FAST SCALE UP USING MICROREACTORS: FROM MICROSCALE TO PRODUCTION

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ABSTRACT

In this study, the excellent scalability of flow chemistry was shown. Selective formation of mono-α-bromoketones was chosen as a model reaction. In a full multivariate optimization experiment, 60 different settings for reaction parameters such as temperature and reaction time were screened, requiring only small amounts of chemicals. A mathematical model of the data was obtained and an optimum set of reaction parameters was selected. These settings were applied on a larger scale continuous flow system and led to a production of the target compound phenacyl bromide at a 1.1 g/hr rate.

KEYWORDS: Flow Chemistry, Microreactors, Scale-up, Bromination

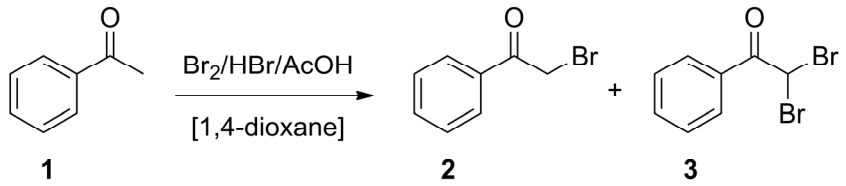

Figure 1. Selective monobromination of acetophenone

INTRODUCTION

Although benefits of flow chemistry using microreactors are now well established[1], the aspect of scalability still remains a relatively unexplored field. In this study, we show that microreactors can be used to optimize a reaction[2], while similar but larger reactors can be employed for chemical production using the same conditions, showing that reaction parameters found in small scale optimization systems can easily be translated to larger scale production systems. Here, we have chosen the selective formation of mono-α-bromoketones **2** as a model reaction (Figure 1), which is difficult to control in conventional batch reactions due to high reaction rates and exothermic kinetics[3] leading to formation of the dibromo byproduct **3**. In a continuous flow microreactor setup (Figure 2), however, this reaction can be performed with high selectivity because of the better mixing and thermal properties of microreactors.

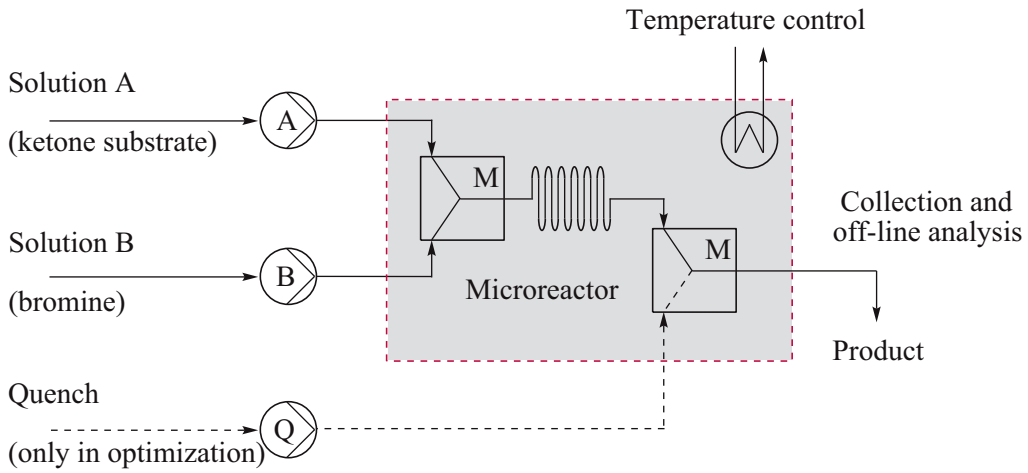

Figure 2. Schematic representation of microreactor setup for both optimization and preparative scale synthesis

Figure 3. View of microreactor with internal volume of 92 µL used for optimization

EXPERIMENTAL

Optimization experiments were conducted in a FutureChemistry C-300 FlowScreen setup equipped with the Basic Quench Microreactor M-121 with an internal volume of 92 µL, maximum channel width of 600 µm and split-and-recombine mixing units (Figure 3). Solutions in 10 mL 1,4-dioxane were prepared: solution A contained acetophenone **1** (2.0 mmol) and hydrogen bromide (33% in acetic acid, 1.0 mmol). Solution B contained bromine (2.0 mmol). Quench solution contained 2-methoxypropene (6.0 mmol). In order to validate flow rates, internal standards were added to the solutions [4]. For data analysis, commercially available optimization software FlowFit was used.

The scale up experiments were conducted in a standard FutureChemistry FlowSyn Q-2010 setup equipped with the FlowSyn Quench Microreactor Q1031 with an internal volume of 0.65 mL, maximum channel width of 1525 µm and split-and-recombine mixing units similar to the 92 µL microreactor (Figure 4). The same solutions were used as in the optimization experiments. For product isolation, solvent and excess reagent was removed under reduced pressure at 50°C. The crude product **2** was dissolved in diethyl ether, run over a 4 cm silica plug, and solvent was removed under reduced pressure.

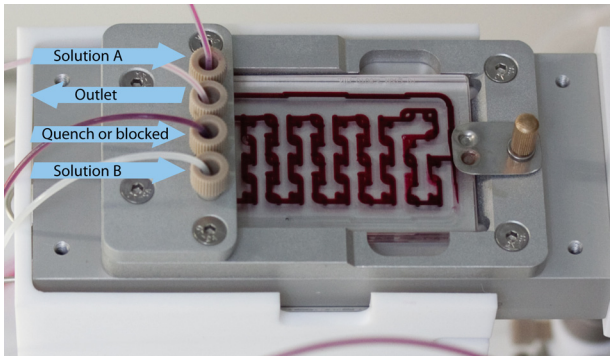

Figure 4. View of microreactor with internal volume of 0.65 mL used for preparative synthesis. Channels are filled with dye to improve visibility

RESULTS AND DISCUSSION

A full multivariate optimization experiment was set up with 60 points spread out across the optimization region with reaction parameters temperature, reaction time and bromine to substrate stoichiometry. The full optimization run only required several milliliters of reaction solutions. After GC analysis of the samples, the data was fit to a polynomial model and visualized in contour plots (Figure 5). Although a local optimum is clearly visible at high temperatures, the actual optimal conditions were found at a temperature of 20°C, a broad optimal bromine stoichiometry of 2.5 to 4.0 and reaction time of 60 seconds.

These settings were successfully validated on a larger scale continuous flow system and employed on a larger preparative scale. Continuous flow production of the target compound phenacyl bromide at the above optimum with the setup depicted in Figure 4 resulted in the continuous production at a 1.1 g/hr rate. A final amount of 1.7 g isolated product **2** was obtained during a 105 min run (100% yield based on GC analysis).

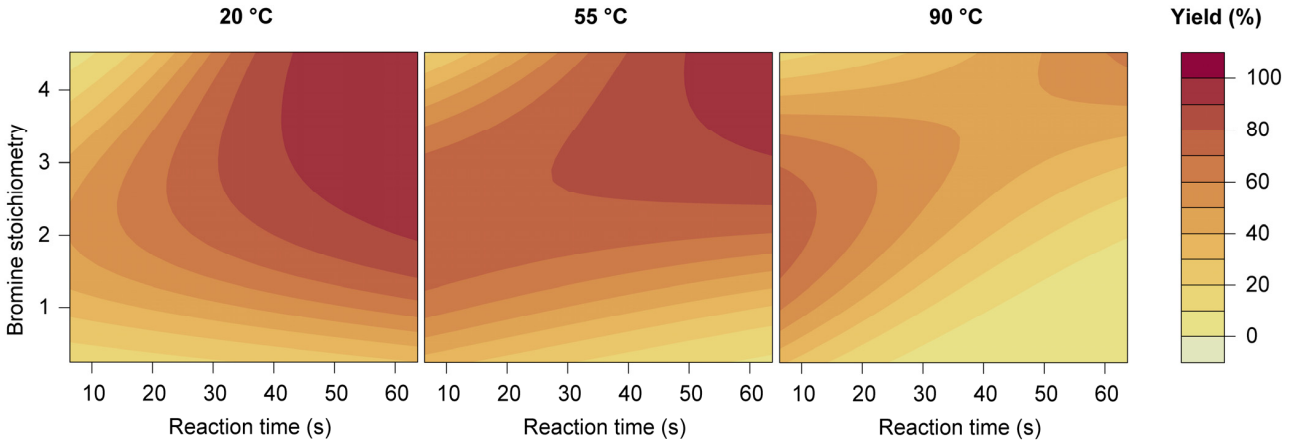

Figure 5. Contour plots reaction data fitted to a polynomial model

CONCLUSION

These results show the feasibility of the integrated flow optimization–production method, while the complete study of microscale optimization to production in larger microreactors was carried out in approximately one week time**.**

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