



On-line flow reaction monitoring of a Wittig reaction using deployable mass detection

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INTRODUCTION

Syrris and Microsaic Systems, both R&D 100 award winning companies, have set up a flow reactor coupled to a mass spectrometry (MS) system to demonstrate all the benefits of using on-line flow reaction monitoring.

For on-line monitoring of flow chemical reactions, MS can be used to analyse in real-time the chemical composition of the flow stream in order to optimize transformations. This specific work-flow provides data to monitor starting materials, identify the presence of reactive transients and impurities, determine steady state conditions of the reaction and optimize transformation improving yield, purity and reaction selectivity. Moreover, flow synthesis offers many advantages compared to batch synthesis particularly when applied to processes which are difficult or have dangerous chemical transformations.

In this application note we report the on-line reaction monitoring of the Wittig reaction of 2-nitrobenzyl-triphenylphosphonium bromide with methyl-4-formylbenzoate using Microsaic 4000 MiD[®] mass detector and Syrris Asia flow chemistry system.

EXPERIMENTAL

The on-line characterisation of the Wittig reaction has been carried out by coupling the Microsaic 4000 MiD[®] mass detector to the Syrris Asia flow chemistry system through MiDas[™] interface module (Figure 1).

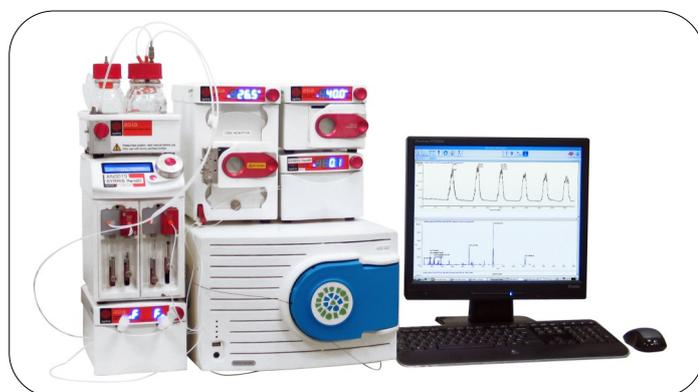


Figure 1. Schematic representation of Microsaic 4000 MiD[®] and Syrris Asia flow chemistry system.

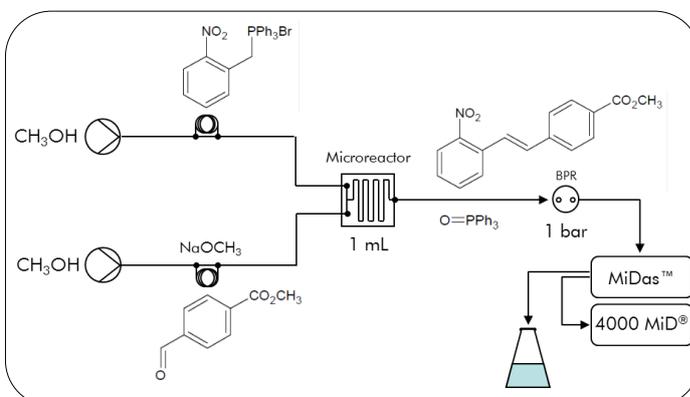
The time taken from installing and connecting the Microsaic 4000 MiD[®] to the Asia flow reactor system to acquiring meaningful data was less than 1 hour. Using a similar set up with a conventional MS system would take anything from 2 to 5 days.

The Wittig reaction was analysed in real-time acquiring in full scan with the mass spectrometer settings reported in Table 1.

Scan mode	Full scan
Mass Range	<i>m/z</i> 80 – 800
Scan Rate	1 Hz
Step size	<i>m/z</i> 0.2
Ion polarity	Positive (ESI)
Tip voltage	850 V
Gas flow	2500 mL/min
Vacuum interface	50 V
Tube lens	10 V
Plate lens	5 V
Ion guide	1 V

Table 1. Microsaic 4000 MiD[®] settings for on-line flow reaction monitoring.

The Wittig reaction of 2-nitrobenzyl-triphenylphosphonium bromide with methyl-4-formylbenzoate (Scheme 1) was carried out under different flow reaction temperatures (from 5 to 60 °C) using the instrument set up reported in Table 2.



Scheme 1. Flow route for the synthesis of methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate.

Bringing mass spectrometry down to size

Reactor	Two input microreactor
Reactor size	1 mL
Pressurization module	1 bar
Mobile phase A and B	Methanol
Flow rate A and B	0.5 mL/min
Reagent A	596 mg of 2-nitrobenzyl-triphenylphosphonium bromide in 12 mL of methanol
Reagent B	216 mg of methyl-formylbenzoate and 2.64 mL of 0.5 M sodium methoxide in 9.36 mL of methanol
Injection volume	0.25 mL (per each reagent)
Make-up pump solvent	Acetonitrile, 0.1% formic acid
Make-up pump flow rate	1 mL/min
Split ratio	3000:1

Table 2. Flow reactor-MS set up for the Wittig reaction of 2-nitrobenzyl-triphenylphosphonium bromide.

RESULTS AND DISCUSSION

The reaction expected is shown in the Figure 2, where 2-nitrobenzyl-triphenylphosphonium bromide (1) is deprotonated by sodium methoxide (2) to generate the phosphonium ylide (3), an intermediate strongly coloured in pink/purple. The ylide reacts then with the methyl-formylbenzoate (4) to yield methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate (5) and triphenylphosphine oxide (6) as reaction products.

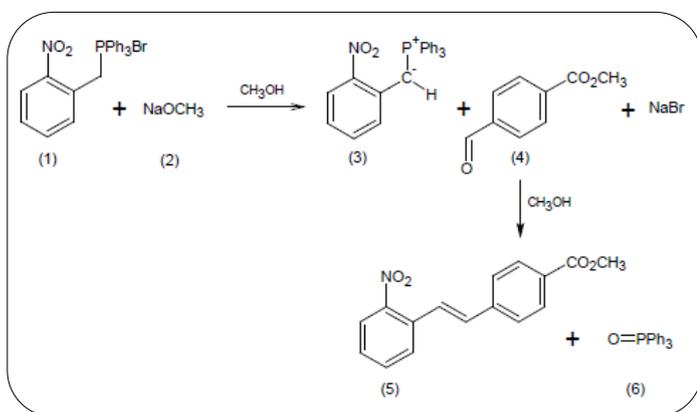


Figure 2. Reaction scheme for Wittig reaction.

After loading the reagents into the flow reactor loops, the reaction is started by changing both reagent loops to the inject position. After a brief pause caused by the time taken to flow from the loop to the visible portion of the microreactor, a pink/purple colouration was seen gradually filling the reactor from the bottom. The rate limiting step of this reaction is the ylide reacting with the methyl-formylbenzoate and the pink colour therefore fades as the reactants reach the top of the reactor. Eventually, the reaction should reach the equilibrium where the pink colour is the strongest at the bottom of the reactor and completely clear at the top. If the temperature of the reactor is increased the rate of the reaction will increase and therefore the intermediate ylide along with its colouration visible on the reactor should fall.

Figure 3 shows the mass spectrum of both reaction intermediate (phosphonium ylide at m/z 398.6) and products ions (methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate adduct with acetonitrile and ammonium at m/z 342.4 and triphenylphosphine oxide at m/z 279.4) at a reaction temperature of 20 °C.

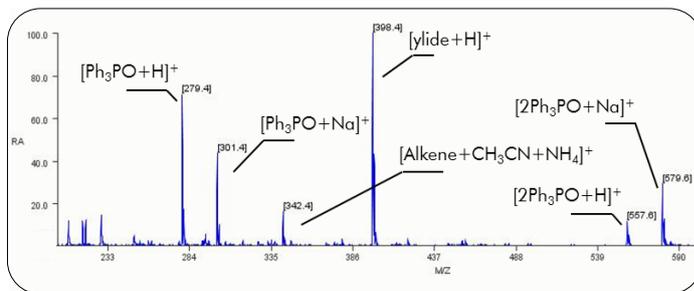


Figure 3. Mass spectrum of protonated phosphonium ylide at m/z 398.4, methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate adduct with acetonitrile and ammonium at m/z 342.4 and protonated triphenylphosphine oxide at m/z 279.4 from on-line monitoring of the reaction at 20 °C. Typical sodium adducts of triphenylphosphine oxide and its dimer are also shown.

Figure 4 shows the formation of the product (methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate, m/z 342.4) and by-product (triphenylphosphine oxide, m/z 279.4) and consumption of the intermediate (phosphonium ylide, m/z 398.4) as a function of the reaction temperature. The temperature profile was obtained in less than two hours from initial experimental set up, reducing significantly the associated costs off-line analysis usually more time consuming. Data was used to identify the optimum reaction temperature, monitor the intermediate and impurity generated in real-time.

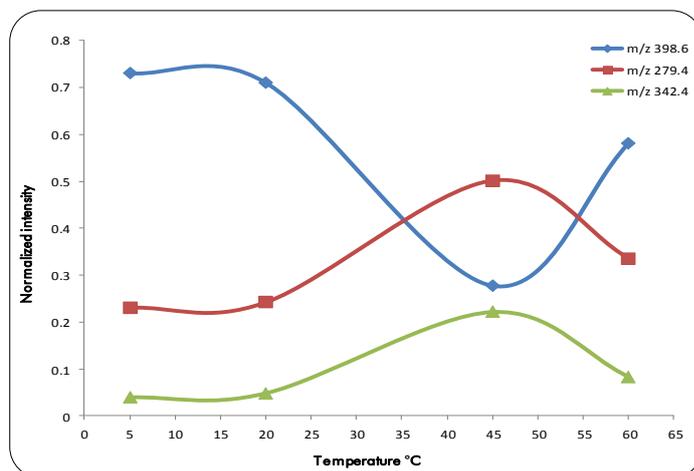


Figure 4. Normalised ion abundance of methyl 4-[(E)-2-(2-nitrophenyl) ethenyl] benzoate (m/z 342.4), triphenylphosphine oxide (m/z 279.4) and phosphonium ylide (m/z 398.4) as a function of the reaction temperature

CONCLUSIONS

With the results presented in this application note, Microsaic Systems and Syrris have successfully demonstrated all the great advantages of using a miniaturised mass detector for on-line flow reaction monitoring.

On-line flow reaction monitoring using the Microsaic 4000 MiD® and Asia flow reactor system has generated instant data used to detect (un)stable intermediates, (by)products, monitor impurities in real-time and optimise the Wittig reaction improving yield and selectivity. Finally, the benefit of using the Microsaic 4000 MiD® to decrease the time to reaction optimisation is clearly apparent since there was no delay waiting for off-line analysis results.