Application Note

SUZUKI REACTION MONITORING

Using Compact Mass Spectrometry with TLC Interface

Advion

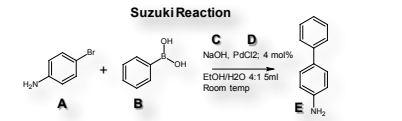
INTRODUCTION

Thin layer chromatography (TLC) is used in many organic synthetic and medicinal laboratories because it is a simple, cost-effective technique that provides chemists with critical information about their synthetic reactions. Structural characterization of the analytes by TLC is not possible by optical methods such as UV or ELSD. Typically, characterization is performed by GC/MS or LC/MS using sample preparation techniques which involves scraping the TLC spot of interest, extraction using suitable solvents, concentration and then reconstitution in MS appropriate solvents.

This application note presents an online TLC/CMS technique using the Advion expression compact mass spectrometer (CMS) and Plate Express™ interface to provide compound structural information without sample preparation after TLC separation. A Suzuki reaction for the synthesis of 4-aminobiphenyl will be demonstrated. The online TLC/CMS technique provides rapid and accurate determination of reaction mixture components without the need for off-line TLC sample preparation procedures.

METHOD

Reactants A and B were mixed at equi-molar amounts in a round-bottom reaction flask and stirred at room temperature. 2mL aliquots were transferred from the flask and spotted onto a Merck TLC Silica gel 60 F254 plate (10x10cm). Chemicals were purchased from Sigma-Aldrich with a purity greater than 99%. MS solvent was LC/MS grade.



	Reactants and Catalyst				Product
	A	B	C	D	E
compound	4-bromaniline	Phenyl Boronic acid	Sodium hydroxide	Palladium chloride	4-aminobiphenyl
Chemical Formula	C_6H_6BrN	$C_6H_7BO_2$	NaOH	$PdCl_2$	$C_{12}H_{11}N$
MW	171	122	40	176	169
moles	0.005	0.005	0.0065	0.005	0.005
mg	855	610	260	35	845

TLC Plate Preparation: Merck TLC Silica gel 60 F254 on Aluminum, 20x20cm - Cut to 10x10cm. TLC plates were baked at 100°C for 10 minutes to displace moisture. A 2 uL aliquot of the reaction mixture was spotted onto the TLC plate at the position of 1 cm away from bottom. The TLC plate was then baked at 80°C for 5 min.

30ml Benzene was added to a TLC plate developing chamber at the level of 0.5 cm. The developing chamber was sealed with a glass lid for 30 min. The separation was stopped when the development solvent front reached a position which was 1 cm away from the top of the TLC plate.

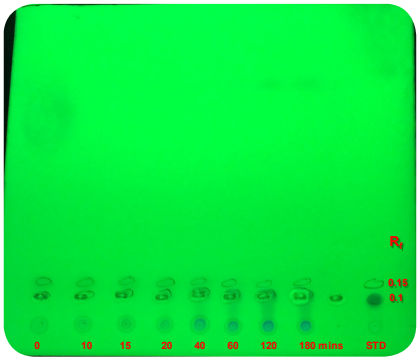


Figure 1. The developed TLC plate with Suzuki reaction mixture under UV 254 nm

The analytes (reactant and product) on the developed plate were observed under UV at 254nm (Figure 1). The Rf value of the product (4-aminobiphenyl) was 0.1; the Rf of the reactant (4-bromaniline) was 0.15.

The TLC/CMS analysis of the Suzuki reaction mixture at different reaction times was performed on Advion's TLC/CMS system (expression CMS-L and Plate Express). A solvent composed of 0.1% formic in methanol was used for the elution of the analytes from the TLC plate. The eluted analytes were directed to the CMS-L for aquisition of the corresponding mass spectra for the reactants and products.

RESULTS

The mass spectra of the reactant and product are shown in Figure 2. The $[M+H]^+$ for 4-bromoaniline was observed at *m/z* 171.9 (^{79}Br) and 173.9 (^{81}Br). Methanol adducts were also detected at *m/z* 204.0 and 206.0 (Figure 2A).

The $[M+H]^+$ for 4-aminobiphenyl was observed at *m/z* 170.1 with a methanol adduct at *m/z* 202.1 (Notice the absence of the bromine doublet peaks in the non-brominated product of p-aminobiphenyl, Figure 2B).

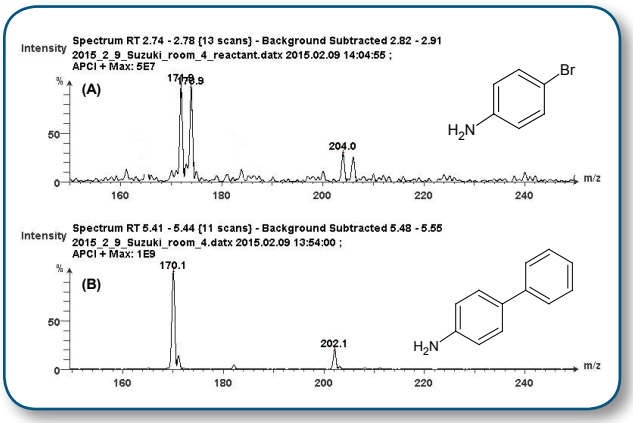


Figure 2. TLC/CMS analysis of reactant and product. (A) The mass spectrum of protonated 4-bromoaniline (reactant) at the *m/z* 171.9 and 173.9. (B) The mass spectrum of protonated 4-aminobiphenyl (product) at the *m/z* 170.1

The extracted ion current of the product ion at *m/z* 170.1 (protonated 4-amionbiphenyl) was monitored over different reaction times from 0 to 180 minutes (Figure 3A) The mass spectrum of the product ion at 120 min is shown in figure 3B. The extracted ion current of the reactant ion at the *m/z* 171.9 (protonated 4-bromaniline(^{79}Br)) is shown in Figure 3C. The intensity of the *m/z* 171.9 decreased over the course of the reaction with respect to the product ion at the *m/z* 170.1 The reactant ion at the *m/z* 171.9 was no longer detected at 180 minutes, indicating the reaction was complete.

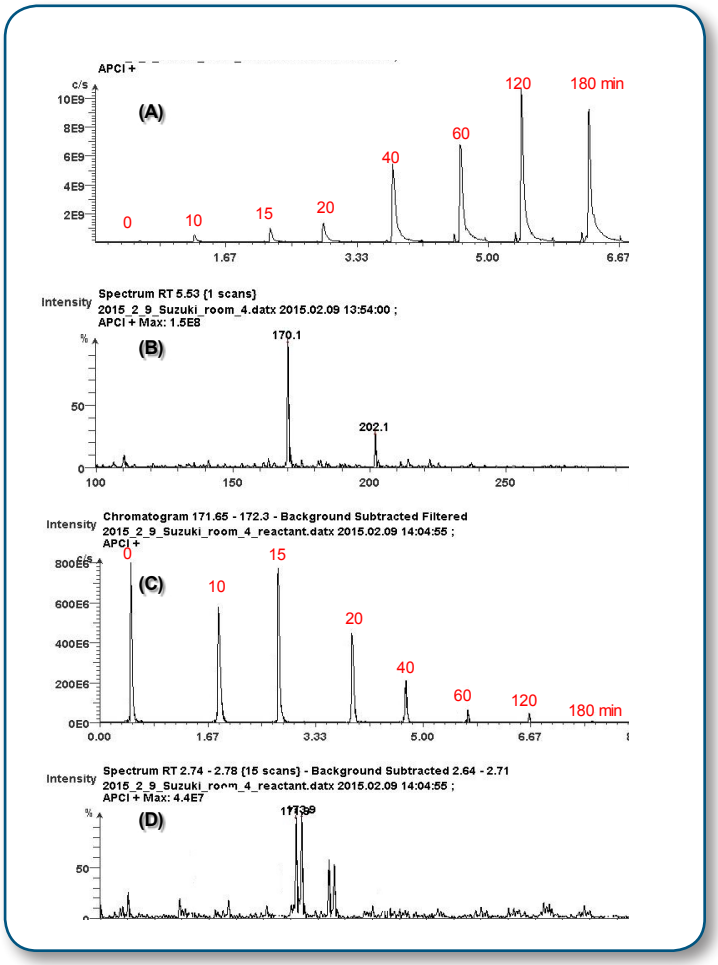


Figure 3. (A) The extracted ion current of product ion (protonated4-aminobiphenyl), the *m/z* 170.1 at different reaction time from 0 to 180 minutes (B). The mass spectrum of the product ion, the *m/z* 170.1 at reaction time of 120 min. (C). The extract ion current of the reactant ion(protonated 4-bromoaniline), the *m/z* 171.9 over different reaction time from 0 to 180 minutes (D) the mass spectrum of the reactant ions, the *m/z* 171.9 and 173.9 at reaction time 15 minutes

SUMMARY

- The Advion expression CMS coupled with Plate Express offers a simple, fast technique to monitor a Suzuki reaction for the synthesis of 4-aminobiphenyl.
- The Advion TLC/CMS system allows the synthetic chemist to monitor the reaction in real-time by evaluating the mass spectra for structural information (i.e., relative intensity of reactants vs. product) directly from the TLC plate.
- The compact size allows it to fit into space-limited labs for direct access and immediate results for chemists requiring mass confirmation, reaction monitoring, quality control and purity analysis.

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