Real-Time Monitoring of a Suzuki Reaction Utilizing a Hood-Based Compact Mass Spectrometer

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Overview

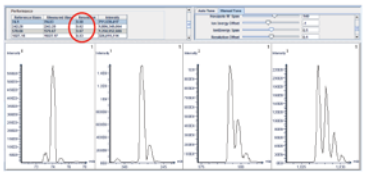
A novel compact single quadrupole mass spectrometer for hood-based applications in the analysis of chemical reactions.

Introduction

Medicinal chemists are routinely faced with personally synthesizing over a hundred new chemical entities (NCE's) 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/UV/MS are routinely used to monitor and guide these reaction outcomes. In most cases the LC/UV/MS technology is only available through a central core facility or via shared open access of systems. A preferred alternative is a personal small LC/MS system located in a hood adjacent to the synthetic reaction apparatus. This presentation will describe such an LC/MS system used to monitor and optimize a Suzuki coupling reaction.

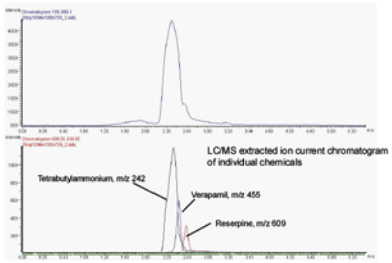
Methods & Materials

Mass Resolution

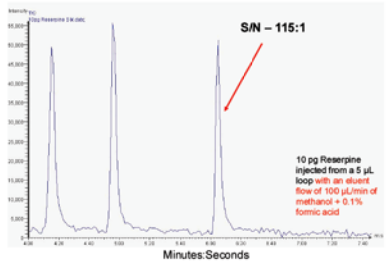


10 pmol/uL Infusion of Quaternary Amine Mix (abundant peaks are tetra alkyl ammonium ions)

Why is Mass Spectrometry Useful?
MS provides selectivity



Sensitivity -10pg Reserpine FIA – SIM Mode

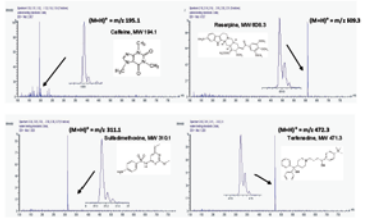


Waters Acquity UPLC/MS with expression CMS

Experimental:

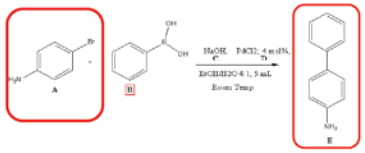
- expression CMS interfaced to Waters Acquity UPLC system
- 800 µL/min flow rate Waters; 4:1 split to CMS
- 5 min gradient: 5/95 ACN/H2O, 0.1% Formic Acid to 95/5 ACN/H2O, 0.1% Formic Acid.
- Waters UPLC test mix used: Acetaminophen, Caffeine, Reserpine, Sulfadimethoxine, Terfenadine.
- Scan speed of 5000 u/s gives 15 data points across 3 s wide peak while scanning 1000 m/z span

UPLC/MS – Five-Component Mix: Representative Mass Spectra



Results

Synthesis Experimental
Suzuki Reaction to prepare p-Aminobiphenyl



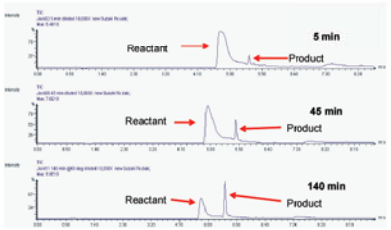
	A	B	C	D	E
Cmpd	C6H6BrN	C6H7BO2	NaOH	PdCl2	C12H11N
MW (g/mol)	171	122	40	178	169
Moles	0.005	0.005	0.0065	0.005 (0.04)	0.005
Grams	0.855	0.61	0.26	0.895	0.845
mg	855	610	260	35	845
Sp. Gr.*	-	1	-	-	-

FF: Formula for p-aminobiphenyl.xls

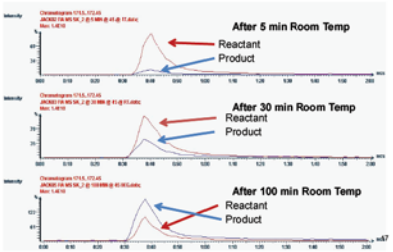
Suzuki Reaction Monitoring
Reaction Procedure

- Set up LC/MS system in hood with mobile phase flowing
- Commence Suzuki reaction stirring at room temperature at 5 mM scale
  - Quantitative yield would be 845 mg in 5 mL aqueous EtOH
- At selected time points:
  - Remove 10 µL aliquot from stirred reaction mixture
  - Dispense the 10 µL into 10 mL water (1,000-fold dilution)
  - Inject 10 µL into LC/MS system
    - Observe reactant/product ratio in 6 min OR
    - Remove LC column
      - get FIA-MS results in 1 min!
- Repeat at selected time points until reaction is optimized under existing conditions

LC/MS Analysis of Suzuki Reaction - Results in 6 minutes



FIA-MS of Suzuki Reaction - Results in 1 minute



Compact and convenient mass spectrometry

Summary

The goal of a synthetic reaction is to produce a high yield of the desired product in a minimum period of time. Monitoring a reaction mixture over the course of time with a selective detector can allow one to optimize this process. This work describes the use of a new compact single quadrupole electrospray mass spectrometer (CMS) to monitor a representative Suzuki coupling reaction in real-time. Aliquots of the crude reaction mixture are taken at sequential time points, diluted with aqueous methanol and analyzed by LC/MS as well as flow injection analysis (FIA) MS. The results demonstrate the proof of principle for this approach for real-time reaction monitoring using mass spectrometry.

- A fresh new perspective and an alternative to traditional MS products
- Fast answers in space-restricted labs
- Does not compromise your performance requirements or your budgets
- A Mass Spec for the Masses