Optimisation and Scale-up of α-Bromination of Acetophenone in a Continuous Flow Microreactor

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To expand the knowledge base for fundamental organic reactions in continuous flow, the α-bromination of acetophenone was successfully transformed from a known batch procedure to a continuous flow process in 99 % yield through D-optimal optimisation and subsequent scale-up of the validated optimum. Using a preparative scale system, a space–time yield of 0.26 kg/m^3/s (comparable literature batch reaction 0.24 kg/m^3/s) was achieved under conditions suitable for laboratory and small-scale industrial application where high yield or purity is required, e.g., when expensive substrates are used.

Keywords: microreactors, flow chemistry, ketone bromination, design of experiment, reaction optimisation, reaction scale-up

1. Introduction

Over the last years, the use of microreactors in synthetic organic chemistry has become well established, leading to an increasing number of scientific articles [1] and patents [2] from both commercial parties and academia. Better yields and selectivity due to inherent faster mixing, more efficient heat transport, and low hold up of (hazardous) intermediates are some of the key advantages microreactor technology has to offer [3]. Also, the relative linearity of the process (as opposed to a batch process) provides the freedom to scale down for screening and scale up for production [4].

For a variety of chemical processes, it has been proven that continuous flow chemistry offers significant advantages over the equivalent procedure in batch chemistry, e.g., in the field of highly reactive intermediates [5,6], reactions prone to thermal runaway [7], and high temperature nanoparticle synthesis [8]. However, for common organic transformations, most organic chemists still routinely use conventional laboratory equipment such as round-bottomed flasks. To expand the knowledge base for fundamental organic reactions in continuous flow, we hereby present the synthesis of α-bromoketones, carried out in a commercially available microreactor system. The closed system employed in continuous flow gives an additional advantage over conventional batch-wise synthesis, as the highly toxic and corrosive bromine is handled in an inherently safe manner.

The synthesis of α-bromoketones is a useful reaction in organic chemistry, as it provides a convenient pathway towards mono-α-substituted ketones through bromide substitution and towards a variety of heterocycles such as thiazoles [9,10], imidazo[1,2-*a*]-compounds [11], and indoles through the Bischler–Möhlau synthesis [12]. The ketone substrate used in this model reaction (Scheme 1) is acetophenone (**1**), which readily undergoes bromination at room temperature within seconds to form the mono-brominated ketone phenacyl bromide (**2**) [13]. This reaction is well known and has been carried out under a variety of conditions: with and without (Brønsted or Lewis acid) catalyst, with coordinating or non-coordinating solvent and neat, and with a variety of brominating agents of which the milder *N*-bromosuccinimide is most often used after bromine itself [14,15]. In any of the above cases, both monobrominated product **2** as well as dibrominated product **3** are formed.

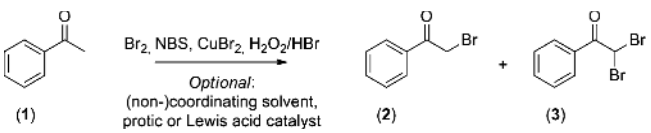
The α-monobromination of ketones has already been subject to investigation by Uniqsis Ltd (UK) in their FlowSyn microreactor system fitted with a static glass mixer, which showed its viability in a continuous flow system [16]. The reaction, however, was not optimised, and the important parameters were not fully investigated. The used three-tier approach in our present study led to a protocol which can be adapted to any viable ketone substrate, and consists of the following steps: (1) design of the continuous flow process, (2) automated reaction optimisation, and (3) out-scaling of the reaction to a preparative synthesis scale. The investigated parameters in the optimisation experiment were reaction time, temperature, and molar ratio of bromine to substrate.

2. Results and Discussion

2.1. Continuous Flow Process Design. Continuous flow synthesis is best carried out from homogeneous stock solutions which react when combined, remain inactive after preparation, and remain stable while conducting the experiments. With this design principle in mind, stock solution A contained the ketone substrate **1** and stock solution B contained the bromine reagent (Scheme 2). 1,4-Dioxane was chosen as a coordinating solvent, thereby avoiding evaporation of toxic and corrosive bromine gasses.

In the analysis of all single-variate and optimisation experiments, multiple-product peaks were observed on gas chromatography (GC) depending on reaction conditions. From these peaks, only substrate **1**, monobromo product **2**, and the internal/external standard compounds (cf. Flow Marker Approach section) were identified and quantified. The remaining peaks, if any, were assumed to be dibromo product **3** and/or other side products. Substrate conversion and product yield were thus measured directly, and from their ratio, reaction selectivity was calculated. During optimisation, however, only yield of **2** was used to determine optimal reaction conditions.

Scheme 1. Generalised reaction equation for the α-bromination of acetophenone



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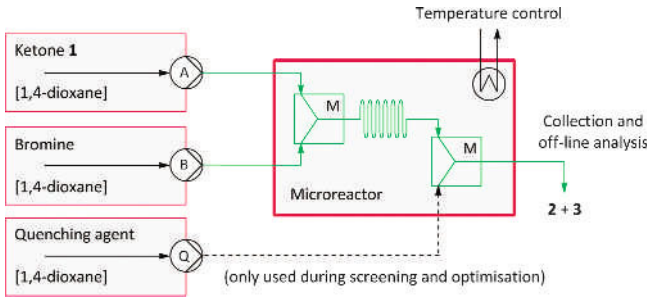
Scheme 2. Continuous flow set-up for preliminary screening of the α-bromination of acetophenone



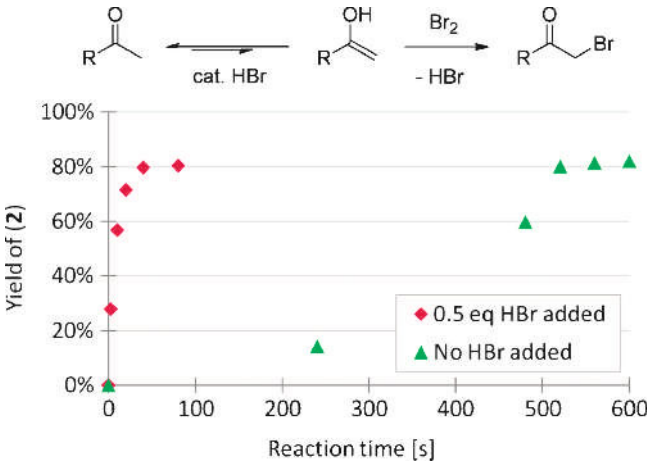


Figure 1. Autocatalytic behaviour of the α-bromination. Top: positive feedback mechanism. Bottom: single-variate reaction time screening with and without autocatalytic behaviour through addition of 0.5 Eq hydrogen bromide to stock solution A (conditions: bromine molar ratio of 1.0 and a temperature of 20 °C)

2.2. Suppressing Autocatalytic Behaviour. During the first screening experiments, it was found that inter-run reproducibility of the process was very poor. Single-variate screening of reaction time showed that the reaction is autocatalytic in hydrogen bromide: as the reaction proceeds, hydrogen bromide is liberated, which in turn catalyses the reaction by accelerating the formation of the reactive enol species of **1**. The overall reaction rate d[**2**]/d*t* is directly proportional to [HBr], which is liberated as **2** gets formed, leading to the sigmoid reactant concentration curves typically observed in autocatalysis. Autocatalytic behaviour was reported earlier by Anslin et al. [16,17], and the observations are summarised in Figure 1. Reproducible inter-run results were obtained by adding 0.5 Eq of hydrogen bromide in acetic acid to stock solution A, effectively removing the autocatalytic behaviour by introducing catalytic conditions from the start of the reaction.

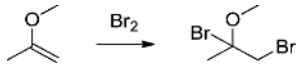
2.3. Design of a Quenching Method. To obtain well-controlled reaction times, a quenching agent was used to consume the excess bromine, which was supplied to the microreactor system as stock solution Q (Scheme 2). This quenching method must follow three general rules: (1) the quenching reaction rate should be many times faster than the main reaction rate; (2) the quenching step should not influence the main reaction in any way, apart from stopping it; (3) to be able to measure both reaction conversion and yield accurately, the quenching reaction should be inert towards both substrate and products and should not interfere with analysis.

The addition of sodium thiosulfate as a quenching agent not only adequately destroyed the bromine reagent, but also gave substitution of the bromide in product **2** [19]. Alternatively, the activated alkene 2-methoxypropene (Scheme 3) proved to be a suitable quenching agent and was used in all continuous flow experiments. The rate constant of bromine addition to the similarly activated alkene α-methoxystyrene (log*k*≈9.0/M/s) [20] gave a good indication that the quenching reaction was sufficiently fast compared to the main reaction (log*k*≈5.0/M/s) [21]. To make sure that all leftover reagent was adequately consumed, 3.0 Eq of quenching agent with respect to bromine was used.

2.4. Single-Variate Parameter Screening. To define a parameter range for performing the optimisation experiments, single-variate screening experiments were conducted to find the influences of all three tested parameters on substrate conversion (Figure 2), aiming at maximal deviation in reaction yield and selectivity to maximise the information (in a mathematical sense) of the full optimisation run. Hence, all three tested parameters – temperature, bromine molar ratio, and reaction time – had a pronounced effect with increasing yield as parameter values increased. The useful parameter ranges were found to be temperature between 20 and 90 °C, bromine molar ratio between 0.7 and 3.0, and reaction time between 10 and 40 s.

2.5. Flow Marker Approach. To obtain accurate concentration measurements of the reaction mixtures and to find deviations from the set flow rates, a flow marker approach was used [22]. To each stock solution, an internal standard was added (*o*-dichlorobenzene and cyclooctane for solutions A and B, respectively). The collection fluid contained an additional standard compound (1-bromonaphthalene), which was coined 'external standard.' The ratios between the internal and external standards determined the actual flow rates. Accurate concentration

Scheme 3. Quench reaction equation



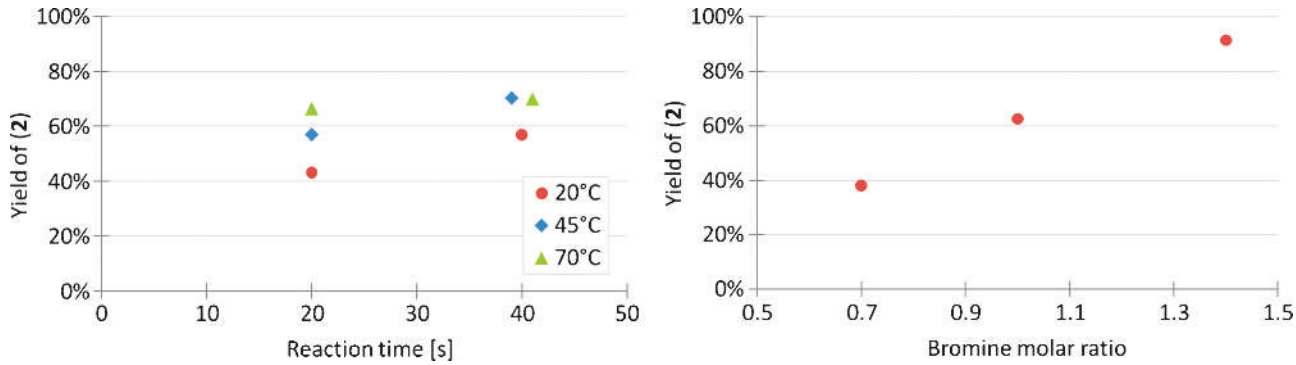


Figure 2. Selected results of the single-variate screening. Left: product yield vs. reaction time at various temperatures (conditions: bromine molar ratio of 1.0). Right: product yield vs. bromine molar ratio (conditions: temperature of 45 °C and a reaction time of 10 s)

Table 1. Parameter levels used in the optimisation experiments

Parameter	Values
Reaction time [s]	10, 25, 40
Temperature [°C]	20, 40, 60, 90
Bromine molar ratio	0.7, 1.85, 3.0

measurements followed from calibration of compounds **1** and **2** with respect to the internal standard of stock solution A.

2.6. Multivariate Analysis. In contrast to batch-wise optimisation of chemical reactions, optimisation in continuous flow offers significant advantages. Firstly, each experiment can be carried out using material in the microgram or nanogram scale, thereby reducing waste and costs. Secondly, automated optimisation using microreactors is a lot less time consuming and more precisely controlled, especially when optimising fast reactions.

2.7. Optimisation and Model Fitting. An optimisation experiment was designed with 60 data points using standard D-optimal algorithms (Design of Experiment, DoE) [23], assuming cubic responses in all parameters. The parameter levels were spread out across the optimisation range as shown in Table 1. The experiment was prepared and conducted in an automated fashion using FutureChemistry's FlowScreen instrument. Afterwards, all samples were analysed with GC, processed, and fitted to a reaction model using FutureChemistry's FlowFit software, which is visualised in Figure 3. The total optimisation procedure (experimentation and data processing) took approximately one working week.

Apart from the formation of the desired product **2**, substrate conversion was also monitored. In general, it was found that at sub-optimal reaction time (<20 s), molar ratio (<1.5), and temperature (<40 °C), mainly product **2** and starting material **1**, were observed. At above-optimal conditions (t_R > 30 s; S > 2.5; T > 50 °C), the main side-products were the doubly brominated compound **3** and traces of unidentified compounds (e.g. benzoic acid through haloform reaction, aldol products, bromide substitution products, or aromatic bromination products).

2.8. Identification of Optimal Parameters. To identify optimal parameters from a reaction model as presented above, some considerations must be taken into account. Firstly, optimality can be an ambiguous term, as it is often not known beforehand what parameters will be of prime importance during production on larger scale. In the α-bromination of ketones, safety issues are minimised by, e.g., minimising the bromine molar ratio and reaction temperature, whereas costs are affected mostly by ease of work-up, raw material consumption, and overall throughput. Secondly, reaction conditions during optimisation differ from the larger scale in the use of a quenching agent, which is undesired in terms of costs. Therefore, the optimal conditions should also hold for the unquenched reaction, which implies that the reaction is driven to completion and the selected optimum shows no decrease in yield at longer reaction times.

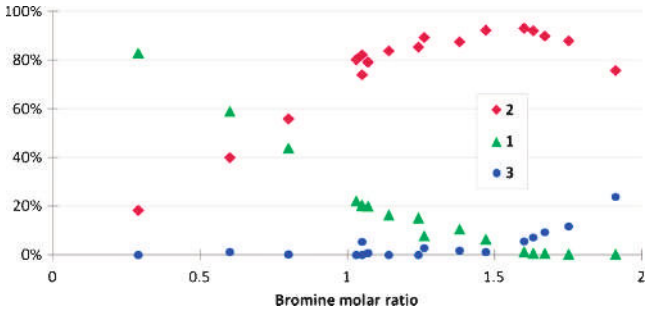


Figure 4. Single-variate screening at preparative scale of compound distribution vs. bromine molar ratio at a temperature of 20 °C and a reaction time of 60 s

With these boundary conditions in mind, optimal reaction conditions were identified at a temperature of 20 °C, bromine molar ratio of 1.5, and reaction time of 60 s.

2.9. Preparative Synthesis. The optimal reaction conditions identified in the optimisation experiment were validated in a larger-scale microreactor system, to make sure that settings in the region at 20 °C and long reaction times indeed would lead to high yields. At a reaction time of 60 s and a temperature of 20 °C, the bromine molar ratio was varied over the range 0.3 to 1.9, and optimal conditions were found at a bromine molar ratio of 1.5, corresponding to the aforementioned optimum (Figure 4).

At these validated optimal conditions, 1.07 g of the monobromo product **2** was synthesised with excellent (>98 %) reaction selectivity. Results of the preparative run are summarised in Table 2.

Table 2. Results of the preparative scale synthesis of **2**

Parameter	Value
Reaction time	60 s
Temperature	20 °C
Bromine molar ratio	1.5
Total runtime	105 min
Yield after workup	1.07 g (99 %)
Microreactor volume	0.65 mL
Space-time yield	0.26 kg/m^3/s

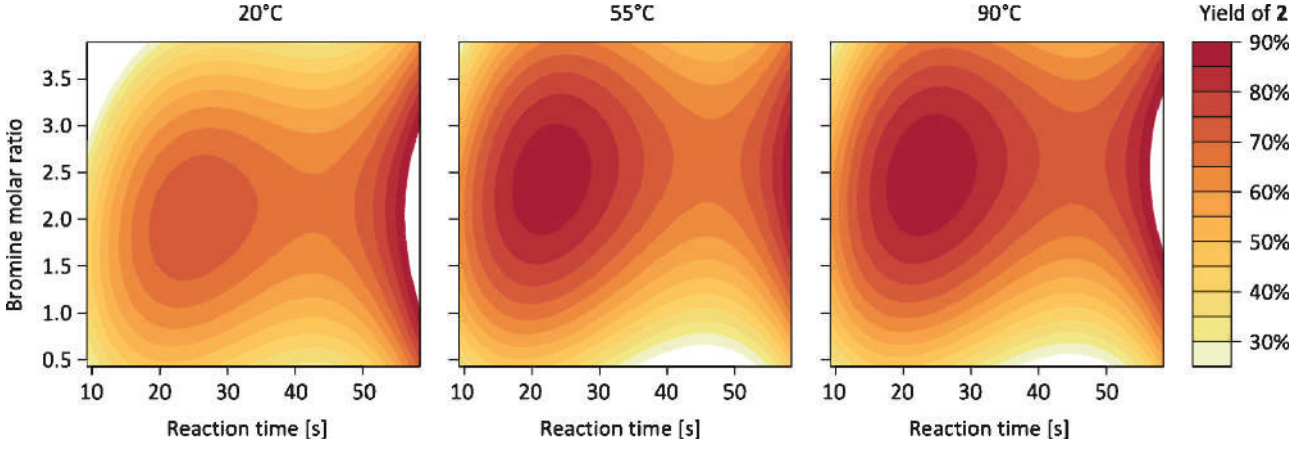


Figure 3. Reaction model fit of the optimisation experiment. Note that due to the DoE assumption of cubic responses in all parameters, some modelling artefacts are visible in the contour plots. At high temperatures, the high-yielding region at long reaction times probably results from the low temperature optimum. At low temperatures, the high temperature optimum is visible as a moderate-yielding local optimum

3. Conclusion

A robust and reproducible continuous flow process for the α-bromination of acetophenone was successfully designed. Using the optimal conditions, selectivity of monobromination was excellent, as no side products could be detected. Autocatalytic behaviour was suppressed by addition of hydrogen bromide. The process was optimised and modelled, and the validated optimal reaction parameters were used to synthesise the target compound on a preparative scale with a space–time yield of 0.26 kg/m^3/s (comparable literature batch reaction 0.24 kg/m^3/s) [13]. The resulting conditions are suitable for (small-scale) industrial application where expensive ketone substrates are used or where high purity and/or yield are/is required to the expense of an increase in bromine molar excess. However, future research could lead to a more intensified process by, e.g., increasing reactant concentrations or the use of an improved catalyst.

4. Experimental Section

All experiments were carried out under ambient atmosphere. All solvents and reagents were bought from commercial suppliers and used without further purification. Bromine purity was 96 ± 0.5 % as determined by titration with sodium thiosulfate/iodine/starch in triplicate, for which no correction was applied.

4.1. Microreactor Set-Up. Three commercial microreactor platforms were used to perform the experiments. All flow process design and single-variate screening experiments were conducted in a FutureChemistry B-400 *Flow*Start Evo set-up, using a Basic Quench Microreactor with internal volume of 92 μL. The multivariate experiment was conducted in a FutureChemistry C-300 *Flow*Screen set-up, using a Basic Quench Microreactor with internal volume of 92 μL. The preparative scale experiments were conducted in a Uniqsis Q-1020 *Flow*Syn, using a FutureChemistry *Flow*Syn Quench Microreactor with an internal volume of 0.65 mL.

4.2. Stock Solutions. Stock solutions were freshly prepared and used within 8 h. Stock solution A contained 0.20 M acetophenone (**1**), 0.10 M hydrogen bromide (33 % *w*/*w* solution in acetic acid), and 24.0 g/L *o*-dichlorobenzene (internal standard) in 1,4-dioxane. Stock solution B contained 0.20 M bromine and 24.0 g/L cyclooctane (internal standard) in 1,4-dioxane. Stock solution Q contained 0.60 M 2-methoxypropene in 1,4-dioxane. Collection solution contained 2.40 g/L 1-bromonaphthalene (external standard) in 1,4-dioxane.

4.3. Small-Scale Experiments. Flow rates were calculated from the desired reaction time and bromine molar ratio. The total flow rate (flow rate of pump A and flow rate of pump B) was set equal to the ratio between microreactor internal volume and reaction time. The ratio between the flow rate of pump B and the flow rate of pump A was set equal to the bromine molar ratio. The flow rate of pump Q was always equal to the flow rate of pump B.

Three glass 5.0-mL syringes were loaded with stock solutions A, B, and Q, and mounted on the *Flow*Start Evo or *Flow*Screen syringe pumps. For each experiment, flow rates were set, pumps were started, and the system was stabilised for 1.5 times the reaction time, after which the microreactor outflow was collected for a total collected volume of stock solution A of 25.0 μL in a vial containing 500 μL collection solution. Each vial was analysed using GC.

4.4. Multivariate Optimisation Experiment. A set of 60 data points was selected in the optimisation range (Table 1) using a D-optimal algorithm (DoE) in Matlab (MathWorks). The experimental procedure was identical to the one used in the small scale experiments, but was used in an automated set-up. Each vial was analysed using GC. The resulting data were transferred to *Flow*Fit software (FutureChemistry), and a reaction model was fitted over the data points (see Supporting Information for analysis data and modelling results).

4.5. Preparative Scale Experiment. Stock solutions were prepared with the same concentrations as in the small scale experiments, without the use of internal standards. No quenching solution and no collection solution were used. Approximately 5 mL of each stock solution was used to purge the system before use. For optimal reaction conditions, flow rates were set to 0.26 and 0.39 mL/min for solutions A and solution B, respectively, and temperature was set to 20 °C. The system was stabilised for 1.5 times the reaction time.

For the preparative run, the microreactor outflow was collected for 105 min, yielding around 70 mL of reaction mixture. Excess reagent was removed under reduced pressure at room temperature; solvent was removed under reduced pressure at 50 °C. The crude product was dissolved in diethyl ether, run over a 4-cm silica plug, and solvent was removed under reduced pressure to give 1.07 g of bromide **2** as white to off-white crystals (99 % yield, >98 % GC pure based on peak area).

4.6. Analysis. All samples were analysed with GC. GC analysis was performed on a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (L 15.0 m, inside diameter 0.10 mm) and flame ionisation detector (*T* 325 °C, H_2 60 mL/min, air 400 mL/min) using a temperature program (0–0.5, min 60 °C; 0.5–2.2 min, 60–230 °C; 2.2–2.7 min, 230 °C) and 1.0 μL injection volume with split ratio 200. Compound retention times: cyclooctane, 0.92 min; *o*-dichlorobenzene, 1.29 min; **1**, 1.43 min; **2**, 1.98 min; 1-bromonaphthalene, 2.11 min.

4.7. Data Analysis. The total amounts of collected stock solutions A and B ($V_{A,coll}$ and $V_{B,coll}$) were calculated from calibration of the internal standards in both stock solutions onto the internal standard in the collection solution. *Actual flow rates* (φ_A and φ_B) were calculated by dividing $V_{A,coll}$ and $V_{B,coll}$ by the collection time t_{coll}. *Actual reaction time* was calculated by dividing the microreactor volume by the sum of actual flow rates. *Actual bromine molar ratio* was calculated by taking the ratio between the actual flow rates. *Actual temperature* was assumed to be identical to the set temperature.

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Supporting information

The supplementary data (raw optimisation data and model fitting procedure) associated with this article can be found on the journal's homepage at www.akademiai.com.

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