

Application Note 9.4

Synthesis of azides from halides



In general, the synthesis of azides is dangerous, as the compounds tend to decompose violently under pressure or raised temperature. A closed microreactor system is therefore the preferred alternative over conventional batch-wise production. The azide substitution reaction was successfully translated from batch to continuous flow in the *FlowStart Evo* microreactor platform, providing a viable alternative to the conventional batch process.

Introduction

The synthesis of azides is a key reaction in organic chemistry, as it provides a good pathway towards triazoles through the Huisgen azide-alkyne cycloaddition. Traditionally, this reaction is carried out using a variety of azide reagents, such as triflyl azide and TMS-azide, which are both explosive and can release the toxic gas hydrazoic acid.

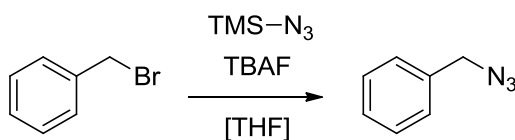


Figure 1: Azide substitution on model substrate using trimethylsilyl azide

In general, azide chemistry is dangerous: depending on substrate, reagent, temperature etc., azides can decompose violently. To be able to handle these potentially explosive compounds in a closed system, FutureChemistry has translated this reaction from a batch process to a continuous flow process. FutureChemistry's typical three-tier approach led to a protocol which can be adapted to any viable amine substrate:

- 1) Translation of batch process to continuous flow process:
 - a) Stock solutions approach, yielding a homogeneous reaction mixture.
 - b) Quenching solution to follow the reaction in time.
- 2) Automated reaction optimisation.
- 3) Out scaling to preparative synthesis.

This *application note* describes the translation of the batch process to the continuous flow process using the *FlowStart Evo B-401*.

Batch to flow conversion

In contrast to batch chemistry, reactions in continuous flow are conducted from stock solutions. These solutions should remain inactive after preparation, but react when combined. In the azide synthesis, solution A contains the halide substrate, solution B contains the tetrabutylammonium fluoride, solution C contains the trimethylsilyl azide and solution Q contains the quenching agent. Solutions A and B are premixed in a T-piece before entering the microreactor. The used flow setup is depicted in Figure 2.

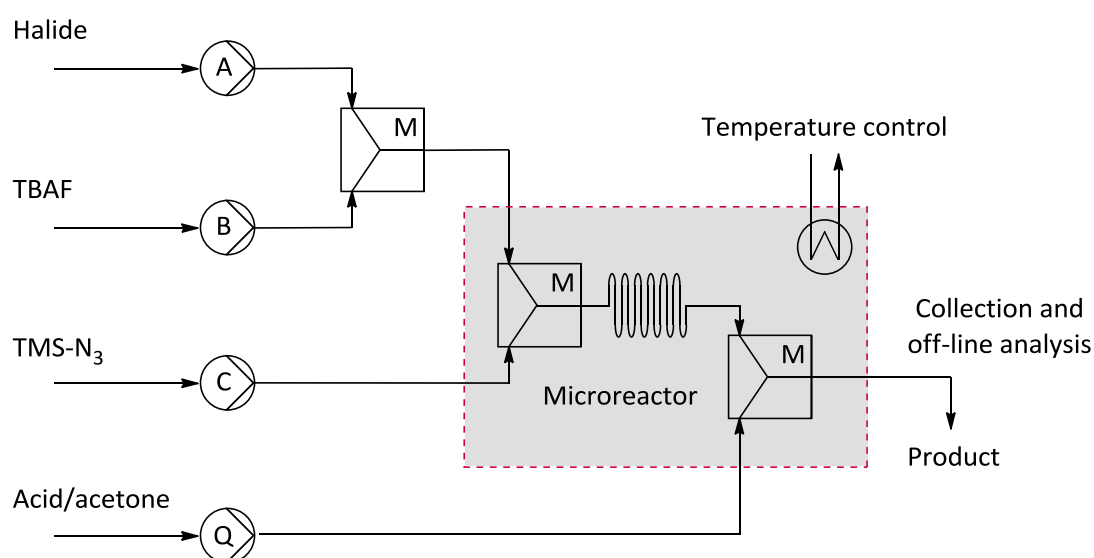


Figure 2: FlowStart Evo setup

To stop the reaction at a certain point in time a quenching agent is needed, which is many times faster than the reaction itself. In the azide synthesis, the tetrabutylammonium fluoride is neutralised with hydrogen chloride and the formed hydrazoic acid is captured with acetone.

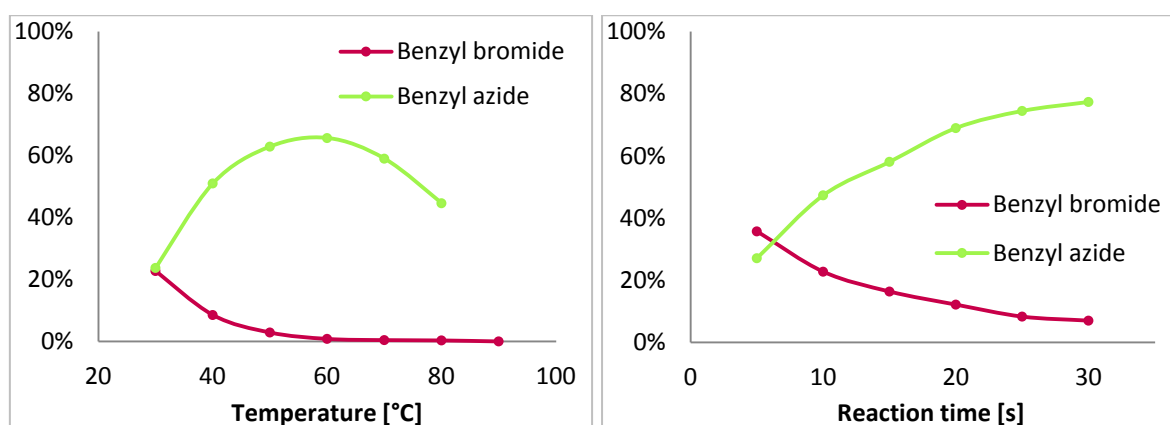


Figure 3: Univariate screening of benzyl azide synthesis.

Left: Product and substrate vs. temperature (azide stoichiometry 1.1, reaction time 10 s)

Right: Product and substrate vs. reaction time (azide stoichiometry 1.1, temperature 40°C)

In the *FlowStart Evo* experiments, temperature and reaction time were varied. With the above parameter values, yields up to 70% were observed (Figure 3), and the azide synthesis was successfully converted from batch to flow.

Method

All experiments were conducted in a standard FutureChemistry *FlowStart Evo* B-401 setup. The microreactor used was custom made with dimensions: L 45 mm, W 15 mm, H 2.2 mm, channel dimensions: L 1325 mm, H 55 μ m and internal volume of 7.02 μ L. Benzyl bromide was used as model substrate.

Solution A (0.74 M): Benzyl bromide (1.27 g, 7.4 mmol) dissolved to a total volume of 10 ml tetrahydrofuran

Solution B (1.0 M): 1.0 M Tetrabutylammonium fluoride in tetrahydrofuran (commercial grade)

Solution C (0.4 M): Trimethylsilyl azide (461 mg, 4.0 mmol) dissolved to a total volume of 10 ml tetrahydrofuran

Solution Q (0.5 M): Solution of hydrogen chloride in ethyl acetate (approx. 1 M)/acetone (1:1)

Four glass 1.0 mL syringes were loaded with solutions A, B, C and Q respectively. For each experiment, the desired flow rates were calculated according to the following equations:

$$\text{Total flow} = \text{microreactor volume} / \text{reaction time}$$

$$\text{Flow A} = \text{total flow} / (1 + 2 * (\text{azide stoichiometry}))$$

$$\text{Flow B} = \text{Flow C} = 0.5 * \text{Flow Q} = \text{Flow A} * \text{azide stoichiometry}$$

All product mixtures were analysed with GC, with retention times according to Table 1. Analysis was performed on a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (L 15.0 m, ID 0.10 mm) and flame ionisation detector, using a temperature program (0-2.0 min 40°C, 2.0-9.0 min 40-75°C, 9.0-10.0 min 75-100°C, 10.0-11.0 min 100-200°C) and 4.0 μ L injection with split ratio 200.

Table 1: GC analysis retention times

Compound	Function	Retention time [min]
benzyl bromide	substrate	8.13
benzyl azide	product	8.32