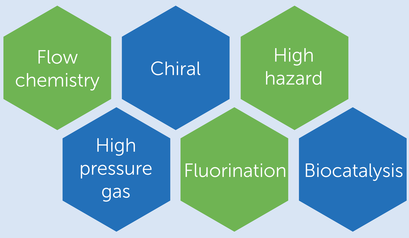
Diazomethane: embracing hazardous chemistry at scale and through the utilisation of flow technology

Embracing the use of efficient, high hazard synthetic techniques can significantly improve project time and cost. With hazard evaluation at the core of chemical development, Sterling Pharma Solutions has developed unrivalled hazardous chemistry capabilities, notably diazomethane and thiophosgene generation.

Technology and innovation at Sterling



Why use hazardous chemistry?

- More efficient, cost-effective synthetic routes
- Avoid lengthy delays and additional costs caused by developing alternative routes that avoid hazardous chemistry
- Provide competitive differentiator

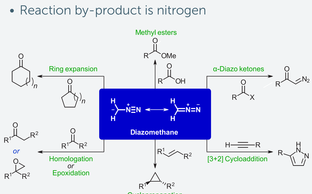
Diazomethane chemistry:

Overview:

- Interest for DAM remains high despite hazard concerns
- Large-scale generation of DAM developed in late 1990s/early 2000s using traditional, high hazard methods
- Several drugs require DAM for synthesis

Advantages of diazomethane chemistry:

- Powerful synthetic tool
  - Methylation, homologation, [3+2] cycloadditions, a-diazo ketone synthesis, epoxidation, aziridination, ring-expansions, cyclopropanations
- Used in synthetic chemistry since 1894
- Generation of reactive species used in the construction of many structural motifs
- Reaction by-product is nitrogen



Challenges of diazomethane chemistry:

- Sensitive, explosive yellow gas
- Incompatible with certain temperatures, light exposures and materials
- Toxic
- Safe generation of DAM is a challenge that requires specific expertise

Generating DAM:

Generating DAM at Sterling:

- Developed with partners
- Sterling precursor is more stable than common alternatives (eg. Diazald)
- High exothermic onset (123 °C)
- Heat of the reaction from KOH is ~8x lower than Diazald
- Can be stored for 6+ months at ambient temperature and pressure

Case study: generating DAM at Sterling:

The project:

- Only DAM is suitable for the project- 300+ conditions screened
- Cyclopropanation of a complex, electron deficient alkene
- Manufacturing is to start in Q3 2019 at >200Kg per batch scale

Chemistry process development:

- Thorough development studies were completed by Sterling, including:
  - DAM generation
  - DAM/ N_2 flow rate and concentration
  - Temperature control for prep, DAM generation and cyclopropanation
  - Influence of ambient light explored
  - Spiking and stressing studies
  - Critical Process Parameters (CPP) study

Optimisation of health, safety and environmental factors:

- DAM quench, scrubbing procedure
- Waste treatment
- Extensive hazard assessment with customers and external safety experts

Diazomethane: continuous/semi-continuous generation

Modern advances in flow chemistry allow technologies, such as DAM generation, to be utilised in more efficient, controlled and safer ways.

Generating diazomethane in flow:

Tube in tube:

- Multi-layer tube system separating substrate mixture from DAM generation mixture through a gas permeable layer.
- DAM gas passed into reaction through permeable layer - no purification or extraction of DAM required
- Simpler and more effective for anhydrous DAM generation

Tube in flask:

- Semi-continuous system
- DAM generated in flow and passed though gas permeable layer into batch reaction mixture.
- Requires less DAM to be generated
- More scalable

Diazomethane in flow at Sterling:

- Advanced development of a flow chemistry alternative to DAM generation
- Collaboration with expert academics in the field of flow chemistry
- Plan for DAM in large-scale continuous manufacturing
- Data expected to validate design plan; installation scheduled for Q1 2019 with process validation in Q2 2019

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