Safety Evaluation of the Copper-Mediated Cross-Coupling of 2-Bromopyridines with Ethyl Bromodifluoroacetate in DMSO

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Why be Concerned with Process Safety?

To avoid scenes like this!

Curtesy of Dr. Will Kowalchyk, Mettler-Toledo AutoChem, Inc.
Process Safety Begins in the Lab

Why?

• Most reactive chemical incidents occur in research laboratories.

• Most incidents involving a chemical reaction could have been prevented, if the process hazards were understood beforehand.

Solution

• Process safety should be considered early to avoid surprises during scale-up. Early identification of significant exotherms should be used to trigger the assessment of thermal hazard risks related to the process before scale-up.

• Personal safety should be considered always. A safe, well-controlled working environment in both the lab and plant is key to avoiding incidents during synthesis, safety studies and manufacturing.

Curtesy of Dr. Will Kowalchyk, Mettler-Toledo AutoChem, Inc.
Chemical Reaction Hazards

- Chemical reactions either release heat or absorb heat.
  - Majority of chemical reactions in industry are *exothermic*.
- Exothermic reactions can lead to thermal runaway when the rate of heat generated exceeds the rate of heat removal.
  - As temperature increases, rate of heat production increases exponentially, but rate of heat removal increases linearly.
- Hazards from endothermic processes can arise due to rapid crystallization or gas evolution.

![Chemical Reaction Hazards Diagram](attachment:diagram.png)
Safe Process Design - Full Criticality Assessment

- Is there a potential runaway scenario?
- If the reaction reaches the MTSR, will that trigger a decomposition reaction?
- The decomposition reaction can be characterized with DSC or ARC.

Stoessel, F. Basel, CH, WILEY-VCH Verlag GmbH & Co. KGaA, 2008
Curtesy of Dr. Will Kowalchyk, Mettler-Toledo AutoChem, Inc.
Criticality Classification of Chemical Processes

- $T_p$: Process temperature
- $T_b$: Boiling point of the solvent
- $\Delta T_{ad}$: Adiabatic temperature rise
- MTSR: Maximum Temperature of a Synthesis Reaction = $T_p + \Delta T_{ad}$
- $T_{D24}$: The temperature at which the reaction will reach the maximum self-heating rate under adiabatic conditions in 24 h
- $\Delta H$: Heat of reaction

• Classes 1-3 do not have thermal potential to reach onset of the secondary reaction through self-heating.
• Classes 4 and 5 have the thermal potential to self-heat to the decomposition onset temperature.

Stoessel, F. Basel, CH, WILEY-VCH Verlag GmbH & Co. KGaA, 2008
Cu-Mediated Cross-Coupling Safety Hazards

- Potential safety hazards with this reaction in DMSO were first reported by Merck scientists; however, detailed information was not disclosed.
- Merck scientists reported that the reaction mixture in DMF was stable, and was scaled up to 4.5 kg of 2-bromopyridine.
- In a reaction performed in a 125-mL reactor without active cooling, the reaction temperature rapidly spiked to ~100 °C from 55 °C upon the addition of 1.3 equiv of ethyl bromodifluoroacetate to a mixture of 50.6 mmol of 2-bromopyridine and 2.1 equiv of copper in 40 mL of DMSO.
The thermogram showed a sharp exothermic event with $-555.3 \text{ J/g}$ energy release.

Significantly lower onset temperature ($\sim 158 ^\circ \text{C}$) compared to neat DMSO ($\sim 270 ^\circ \text{C}$).
DSC Analysis of Post-Reaction Mixture in DMF

- DSC indicated that the reaction mixture in DMF was stable at up to 400 °C

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• A major exothermic event with an onset temperature of 115.5 °C was detected.

• This decomposition gave an estimated heat release of $-597 \text{ J/g}$ with a maximum self-heating rate of 143 °C/min and a $\Delta T_{ad}$ of 284 °C.

• The ARC test reached the maximum cut-off pressure during the evaluation with a cool down pressure of 414.6 psia at 29.4 °C.
Reaction Calorimetry by HF Cal

\[ \Delta H = -13.5 \text{ kJ}. \quad \Delta T_{ad} = 129.5 \degree C, \quad \text{MTSR} = 189.5 \degree C \gg \text{onset temperature of DMSO decomposition} \]

• Without sufficient cooling, the system could self-heat to quickly trigger the decomposition of DMSO to result in a runaway reaction.

## Substrate Scope of Exotherm

A Cu (2.1 eq), solvent, temperature

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<th>R</th>
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<th>Temp. (°C)</th>
<th>Method</th>
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<th>ΔH (kJ)</th>
<th>ΔT_{ad} (°C)</th>
<th>MTSR (°C)</th>
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Substrate Scope of Exotherm
Cu-Mediated Coupling Safety Hazards Summary

• Significant exothermic events were observed during the copper-mediated cross coupling of 2-bromopyridines with ethyl bromodifluoroacetate in the studied systems.

• The onset temperature of the decomposition of DMSO in the reaction mixture was much lower than that of neat DMSO.

• In all reactions in DMSO, the MTSR exceeded the onset temperature of the decomposition of DMSO.

• In the absence of active cooling, the system could quickly trigger the decomposition of DMSO resulting in a runaway reaction.
DSC Analysis of Post-Reaction Mixture in DMSO

- In both experiments, significantly lower onset temperatures (~223 °C) were detected compared to that of neat DMSO (273 °C).
- In the case of 9:1 DMSO/water, the peak temperature representing the main DMSO decomposition reaction was shifted to a much lower temperature.

ARC Analysis of Post-Reaction Mixture

Two independent exothermic events were detected for the reaction mixtures in anhydrous DMSO and 9:1 DMSO/water.

The small exothermic events (around 150 °C) in both reaction mixtures were consistent with the polymerization of the styrene product.

The major exothermic events were comparable for the reaction mixtures in DMSO and 9:1 DMSO/water (190.7 °C and 196.0 °C), respectively.

Thermal Instability of NaH/DMSO by ARC

[Graphs and images showing heat rate and pressure changes over temperature, indicating ARC cell rupture.]
Thermal Instability of NaH/DMSO by DSC

- 10.3% NaH + 6.9% Mineral oil + 82.8% DMSO
- Neat DMSO

- 14°C 39°C 99°C 120°C 255°C 278°C 285°C 93.193J/g 1223.7J/g
- 13.67J/g 18°C 20°C

- 320°C 396°C

111.59J/g

Temperature $T \, (^{o}C)$

Heat Flow (Normalized) $Q \, (W/g)$

Dimethyl Sulfoxide

Ethylene

Dimethyl Sulfide
DMSO is a Widely Used Solvent; However……

- The thermal decomposition of DMSO has been a growing concern in the chemistry community.
- DMSO undergoes a severe exothermic decomposition just above its atmospheric boiling point.
- This thermal decomposition can be autocatalytic in the presence of acids, bases, and/or halogenated organic compounds.
- Researchers at Merck report that several processes using DMSO as solvent were found to have significantly lower onset temperatures of decomposition compared to neat DMSO.
- When two bromo compounds are coupled using copper powder in DMSO at 50 °C, ARC analysis on the pre-reaction mixture showed two exotherms starting at 50 and 70 °C, and the second exotherm generated heat and pressure at an extremely high rate.
- When a fluoro compound and a quinone were coupled in the presence of KOt-Bu in DMSO at 150 °C for 20 h, an isothermal age ARC at 170 °C revealed a thermal runaway after 23 h.
DMSO is also Incompatible with……

- Violent or explosive reaction with many acyl, aryl, and nonmetal halides (e.g., AcCl, BsCl, bromobenzoyl actanilide, cyanuric chloride, iodine pentafluoride, Mg(ClO$_4$)$_2$, CH$_3$Br, NiO$_4$, oxalyl chloride, P$_2$O$_3$, PCl$_3$, POCl$_3$, AgF, NaH, SO$_2$Cl$_2$, SiCl$_4$, and SOCl$_2$).

- Violent or explosive reaction with boron compounds (e.g., BH$_3$, nonahydrononaborate (2-) ion), 4(4'-bromobenzoyl)acetanilide, carbonyl diisothiocyanate, dinitrogen tetraoxide, hexachlorocyclotriphosphazine, Cu/TCA, metal alkoxides (e.g., KOt-Bu, sodium i-propoxide), TFAA.

- Forms powerfully explosive mixtures with magnesium perchlorate, aluminum perchlorate, sodium perchlorate, and iron (III) nitrate, perchloric acid, periodic acid, SO$_3$.

Recommendations

- Identify replacement solvents for DMSO if possible.

- Evaluate thermal stability of the reaction mixtures if DMSO is used as the solvent.

- Design procedure accordingly to mitigate potential risks.
## Acknowledgements

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