Organic azide synthesis in microreactors: from optimization to lab scale production

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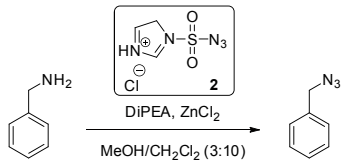
Organic azides play an increasingly important role in the chemical industry[1]. Because azides are prone to explosive decomposition[2], production and handling must proceed with great caution. Flow chemistry offers a benefit in the production phase, because better heat and concentration control avoid building up of hot spots[3]. Furthermore, the technology is ideal for reaction screening, since it allows testing of reaction parameters in a fast and efficient way. In this study, formation of benzyl azide by diazotransfer to benzyl amine was screened and subsequently scaled up using continuous flow chemistry.

Benzyl azide synthesis

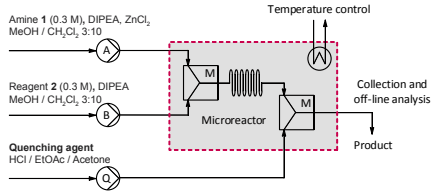


We investigated the synthesis of benzyl azide (3) as a general procedure for the synthesis of organic azides in flow. Benzyl azide was prepared from benzyl amine (1) in a diazotransfer reaction. Imidazole-1-sulfonylazide hydrogen chloride (2) was used as diazotransfer reagent. This reagent was synthesised according to literature procedure[4].

Step 1: Batch scale

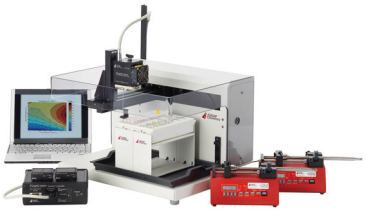
A quenching method to stop the reaction was developed to ensure well-defined reaction times in a continuous flow system. Hydrochloric acid in ethyl acetate and acetone was found to be an adequate quenching agent. Furthermore, a fast GC analysis method was developed.

Step 2: Continuous flow system



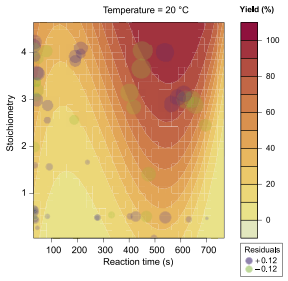
Experimental conditions for continuous flow were determined. A methanol/dichloromethane mixture was used as a solvent. Trial runs were performed to ensure robust behaviour of the liquids in the flow system. The ranges of parameters to be optimised were determined in single variate experiments.

Step 3: Optimisation in a microreactor system



FutureChemistry's *Flow*Screen automated optimisation setup was used.[4] The system was equipped with glass microreactors with volumes of 7.0 and 92 µL in order to cover a wide range of reaction times.

Step 4: Data processing



Parameters screened:
- Temperature: 0 - 70 °C
- Reaction time: 30 - 600 s
- Reagent stoichiometry: 0.5-3.5

Number of experiments: 60

Optimal parameters
(97 % yield based on GC):

Temperature: 20 °C
Reaction time: 600 s
Reagent stoichiometry: 4.6
Total flow: 2 mL/min

Step 5: Lab scale continuous flow

The reaction was performed in a Uniqsis *Flow*Syn continuous flow system. Optimal parameters, established in step 4, were used.

Total yield of azide: 1.45 g
(80% isolated yield, workup procedure not optimised)

Total run time: 95 min

Conclusions

The diazotransfer reaction could easily be translated to flow chemistry. Optimal conditions for the reaction were obtained using small scale, automated microreactor hardware, and were successfully used to perform a lab scale flow experiment.

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[2] J.H. Boyer, R. Moriarty, Darwent. B. de B., P.A. Smith, Handle Azide Compounds with Caution, *J. Chem. Eng. Data*. 9 (**1964**) 480.
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