Examples of Early Phase Implementation of PAT Tools: Meeting Short Term Goals While Setting the Stage for Long-Term Process Understanding and Control

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Wyeth Research 2001-2009

• Since 2001, Wyeth has pursued a productivity model that had as its objective the submission of two New Drug Applications (NDAs) for New Molecular Entities every year

• To support this goal, Wyeth Research increased the number of compounds entering clinical development each year

• The annual Wyeth Research goals became
  – 13 compounds enter Phase 0
  – File 10 INDs
Chemical Development: Timing and Deliveries

- Pre-development Track Declaration
- Lead Selection
- Development Track Declaration
- IND/FIH

- Pre-Selection (Discovery)
- Pre-Development
- Ph 0
- Ph I

- 5 g (Multiple Leads)
- 25 g (Single Lead)
- IDM
- RSE Mtg
- RSE (~5 g)
- LLM
- LLM
- LLM
- API Tech Review
- ~500 g
- 2-10 kg

IDM: Initial Discovery Meeting
RSE: Rapid Synthesis Evaluation
LLM: Lessons Learned Meeting
Chemical Development: Challenges and Drivers

- More reactions in shorter time
  - Parallel reaction screening
- Learn more from each reaction
  - Heat flow – Qr and Tr-Tj
  - in-situ FTIR
Enolization-Azidation Sequence

Initial Procedure:
1. 1 equiv KHMDS (0.5 M in toluene) added to substrate in 6.5 vol THF at -65 °C
2. Trisyl Azide in 4 vol THF added to cold solution
3. Reaction quenched with acetic acid and water, warmed to room temperature

Scale-Up Issues:
1. Product is an oil, necessary to telescope to amine
2. Use and generation of azides – process safety issue?
3. Low temperature (min -50 °C cooling fluid on reactor)
4. Low throughput (50 L Vmax on reactor)
Azidation – Process Safety Data for Trisylazide

Exotherm starts at 120 °C, Max temperature rise 150 °C/min, Max pressure rise 21 bar/min
Azidation – Process Safety Data Azido int.

Sample ID: L34849-14, 2 mL viscous oil mixture of WAY-121609
TSU1-200610251.dat

Shallow exotherm at ~140 °C
Target Kilolab Vessel
Azidation: Process Development

Process Improvements:

- KHMDS sourced as 0.91 M solution in THF (vs 0.5 M in toluene)
- Trisyl Azide sourced as 30 wt% solution in toluene
- Reduced solvent required to dissolve substrate from 6.5 to 2.5 vol
- Overall throughput improved from 2.8 kg input to 5 kg

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Base Addition Time (min)</th>
<th>Enolate Hold Time (min)</th>
<th>Trisylazide solution (°C)</th>
<th>Hold Time</th>
<th>Assay Yield (%)</th>
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Azidation: ReactIR™ Monitoring

IR Spectral Region of Interest

- Starting material carbonyl stretch: 1775-1825 cm\(^{-1}\)
- Enolate carbonyl stretch: 1715-1740 cm\(^{-1}\)
- Azide stretch: 2090-2150 cm\(^{-1}\)
Azidation: ReactIR™ Monitoring

- ReactIR Profile at -45 °C for KHMDS and Trislyazide Additions

![Graph showing ReactIR Profile at -45 °C for KHMDS and Trislyazide Additions]

- KHMDS addition
- Trisylazide addition

Legend:
- Peak 1 1775-1825 cm⁻¹
- Peak 2 1715-1740 cm⁻¹
- Peak 3 2090-2150 cm⁻¹
Azidation: ReactIR™ Monitoring

Stability: Enolate held at -45 °C for 4 h

- Intensity of enolate signal decreased 18% over 4 h
- Half life ~ 12 h @ -45 °C
Azidation: ReactIR™ Monitoring

ReactIR Profile at -10 °C for KHMDS and Trisylazide Additions

Half life ~ 3h @ 10 °C
Enolization – Azidation Performance

- **14 kg of KHMDS (20 wt% in THF) added over 45 minutes**
  - Reactor temp: -47 to -42 °C
  - Jacket temp: -50 to -45 °C

- **17 kg trisylazide (30 wt% in toluene) added over 1 h**
  - Reactor temp: -46 to -40 °C
  - Jacket temp: -55 to -50 °C
Telescoped Azidation - Reduction

Telescoping through hydrogenation

- Run reaction at -40 °C
- Sulfinic acid byproduct removed with basic washes (0.25 M K$_3$PO$_4$)
- Solvent replaced with ethanol
- Hydrogenation with 10% Pd/C 50% wet catalyst
## Kilo-lab Performance

![Chemical structures]

<table>
<thead>
<tr>
<th>Step</th>
<th>Lab demo</th>
<th>Kilolab</th>
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</thead>
<tbody>
<tr>
<td>5-6  (KHMDS-ArSO₂N₃⁻H₂))</td>
<td>168.5 g (74.9%) A%: 98.3%, LSI 1.6%</td>
<td>3.7, 3.2, 4.2 kg (62.7%) A%: 98.5%, LSI 1.5%</td>
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Summary

- *In-situ* FTIR used in combination with parameter ranging experiments to define preferred operating range for low-temperature enolization-azidation sequence
- Process shown to be stable at operating temperatures between -40 to -50 °C
- *In-situ* FTIR also highlighted that trisylazide did not accumulate during addition
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