COMPACT MASS SPECTROMETRY: A COMPLETE REACTION MONITORING SOLUTION

WHITEPAPER

MS Method: expression CMS

Advion, Inc.

Advion's expression Compact Mass Spectrometer (CMS) addresses the need for organic and synthetic chemists to understand the optimal time to quench a reaction mixture. The CMS fully integrates with the industry's broadest range of innovative sampling technique allowing chemists to obtain answers within minutes or even seconds.

REAL-TIME REACTION MONITORING ANSWERS

Reaction monitoring is a key aspect in a range of chemistry environments from chemical synthesis to drug discovery to understanding natural products to protein synthesis. Understanding the optimal time to quench a reaction for maximum yield, as well as monitoring a reaction in real-time are vital to many medicinal and synthetic organic chemists. Advion's expression CMS was developed with the chemist in mind to optimize their workflow directly at the bench. It is an easy-to-use and maintain single quadrupole detector that integrates with the industry's broadest range of innovative sampling techniques from direct probe analysis to ultra-high performance liquid chromatography. Users can rapidly switch between the many different sampling techniques required throughout the chemist's workflow.

APPLICATION: REAL-TIME MONITORING OF A SUZUKI REACTION VIA LC/CMS AND FIA

Medicinal chemists are routinely faced with personally synthesizing over a hundred new chemical entities (NCEs) each year for testing as future pharmaceutical drug candidates. The goal is to prepare a high-yield, relatively pure product via an optimized synthetic route. TLC and LC/MS are routinely used to guide these reaction outcomes, but are typically only available through a central core facility or a shared open access of systems. For real-time monitoring and rapid answers, the CMS can fit directly in a fume hood for hood-based applications in the analysis of chemical reactions employing either LC/CMS or flow injection analysis (FIA).

Figure 1: The CMS with reaction equipment directly inside of a fume hood.

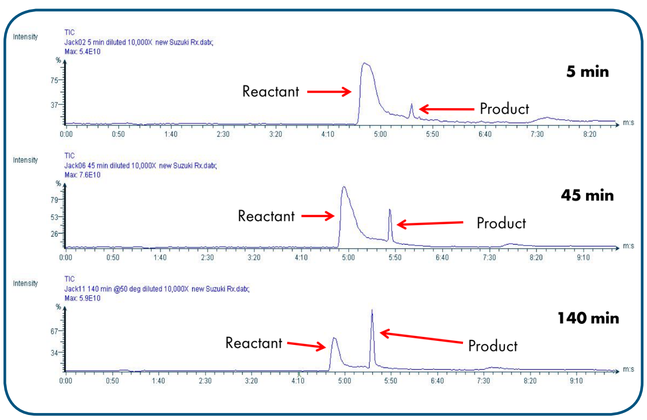

Figure 2: LC/CMS analysis of Suzuki reaction.

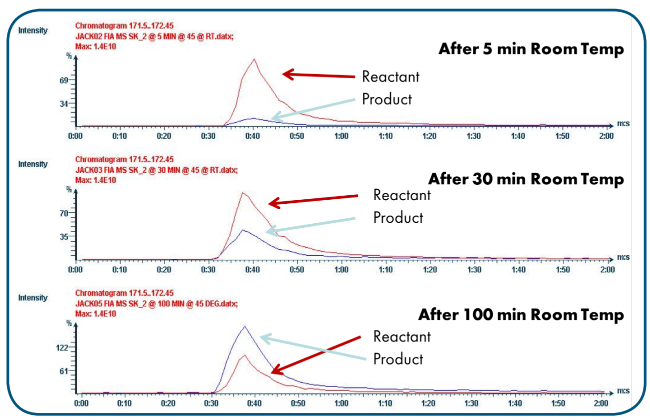

Figure 3: FIA analysis of Suzuki reaction.

The results shown for the LC/CMS analysis (Figure 2) and FIA analysis (Figure 3) of the Suzuki reactions to prepare p-Aminobiphenyl demonstrate proof of principle for real-time reaction monitoring. Both results show the increase of product/reactant ratio over time. Real-time monitoring of the reaction mixture with a selective detector optimizes the chemist's workflow to produce a high yield of the desired product in a minimal period of time.

APPLICATION: REACTION MONITORING VIA TLC

Thin layer chromatography (TLC) is a simple, cost-effective technique that provides critical information about synthetic reactions, and is often employed for reaction monitoring in medicinal and organic synthetic labs. Advion's Plate Express® TLC Plate Reader seamlessly integrates with the CMS and provides compound structural information directly from TLC plates without additional preparation.

Figure 4: Experimental set up of the CMS and Plate Express.

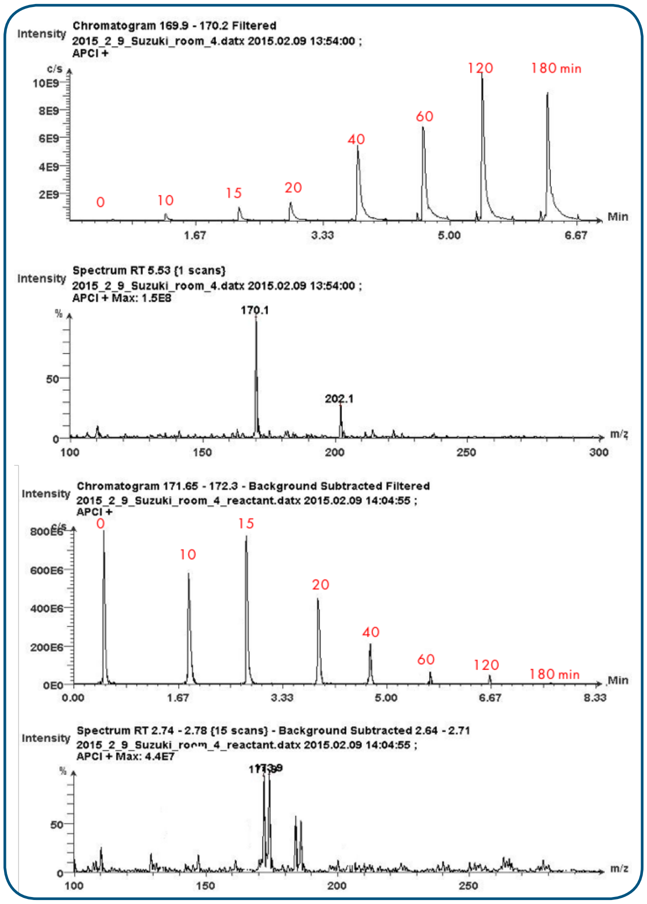

Figure 5: XIC of the synthesis of 4-aminobiphenyl.

The results of a Suzuki reaction for the synthesis of 4-aminobiphenyl show an extracted ion chromatogram (XIC) of the increasing of the product ion and the decrease of the reactant ion over time demonstrating real-time monitoring. The reactant ion was no longer detected at 180 minutes indicating the reaction was complete. The CMS coupled with the Plate Express allows users to monitor reactions in real-time by evaluating the mass spectra for structural information directly from the TLC plate.

APPLICATION: MONITORING SYNTHETIC REACTIONS VIA ASAP

Advion's Atmospheric Solids Analysis Probe (ASAP®) offers direct and instant mass analysis. Simply dip the ASAP into a liquid or swipe across a solid, and insert the probe directly into the ASAP-enabled APCI ion source of the CMS for analysis (Figure 6). The ASAP requires no sample preparation, no chromatography, and provides sensitive analysis of a wide range of compounds in less than 30 sec.

Figure 6: ASAP with sample inserted into the ASAP-enabled APCI ion source of the CMS.

Two experiments were demonstrated with the ASAP. In the first experiment, the synthesis of 4-iodoisoquinoline using the methods of Artis and Buchwald[1] could not be monitored by TLC. However, with the ASAP, the reaction product is readily seen after reacting at 110 °C for 22 hours at m/z 256.02 (Figure 7).

The results of the second experiment to determine the optimum stop time for the reaction based on the work of Yaetko et al[2] show an increase in the formation of 6-iodotryptophan and the acetamide-protected version of 6-iodotryptophan product ions as the presence of 6-iodoindole reactant ions decrease (Table 1). The timed study show that the reaction was reaching a plateau at approximately 60 min, indicating the reaction could have been stopped at 60 min.

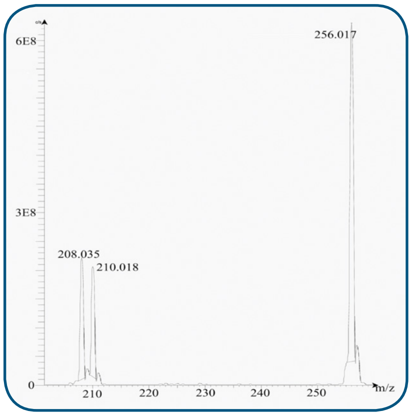

Figure 7: Mass spectra of the synthesis of 4-iodoisoquinoline.

Table 1: Presence of reactant and product ions over time.

TIME (MIN)	% 6-IODOINDOLE	% 6-IODOTRYPTOPHAN	%6-IODOTRYPTOPHAN PROTECTED
1	99.73	0.15	0.12
30	94.44	4.62	0.94
60	20.20	65.17	14.63
120	15.2	60.67	24.12

APPLICATION: MONITORING AIR-SENSITIVE REACTIONS VIA iASAP

The inert ASAP (iASAP®) is a modification of this technique that allows for easy sampling of air-sensitive compounds from reactions directly from a glove box or Schlenk line (Figure 8). Metal based compounds have found utility in various fields such as clinical, energy, food safety and environmental to name a few. Creating the metal complex is the last step in a synthetic process, when ligands are bound to the metal center. Once made, these metal complexes can be used anywhere from stereospecific synthesis to anti-cancer drugs. It is critical that reaction conditions are providing the desired product and that side products are kept to a minimum to maximize yield.

Figure 8: The iASAP, an inert modification developed for the original ASAP, for CMS analysis of air-sensitive samples.

During synthesis for a Molybdenum complex, the product crystals precipitate from the solvent, making direct product monitoring difficult, but the formed reaction products remain in solution and can be monitored. When the reaction was exposed to air, the formation of lower mass Mo monomers were reduced (Figure 10) compared to when the reaction was protected from air (Figure 9). Even without directly monitoring product formation, the byproduct from the reaction indicates reaction progress.

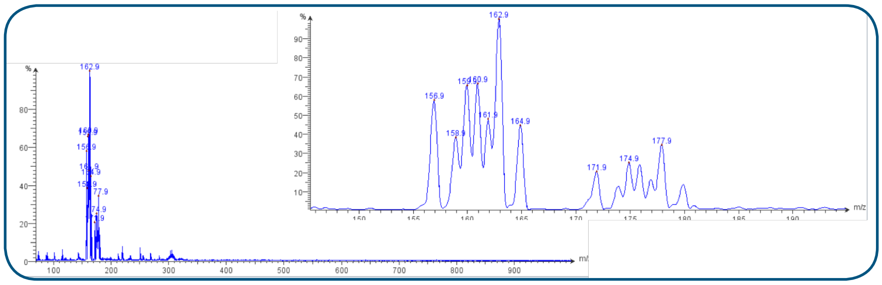

Figure 9: Mass spectra of reaction under nitrogen protection from air.

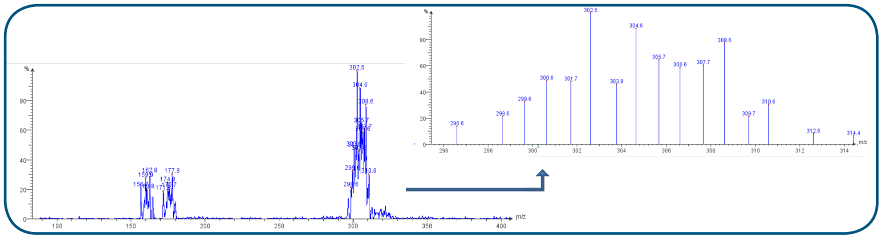

Figure 10: Mass spectra of reaction with air introduced.