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Agriculture Division of DowDuPont

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.

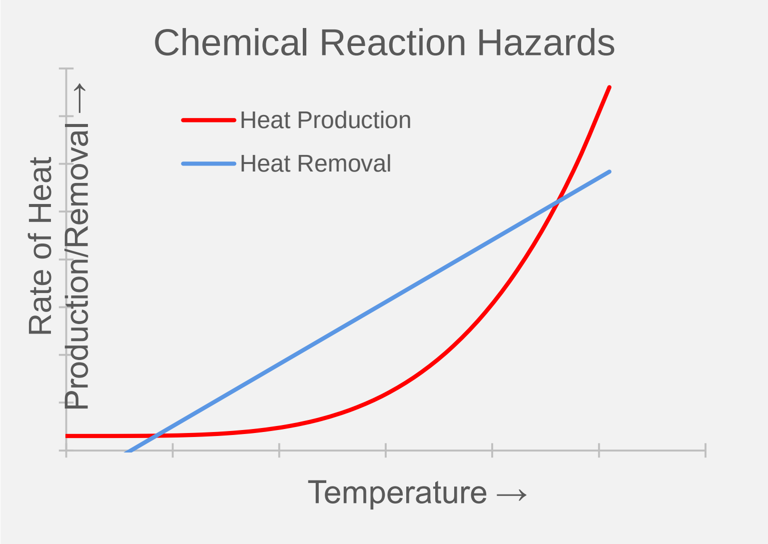
The 12 Principles of Green Chemistry

- Prevent Waste
- Design Safer Chemicals and Products
- Design Less Hazardous Chemical Syntheses
- Use Safer Solvents/ Reaction Conditions
- Increase Energy Efficiency
- Use Renewable Feedstocks
- Design Chemicals and Products that Degrade After Use
- Minimize the Potential for Accidents
- Analyze in Real Time to Prevent Pollution
- Use Catalysts, Not Stoichiometric Reagents
- Maximize Atom Economy
- Avoid Chemical Derivatives

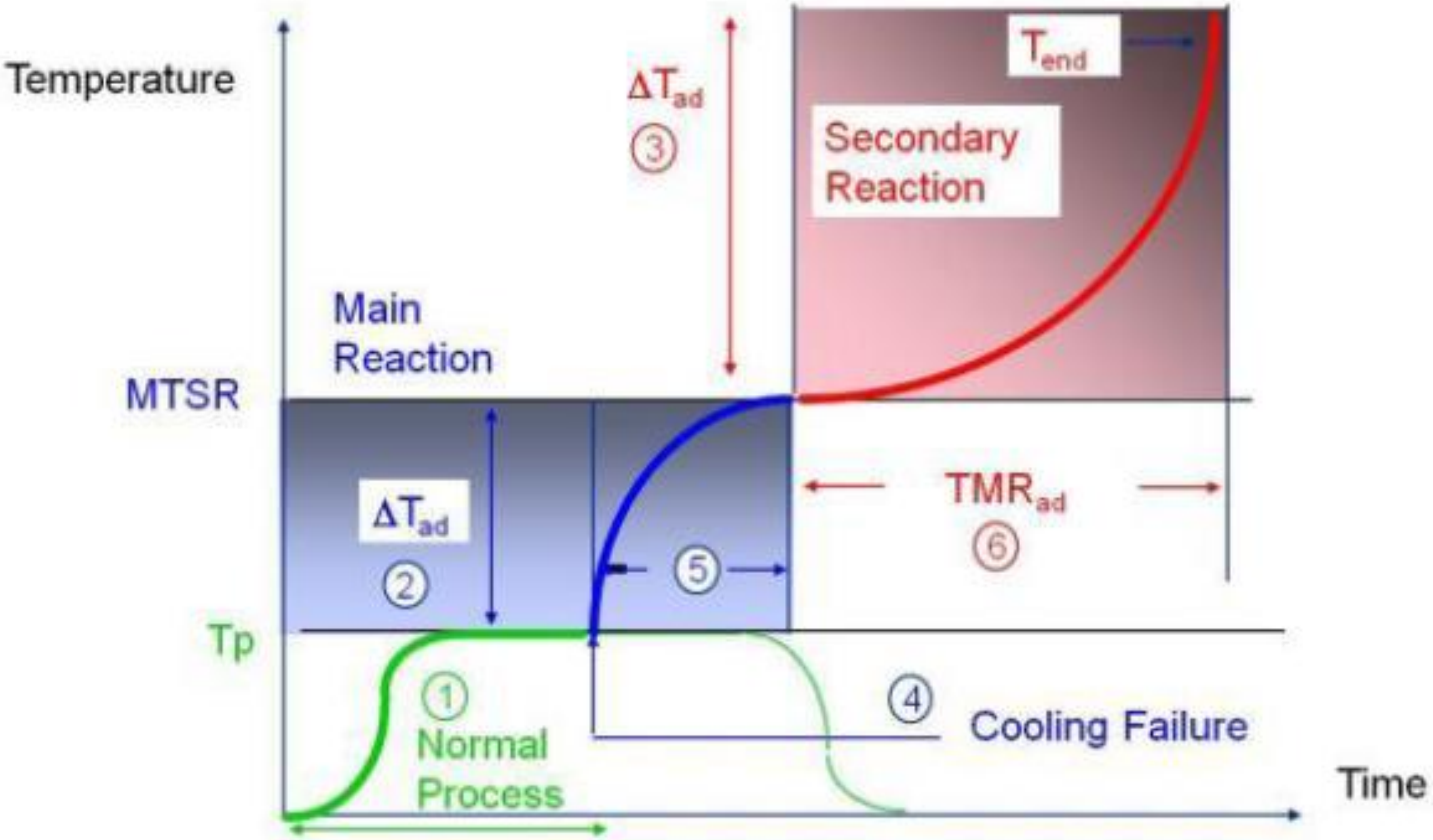
Curtesy of Dr. Will Kowalchyk, Mettler-Toledo AutoChem, Inc.

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.



Safe Process Design - Full Criticality Assessment



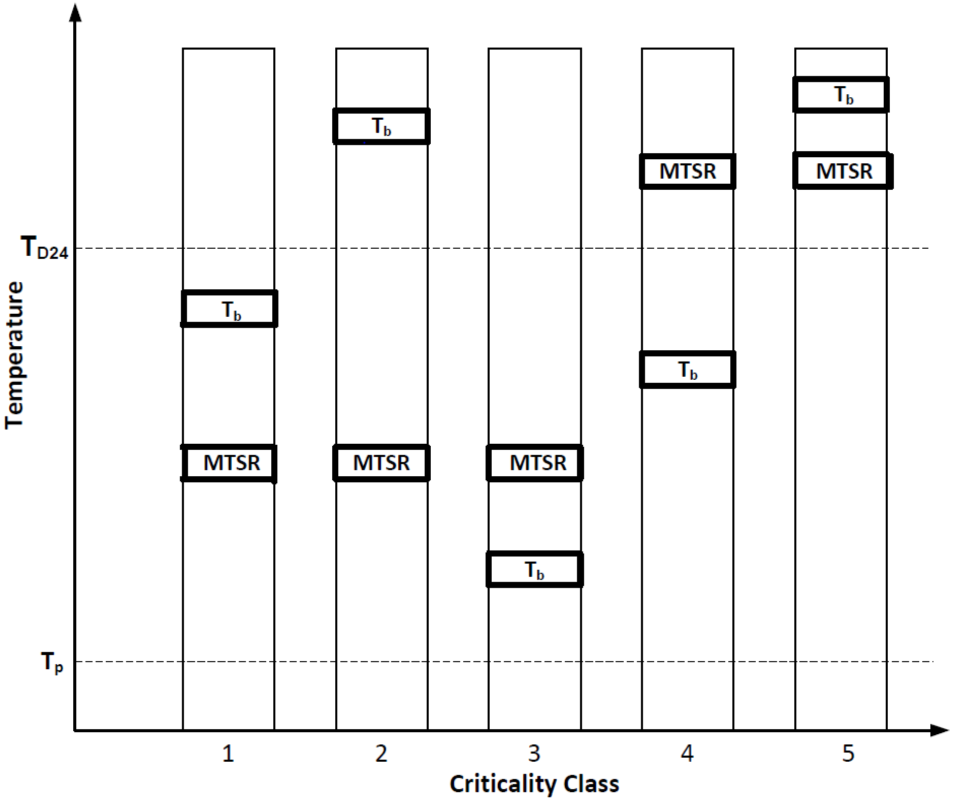
- Is there a potential runaway scenario?
- If the reaction reaches the MTSR, will that trigger a decomposition reaction?
- The decomposition reaction can be characterized with DSC or ARC.

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

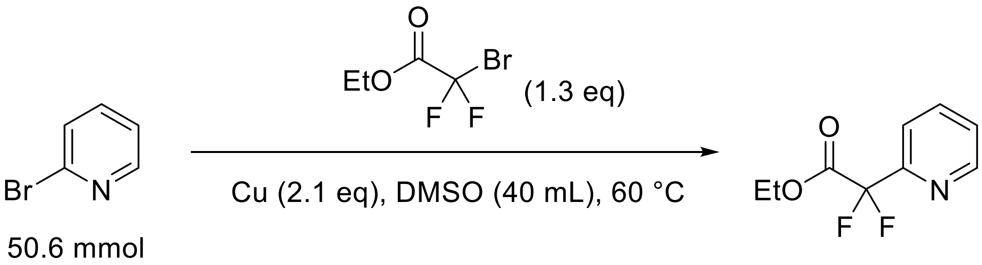
- T_p: Process temperature
- T_b: Boiling point of the solvent
- ΔT_{ad}: Adiabatic temperature rise
- MTSR: Maximum Temperature of a Synthesis Reaction = $T_p + \Delta T_{ad}$
- T_{D24}: The temperature at which the reaction will reach the maximum self-heating rate under adiabatic conditions in 24 h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

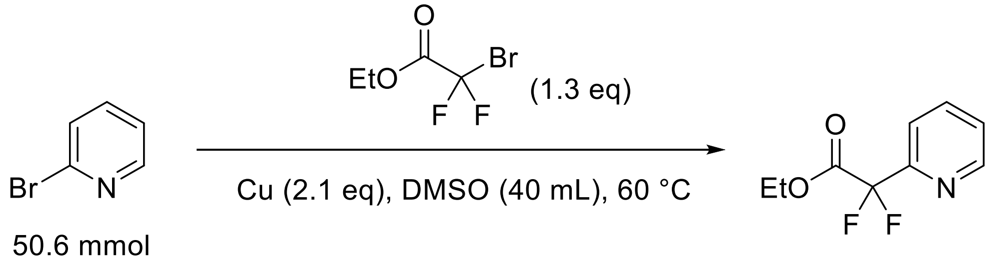
Stoessel, F. Basel, CH, WILEY-VCH Verlag GmbH & Co. KGaA, 2008

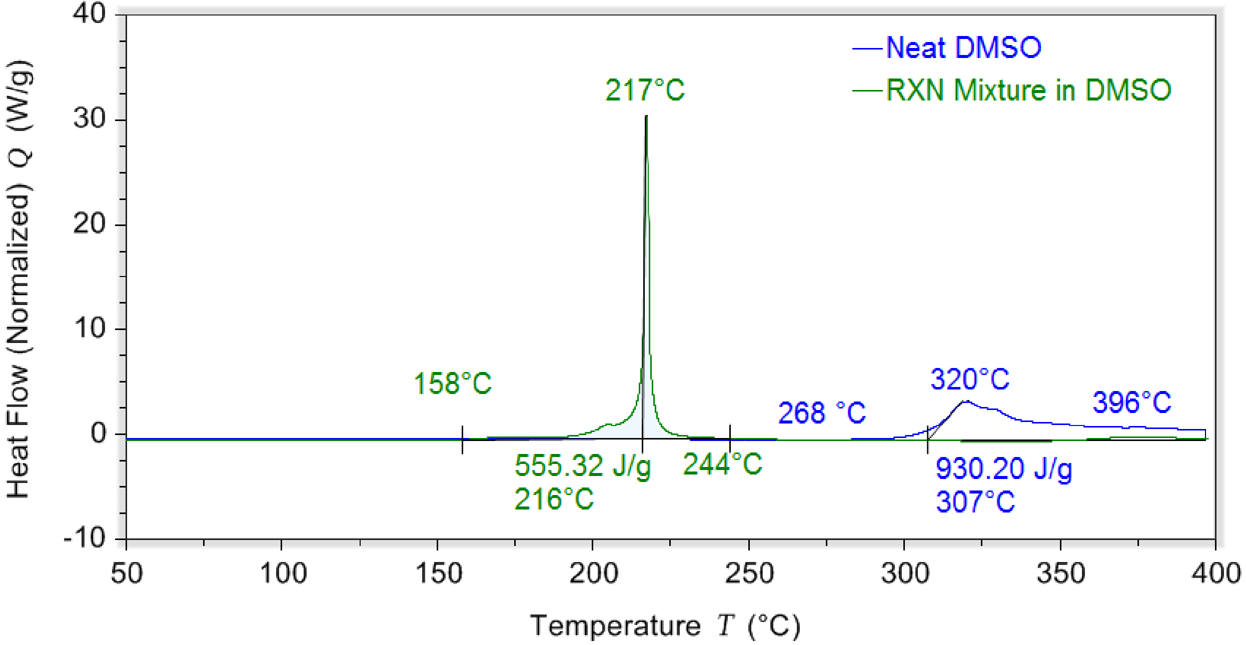
Cu-Mediated Cross-Coupling Safety Hazards



- 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.

DSC Analysis of Post-Reaction Mixture in DMSO





- The thermogram showed a sharp exothermic event with –555.3 J/g energy release.
- Significantly lower onset temperature (~158 °C) compared to neat DMSO (~270 °C).

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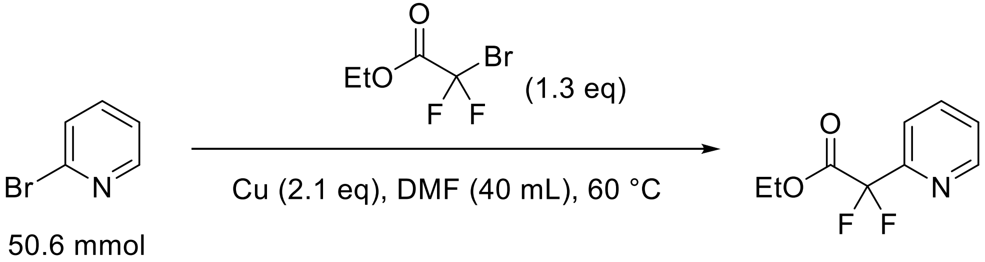
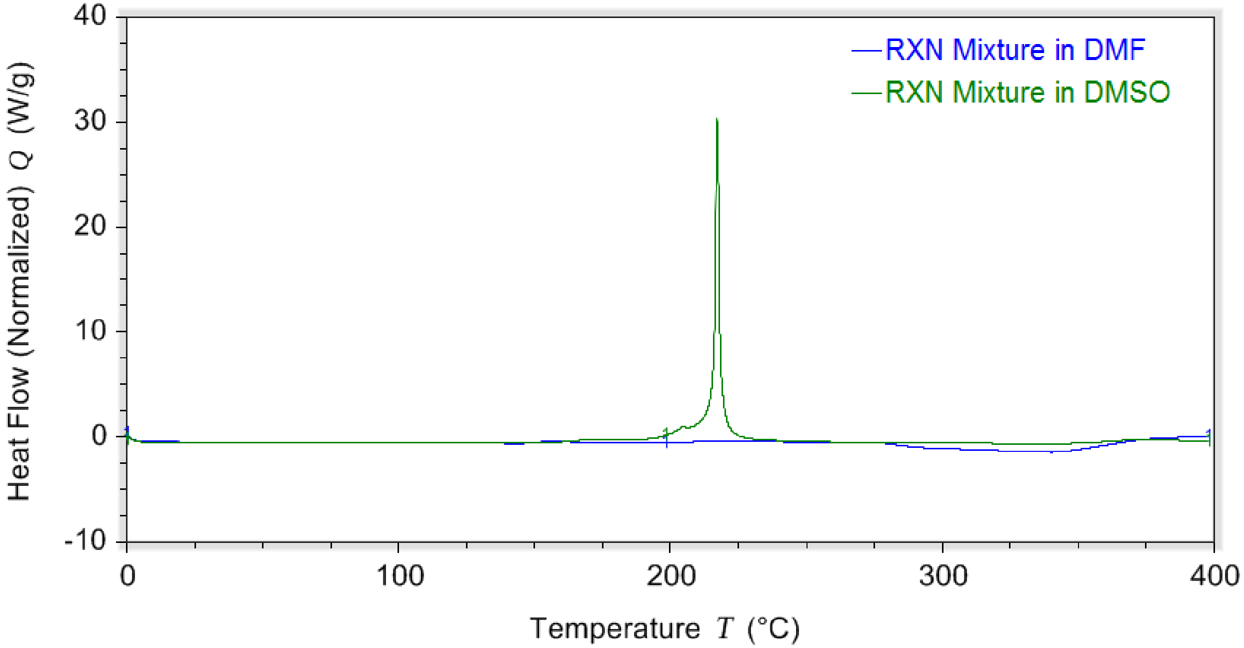
DSC Analysis of Post-Reaction Mixture in DMF





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

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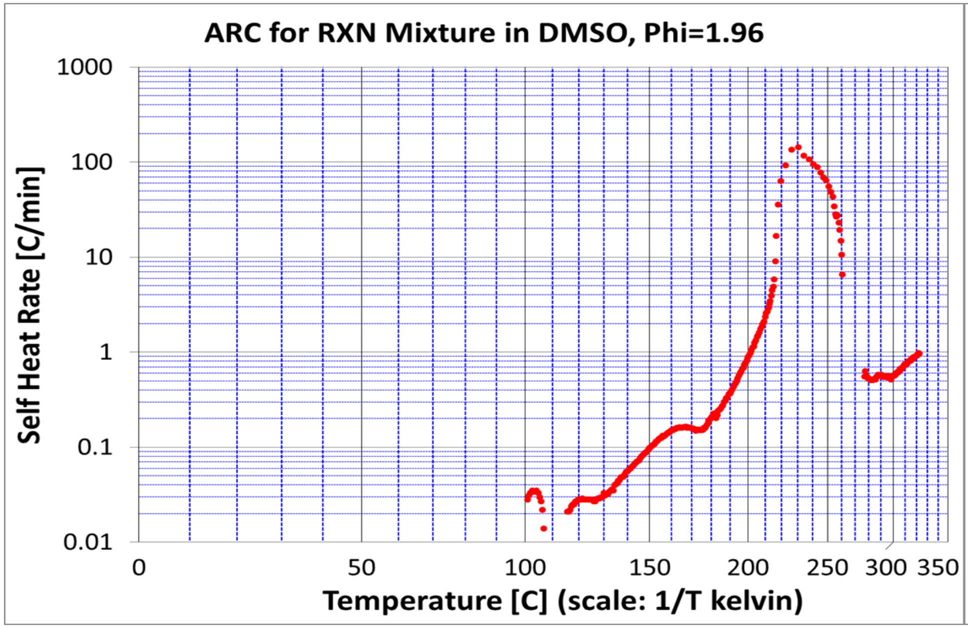
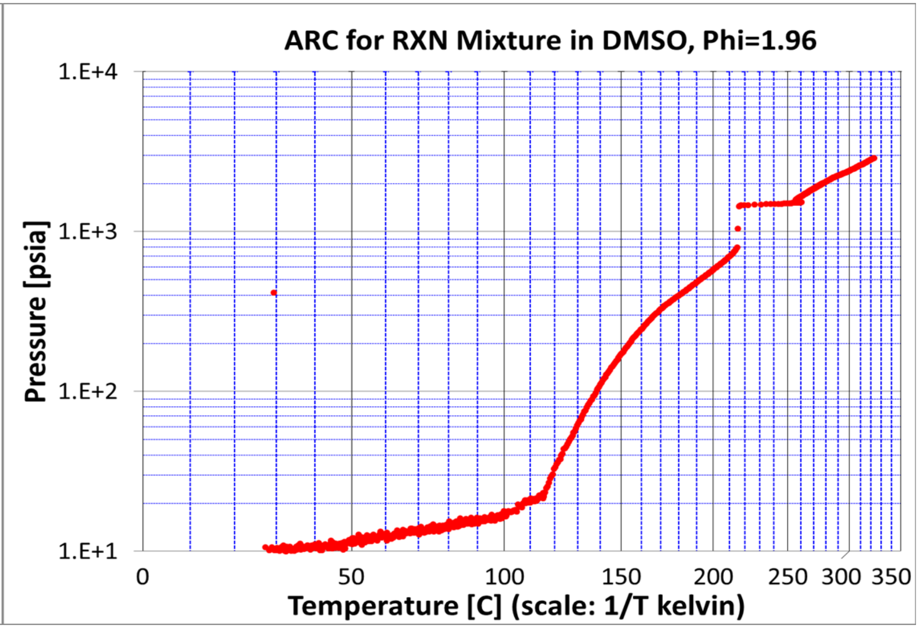
ARC Analysis of Post-Reaction Mixture in DMSO





- A major exothermic event with an onset temperature of 115.5 °C was detected.
- This decomposition gave an estimated heat release of –597 J/g with a maximum self-heating rate of 143 °C/min and a ΔT_{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.

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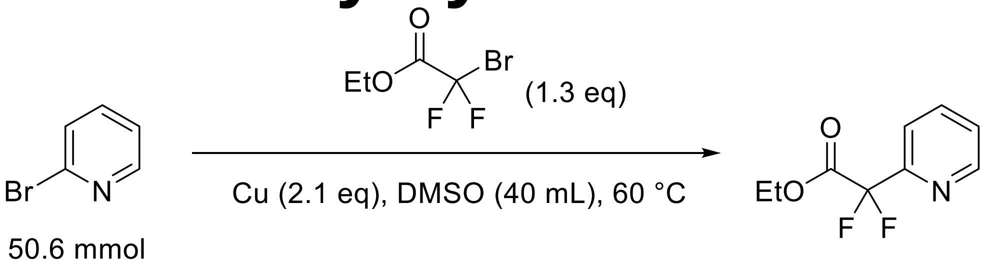
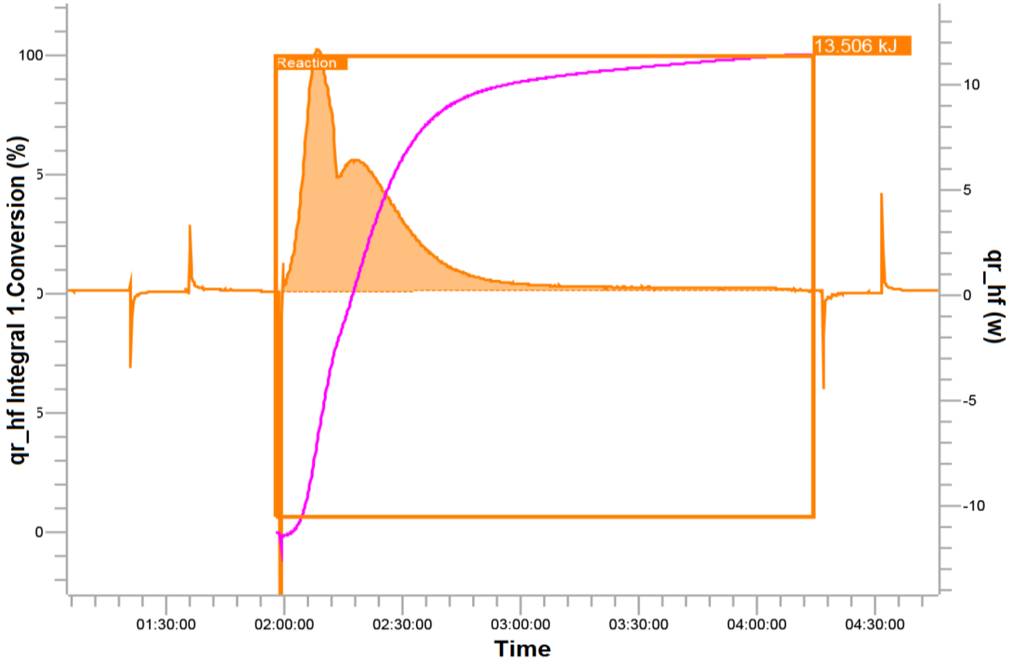
Reaction Calorimetry by HF Cal





- ΔH = –13.5 kJ. ΔT_{ad} = 129.5 °C, MTSR = 189.5 °C >> 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.

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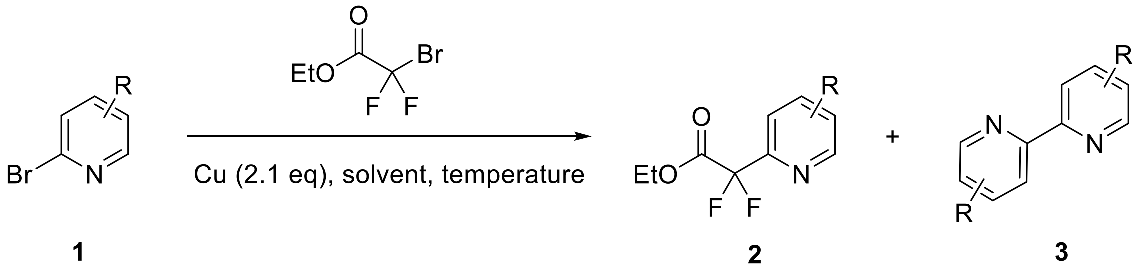
Substrate Scope of Exotherm



Entry	R	Solvent	Temp. (°C)	Method	GC (% AUC)			ΔH (kJ)	ΔT_{ad} (°C)	MTSR (°C)
					1	2	3			
1	H	DMSO	60	A	0	>99.9	0	–13.5	129.5	189.5
2	H	DMF	60	A	3.2	96.8	0	–13.0	163.1	223.1
3	3-Me	DMSO	40	B	0	98.3	1.7	–13.5	130.4	170.4
4	3-CF_3	DMSO	60	A	0	67.1	32.9	–11.9	119.2	179.2
5	3-CF_3	DMSO	60	B	0	85.2	14.8	–13.0	134.2	194.2
6	4-Me	DMSO	40	B	0.2	98.6	1.2	–13.7	138.9	178.9
7	4-F	DMSO	60	A	0	90.5	9.5	–13.3	136.4	196.4
8	5-Me	DMSO	40	B	0	98.3	1.7	–13.4	132.6	172.6
9	5-CF_3	DMSO	60	A	0	90.3	9.7	–13.6	136.2	196.2
10	5-Cl	DMSO	60	A	0.7	99.3	0	–13.9	141.1	201.1
11	6-OMe	DMSO	40	B	9.6	90.4	0	–12.4	128.6	168.6
12	6-OMe	DMSO	60	A	8.1	91.9	0	–12.9	133.8	193.8
13	6-CF_3	DMSO	60	A	14.4	85.6	0	–12.2	121.8	181.8
14	6-Cl	DMSO	60	A	7.8	92.2	0	–12.7	121.7	181.7

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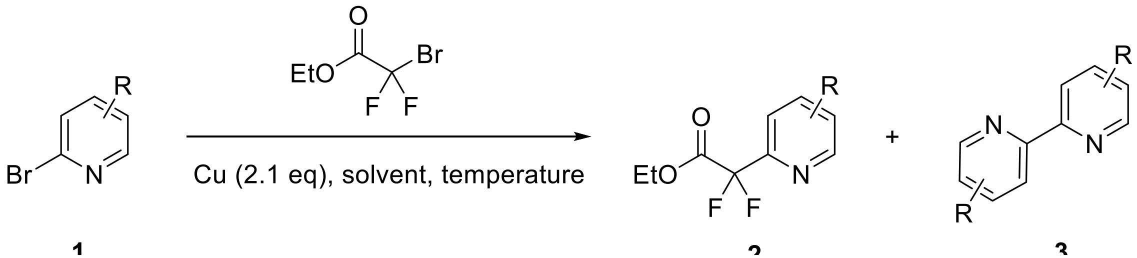
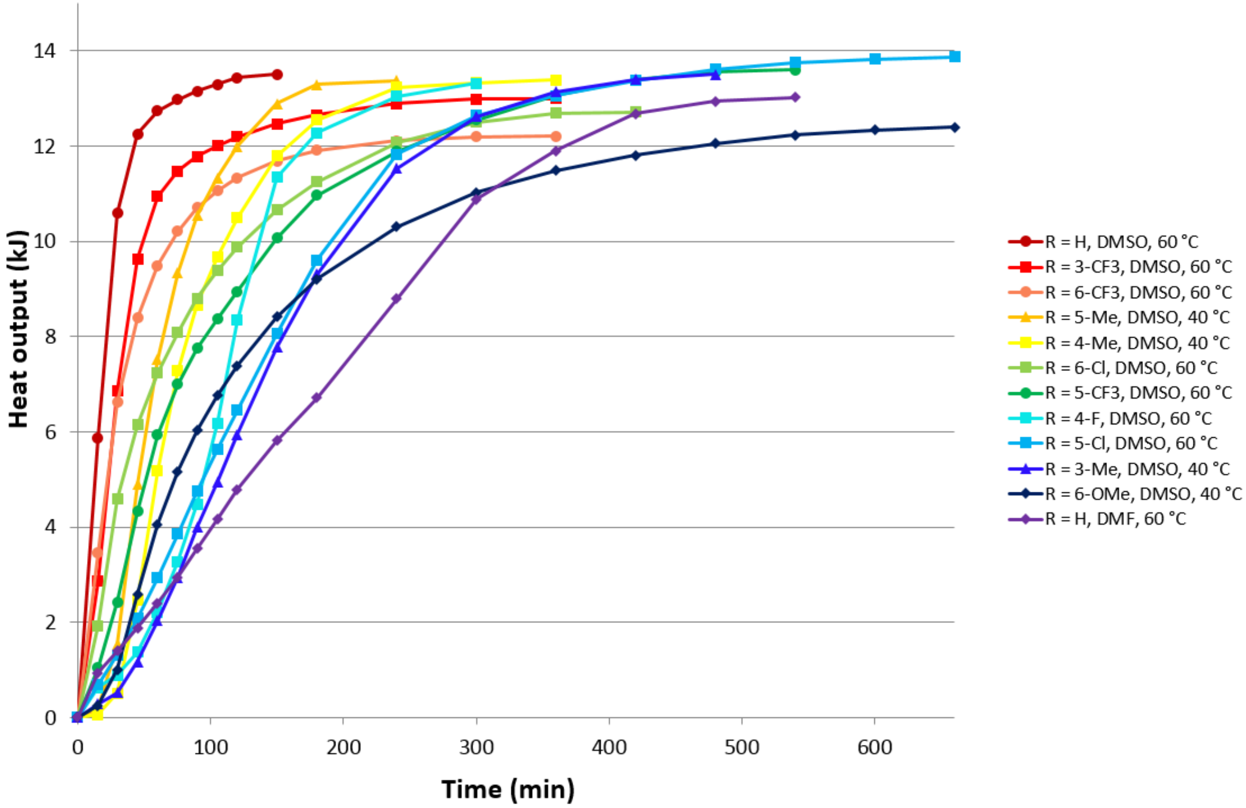
Substrate Scope of Exotherm



Cu (2.1 eq), solvent, temperature

1 2 3



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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.

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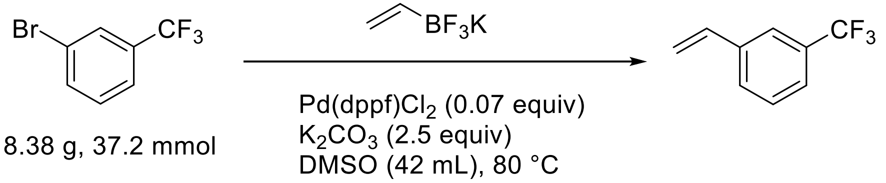
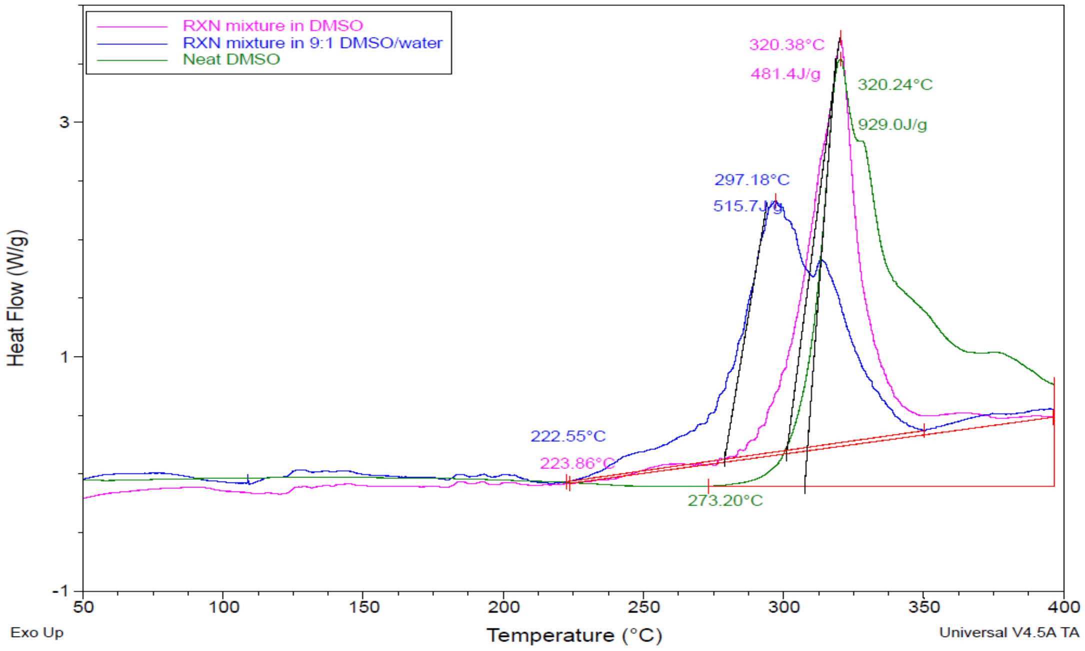
DSC Analysis of Post-Reaction Mixture in DMSO



8.38 g, 37.2 mmol

Pd(dppf)Cl_2 (0.07 equiv)
K_2CO_3 (2.5 equiv)
DMSO (42 mL), 80 °C



- 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.

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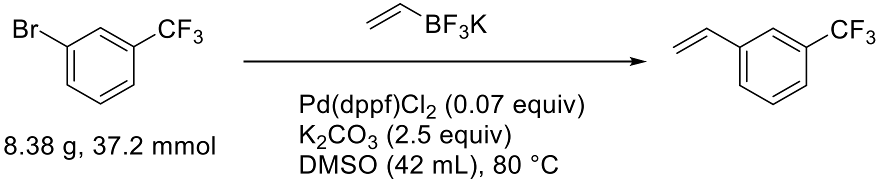
ARC Analysis of Post-Reaction Mixture



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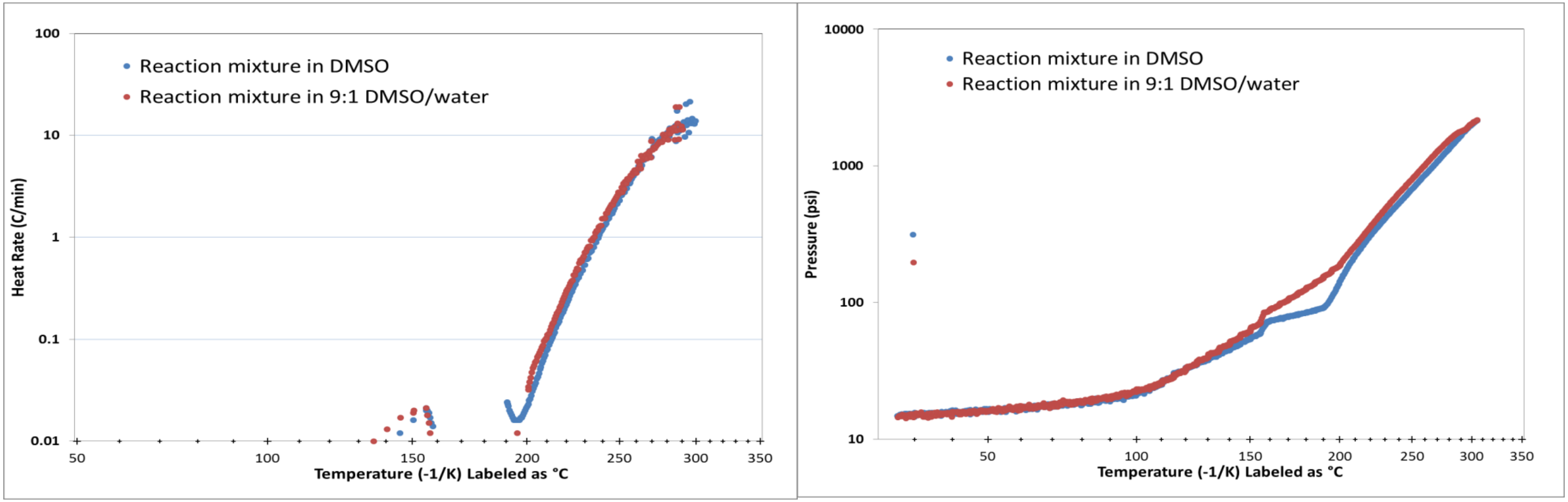

- Two independent exothermic events were detected for the reaction mixtures in anhydrous DMSO and 9:1 DMSO/water.
- The small exothermic events (around 150 °C) in both reaction mixtures were consistent with the polymerization of the styrene product.
- The major exothermic events were comparable for the reaction mixtures in DMSO and 9:1 DMSO/water (190.7 °C and 196.0 °C), respectively.

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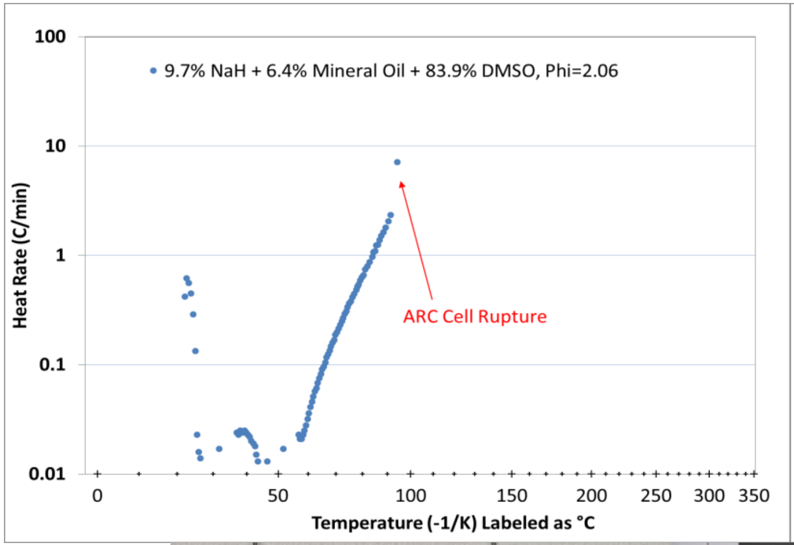
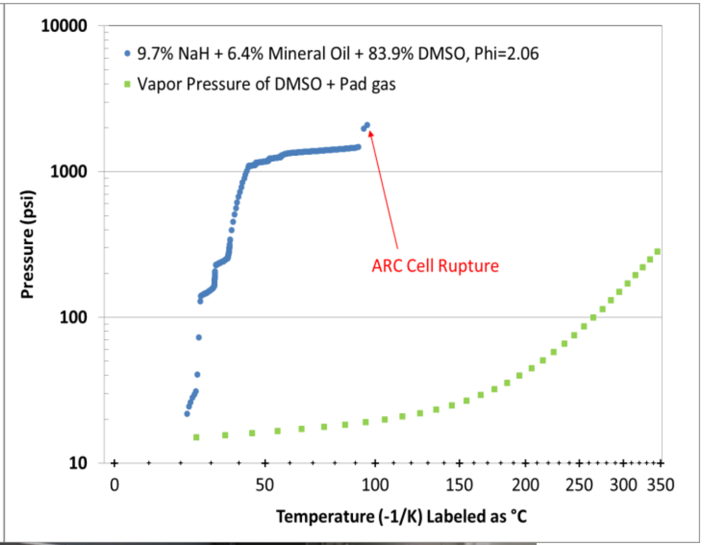
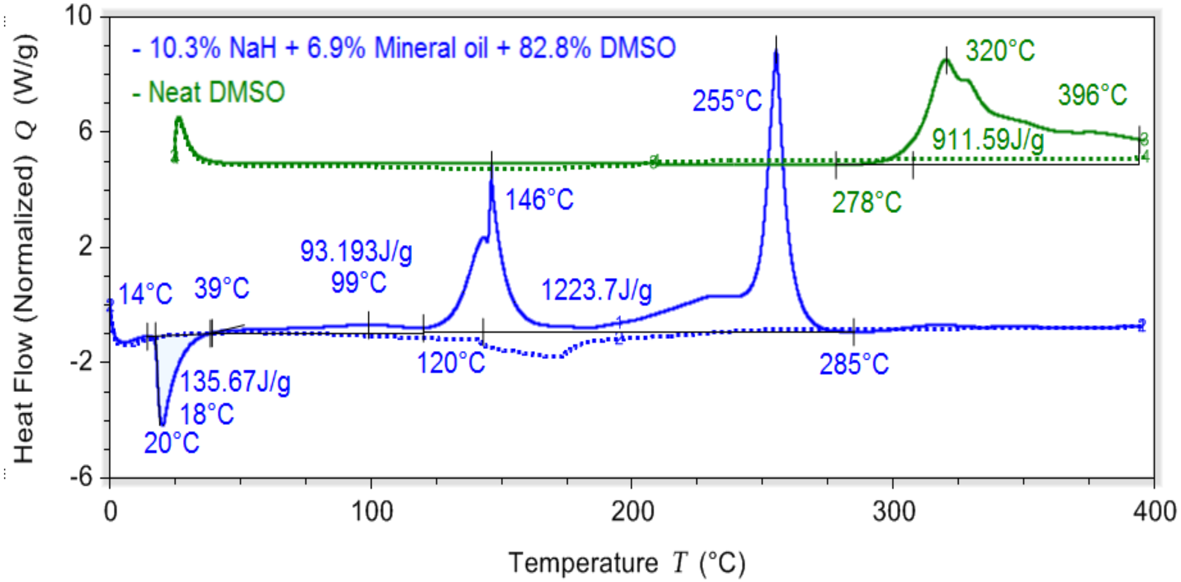
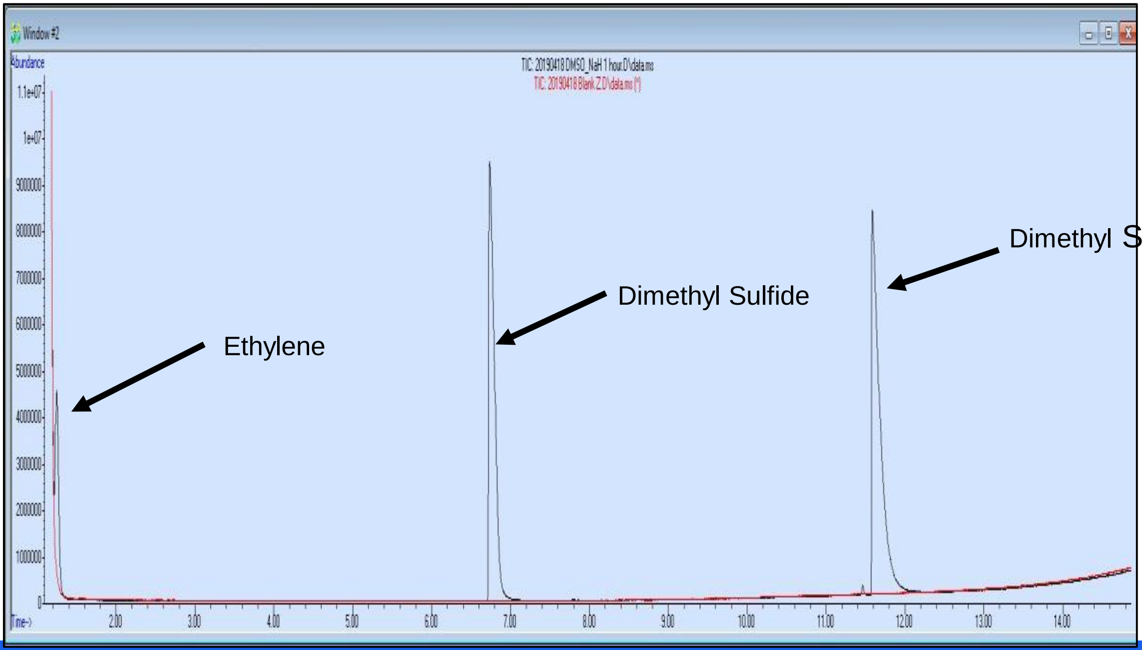
Thermal Instability of NaH/DMSO by ARC





Thermal Instability of NaH/DMSO by DSC





Ethylene

Dimethyl Sulfide

Dimethyl Sulfoxide

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 KO*t*-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_3Br, NiO_4, oxalyl chloride, P_2O_3, PCl_3, $POCl_3$, AgF, NaH, SO_2Cl_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., KO*t*-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.

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Cu-mediated coupling safety hazards

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