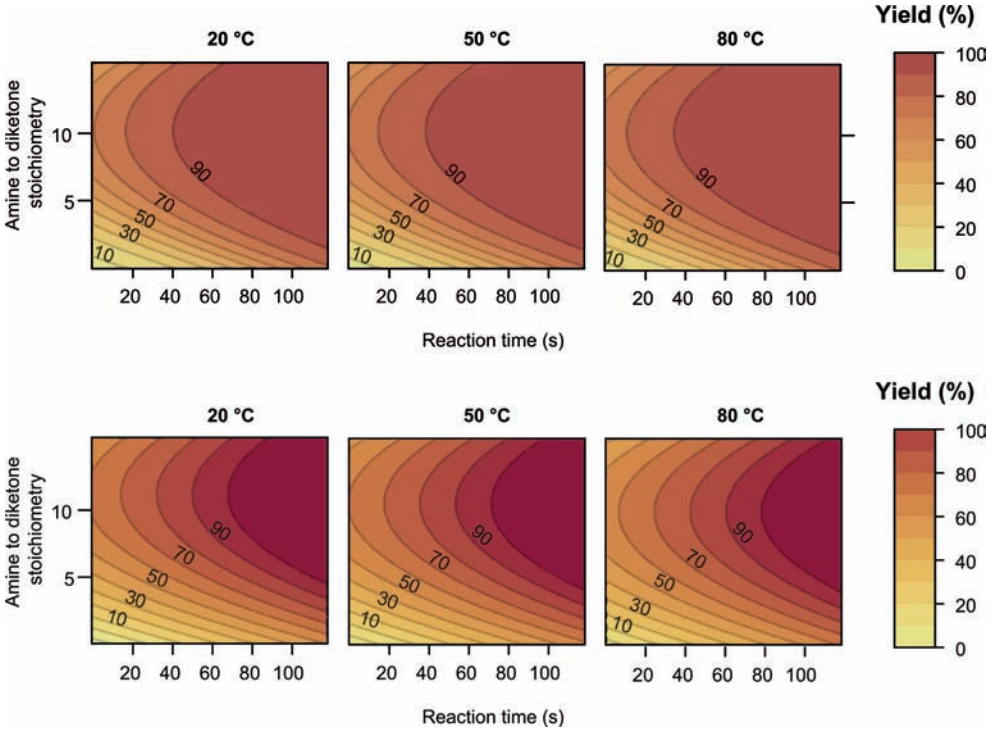

Figure 3. Contour plots of data from multidimensional screening experiments, modelled to a polynomial fit. (Top) Optimization run with substrate ethanolamine 2. (Bottom) Optimization run with substrate ethylamine 3.

Figure 4. Microstructured flow reactor. Internal volume: 2.4 mL.

Leave one out cross validation (LOOCV) was used to evaluate model quality. Values of 70.3% and 63.9% were found for the ethanolamine and ethylamine substrates, respectively. These numbers represent reasonable model prediction, indicating that conclusions can be drawn from the shape of the model. On the basis of the need for model quality, validation was required, which was performed in the next phase.

In addition, the quality of the model fit was visualized by a true vs predicted scatter plot (avaliable in Supporting Information). These scatter plots show a random distribution of residuals, indicating that the model correctly predicts trends in the data.

Phase 3. With optimal conditions for flow chemistry established, the reaction was scaled up and validated at milliliter-scale using a microstructured flow reactor (Figure 4) with an internal volume of 2.4 mL. While maintaining a sufficiently large surface to volume ratio, the lateral dimensions of this reactor were enlarged 1−2 mm. Mixing due to diffusion was no longer sufficient at these scales; therefore adequate, mixing was established by the integration of folding flow-type mixers[19] over the total length of the channel.

Table 1. Larger-scale validation experiments

	ethanolamine **2**		ethylamine **3**	
	optimized point	validation point	optimized point	validation point
reaction time	100 s	10 s	100 s	40 s
amine:diketone stoichiometry	5.0	2.5	10	5
temperature	20 °C	20 °C	20 °C	20 °C
conversion predicted[a]	100%	54%	100%	50%
conversion observed	100%	57%	93%	54%

[a] Prediction based on polynomial model obtained in phase 2.

In order to obtain confidence for scalability, two validation experiments were performed with the milliliter-scale system. In the first experiment, reaction conditions were chosen that matched the optimal conditions found in the previous step. In the second one, arbitrary validation points were used which yielded 50% conversion with the optimization study. Parameters and results of these points are summarized in Table 1. Only small deviations from the predicted values were observed.

Subsequently, four of the same microstructured flow reactors were placed in parallel and integrated into a single parallel multilayered reactor module (Figure 5), resulting in a total internal volume of 9.6 mL. A full-scale reaction run was performed with ethanolamine **2** as the amine substrate. Again, reaction conditions were validated with optimal settings, and 100% conversion was observed. With a total feed of 5.4 mL/min

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Figure 5. Parallel multilayered microstructured reactor. Internal volume: 9.6 mL.

and a run time of 60 min, a total isolated yield of 55.8 g of pyrrole product **4** (96%) was obtained as yellow crystals. In phase 1, total conversion was reached in a microreactor with an internal volume of 7.02 μL at total feed of 4.0 μL/min. Therefore, a scale-up factor of 1367 could be achieved.

CONCLUSION

With these results we have clearly demonstrated the feasibility of the continuous flow optimization-scale up approach for the Paal−Knorr reaction, where the complete trajectory of micro-scale optimization to production in parallel microreactors was carried out successfully. We foresee that this approach will be applicable to a wide range of chemical processes. This emphasizes a double benefit of flow chemistry: highly exothermic processes can be better controlled, while scale-up steps require lower investments.

EXPERIMENTAL SECTION

General. All reactor volumes stated describe the active reaction zone from the point of mixing diketone and amine, up to the point at which the quench liquid is added. The volume of the quenching zone was typically one-third of that of the active reaction zone.

GC Analysis. All GC analyses were performed off-line. The effluent of the microreactor was collected in vials and diluted using acetone marked with an internal standard (1-bromonaphthalene, 0.6% v/v) in order to constantly monitor flow rates as previously demonstrated.[20] GC analysis was performed on a Shimadzu GC 2010 GC-FID equipped with a Quadrex 007 1701 column (length: 10 m, internal diameter: 0.1 mm, film thickness: 0.1 μm), using a temperature program starting at 70 °C for 0.85 min with ramping to 90 °C with 25 °C/min and final ballistic heating with a set temperature of 270 °C for 1.0 min, a linear flow rate of 1 m/s, and a split ratio of 667 with an injection volume of 0.2 μL.

The phase 1 univariate screening experiments were conducted in a standard FutureChemistry *Flow*Start B-200 setup, consisting of syringe pumps, a microreactor holder, and temperature controller. Three syringes (Harvard Apparatus: high-pressure syringe, 2 mL; for quench flow: Henke Sass Wolf NORM-JECT 10 mL) were mounted on the syringe pumps: one for the diketone substrate, one for the amine reagent, and one for the quench liquid. All pumps were connected to the microreactor's corresponding inlet by FEP tubing (ID: 0.25 mm), while the outlet was connected to similar tubing, which was manually operated to collect samples. Reaction parameters were changed manually by setting the reaction temperature on the controller and flow rates on the syringe pumps. For the phase 2 multivariate screening experiments, a standard FutureChemistry *Flow*Screen C-300 setup was used, which is similar to the setup used in phase 1 but with the outlet directly connected to a sampling robot's needle, delivering outflow samples to HPLC vials. The computer-controlled sampling robot was used to sample all effluents from different parametric settings. The parameters were controlled automatically by the computer, changing the temperature and flow rates according to a preset reaction screening sequence.

The microreactor used in both phases 1 and 2 was custom-made with dimensions: L 45 mm, W 15 mm, H 2.2 mm, channel dimensions: L 1325 mm, H 55 μm, and internal volume of either 0.13 or 7.02 μL (to achieve reaction times of less than 1 s or more than 1 s, respectively).

Phases 1 and 2. The first syringe was loaded with liquid A containing 2,5-hexanedione **1** (11.0 g, 96 mmol) and 2-bromotoluene (1.78 g, internal standard) dissolved in methanol (total stock volume 25 mL). The second syringe was loaded with liquid B containing ethanolamine **2** (10.1 g, 166 mmol) and dimethoxy ethane (2.17 g, internal standard) dissolved in methanol (total stock volume 25 mL). The third syringe was filled with acetone (analysis grade, neat). The sample preparation mixture was prepared by dissolving 1-bromonaphthalene (6.0 g, internal standard) in acetone (total stock volume 1 L). Syringes with liquids A−C were then connected to the respective microreactor system. In phase 1, the outlet tubing was manually held in collection vials during the collection times, whereas in phase 2 this process was automated by a sample robot. Before collection commenced for each sample, the system was stabilized during a time defined by the flows of liquid A and B flushing the microreactor approximately 2.5 times. For each data point, the collection time was set so that 50 μL of liquid A was collected in 1.0 mL of liquid D All reaction conditions were randomized. All samples were analyzed with GC. Retention times were 0.39, 0.68, 1.26, 1.36, 1.99, and 2.19 min for dimethoxyethane, amine **2**, diketone **1**, 2-bromotoluene, product **4**, and 1-bromonaphthalene, respectively. The collected data was processed using FutureChemistry *Flow*Fit software, based on multidimensional polynomial curve fitting. The software used a polynome degree of three (cubic) for all parameters. The Bayesian Information Criterion method was used to automatically optimise the curve fitting.

Phase 3. All experiments were conducted in a standard FutureChemistry *Flow*Syn setup, using a 2.4 mL glass microreactor for first validation and 9.6 mL glass microreactor for final scale-up, respectively. Flow markers were used during the validation experiments in the same way as in phases 1 and 2; no flow markers were used in the preparative run. No quenching liquid was used, since the reaction was driven to full completion.

Preparative Run. These experiments were conducted on a custom setup consisting of 20 mL/min syringe pumps (Syntics) and a 9.6 mL internal volume glass microreactor (Micronit Microfluidics). Two bottles were filled with solutions A′ (**1**, 4.4 M in methanol, no internal standard) and B′ (**2**, 8.3 M in methanol, no internal standard). Pump rates were set to 1.53 and 3.87 mL/min, respectively. The experiment was run for 60 min, and the product mixture gave 100% yield based on GC analysis. The reaction mixture was concentrated, diluted with ∼50 mL of water, extracted with diethyl ether (3 × 100 mL), washed with 1 M HCl (150 mL) and brine (50 mL), dried, and filtered, and the solvent was removed under reduced pressure. The resulting

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yellow oil crystallized to yield 55.8 g of the desired product in a 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 2.24 (s, 6H), 1.60 (br s, 1H, OH). This is identical to literature data.[21]

■ ASSOCIATED CONTENT

Supporting Information. Raw data of optimization runs and model evaluation. This material is available free of charge via the Internet at http://pubs.acs.org.

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