

# Use of Real Time Mid-IR Analytics for Enhanced Development of Flow Chemistry



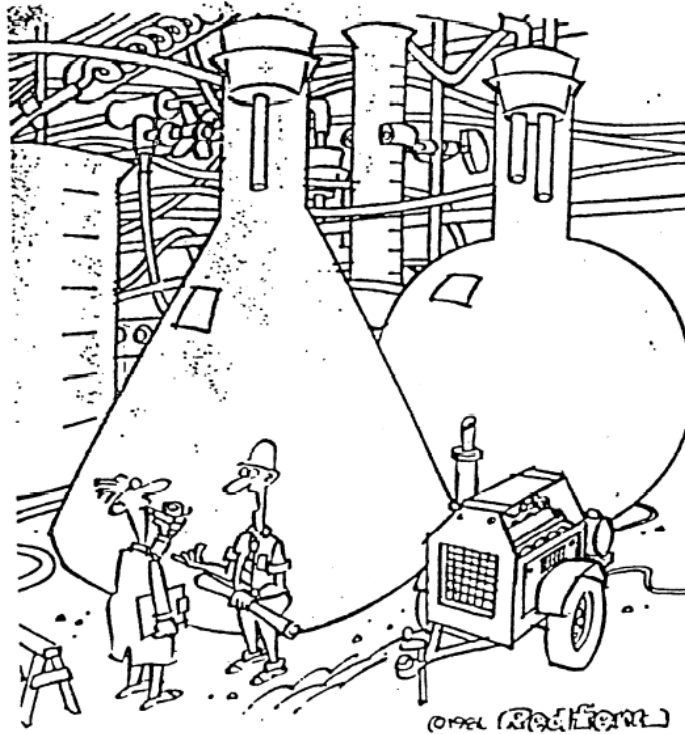
Paul Scholl

14<sup>th</sup> NIChE Conference

September 21 -23, 2009

**METTLER TOLEDO**

# Introduction



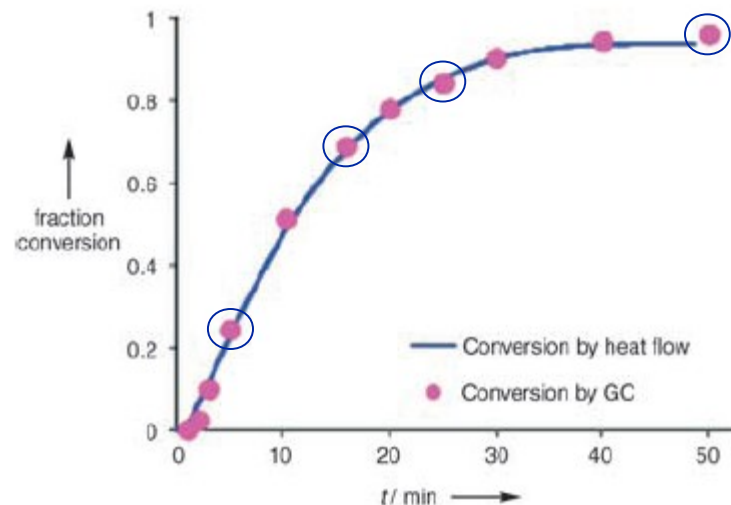
*"Got a few problems going from lab scale up to full-scale commercial."*



# Introduction

## The importance of real time reaction analysis

- Did the reaction work?
  - Understand selectivity and reactivity
  - Identify intermediates or by-products
- How long did it take?
  - Endpoint, initiation-point, stall-point
- Can this process be scaled-up?
  - Identify key control parameters
  - Understand reaction kinetics

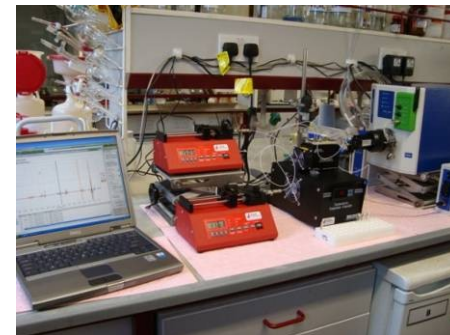


- No need for a chromatography method
- Compounds can be unstable, sensitive, toxic,...
- No need for sampling at low/high temperature/pressure

# *In Situ* Reaction Analysis for Flow Chemistry

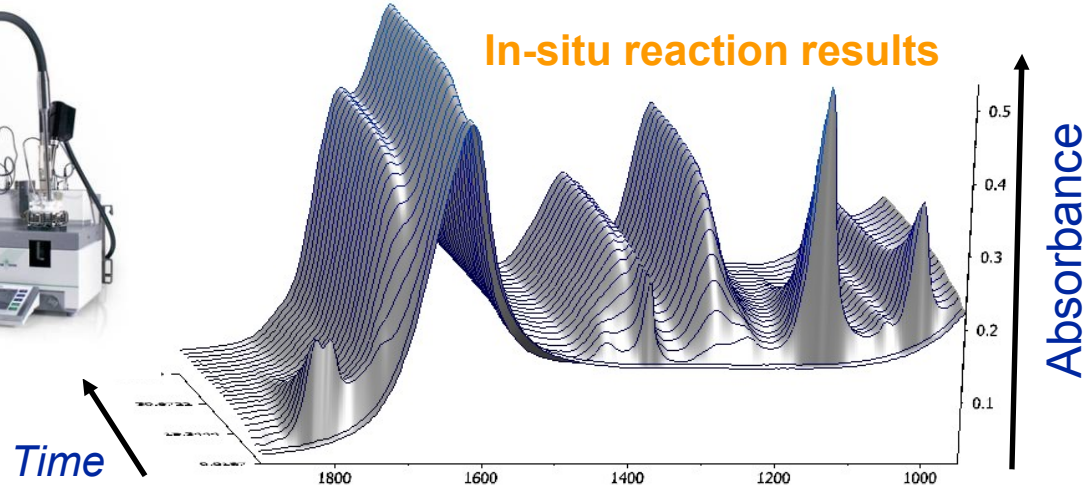
## ■ Current challenges

- Most systems require grab sampling for analyses
  - ▶ Developing flow processes of novel compounds “blind”
  - ▶ Decreased efficiency, potential alteration of sample
- UV detection systems have limited chemical detectivity
- Increasing pressure and number of chemistries to convert to flow processes



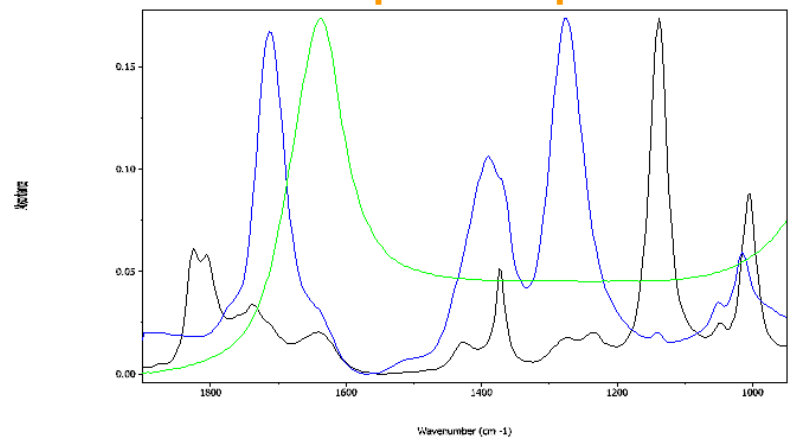
- Faster structural information in real time
  - Reaction mechanism/pathway
  - Immediate reaction Start/End points
  - Detection of transient intermediates
  - Eliminates sampling
  - Universal (fits with any flow system)
  - Multi-stage flow capability (MultiplexIR)

# Reaction Monitoring and Characterization

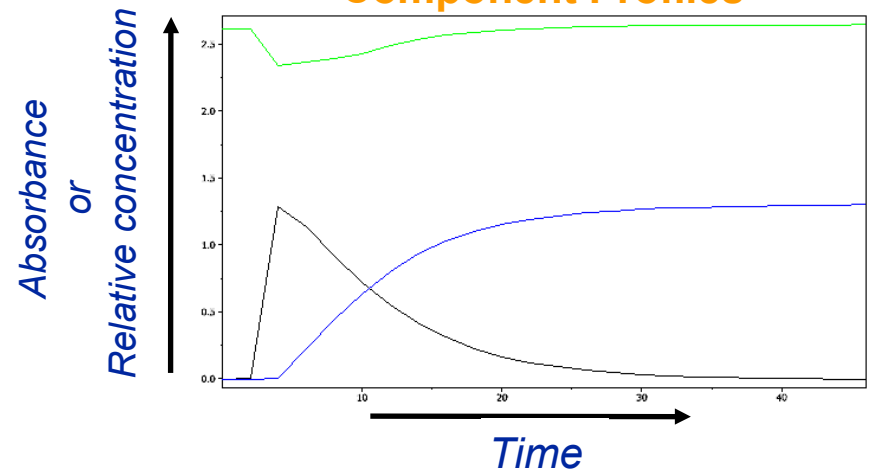


- ConclRT live
- Peak height profiling
- Quantitative model

**Component Spectra**



**Component Profiles**



# Case Study: FTIR, PAT Tool in Pharma Development

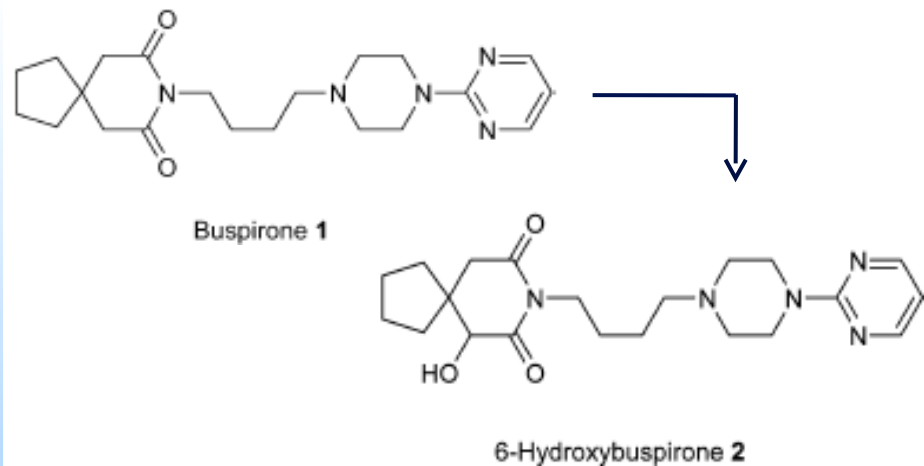
## Development of a Safe and Scalable Oxidation Process for the Preparation of 6-Hydroxybuspirone

### ■ Introduction

Active metabolite of Buspirone, manufactured and marketed as Buspar, employed for the treatment of anxiety disorders and depression

Multi Kg amount needed for clinical dev.

Process lack of ruggedness and unreliable product quality



# Case Study: FTIR, PAT Tool in Pharma Development

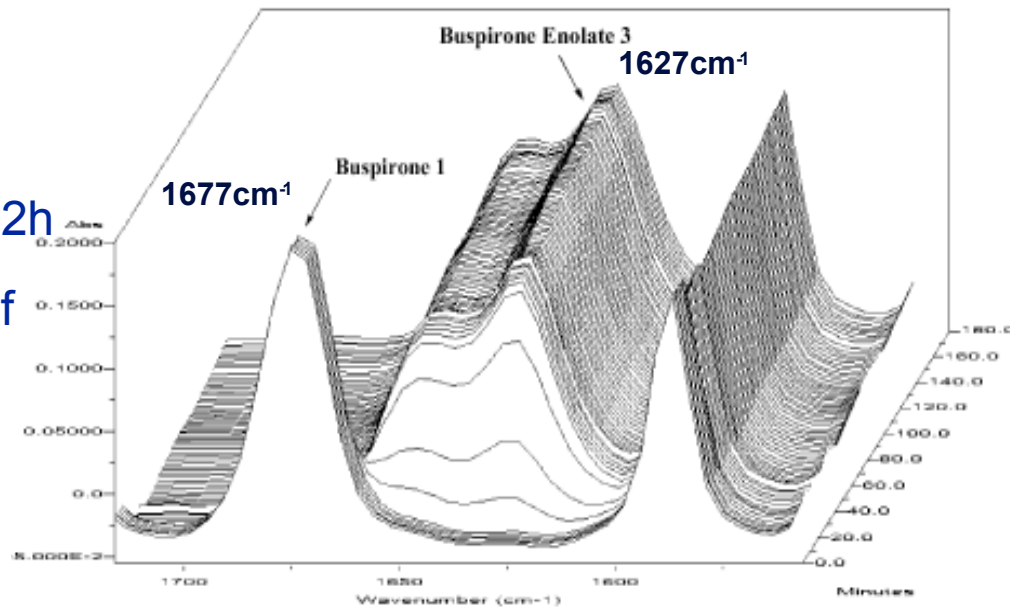
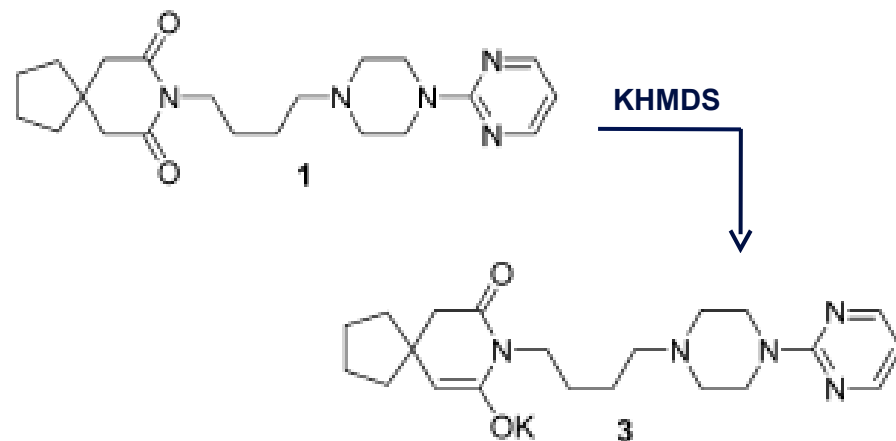
## ■ Challenges

Monitor deprotonation of **1** for:

- More precise determination of endpoint to minimize bis-deprotonation
- Allow for variations in the base titer, water content, and phosphite quality

## ■ Observations

- Deprotonation complete within 5'
- Enolate anion **3** stable at -25°C for 12h
- Addition of P(OEt)<sub>3</sub> before addition of the base → no impact on IR signal
- Kinetics of enolate degradation



# Case Study: FTIR, PAT Tool in Pharma Development

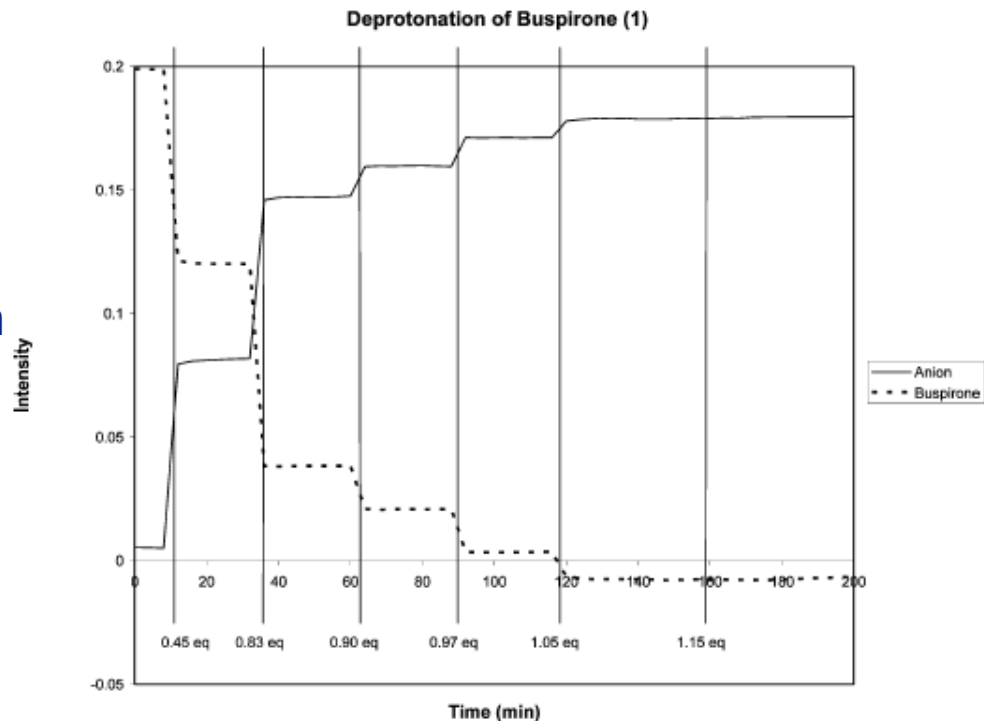
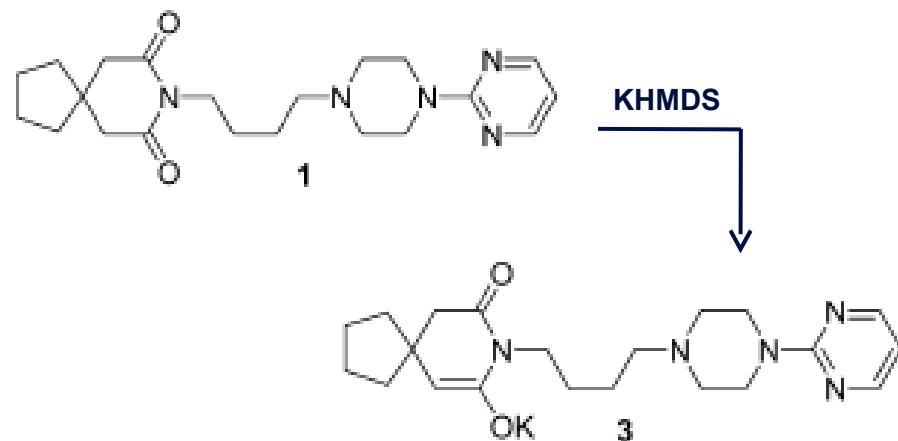
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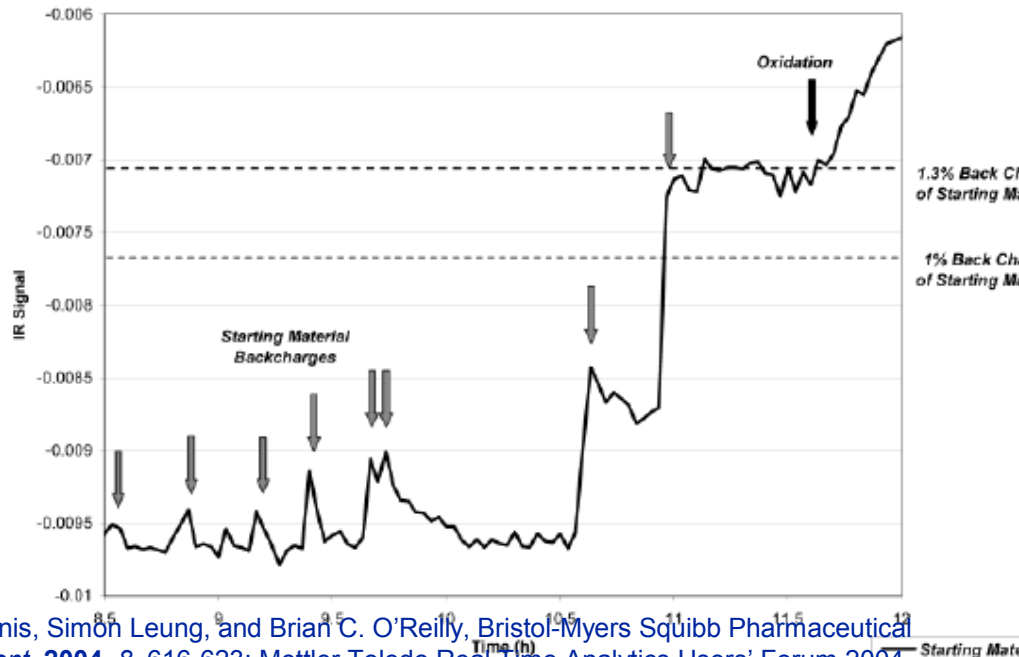
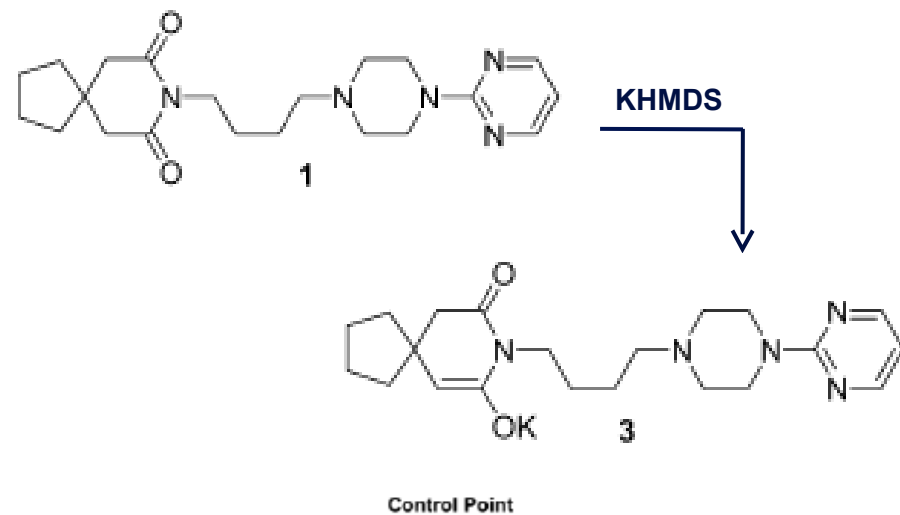
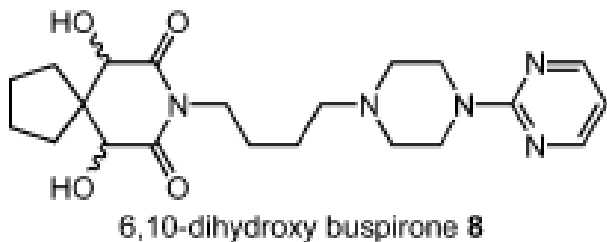
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# Case Study: FTIR, PAT Tool in Pharma Development

## ■ Improved process

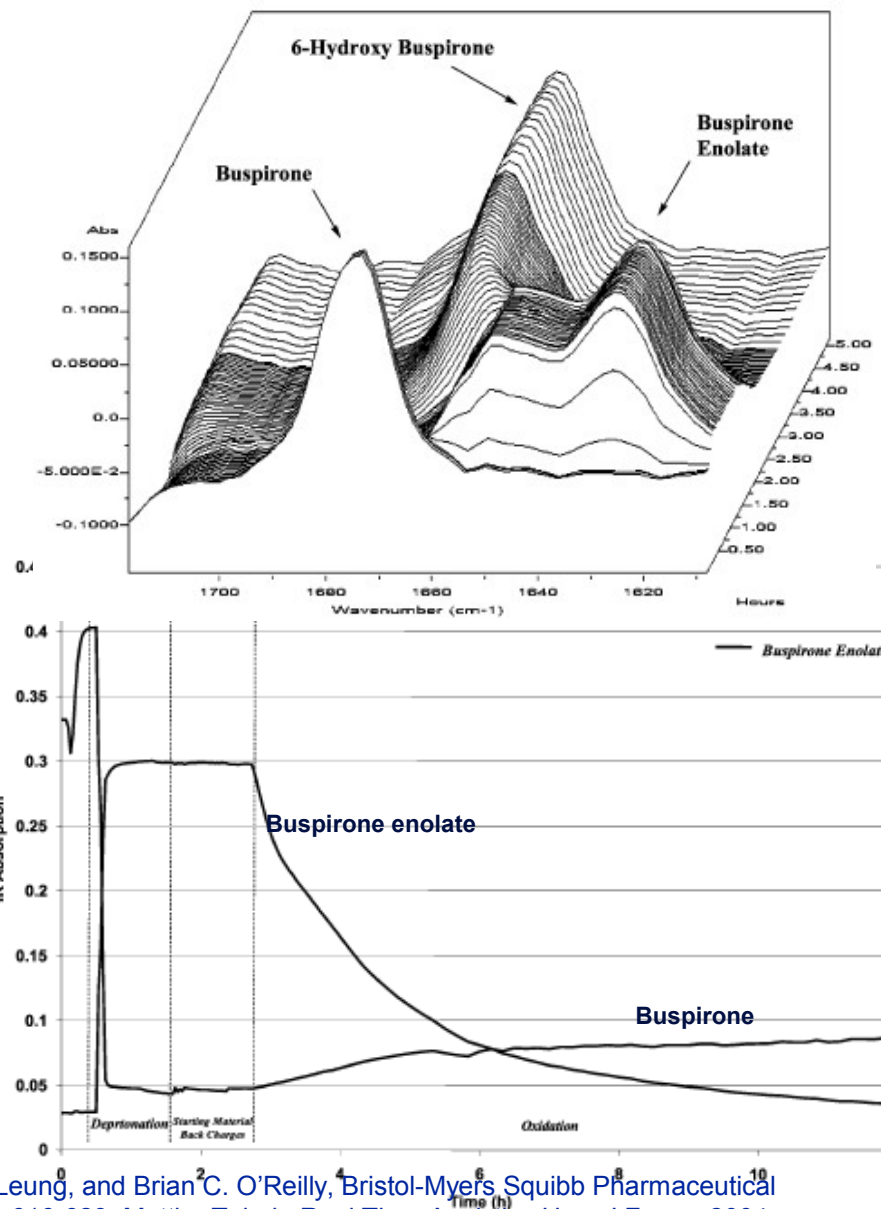
- Charged the base to **1** until complete consumption → Stable signal ( $1677\text{cm}^{-1}$ )
- **1** / THF charged back to the vessel until the signal increased → 1-3% excess of the starting material (quantified FTIR)
- Result: Impurity **8** is minimized



# Case Study: FTIR, PAT Tool in Pharma Development

## ■ Conclusion

- ReactIR™ allowed titration of the correct amount of base, prevented accidental overcharge due to ambiguous concentration
- Implementation to the pilot plant (13Kg)
- 69% yield and >99 area %, need for recrystallization eliminated
- Robust, superior process & crystallization thanks to the successful use of PAT



# Case Study: FTIR as PAT Tool for Continuous Process

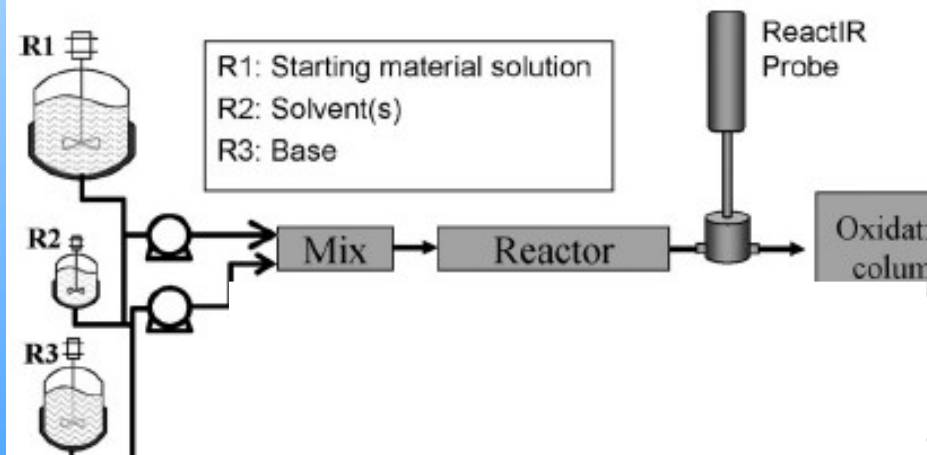
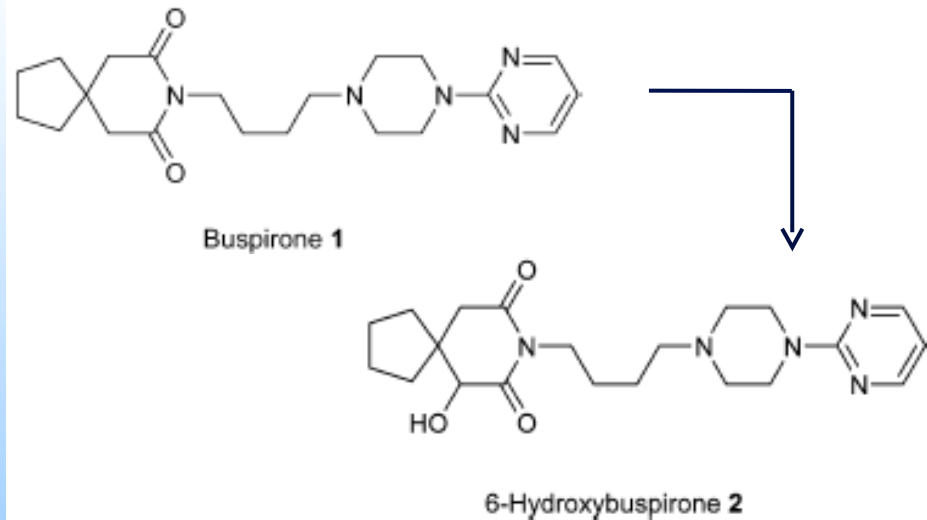
## Development and Scale-up of Three Consecutive Continuous Reactions for Production of 6-Hydroxybuspirone

### ■ Introduction

Control base / buspirone stoichiometry is critical to product quality

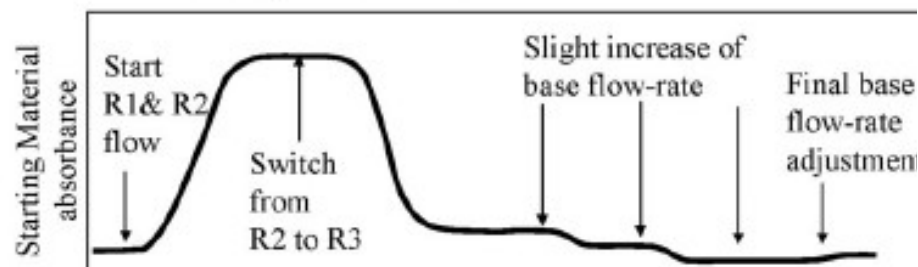
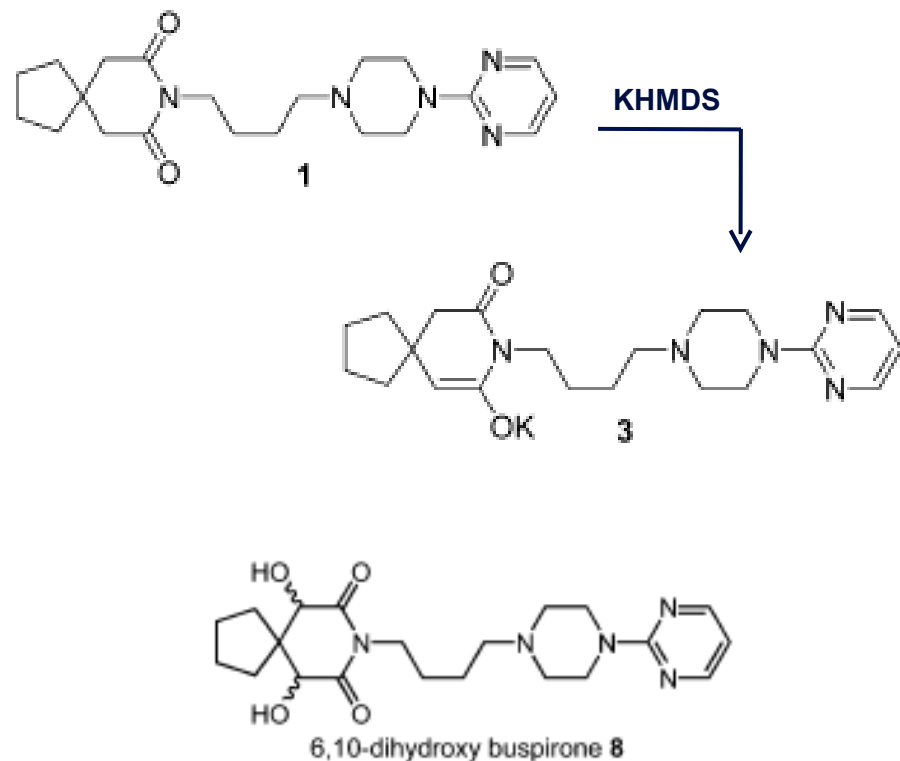
Optimization based on offline analysis is time consuming and wasteful

Actual feed rate adjusted based on the feedback from inline FTIR: Flow cell and ReactIR™ DiComp probe



# Case Study: FTIR as PAT tool for Continuous Process

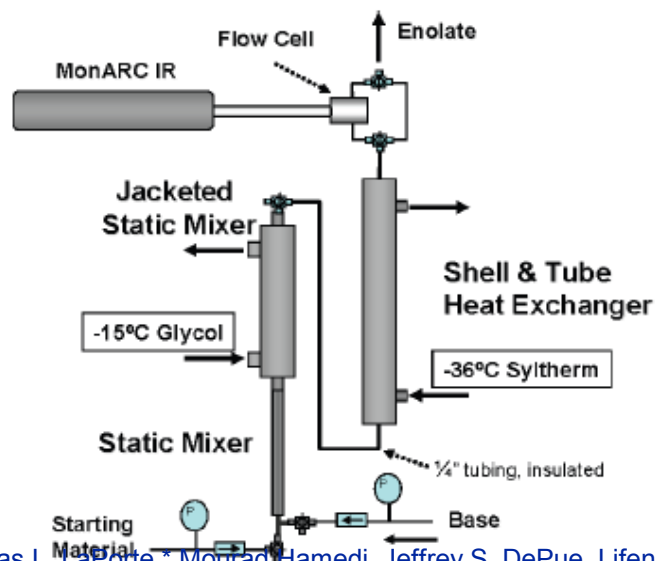
- Implemented startup strategy
  - Start with slight undercharge of base (feed rate) to reduce diol **8**
  - Flow rate increased at 1% increments until no decrease of Buspirone **1** signal is observed
  - Base feed rate was reduced 1-3%
  - Works well because enolization fast, equilibrium reached within minutes



# Case Study: FTIR as PAT Tool for Continuous Process

## ■ Outcome

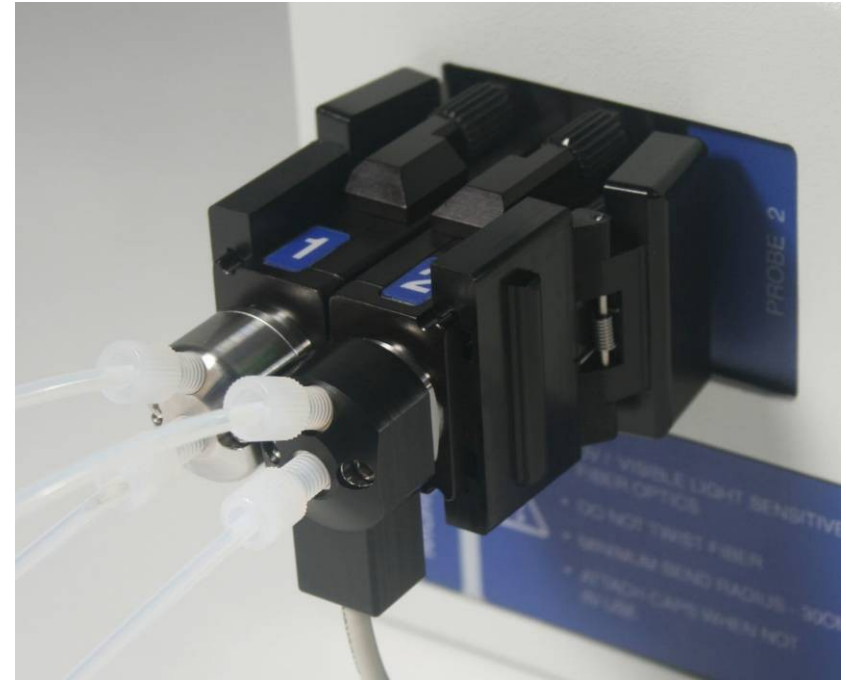
- Ensure product quality via proper ratio and base feed rate
- Minimize waste of starting material
- Faster reach of steady state via real-time detection of phase transitions
- FTIR also used for enolization monitoring during steady state



## ■ Scale-up

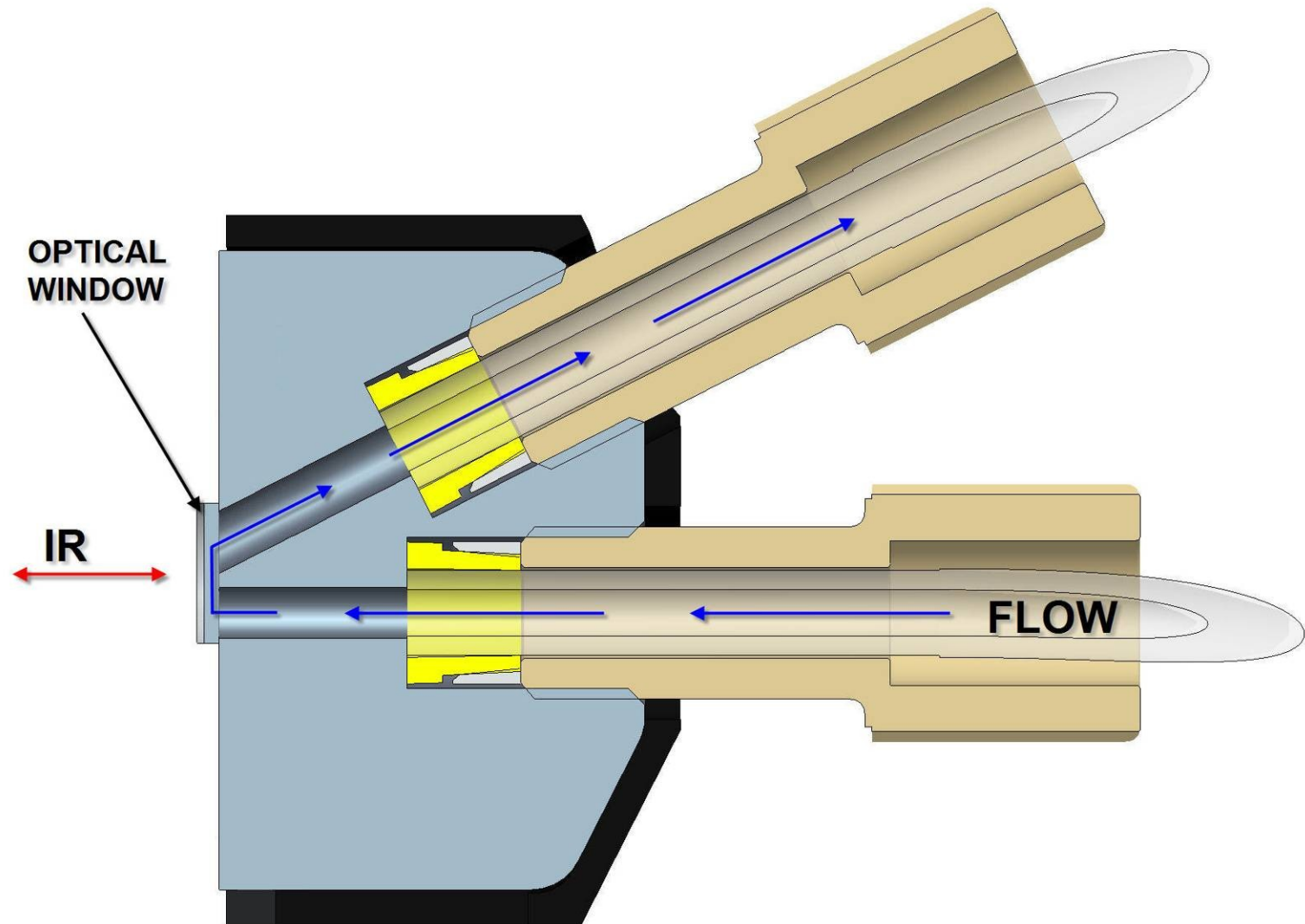
- Lab reactor: Over 40 hours at steady state
- Pilot-plant reactor: Successful implementation (3-batch, 47kg/batch)

# Technology Development: MultiplexIR & DS Series Flow Cells



- **Multiplexing**
  - Monitor multi-step chemistry
  - Monitor up to 2 different flow systems
- **Built-in modularity allows enhanced usability for process development**
  - Plug-n-play technology permits use of probe based ReactIR™ reaction monitoring technology with the same system

# DS Series Flow Cell Schematic



# Conclusion

Organic synthesis lab at the turn of the century...



...which century?