

On-line monitoring of continuous flow chemical synthesis using a portable, small footprint mass spectrometer

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Introduction

For on-line monitoring of chemical reactions (batch or continuous flow) mass spectrometry (MS) can provide data to (i) determine the fate of starting materials and reagents, (ii) confirm the presence of the desired product, (iii) identify intermediates and impurities, (iv) determine steady state conditions and (v) speed up process optimisation. Recent developments in portable mass spectrometers further enable this coupling as the MS system can be positioned with any reaction system to be studied. A major issue for this combination is the transfer of a sample that is representative of the reaction and also compatible with the mass spectrometer. This is particularly challenging as high concentrations of reagents and products can be encountered in organic synthesis. The application of a portable mass spectrometer for on-line characterisation of flow chemical synthesis has been evaluated by coupling a Microsaic 4000 MiD to the Future Chemistry Flow Start EVO chemistry system.

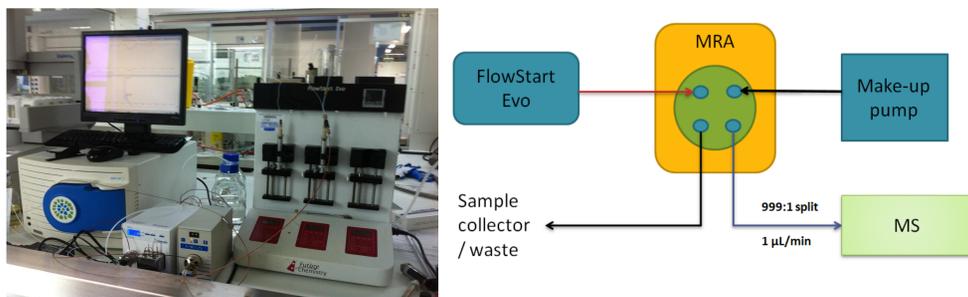


Figure 1: Photograph showing the combination of the Microsaic 4000 MiD coupled to the Flow Start EVO and a schematic diagram of the experimental set-up.

Experimental

The potential of this approach was investigated using the Hofmann rearrangement shown in Figure 2.



Figure 2: A generic representation of the Hofmann Rearrangement.

A number of flow chemistry and MS experimental parameters were varied and their effect monitored on-line using the 4000 MiD MS.

Flow Reaction conditions:

20°C, 30°C, 40°C, 50°C, 60°C, 70°C and 80°C (data acquisition time for each temperature was on average 6 minutes).

The reaction was studied with and without the HCl quench.

Reaction flow rates: Reagent 1 = 49.9 µl/min and Reagent 2 = 50.1 µl/min.

MS Conditions:

Composition of the make-up flow (1 ml/min):

- MeCN: H₂O (50: 50) + 0.1% formic acid.
- H₂O: MeCN (80: 20) + 0.1% formic acid.
- MeCN: H₂O (50: 50) + 0.05% TFA.

Sample dilution factors: 1000:1, 500:1, 250:1, 100:1.

Results and discussion

(i) On-line monitoring of the formation of the isocyanate intermediate.

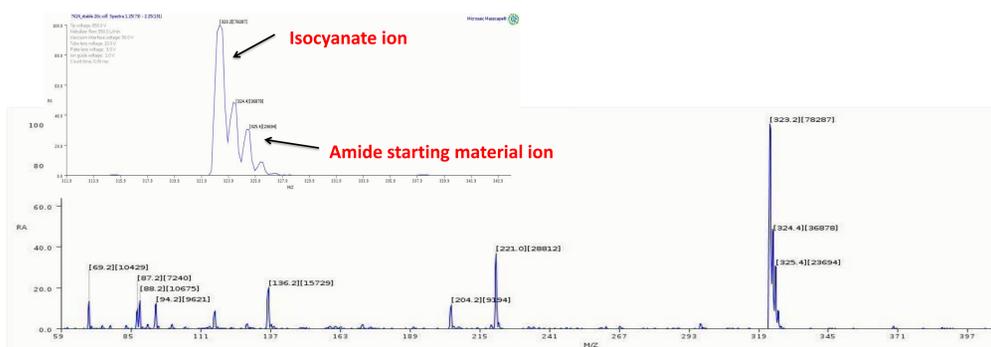


Figure 3: Mass spectra from on-line monitoring of the formation of the isocyanate intermediate (m/z 323) at a reaction temperature of 20°C and recorded using a make-up flow of MeCN: H₂O (50:50) + 0.1% HCOOH.

Acknowledgements

Our sincere thanks go to Bryan McCullough and Alessio Zammataro at Microsaic for their excellent support and advice throughout this project.

The consumption of the amide starting material as a function of reaction temperature is shown in Figure 4, which illustrates that steady state reaction conditions were established.

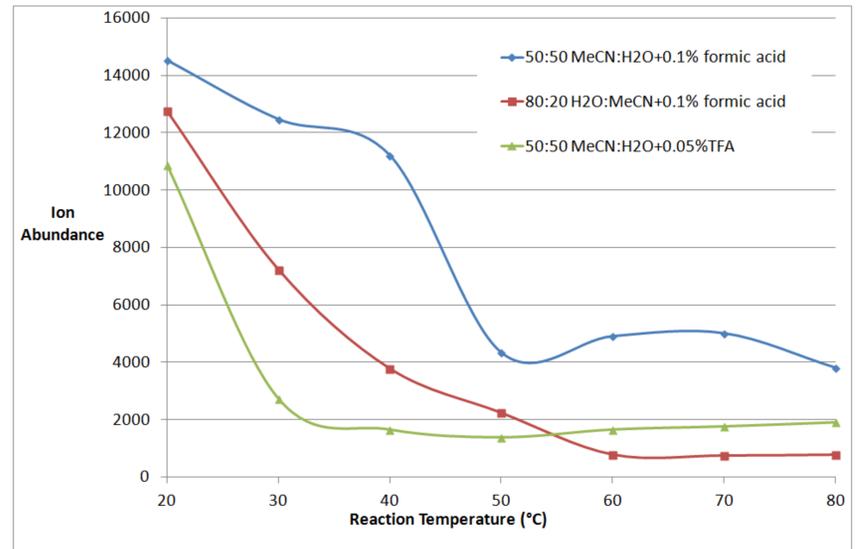


Figure 4: Plots of the abundance of m/z 325 (amide starting material ion) as a function of reaction temperature and using different make-up flow compositions (1000:1 sample dilution).

(ii) On-line monitoring of the formation of the amine product.

The formation of the amine product following an in-line HCl reaction quench was also monitored on-line by MS. Figure 5 shows two representative mass spectra which contain both product and impurity ions.

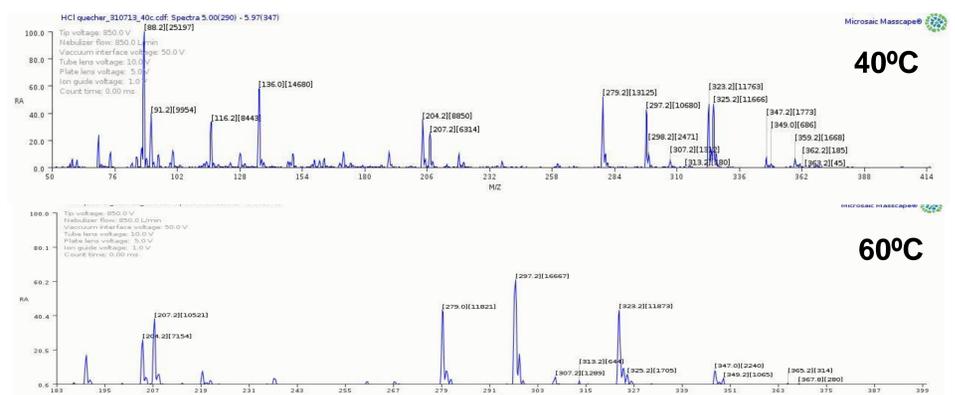


Figure 5: Mass spectra from on-line monitoring of the reaction at temperatures of 40°C and 60°C, recorded using a make-up flow of H₂O:MeCN (80:20) + 0.1% HCOOH

Figure 6 shows the formation of the amine product (m/z 297) and consumption of the amide starting material (m/z 325) as a function of reaction temperature.

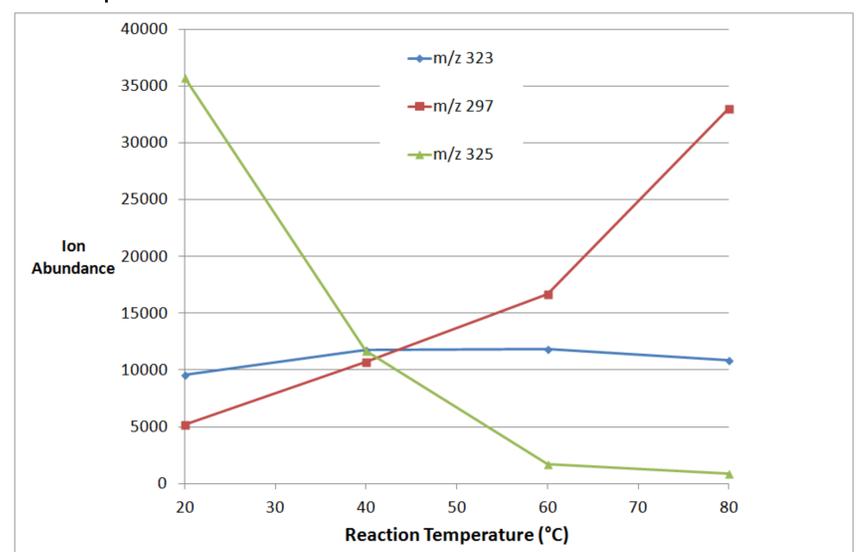


Figure 6: Plots of the ion abundance of m/z 325, m/z 323 and m/z 297 as a function of reaction temperature using a make-up low of H₂O:MeCN (80:20) + 0.1% HCOOH.

Conclusion

The Microsaic 4000 MiD MS has been successfully coupled to the Flow Start EVO chemistry system for on-line monitoring of the Hofmann Rearrangement reaction. The data was used to identify the optimum reaction temperature and the impurities formed in real time.