Application Note

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Online LC Reaction Monitoring of Radical Bromination of an Aromatic Sulfonyl Chloride

Monitoring of a flow chemistry reaction by the Agilent InfinityLab Online LC Solution

Authors

Conor Burke, Hajeeth Thankappan, Melba Simon, and Brian Glennon
APC Ltd.
Dublin, Ireland

Edgar Naegele and Daniel Kutscher
Agilent Technologies, Inc.
Waldbronn, Germany

Abstract

This application note demonstrates the connection of the Agilent InfinityLab Online LC Solution with a flow chemistry reactor system. The fast and highly precise sampling by the Agilent 1260 Infinity II Online Sample Manager allows users to monitor reactions in real time and change reaction parameters as needed. The Agilent Online LC Monitoring Software offers full control for sampling and analysis. This setup enables complete automation of experiment monitoring in a safe and economic way.

Introduction

For the final synthesis of modern complex small molecule pharmaceutical compounds, the effective synthesis of so-called building blocks is important. Classically, they are produced in reaction vessels batch-by-batch. A significant improvement is possible if these compounds can be produced in a continuous way by flow reaction chemistry.

Flow reaction chemistry offers a more economical way to generate small molecule compounds. To keep a constantly high yield and high product quality, continuous monitoring of the reaction is necessary.

This application note describes the use of the Agilent InfinityLab Online LC Solution to monitor a flow chemistry reaction. As an example, the radical bromination of 4-methylbenzenesulfonyl chloride was chosen. The products include the desired 4-(bromomethyl) benzenesulfonyl chloride and an unwanted dibrominated by-product (Figure 1).[1]

The Agilent Online LC Monitoring Software orchestrates the online analysis of the experiment. With the resulting data, the reaction can be optimized to maximize the desired product yield.

Experimental

Instrument

- Agilent 1290 Infinity II High-Speed Pump (G7120A)
- Agilent 1260 Infinity II Online Sample Manager Set (G3167AA): Agilent 1260 Infinity II Online Sample Manager (G3167A) clustered with external valve (part number 5067-6680) located at the Agilent 1290 Infinity Valve Drive (G1170A) and Agilent Online LC Monitoring Software
- Thermostat for 1260 Infinity II Online Sample Manager (G7167-60005)
- Agilent 1290 Infinity II Multicolumn Thermostat (G7116B) with Agilent InfinityLab Quick Connect heat exchanger, standard flow (part number G7116-60051)
- Agilent 1290 Infinity II Diode Array Detector (G7117B) with Agilent InfinityLab Max-Light Cartridge Cell, 10 mm (part number G4212-60008)

Software

- Agilent OpenLab CDS, version 2.6 or later
- Agilent Online LC Monitoring Software, version 1.0

Column

Helix Chromatography Heritage MA mixed-mode column, 4.6 × 50 mm, 5 µm

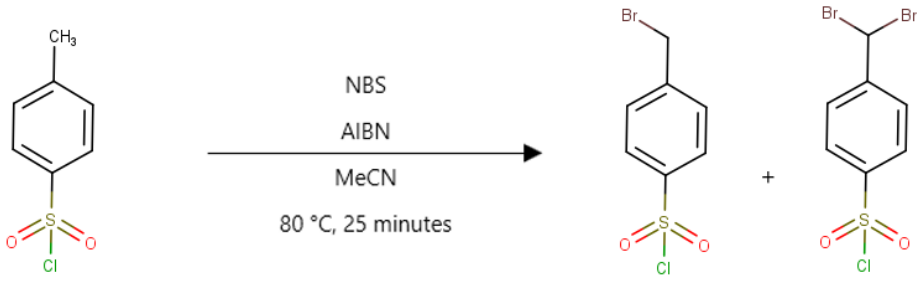

Figure 1. Radical bromination of the educt 4-methylbenzenesulfonyl chloride (1) to the product (2) and the dibrominated impurity (3). NBS refers to N-bromosuccinimide, AIBN to 2,2'-azobis(isobutyronirtile), and MeCN to acetonitrile.

Analytical method

Parameter	Value
Solvents	A) 80 mM ammonium formate in water/acetonitrile 70/30 (pH 3) B) acetonitrile
Analytical Flow Rate	1 mL/min
Gradient	Time (min) %B 0 5 5 50 5.01 5 6 5
Stop Time	7 min
Column Temperature	55 °C
Flowthrough Injection	Draw speed: 100 µL/min Eject speed: 400 µL/min Wait time after draw: 1.2 s
Sample Volume	3 µL
Needle Wash	3 s, water/acetonitrile 50/50 (S1)
Sampling	See sampling method
Diode Array Detector	255 ± 4 nm, Ref. off, data rate 2.5 Hz

Sampling method from reactor stream

Parameter	Value
Draw Speed	Setting 2 (draw speed 100 µL/min, wait time 3.6 s)
Target Volume	800 µL
Dilution Factor	100
Dilution Speed	10,000 µL/min
Dilution Solvent	S1, water/acetonitrile 50/50
Sampling Interval	Samples were collected in the region of approximately 30 seconds to one- or two-minute intervals (varying at times due to the rate of a given experiment).

- Samples were vialed and banked in the tray and then immediately injected in sequential order.
- Injection intervals were governed by the bromination LC method run time (approximately a seven-minute turnaround between injections to allow column equilibration from the steep organic gradient between injections).

Flow chemistry reaction

The applied Vapourtec R-Series modular flow chemistry system consisted of an R2 pumping module with two pumps and an R4 flow reactor heater/cooler module with a heated flow capillary (Figure 2).[2]

Solvents and chemicals

- All solvents were purchased from Merck, Germany.
- Chemicals were purchased from VWR, Germany.
- Fresh ultrapure water was obtained from a Milli-Q Integral Water Purification System equipped with LC-Pak polisher and a 0.22 µm membrane point-of-use cartridge (Millipak).

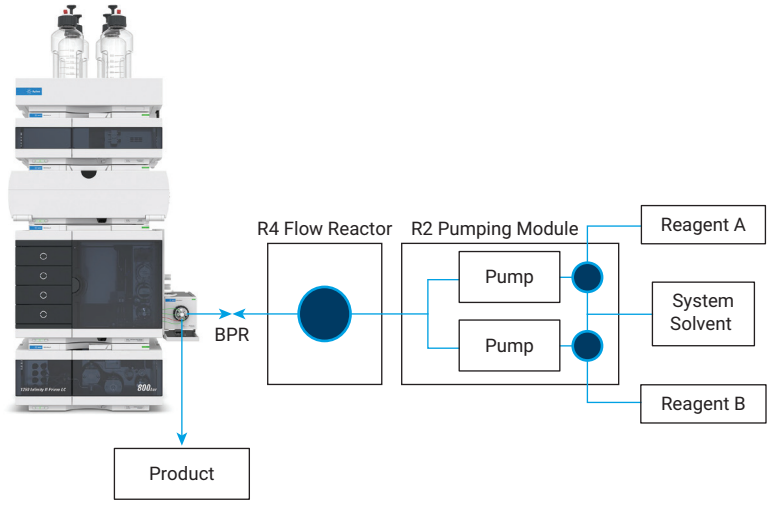

Figure 2. Schematic of the Vapourtec R-Series modular flow chemistry system connected to the Agilent InfinityLab Online LC Solution. BPR refers to the backpressure regulator.

Results and discussion

For the monitoring of the described flow chemistry reaction, a short 5 minute chromatographic separation with a total run time of 7 minutes including reconditioning was developed (Figure 3). This method was able to separate the product from starting material, which was challenging due to the similarities in their chemical properties (Figure 1). In addition, by-products from additional bromination could have been generated and therefore also had to be separated.

For the optimization of the product yield during the flow chemistry reaction, different conditions and reagent concentrations were applied to the chemical reaction. The amount of the bromination reagent (NBS), the molar equivalent of the radical reaction starter (AIBN), the residence time in the flow reactor, and the reaction temperature were varied under flow mode, and the resulting changes were monitored.

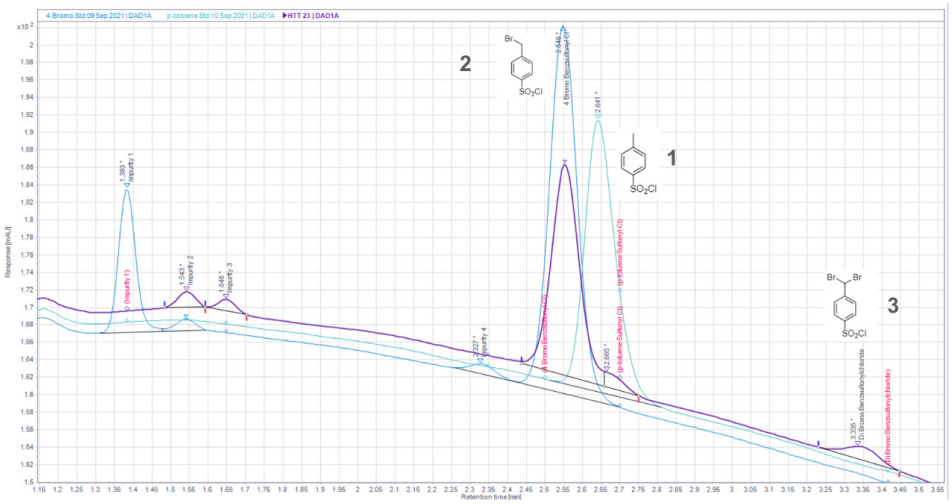

Figure 3. Separation of the educt 4-methylbenzenesulfonyl chloride (1, RT = 2.653 min) and the product 4-(bromomethyl)benzenesulfonyl chloride (2, RT = 2.554 min) of the radical bromination reaction. In addition, some impurities (3) and succinimide can be separated. The overlay shows the reaction mixture (purple), educt (turquoise), and product standard (blue).

With an increasing concentration of the bromination reagent, an increase in conversion to the product could be achieved (Figure 4). At a concentration of 0.5 M NBS, the conversion to the desired product (2) reached a maximum at 86%, which was determined by HPLC measurement. Further NBS concentration increase declined the product conversion and instead increased the content of the by-product (3) achieved from a dibromination reaction.

The effect of the reaction temperature on the conversion was examined by increasing the reaction temperature. The conversion to the product (2) reached a maximum of 86% conversion at a reaction temperature of 80 °C. At that level, the conversion to the dibromide by-product was at 7%, which increased with further increase of the reaction temperature (Figure 5).

The effect of decreasing the AIBN below 0.1 eqv. leads to a decrease in product formation and an increase in residual starting compound (Figure 6). On the other hand, the by-product of a dibromination at the methyl group starts to increase for higher equivalents of AIBN.

The last parameter of the flow chemistry reaction that was varied was the residence time in the flow reactor. The residence time was varied from 2.5 to 25 minutes. The maximum conversion to the desired product was 86%, which was achieved with a residence time of more than 10 minutes. The formation of the dibromide impurity (3) was only 7% under these conditions (Figure 7).

To find a preferred reaction mode, the achieved conversion was compared between flow reaction conditions and batch reaction conditions (Table 1).

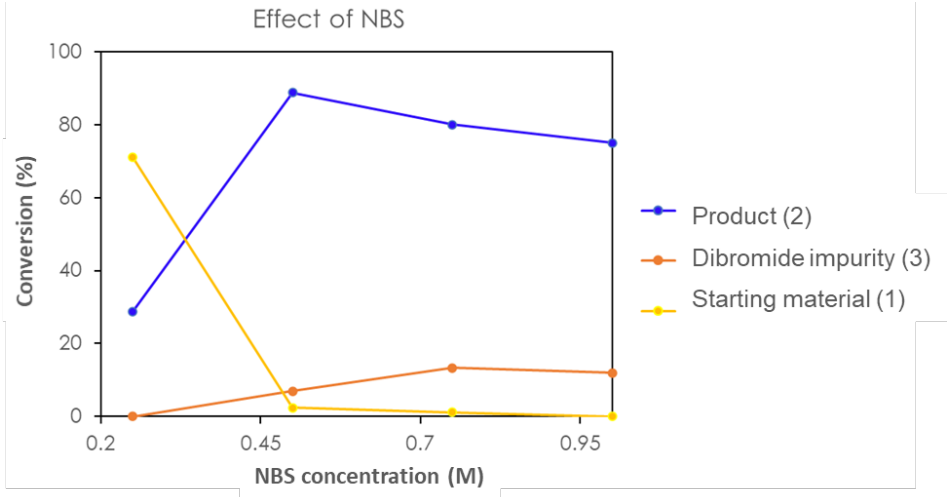

Figure 4. Influence of NBS concentration on product yield. Product conversion increases with higher NBS concentration (up to 0.5 M). Further increase in NBS concentration leads to formation of the dibromide impurity (3) and a decline of the product. Other reaction conditions include: 0.5 M starting material (1), 80 °C temperature, 0.047 M AIBN (0.1 eqv.), and 25 min residence time.

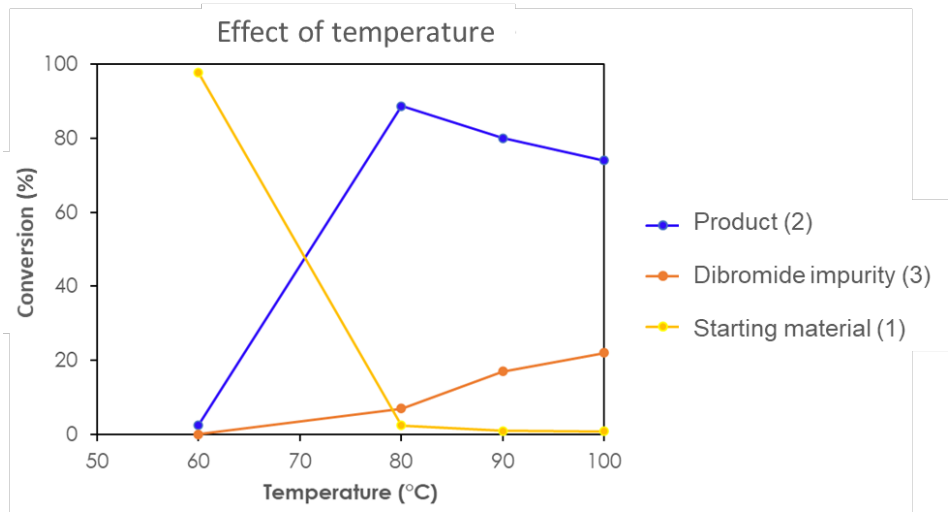

Figure 5. Influence of reaction temperature on product yield. Maximum conversion is achieved at 80 °C with the absence of the educt 4-methylbenzenesulfonyl chloride (1). Increasing conversion to the dibromide impurity is observed at temperatures higher than 80 °C. Other reaction conditions include: 0.5 M starting material (1), 0.5 M NBS, 0.047 M AIBN (0.1 eqv.), and 25 min residence time.

Table 1. Comparison of the radical bromination reaction under flow chemistry reaction conditions and batch reaction conditions.

Mode	Educt (1)(M)	NBS (M)	AIBN (eqv.)	Res. Time (min)	Conv. (%) by HPLC	Impurity (3)(%)	Yield (%)
Flow	0.5	0.5	0.1	12	86	6.57	68
Batch	0.5	0.5	0.1	300	45	28	48

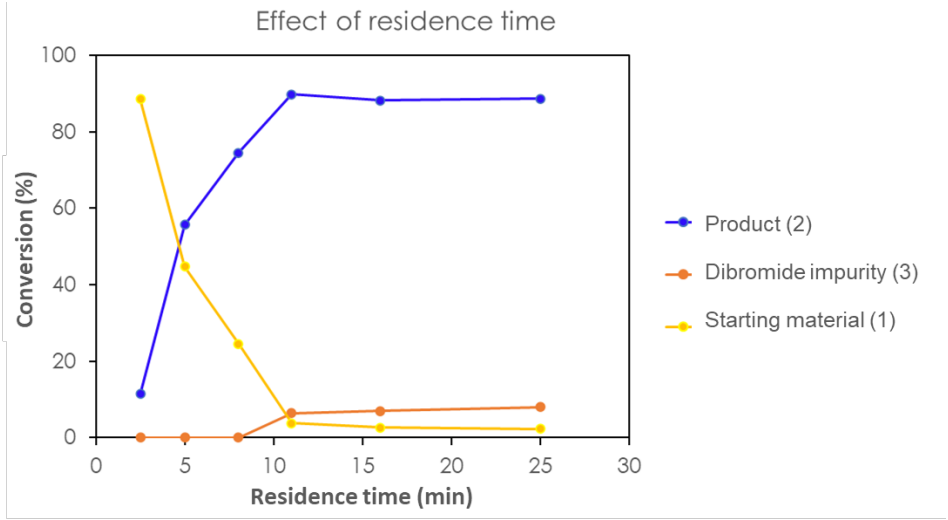

Figure 6. Effect of AIBN on the conversion of the educt. Decreasing AIBN below 0.1 eqv. leads to a decrease in product formation and an increase in residual starting compound. Other reaction conditions include: 0.5 M starting material (1), 80 °C temperature, 0.5 M NBS, and 25 min residence time.

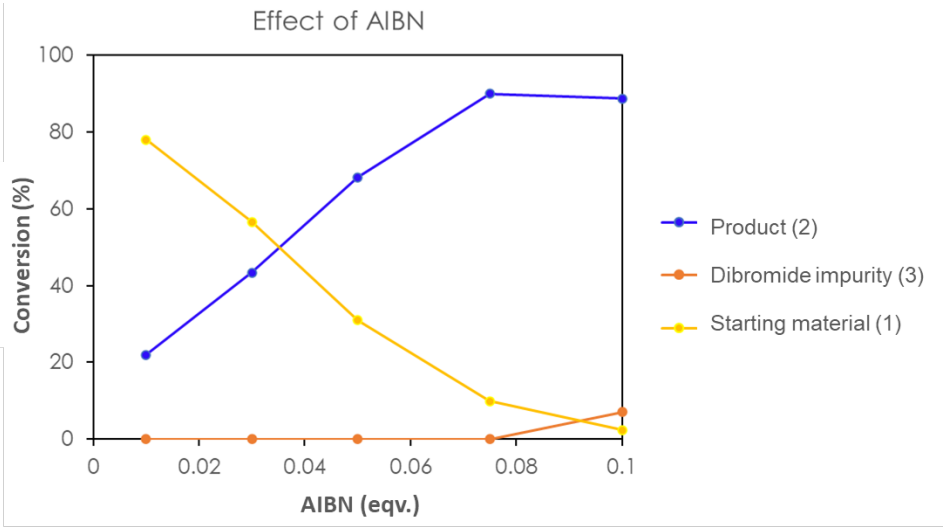

Figure 7. Effect of residence time in the flow reactor on product yield. The maximum conversion was achieved at more than 10 minutes with 86% conversion to the desired product (2). Other reaction conditions include: 0.5 M starting material (1), 80 °C temperature, 0.047 M AIBN (0.1 eqv.), 0.5 M NBS, and residence time varied from 2.5 to 25 min.

The optimized flow chemistry reaction showed a conversion of 86% with a 10 minute flow reactor residence time, while the batch reaction showed 45% of the desired product in a reaction time of 5 hours.

Conclusion

This application note demonstrates the use of the Agilent InfinityLab Online LC Solution with a flow chemistry reactor for continuous bromination of an arylsulfonyl chloride by a radical reaction. The Online LC System was used to determine the optimal reaction conditions to maximize the desired brominated product yield. With the Agilent InfinityLab Online LC Solution and the Agilent Online LC Monitoring Software, the experiment can be controlled in an automated way under safe and economic conditions. The highly precise and fast sampling capabilities of the Agilent 1260 Infinity II Online Sample Manager enable direct injection and sampling of the flow reactor effluent to characterize and optimize the reaction parameters for optimal yield.

References

1. Gensini, M; *et al.* Solvent Dependent Benzylic Radical Bromination of Aromatic Sulfonyl Chlorides. *Letters in Organic Chemistry* **2006**, *3(3)*, 191–194.
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