Continuous flow azide formation: Optimization and scale-up

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Abstract

The intrinsically small volumes and highly controlled reaction conditions render continuous flow microreactors ideal systems for the synthesis of potentially explosive compounds such as organic azides. In this article, we report the formation of benzyl azide from benzylamine using imidazole-1-sulfonyl azide hydrochloride as diazotransfer reagent. In a small scale (semi-automated) continuous flow setup the diazotransfer reaction was optimized using minimal amounts of reagents; less than 400 mg of benzylamine was required to perform 60 optimization reactions. The optimal reaction conditions were indentified to be room temperature, 600 s of residence time and an imidazole-1-sulfonyl hydrochloride to benzylamine stoichiometric ratio of 3 to 4. Furthermore, we successfully scaled up the reaction with a factor of 200 to gram scale using one single continuous flow reactor.

1. Introduction

The number of applications of continuous flow systems in synthetic organic chemistry is rapidly increasing [1–12]. This trend is stimulated by the vision that fine chemical and pharmaceutical processes could strongly benefit of microreactor technology leading to increased selectivity and efficiency of reactions and consequently higher yields [13,14]. The high surface-to-volume ratio and the absence of heat and mass transport limitations are the main advantages of continuous flow microreactors over larger scale batchwise processes. In small scale continuous flow experiments, reaction conditions can be accurately controlled which enables a straightforward and thorough reaction optimization. The optimal conditions indentified on small scale can then be directly implemented in larger scale continuous flow systems [9,12,15]. An additional advantage of microreactor synthesis is the small amount of chemicals required to perform a reaction. Furthermore, the closed system combined with small hold-up volumes offer an intrinsically safe environment for chemicals prone to explosive decomposition.

Organic azides constitute such a compound class with potentially explosive properties. Trace amounts of acid or certain metal salts may catalyze explosive decomposition due to the formation of molecular nitrogen. In addition, organic azides may also be shock and/or heat sensitive and will generally decompose on exposure to UV light [16,17]. Nevertheless, organic azides have been shown to be valuable and versatile intermediates in organic synthesis [18–22]. In 2009, Kopach et al. reported the synthesis of 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene in batch and microreactor equipment by substituting a halide with an inorganic azide [23]. This reaction was performed with an aqueous solution of sodium azide at a temperature of 90 °C. Both the high reaction temperature and the requirement of toxic sodium azide [16,17] significantly decrease the applicability of this method. An alternative route to organic azides proceeds via diazotransfer onto amine functionalities. The most commonly used diazotransfer reagent is triflyl azide, which in neat form is highly explosive. Due to its reactive nature, it has a relatively short shelf life and needs to be prepared directly prior to use [24]. In 2007, Goddard-Borger and Stick invented a new diazotransfer reagent, imidazole-1-sulfonyl azide hydrochloride (2) [25], which is stable and easy to prepare, and eventually cheaper compared to triflyl azide. In addition, reagent 2 can be prepared in large amounts and was reported to be non-explosive. As a result, the latter diazotransfer reagent can be handled in pure form rather than in solution.

2. Materials and methods

2.1. Benzyl azide synthesis

We investigated the synthesis of benzyl azide (3) as a general procedure for the synthesis of organic azides in a continuous flow
system. Benzyl azide (3) was prepared from benzylamine (1) using imidazole-1-sulfonyl azide hydrochloride (2) as the diazotransfer reagent [25].

2.2. Microreactor setup

A schematic representation of the microreactor setup is shown in Fig. 1. All parts within the dotted line consist of a single glass microreactor with an internal volume of 92 µL, a channel width of 600 µm, a channel depth of 500 µm and an effective channel length of 360 mm. The channel layout contains two mixing units M, being of the folding flow type [26]. The reactor temperature was controlled by Peltier elements and sensed by a Pt1000 temperature sensor. In case of short reaction times, experiments were performed in a microreactor with an internal volume of 7.0 µL, a channel width of 120 µm, a channel depth of 55 µm and an effective channel length of 1325 mm. This channel layout contained no separate mixing units as the small internal diameter led to sufficient mixing by diffusion. In all cases, the reactor temperature was controlled by Peltier elements and sensed by a Pt1000 temperature sensor.

2.3. Reaction optimization

A FutureChemistry FlowScreen (C-300) was used to perform the screening of reaction conditions. Three glass syringes with an internal volume of 1 mL were used in pumps P1, P2 and P3 as indicated in Fig. 1. Pump P1 contained solution of benzylamine (1, 328 µL, 3.0 mmol), diisopropylamine (DIPEA, 1.57 mL, 9.0 mmol), ZnCl2 (183 µL of 2.19 g/L MeOH/CH2Cl2 (10:3), 3.0 mmol) and 2-bromotoluene (250 µL, internal standard A) in MeOH/CH2Cl2 (10 mL; 10:3, v/v). Pump P2 contained a solution of imidazole-1-sulfonyl azide hydrochloride (2, 625 mg, 3.0 mmol), DIPEA (524 µL, 3.0 mmol) and 5-bromo-m-xylene (250 µL, internal standard B) in MeOH/CH2Cl2 (10 mL; 10:3, v/v). In order to quench the reaction at the end of the channel, ensuring well-defined residence times, pump P3 contained a solution of HCl (500 µL, 37% concentrated HCl) in EtOAc/acetone (10 mL; 1:1, v/v), which was added to the reaction after the residence time channel (shown as meander channels in Fig. 1). The product (5 µL) was collected in CH2Cl2 (100 µL) containing 2% cyclooctane as an external standard.

2.4. Scale-up reaction

A scale-up experiment was performed in a Uniqsis FlowSyn (FC-UQ-1020) equipped with a 20 mL stainless steel coil reactor. With a flow A of 0.4 mL/min and flow B of 1.6 mL/min, a residence time of 10 min was obtained. The product was collected for 95 min after 15 min of stabilization. Pump P1 continuously pumped a solution of benzylamine (1, 3.28 mL, 30 mmol), DIPEA (15.7 mL, 90 mmol) and ZnCl2 (1.87 mL of 2.19 g/L MeOH/CH2Cl2 (10:3, v/v), 30 µmol) in MeOH/CH2Cl2 (100 mL; 10:3, v/v). Pump P2 was used for the solution containing imidazole-1-sulfonyl azide hydrochloride (2, 12.5 g, 60 mmol) and DIPEA (10.5 mL, 60 mmol) in MeOH/DCM (200 mL; 10:3, v/v). In contrast to the optimization setup, no quench pump was used because the residence time in the larger setup could easily be determined. In order to stop the reaction, the product was simply collected in a quenching solution, 1 M HCl in EtOAc/acetone (230 mL; 1:1, v/v). After collecting the product for 95 min, the reaction mixture was slowly concentrated under reduced pressure (max. 200 mbar in a 40 °C water bath) to 30 mL. Care should be taken during this process due to the low vapor pressure of benzyl azide. The residual yellow oil was filtered over silica (7 cm x 10 cm) using Et2O as the eluent. Bulk solvent was gradually removed under reduced pressure (600 mbar in a 40 °C water bath) up to 50 mL and the residual crude product was washed with 1 M HCl (3 x 50 mL) and brine (50 mL), dried over Na2SO4, filtrated and concentrated under reduced pressure (600 mbar in a 40 °C water bath). The remaining oil was then diluted with 15 mL Et2O and again washed with 1 M HCl (3 x 10 mL) dried over Na2SO4, filtrated and concentrated under reduced pressure (max. 180 mbar in a 40 °C water bath) to yield a solution of 993 mg (7.4 mmol) benzyl azide (3) in Et2O. This is in accordance with a calculated yield of 65% based on 1H NMR analysis.

2.5. Analysis

Off-line GC-analysis was performed with a Shimadzu gas chromatograph (GC-2010) equipped with a Quadrex 007 1701 column (length: 15 m; internal diameter: 0.1 mm; film thickness: 0.1 µm) and a flame ionization detector. An injector temperature of 250 °C and a detector temperature of 325 °C were employed. An initial column temperature of 80 °C for 0.5 min was followed by a temperature ramp of 80 °C/min for 2.25 min and a final temperature of 260 °C was maintained for 0.25 min. The total GC program took 3 min. The product sample obtained from the microreactor was collected in dichloromethane containing 2% cyclooctane as an external standard. Accurate flow rates were calculated using our recently developed flow marker methodology [27].

3. Results and discussion

3.1. Batch scale

The synthesis of benzyl azide (3) was investigated as a representative procedure for the synthesis of organic azides in microreactors (Scheme 1). Nyfeler et al. described the use of two catalysts, zinc chloride and copper sulfate [24]. In some cases, zinc chloride provided better results in yield and reaction time than copper sulfate. Since the difference in catalyst in our hands had no influence on the formation of benzyl azide (3), zinc chloride was chosen as catalyst for the diazotransfer reaction.

In order to ensure well-defined residence times in the continuous flow system, batch scale experiments were performed to develop a suitable quenching method. Adding a 1 M solution of hydrochloric acid in ethyl acetate/acetonitrile (1:1) to the reaction mixture was identified as an adequate method to quench the reaction.
Analysis of the samples was performed using a fast GC method (Section 2.5).

### 3.2. Microreactor system

Initial continuous flow experiments were performed using a water/methanol/dichloromethane (3:10:3) solvent system for both flows. Unfortunately, irreproducible GC yields were obtained probably due to high flow rate deviations. This might be caused by gas formation in the syringe containing solution B (imidazole-1-sulfonyl azide hydrochloride) due to high flow rate deviations. This might be caused by gas formation in the syringe containing solution B (imidazole-1-sulfonyl azide hydrochloride) which was confirmed by running NMR experiments at room temperature and 80 °C. A broad and robust optimal temperature range was found between 0 and 40 °C. This is practical for performing the reaction at production scale since no cooling or heating is required. Decomposition of diazotransfer reagent [2] earlier suggested implies the need of a large excess of this compound in order to obtain benzyl azide (3) in high yields. This is in compliance with the optimum found for the stoichiometric ratio, namely 3 to 4.

A third observation was a relatively long optimal residence time of around 600 s required to obtain the product in high yield. In addition, contour plot b showed a decrease in yield at long residence times (>700 s). However, the model fit shows a high uncertainty of the model in this time range. This region should therefore be ignored when making concluding remarks.

For each experiment performed in the optimization screening, an average of 6 mg of benzylamine (1) and 17.5 mg of diazotransfer reagent [2] was used. Consequently, less than 400 mg of benzylamine (1) and 1 g of imidazole-1-sulfonyl azide hydrochloride (2) was required to perform a sixty experiments multivariate reaction optimization.

### 3.4. Continuous flow on gram scale

Based on the results and data interpretation of the small scale multivariate optimization experiments, a gram scale experiment was performed using a Uniqsis FlowSyn reactor. The reaction was performed at room temperature; requiring no additional cooling or heating. Due to the slightly elevated temperature applied with respect to the optimal set in which 1.8 °C was found; a stoichiometric ratio of 4 was chosen. Furthermore, this stoichiometric ratio is less than in the optimal set to decrease production costs. For the synthesis of benzyl azide (3), a reaction temperature of 80 °C was chosen requiring a total flow rate of 2 mL/min in a stainless steel coil reactor of 20 mL. The crude product (3) was collected in 230 mL of quenching solution for 95 min. In order to perform the reaction 1.4 g benzylamine (1) and 4.2 g imidazole-1-sulfonyl azide hydrochloride (2) was required, an increase of more than 200 times compared to the optimization experiments. A validation experiment before the actual scale-up, including the use of inter-
nal standards, proved to have a GC yield of 97%. After the actual scale-up experiment and a batch work-up procedure, benzyl azide (3) was obtained as a 73% solution in diethyl ether according to $^1$H NMR (1.36 g, 65% isolated yield). Most likely, the relatively low yield is due to the low vapor pressure of benzyl azide (3) in combination with the need to evaporate the solvent(s) multiple times. For this reason, we refrained from completely evaporating the solvent.

4. Conclusion

In a small scale continuous flow setup, the reaction conditions for the conversion of benzylamine into benzyl azide were optimized. The optimization was performed using a semi-automated microreactor system and D-optimal-based design of experiment resulting in an optimal set the three reaction parameters varied. The optimal reaction conditions were identified to be room temperature, 600 s residence time and an imidazole-1-sulfonyl azide hydrochloride (2)/benzylamine (1) stoichiometric ratio of 3 to 4. In addition, we successfully scaled up the reaction by a factor of 200, resulting in the production of approximately 1 g of benzyl azide (3) per hour using one single flow reactor. Currently, we are extending this continuous flow method to a range of amines, including incorporation of follow-up reactions in the same microreactor. Furthermore, we are aiming at integrating work-up steps in the same reactor.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cej.2010.08.087.

References

[29] This software is commercially available from FutureChemistry.