

IMPROVING SYNTHESIS LAB PRODUCTIVITY USING THERMAL DESORPTION/MASS SPECTROMETRY TO RAPIDLY MONITOR CHEMICAL REACTIONS

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INTRODUCTION

To improve organic synthesis efficiency, timely chemical analysis data are required for making important decisions to maximize product yields. Information on reaction progress and the components of each fraction in the purification processes is critical to these decisions. Reactions are typically monitored by TLC, which does not provide structural information and often requires mobile phase optimization. Conventional analytical tools, such as NMR, LC or LC/MS, require time-consuming workup procedures including extraction, filtration, separation, and evaporation. Atmospheric pressure solids analysis probe (ASAP), an ambient thermal desorption ionization technique, can provide mass spectra of reaction mixtures liberally within seconds of the reaction sampling point.¹ This presentation demonstrates time-saving and cost benefits of using ASAP to monitor the reaction progress and identify components of chromatography separation fractions.

Reductive amination and amide formation reactions are widely used in multiple-step organic syntheses to make agricultural chemicals, drugs, and food additives. A reductive amination reaction (Figure 1) was conducted by mixing acetophenone with aniline in methanol, then adding HCl to form an iminium intermediate, and finally adding the reducing agent NaBH₃CN to produce phenyl(phenylethyl)amine.² The step-by-step reaction procedures were successfully monitored with ASAP by following the disappearance of acetophenone and aniline ion peaks and the increase in proportion of phenyl(phenylethyl)amine ion peak in the mass spectra. Another experiment, an amide formation reaction was conducted and the reaction mixture was separated with a Waters 20 cc PoraPak Rxn CX cartridge (Figure 2). Frequently, organic reaction mixtures are separated using preparative scale liquid chromatography (Prep-LC) to isolate and purify target compounds. Acidic modifiers, such as trifluoroacetic acid (TFA) are often used in the mobile phase for the Prep-LC separation. Simply removing the mobile phase from the collected fractions, an equivalent amount of TFA will remain associated with any basic products. Residual TFA has been linked to the degradation of basic compounds. TFA can be easily removed by using a PoraPak Rxn CX cartridge. ASAP was used to ensure the full utilization of the cartridge loading capacity and the removal of TFA from basic products (Figure 3).

METHODS

ASAP coupled to a TQD mass spectrometer was used to directly analyze reaction mixture (Figure 4). The sample was loaded onto the sealed glass melting point capillary tube of the ASAP probe. The probe was inserted into the sealed MS source enclosure and the desolvation gas was rapidly heated to 400 °C. Data were acquired using both ESI positive and negative mass scan modes at 2V cone voltage and 120 °C source temperature with a 40 seconds run time. MS/MS spectra were acquired for the product peak structure elucidation. The low cone voltage is applied to avoid in-source fragmentation.

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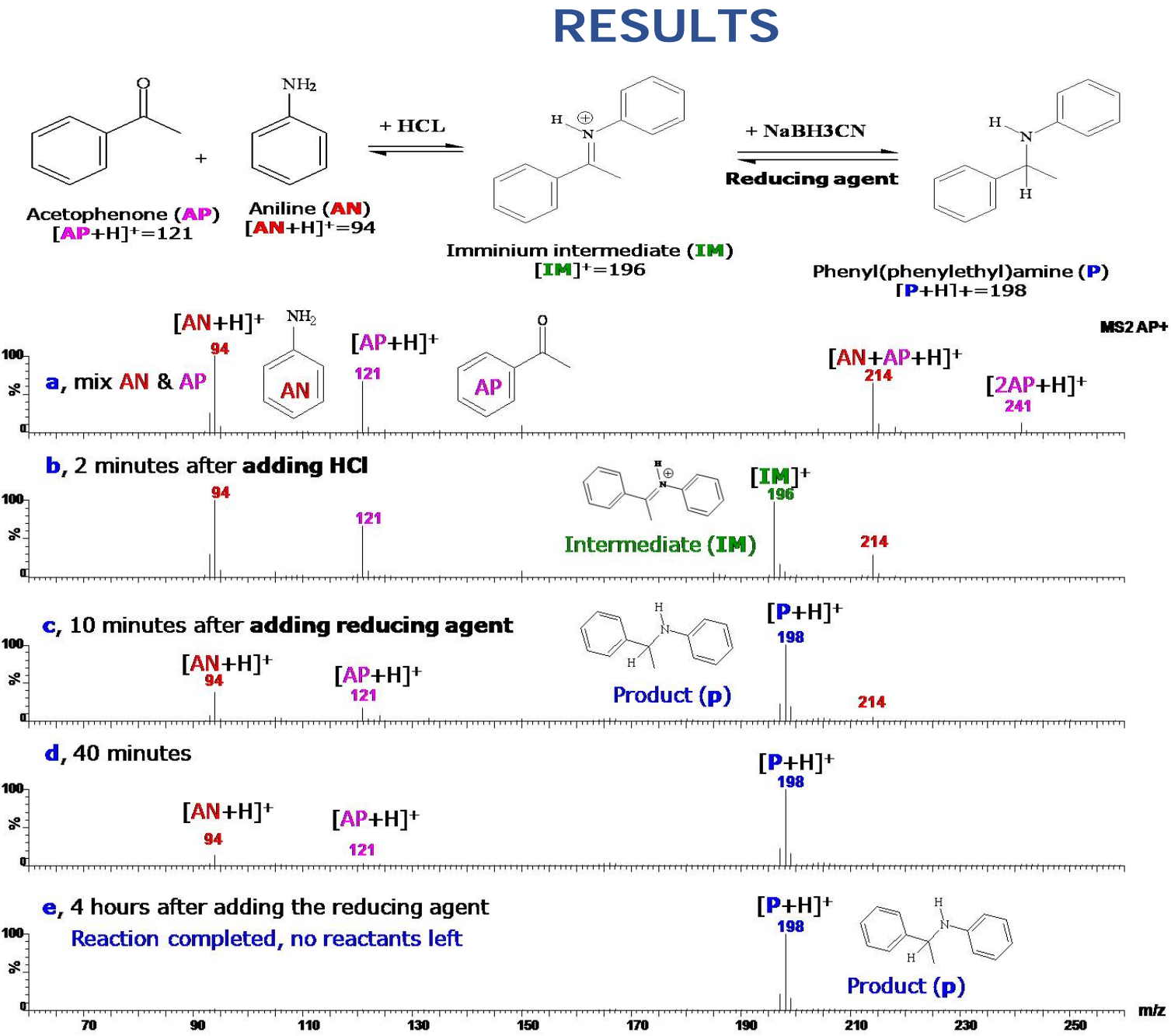


Figure 1, ASAP Monitoring Reductive Amination: Spectrum **b** confirms the formation of the expected iminium intermediate (IM), spectrum **e** indicates the completion of the reaction.

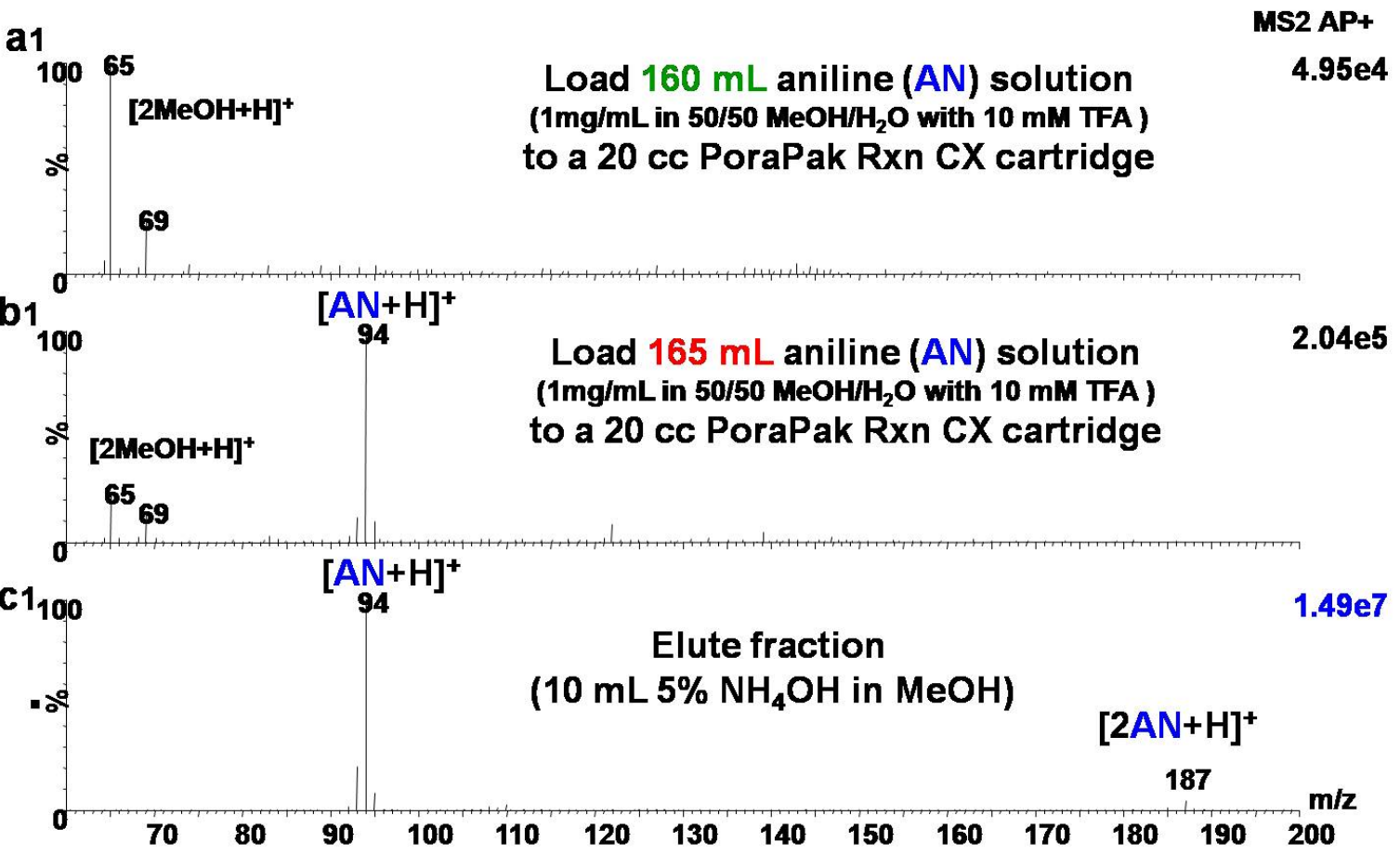


Figure 3, ASAP Monitoring TFA Removal and Amine Purification: aniline/TFA solution (1mg/mL) was loaded in 5 mL increments onto a 20 cc PoraPak Rxn CX cartridge and the pass-through solvent was examined with ASAP using both positive and negative full scan modes. Spectra **a1** and **b1** indicate that a maximum of 160 mL aniline solution can be loaded onto the cartridge without breakthrough. Spectrum **c1** and **c2** show the aniline was recovered as a freebase without the presence of TFA.

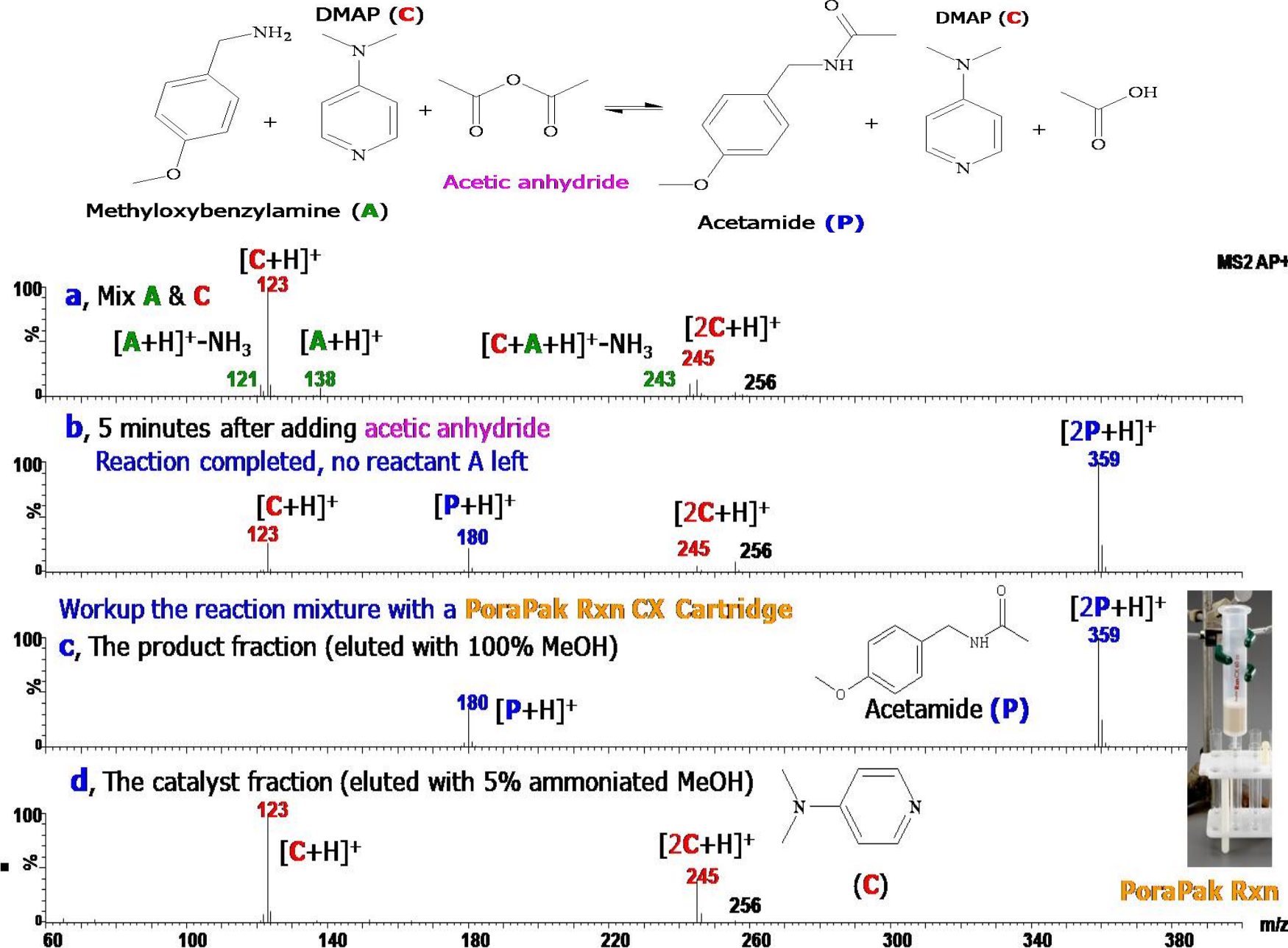
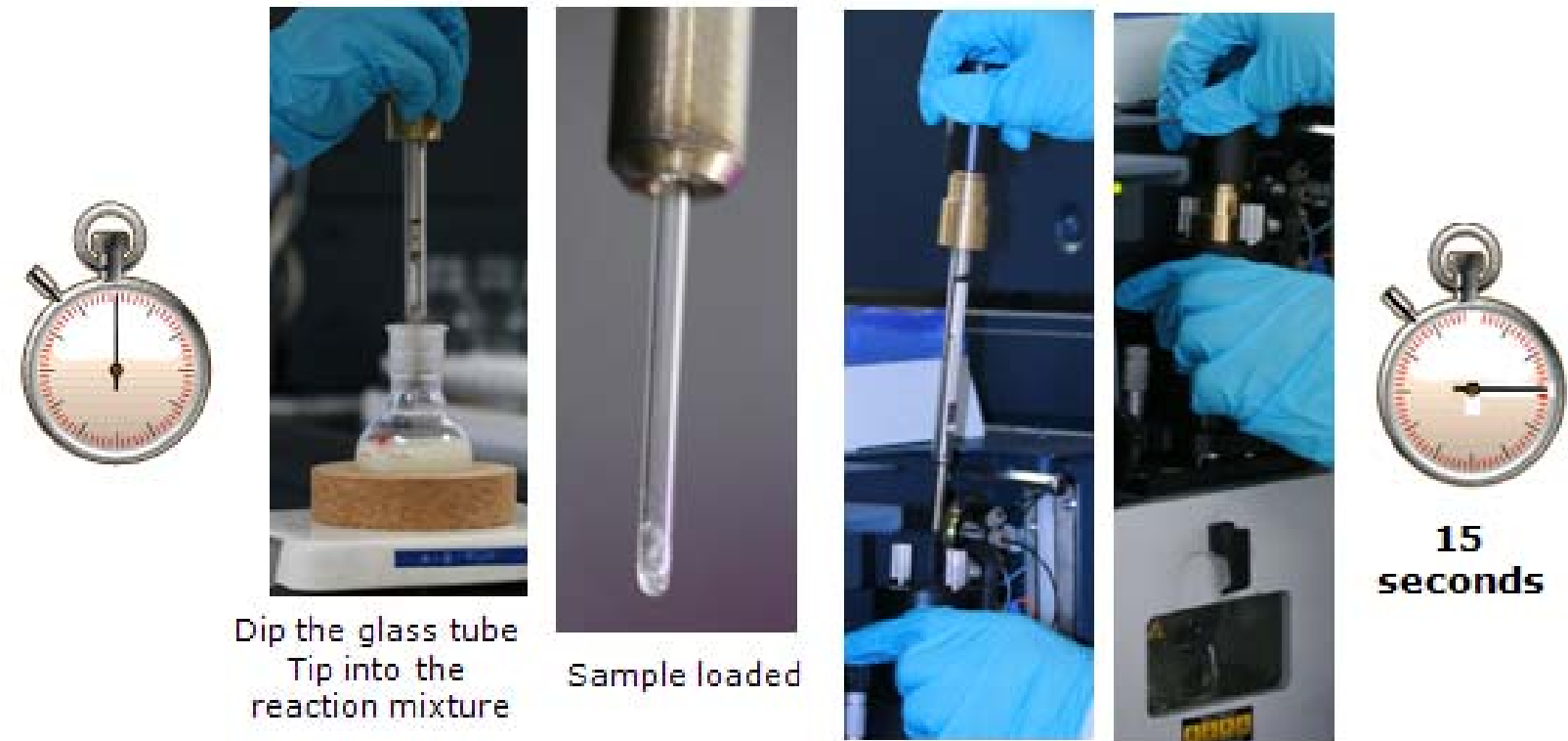
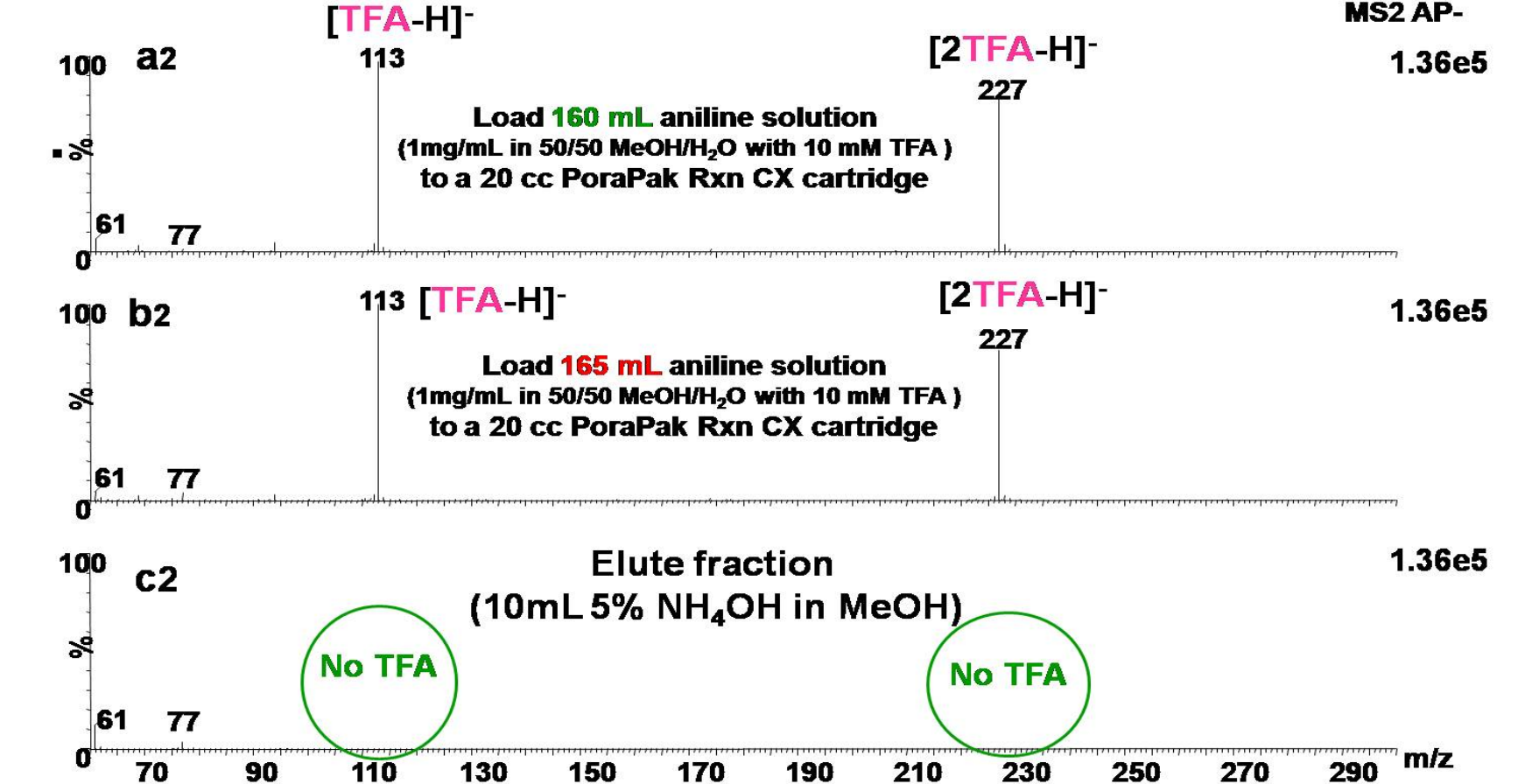


Figure 2, ASAP Monitoring Amide Formation: Spectrum **b** shows that the ion peak of **A** disappeared after 5 minutes, indicating the completion of the reaction, spectrum **c** and **d** show the product acetamide was successfully separated from catalyst DMAP with a PoraPak Rxn CX cartridge.



No Sample Preparation

Direct Detection

Figure 4, ASAP Sample Loading Procedures

CONCLUSION

- Step-by-step reaction procedures of reductive amination and amide formation reactions were successfully monitored with ASAP.
- ASAP can be used to rapidly confirm the structures of organic synthesis starting materials, examine the reaction progress, and identify product fractions in less than one minute without sample extraction, sample dilution, and chromatographic separation.
- PoraPak Rxn cartridges can be used to rapidly isolate and purify targeted compounds.
- Residue of acidic mobile phase modifier, TFA, can be easily removed from basic products using PoraPak Rxn CX cartridge.
- The data illustrate the benefits of using ASAP in organic synthesis environment to greatly increase lab productivity through analytical time savings and reduce lab operating costs.
- In addition, the ASAP approach lessens the impact on the environment by reducing solvent consumption.

REFERENCE

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2. R. F. Borch, M. D. Bernstein, H. D. Durstlb, J. Amer. Chem. Soc., 93, 2897, (1971)