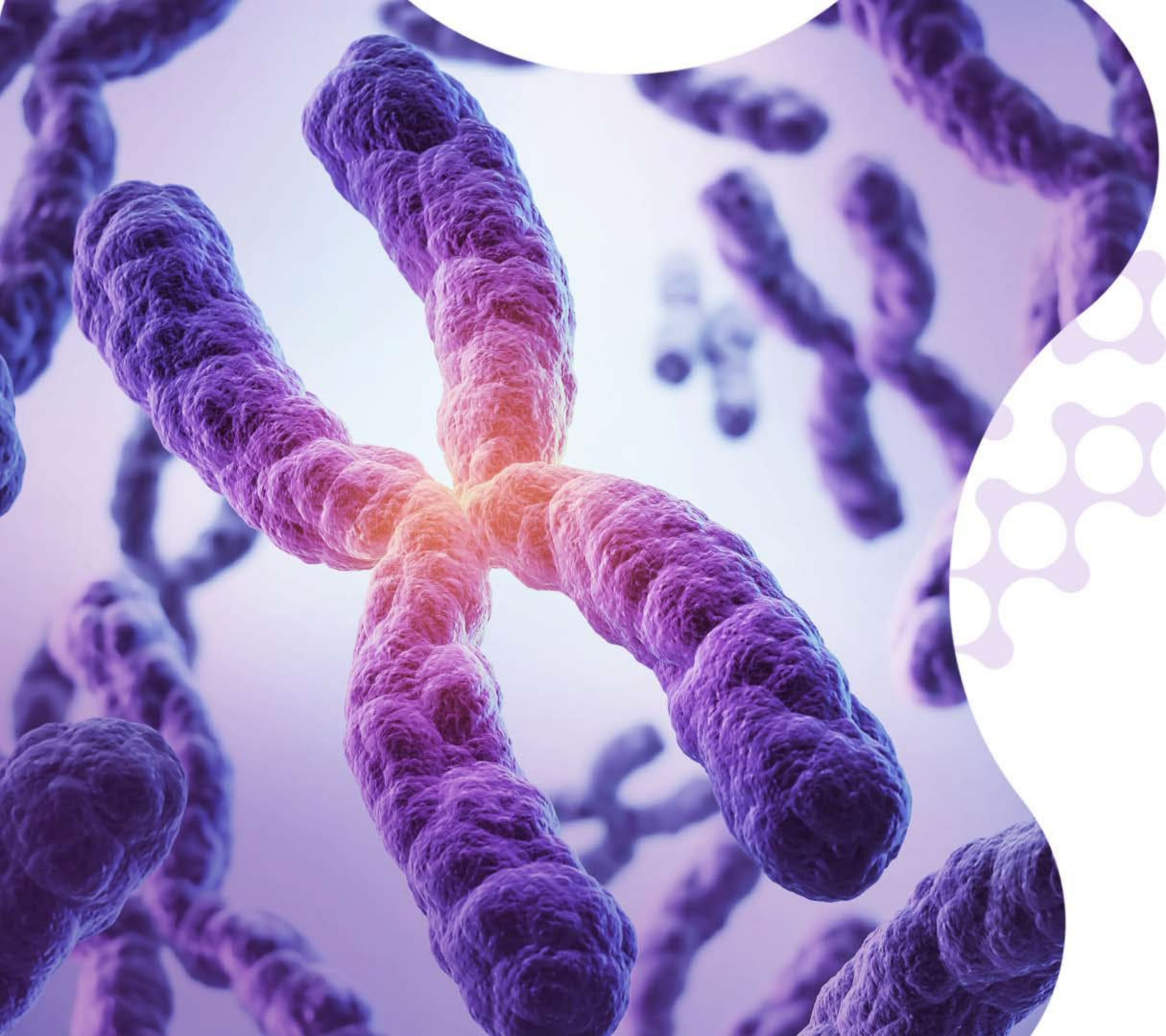
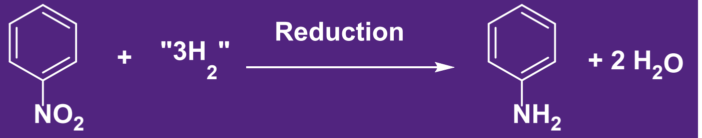


Process Safety Considerations for Tetrahydroxydiboron Reductions of Aromatic Nitro Groups

Jeffrey Sperry and Connor Barrett

Nitro Reductions

- The conversion of Ar-NO_2 to Ar-NH_2 is very common in the pharmaceutical industry
- This conversion is often performed with hydrogen via precious or non-precious metal catalysis
- Newer metal-free conditions involving flavin-dependent nitroreductases are also known
- In 2022, tetrahydroxy diboron (THDB) and 4,4’-bipyridine were reported to be effective for the chemoselective reduction of aromatic nitro groups at room temperature



Nitro Group Reduction Method	Pros	Cons	Process Safety Considerations
Hydrogenation via Precious Metal Catalysis (Pd, Pt)	• Catalysts widely available • Well understood	• Costs • Removal of metal required to ppm levels	• Catalysts flammability • Use of pressure vessels • Use of hydrogen
Hydrogenation via Non-Precious Metal Catalysis (Fe, Ni)	• Lower Catalysts costs • Considered “Greener” alternatives	• More limited substrate scope • Challenging workups	• Use of Pressure vessels • Use of hydrogen
Biocatalysis	• Green alternative • Usually highly selective	• Bioengineered enzymes • More process development work required	
Tetrahydroxy diboron/4,4’-bypyridine	• No hydrogen required • Low-cost reagents	• Mechanism not fully understood	• Exotherms? • Thermal stability of THDB

The Near Miss

“Hey, have you seen this paper??”

“Hey, have you seen this paper??”

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Metal-Free, Rapid, and Highly Chemoselective Reduction of Aromatic Nitro Compounds at Room Temperature

Mingyeong Jang,[†] Taeho Lim,[†] Byoung Yong Park,[†] and Min Su Han*

Cite This: *J. Org. Chem.* 2022, 87, 910–919 Read Online

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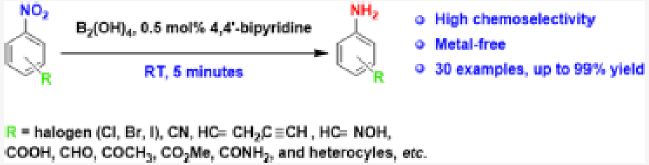
ABSTRACT: In this study, we developed a metal-free and highly chemoselective method for the reduction of aromatic nitro compounds. This reduction was performed using tetrahydroxydiboron [$B_2(OH)_4$] as the reductant and 4,4′-bipyridine as the organocatalyst and could be completed within 5 min at room temperature. Under optimal conditions, nitroarenes with sensitive functional groups, such as vinyl, ethynyl, carbonyl, and halogen, were converted into the corresponding anilines with excellent selectivity while avoiding the undesirable reduction of the sensitive functional groups.



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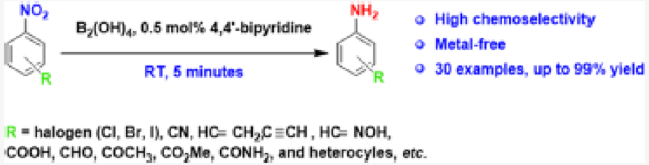

The Near Miss

- A chemist was performing the published procedure as described in the paper on a proprietary nitro compound on multi-gram scale
- After charging all of the reagents, the reaction experienced a significant exotherm that caused the mixture to exit the top of the flask “like a volcano”
- No injuries, no damage to equipment
- Chemist reached out for process safety assistance

Gram-Scale Reaction for the Reduction of the Nitro Compound. (*E*)-4-Nitrostilbene (15 mmol, 3.3786 g), $B_2(OH)_4$ (45 mmol, 4.0343 g), and 4,4′-bipyridine (0.075 mmol, 0.0117 g) were dissolved in 100 mL of DMF. The reaction mixture was stirred at room temperature for 5 min under air conditions. The reaction mixture was diluted with water and ethyl acetate. The organic layer was collected and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under

The Near Miss – Investigation and Data Gathering

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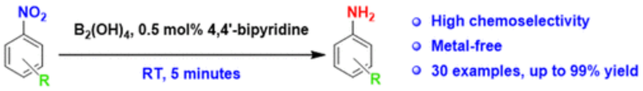
The Near Miss – Investigation and Data Gathering

Process Safety Concerns:

1. The title of the publication
2. Lack of understanding of reaction mechanism



R = halogen (Cl, Br, I), CN, HC= CH_2,C≡CH , HC= NOH, COOH, CHO, $COCH_3$, CO_2Me, $CONH_2$, and heterocycles, *etc.*

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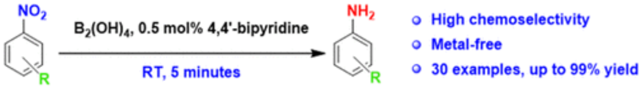

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Experiments were then conducted to investigate the reaction pathway of our protocol. First, deuterium labeling experiments were conducted using 1-bromo-4-nitrobenzene (**1e**) (Figure 1). Crude samples were analyzed by ^{1}H NMR by taking aliquots of the reaction mixture and dissolving in $CDCl_3$. In the ^{1}H NMR spectrum of **2e**, the peak at ∼δ 3.8 ppm is the signal representing the H atoms in the $-NH_2$ group, and its ideal integral value is two compared to those of the aromatic proton signals presenting an integral value of four. If an $-ND_2$ moiety had been generated, the integral value was expected to have been much lower than an ideal value of two. For control experiment and experiment using DMF-d_7 the integral values of the peaks representing the amine protons of **2e** were 1.88 and 1.91, respectively (Figure 1a,b,d). These results indicated that the H atoms in $-NH_2$ did not originate from DMF. As shown in Figure 1c,d, when $B_2(OD)_4$ was used instead of $B_2(OH)_4$, the integral value of the signal corresponding to the H atoms in $-NH_2$ decreased to 0.72. This value indicates that the H atoms were derived from $B_2(OH)_4$. The effects of radical inhibitors were also studied to determine if the reaction proceeds via a radical pathway. Three inhibitors [2,6-di-*tert*-butyl-4-methylphenol (BHT), hydroquinone, and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)] were selected and added during the reduction (Table S5). BHT and hydroquinone did not affect the reaction, but a diminished yield was observed when TEMPO was used. This was attributed to the decomposition of $B_2(OH)_4$ by TEMPO (Figure S2). Therefore, the reaction mechanism likely does not proceed via a radical pathway. Through this study, the source of the H atoms of the amine products was identified, and a radical pathway was excluded as the potential mechanism. However, because mechanisms can be complex and involve more than one pathway, further studies are needed to determine the mechanism of the reactions presented in this work.

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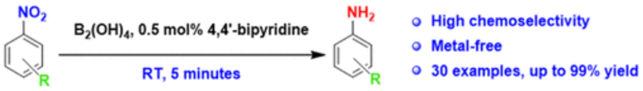

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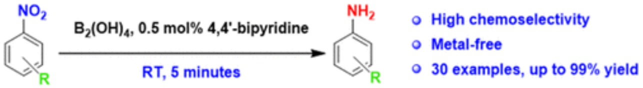

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The Near Miss – Investigation and Data Gathering

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2. Lack of understanding of reaction mechanism
3. No mention of exothermic activity

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3. No mention of exothermic activity
4. Use of polar aprotic solvents (DMF, and DSMO)

Sample	T_{onset} (°C)	ΔT_{ad} (°C)	$P_{residual}$ (bar)	$(dP/dt)_{max}$ (bar/min)	$(dT/dt)_{max}$ (°C/min)
DMSO	199.4	51.4	15.8	0.56	0.76
DMSO + DMF (13 wt%)	196.5	114	15.8	1.8	2.43
DMSO + 10 wt% NaOH	193.4	61.8	16.9	12.1	57.6
DMSO + 10 wt% KBr	154.5	73.6	32.45	94.6	89.6
DMSO + 10 wt% $FeCl_3$	166.7 267.6	147 N/A[a]	N/A	1204.9	331.0

Note a. Explosion during second exotherm

Thermochimica Acta, **2013**, 76-81

The Near Miss – Investigation and Data Gathering

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2. Lack of understanding of reaction mechanism
3. No mention of exothermic activity
4. Use of polar aprotic solvents (DMF, and DSMO)
5. Use of THDB

ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
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Thermal Stability of Tetrahydroxydiboron

Shasha Zhang,* Simon Shun Wang Leung, and Dale Vanyo

Cite This: *Org. Process Res. Dev.* 2024, 28, 2854−2861 Read Online

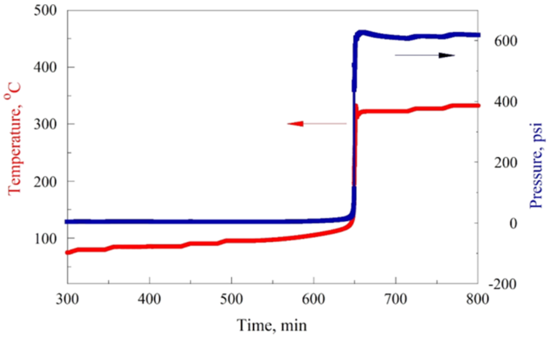

Figure 6. Temperature and pressure traces were measured from DARC.

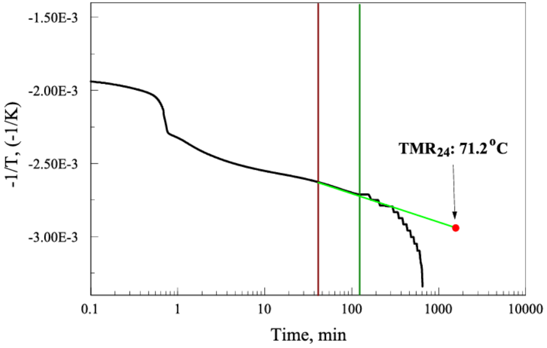

Figure 7. TMR extrapolation is based on the temperature curve shown in Figure 6.

Org.Process Res.Dev. **2024**, *28*, 2854−2861

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ❑ Starting material
   - ❑ THDB
   - ❑ 4,4’-bipyridine
   - ❑ Product
2. Thermal stability of reaction mixtures
   - ❑ Starting material in DMF
   - ❑ Stating material and 4,4’-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction

The Near Miss – Investigation and Data Gathering

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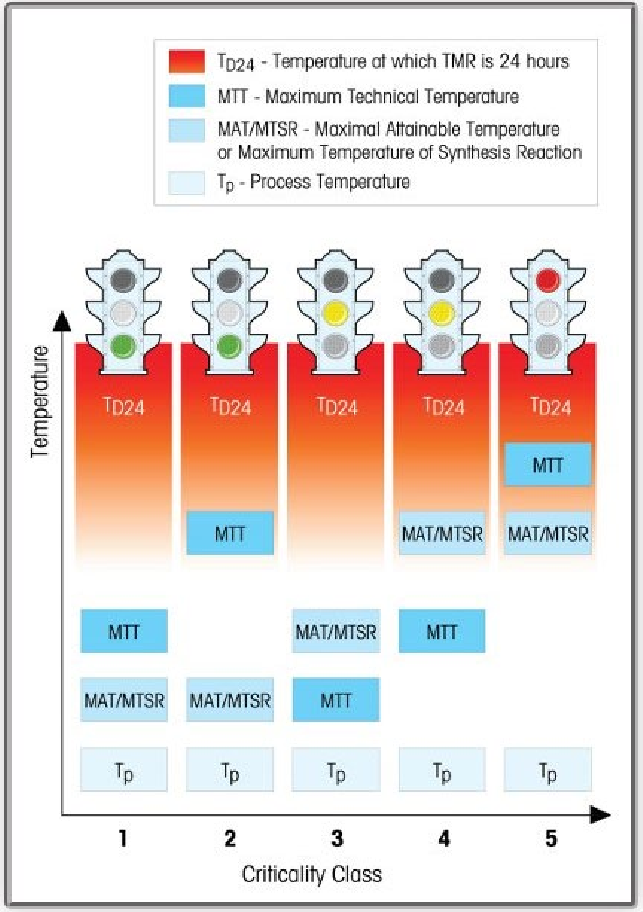

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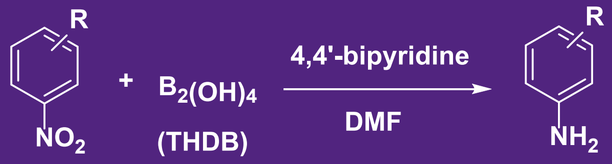
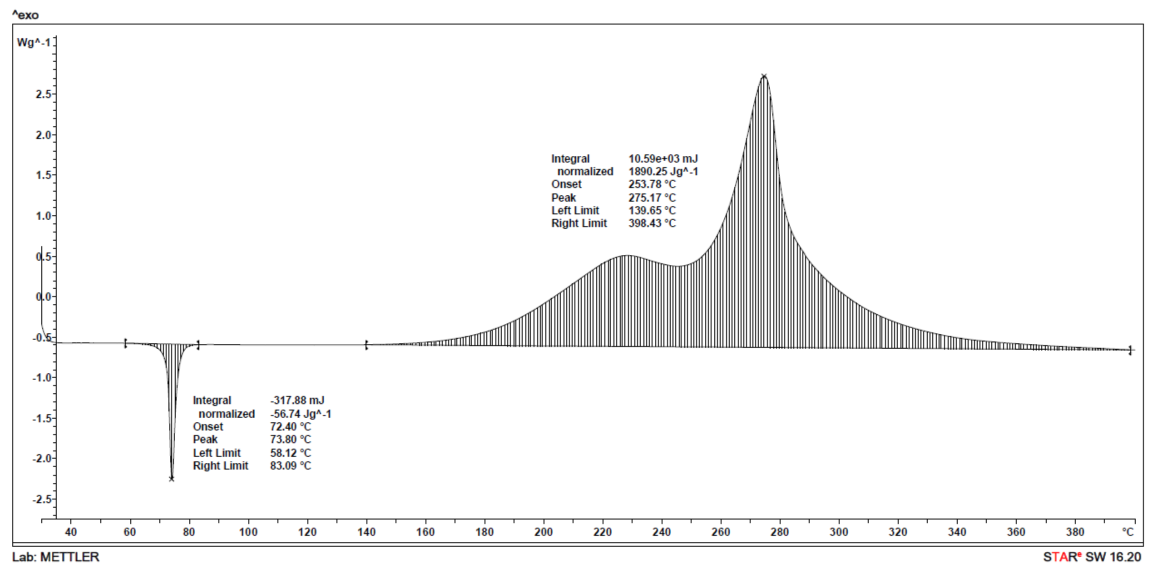


(Starting Material) (Product)



Starting material

Left Limit: 139 °C

Decomposition energy: 1,890 J/g

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

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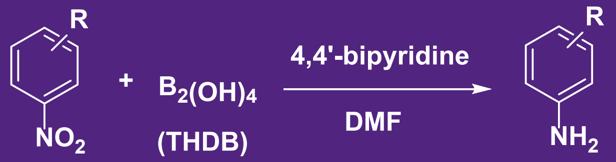
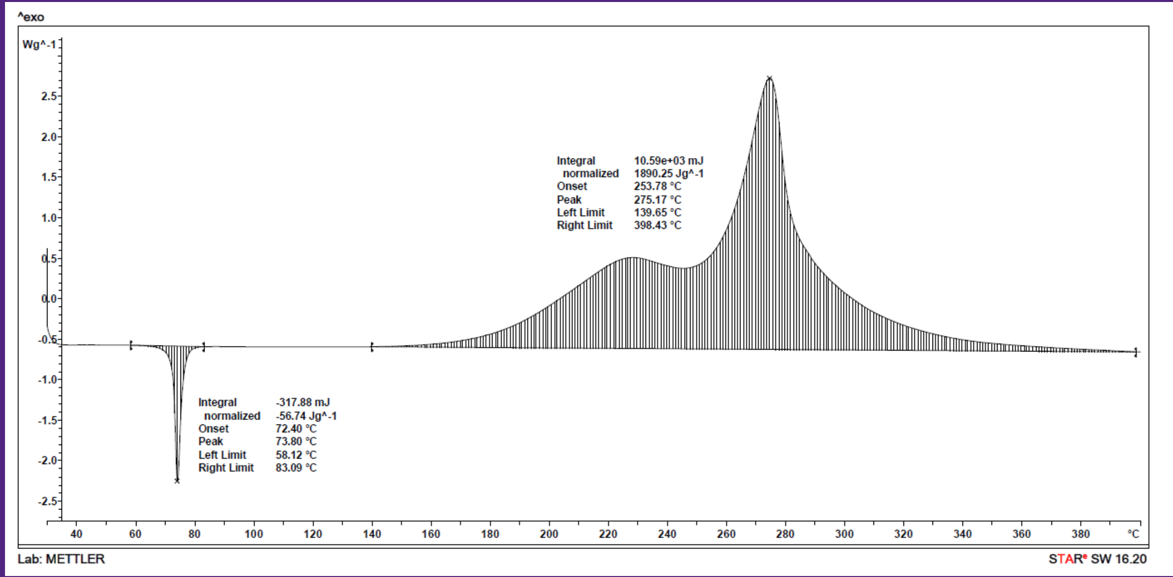


(Starting Material) (Product)



Starting material — Medium to High Risk

Left Limit: 139 °C

Decomposition energy: 1,890 J/g

The Near Miss – Investigation and Data Gathering

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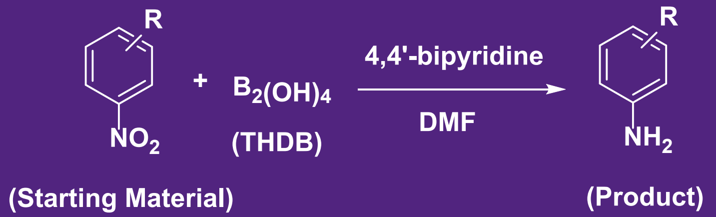

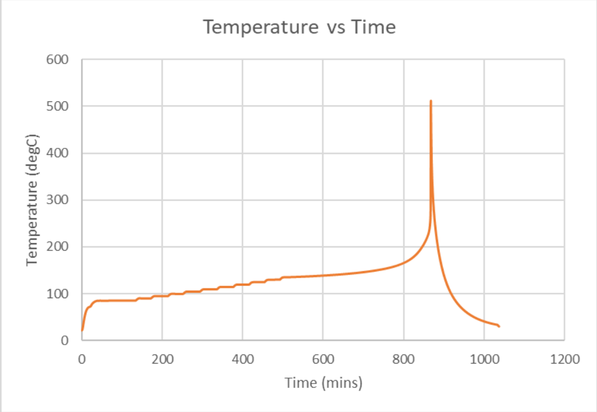

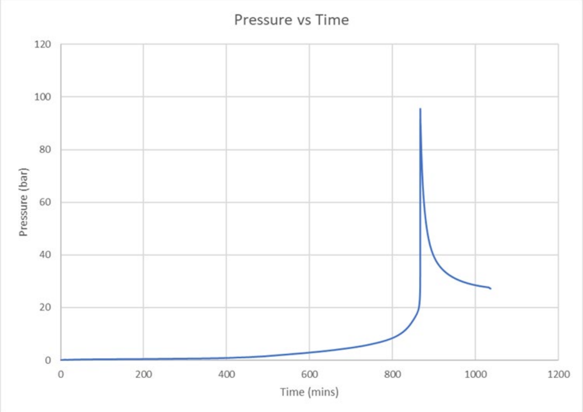

Phi Tec I of Starting material

Max Pressure rise rate = 290 bar/min

Left Limit: 135 °C

Decomposition energy: 2,397 J/g

Temperature for TMR_{24} = 91 °C

Max Temperature rise rate = 931 ° C/min

Risk: High

The Near Miss – Investigation and Data Gathering

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   - ❑ 4,4’-bipyridine
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   - ❑ End of reaction
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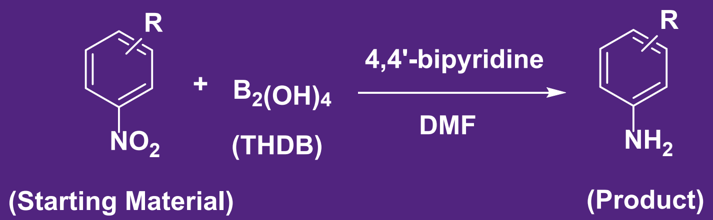

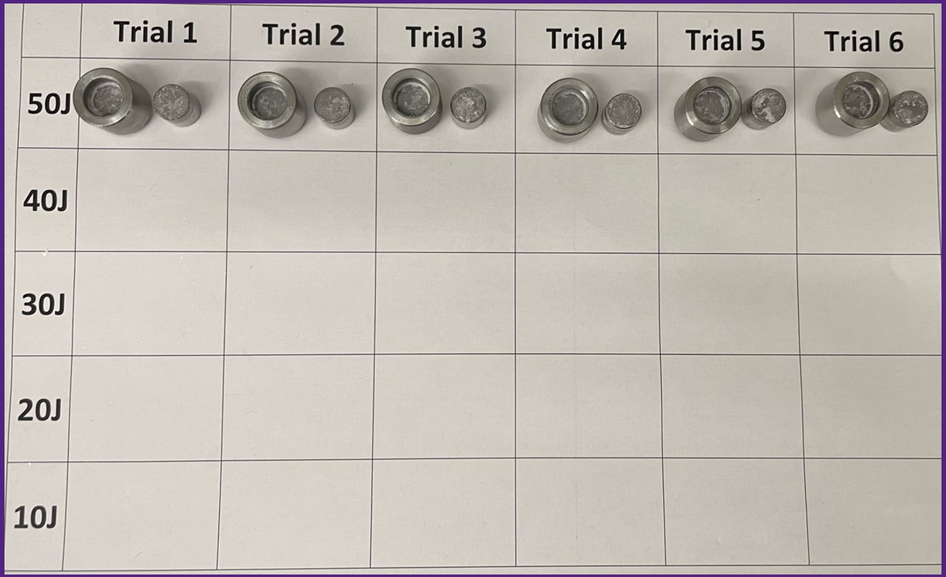

Impact Testing of Starting material

No reaction at ~50 J

Risk: Low

The Near Miss – Investigation and Data Gathering

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   - THDB
   - 4,4'-bipyridine
   - Product
2. Thermal stability of reaction mixtures
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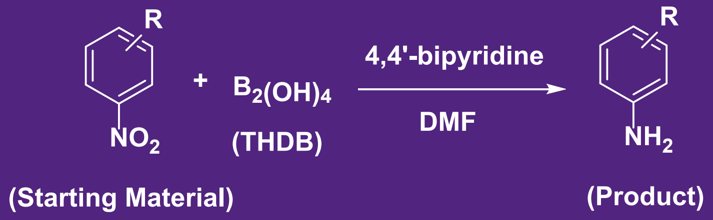
3. Heat of Reaction



Sample Size: ~10 mm^3

Room Temperature: 23 °C
Date of test: September 20, 2024

Weight (kg)	Notch #	Resulting Load on the Sample (N)	Trial Results						Comments
			1	2	3	4	5	6	
10.08	6	360	NR	NR	NR	NR	NR	NR	discoloration

Friction Testing of Starting material

No reaction at 360 N

Risk: Low

The Near Miss – Investigation and Data Gathering

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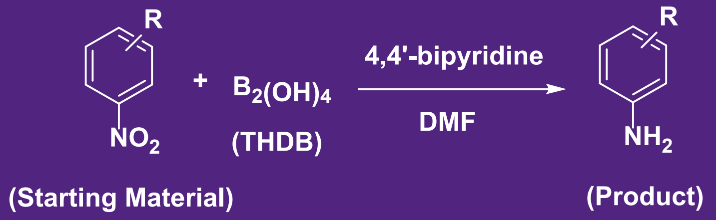
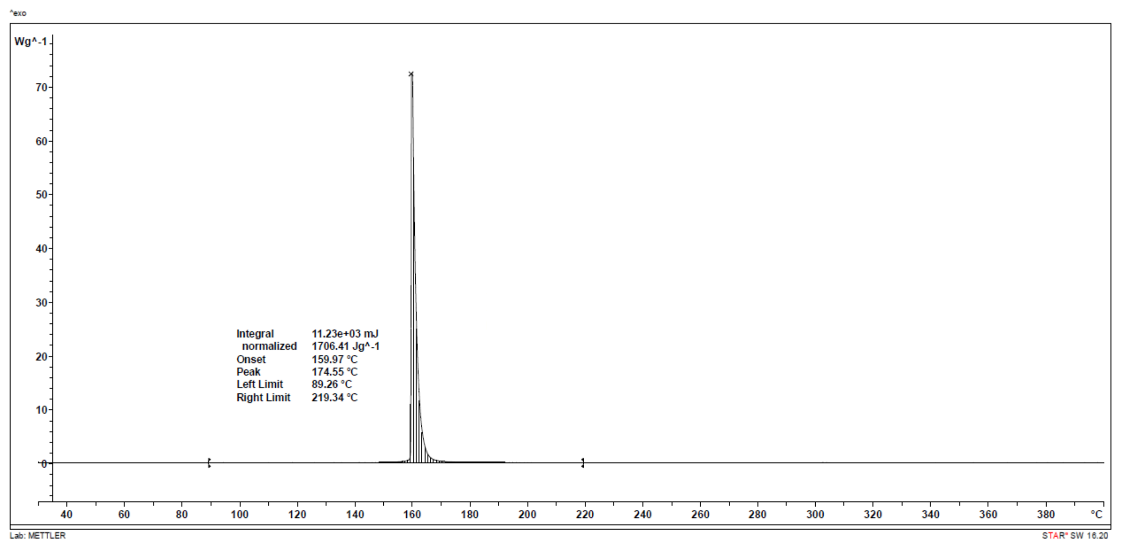
3. Heat of Reaction





DSC of THDB

Left Limit: 89 °C

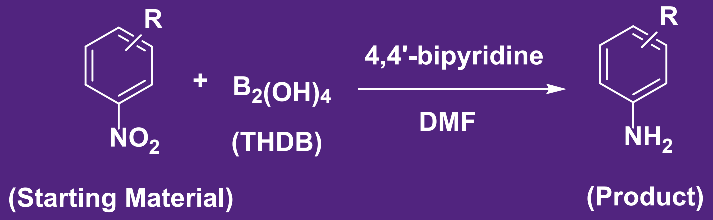
Decomposition energy: 1,706 J/g

Risk: High

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ❑ THDB
   - ❑ 4,4’-bipyridine
   - ❑ Product
2. Thermal stability of reaction mixtures
   - ❑ Starting material in DMF
   - ❑ Stating material and 4,4’-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction



Impact Testing of THDB

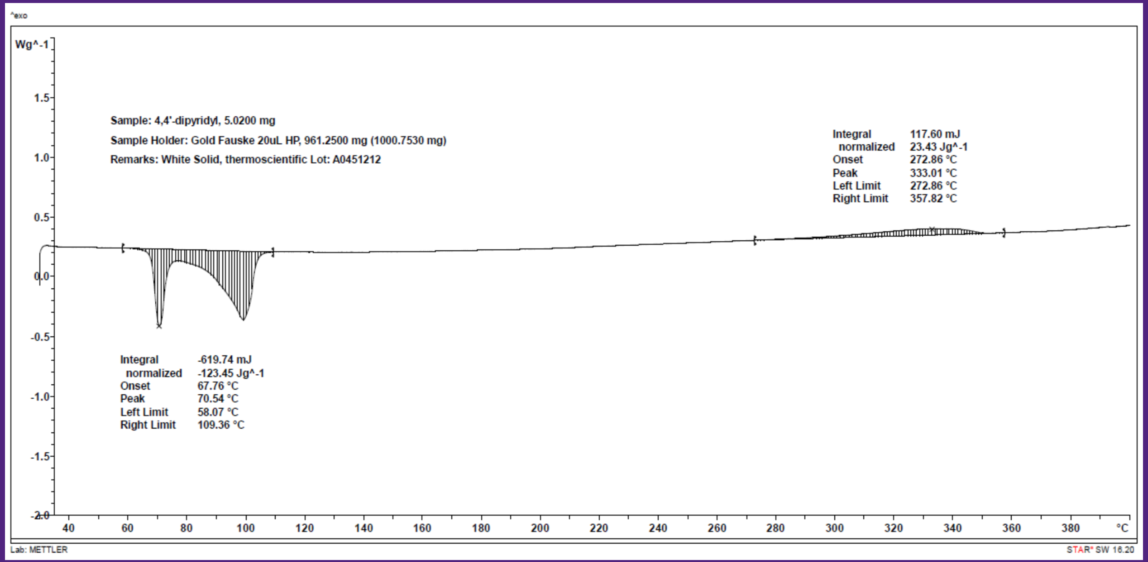
No Reaction at ~50 J

Risk: Low

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ❑ 4,4’-bipyridine
   - ❑ Product
2. Thermal stability of reaction mixtures
   - ❑ Starting material in DMF
   - ❑ Stating material and 4,4’-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction



DSC of 4,4’-bipyridine

Left Limit: 272 °C

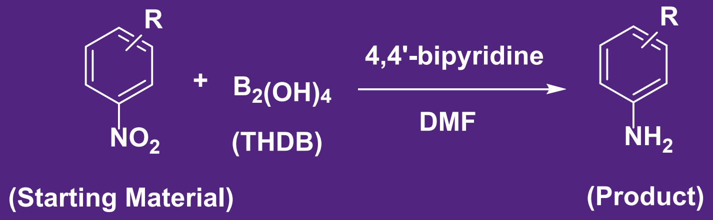
Decomposition energy: 23 J/g

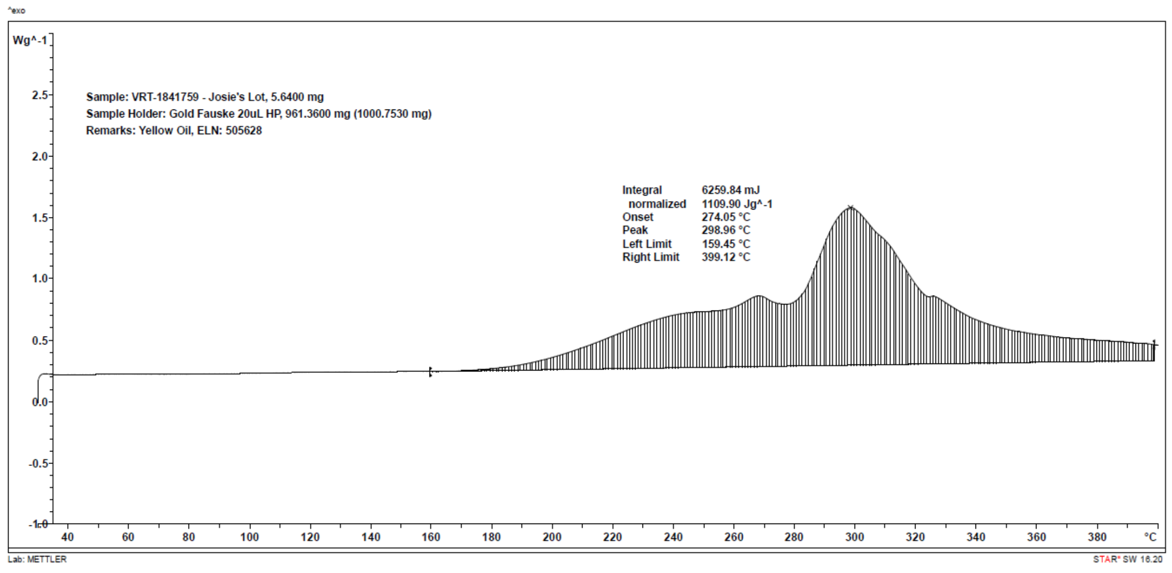
Risk: Low

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4'-bipyridine
   - ❑ Product
2. Thermal stability of reaction mixtures
   - ❑ Starting material in DMF
   - ❑ Stating material and 4,4'-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4'bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction





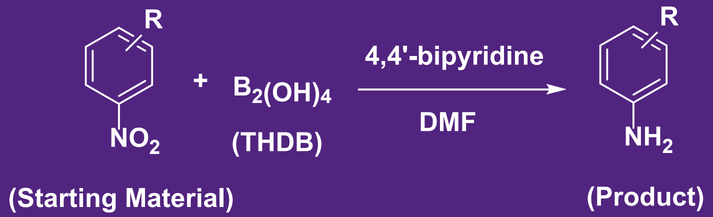
DSC of Product

Left Limit: 159 °C

Decomposition energy: 1,110 J/g

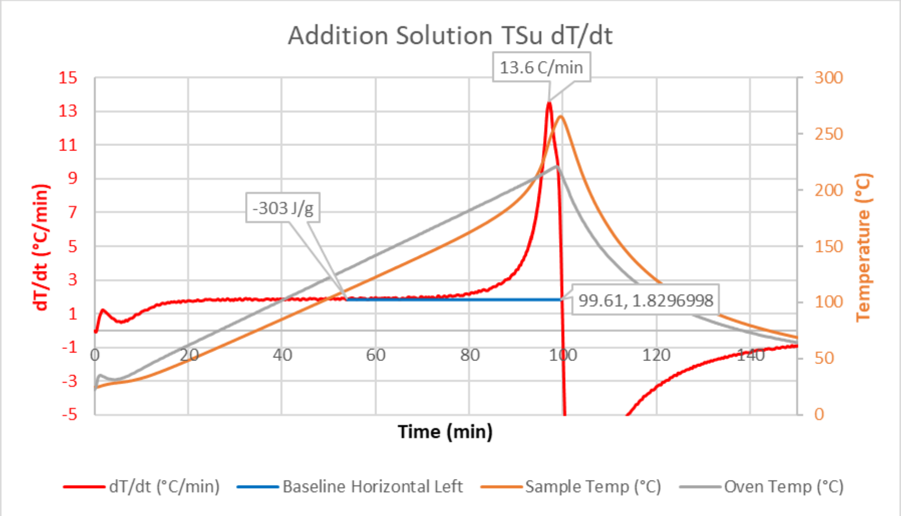
Risk: Medium

The Near Miss – Investigation and Data Gathering



Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4'-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ❑ Starting material in DMF
   - ❑ Stating material and 4,4'-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4'bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction



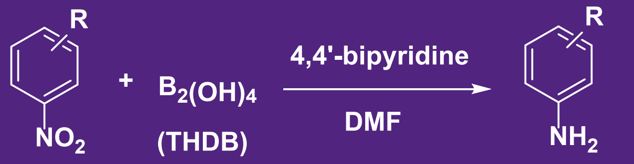
Risk: High

Sample Name	Max OP T °C	Reaction(s)					Pressure		
		Temp °C	J/g* -Exo +Endo	Max dT/dt °C/min	Cp J/g*K	ΔTad °C	Onset Temp °C	Max dP/dt psi/min	Residual Pressure psi
SM in 1 vol DMF	10	110	-303	13.6	1	300+	90	345.6	696.9

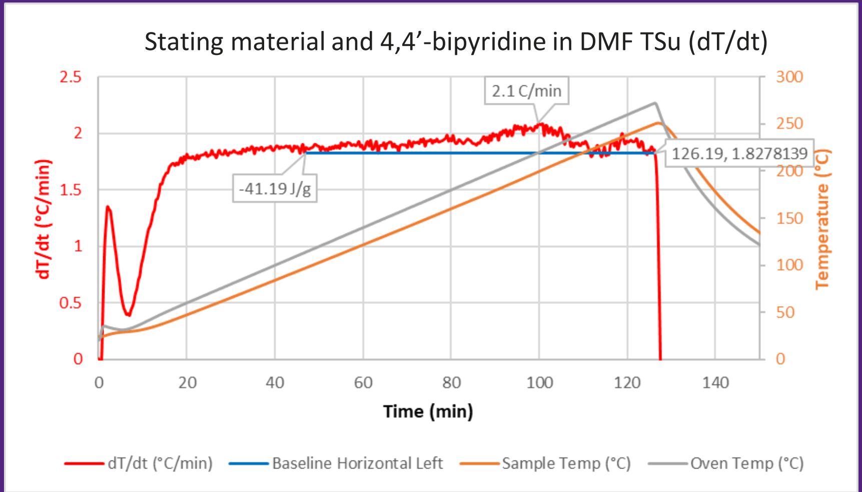
The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ❑ Stating material and 4,4’-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction



(Starting Material) (Product)



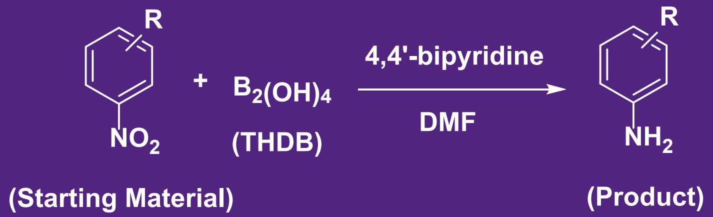
Risk: Low

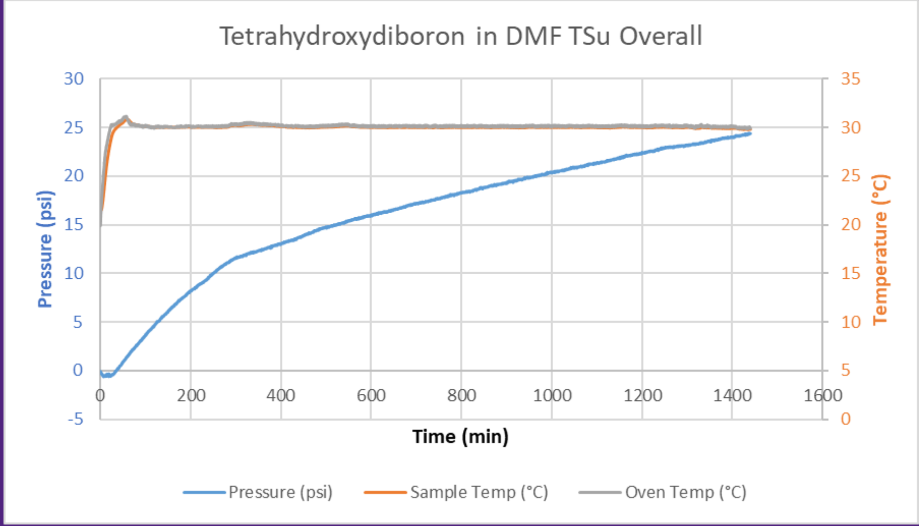
Sample Name	Max OP T °C	Reaction(s)					Pressure		
		Temp °C	J/g* -Exo +Endo	Max dT/dt °C/min	Cp J/g*K	ΔTad °C	Onset Temp °C	Max dP/dt psi/min	Residual Pressure psi
SM in 1 vol DMF	10	97	-41	2.1	1	40+	100	11.3	92.3

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4'-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ✓ Stating material and 4,4'-bipyridine in DMF
   - ❑ THDB in DMF
   - ❑ THDB and 4,4'bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction





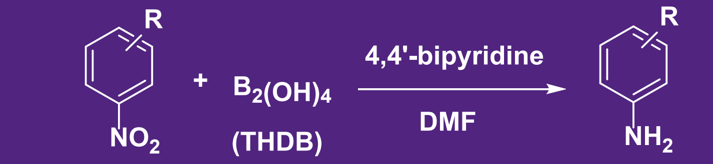
Risk: High

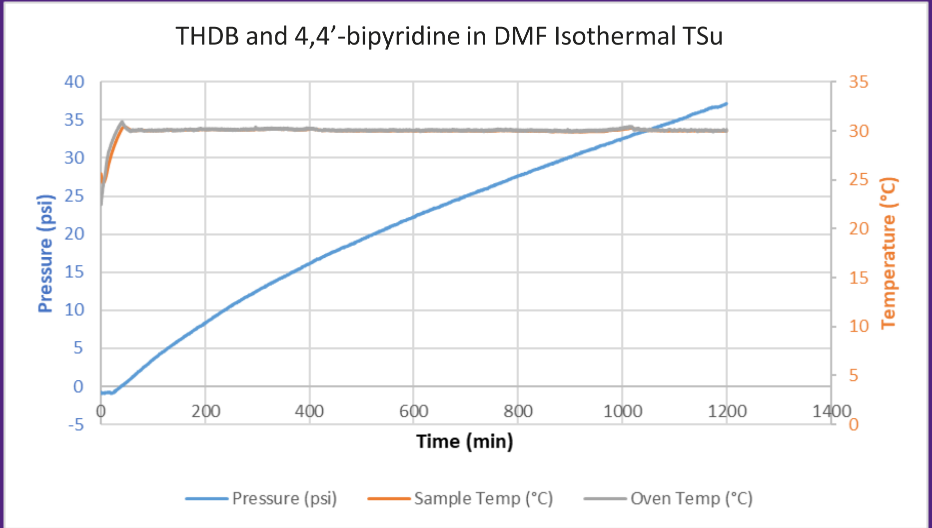
Sample Name	Isotherm Temp (°C)	Isotherm Length (hr)	Pressure		
			Onset Temp (°C)	Max dP/dt (psi/min)	Residual Pressure (psi)
Tetrahydroxydiboron in DMF – 30C – 1 day	30	24	30	0.1	27.4

The Near Miss – Investigation and Data Gathering

<u>Process Safety Testing Plan:</u>

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ THDB in DMF
   - ❑ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction





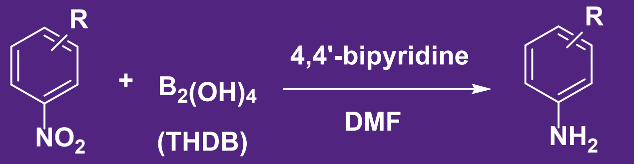
Risk: High

Sample Name	Isotherm Temp (°C)	Isotherm Length (hr)	Pressure		
			Onset Temp (°C)	Max dP/dt (psi/min)	Residual Pressure (psi)
Tetrahydroxydiboron and 4,4’-bipyridine in DMF – 30C – 20 hr	30	20	30	0.1	38.0

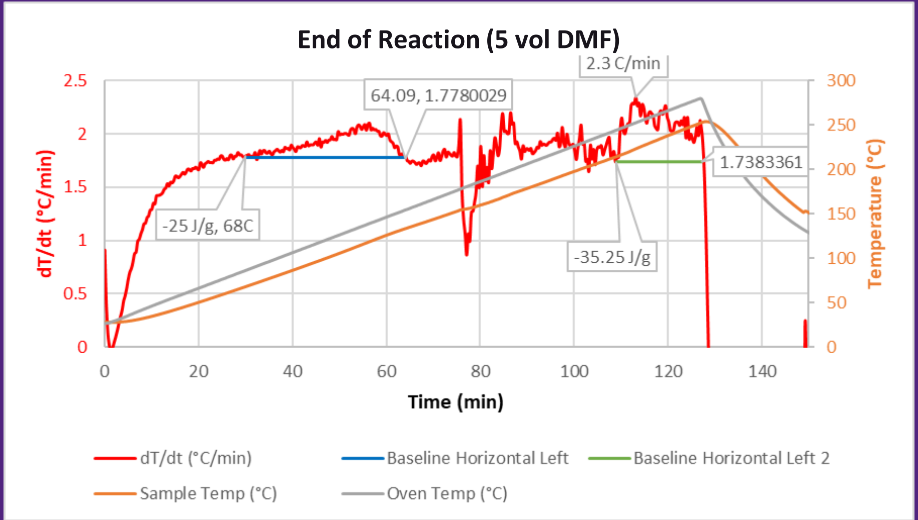
The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ THDB in DMF
   - ✓ THDB and 4,4’bipyridine in DMF
   - ❑ End of reaction
3. Heat of Reaction



(Starting Material) (Product)



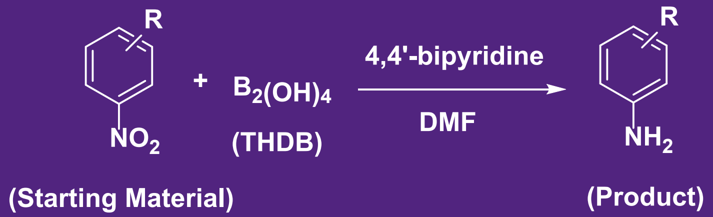
Risk: Medium

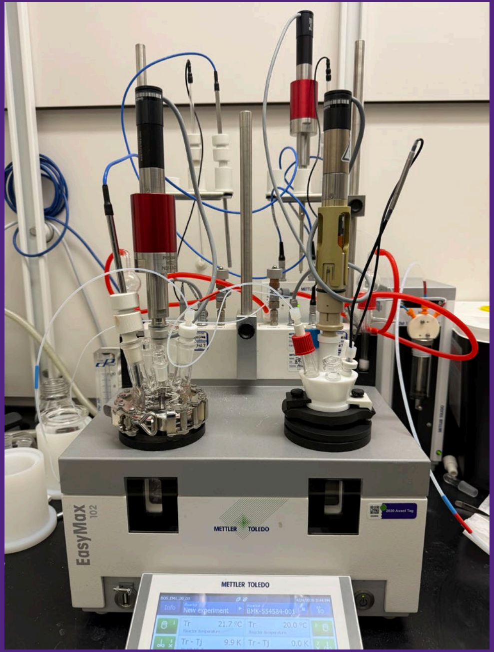
Sample Name	Max OP T °C	Reaction(s)					Pressure		
		Temp °C	J/g* -Exo +Endo	Max dT/dt °C/min	Cp J/g*K	ΔTad °C	Onset Temp °C	Max dP/dt psi/min	Residual Pressure psi
End of Reaction (5 vol DMF)	23	68 214	-25 -35	2.3	1	25+	90	12.7	106.3

The Near Miss – Investigation and Data Gathering

<u>Process Safety Testing Plan:</u>

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ THDB in DMF
   - ✓ THDB and 4,4’bipyridine in DMF
   - ✓ End of reaction
3. Heat of Reaction





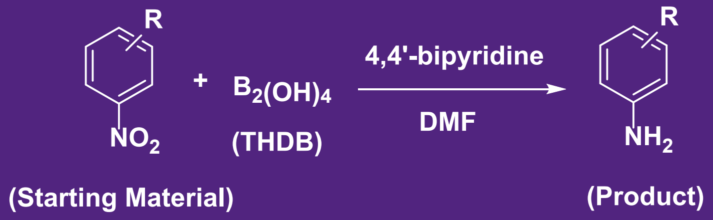
For the addition of the Starting Material in 1 volume of DMF into a solution of THDB and 4,4’-dipyridine in 4 volumes of DMF, the adiabatic temperature rise was determined to be 148 °C.

Risk: High

The Near Miss – Investigation and Data Gathering

Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ THDB
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ Starting material in DMF
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ THDB in DMF
   - ✓ THDB and 4,4’bipyridine in DMF
   - ✓ End of reaction
3. Heat of Reaction

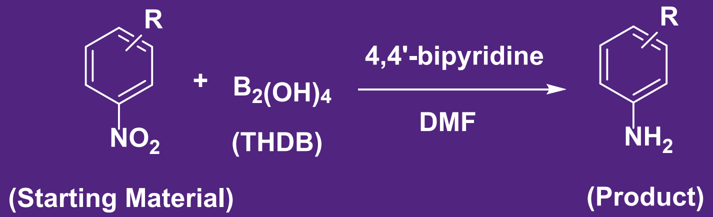


The Near Miss – Investigation and Data Gathering

<u>Process Safety Testing Plan:</u>

1. Thermal stability of:
   - ✓ Starting material
   - ✓ **THDB**
   - ✓ 4,4'-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ **Starting material in DMF**
   - ✓ Stating material and 4,4'-bipyridine in DMF
   - ✓ **THDB in DMF**
   - ✓ **THDB and 4,4'bipyridine in DMF**
   - ✓ End of reaction
3. **Heat of Reaction**

Risk: High, Medium, or Low

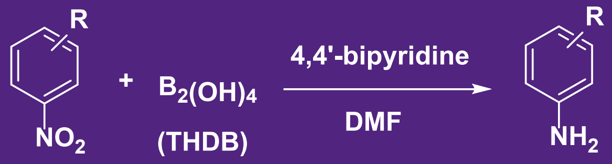


The Near Miss – Investigation and Data Gathering

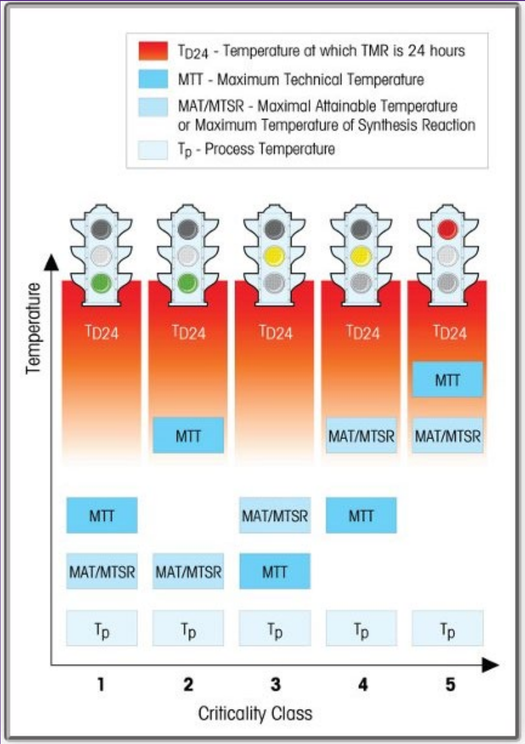
Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ **THDB**
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ **Starting material in DMF**
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ **THDB in DMF**
   - ✓ **THDB and 4,4’bipyridine in DMF**
   - ✓ End of reaction
3. **Heat of Reaction**

Risk: High, Medium, or Low



(Starting Material) **(Product)**

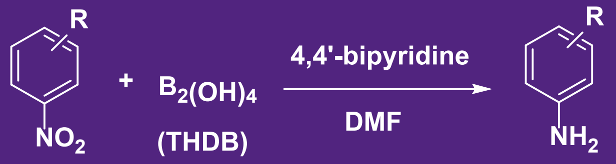


The Near Miss – Investigation and Data Gathering

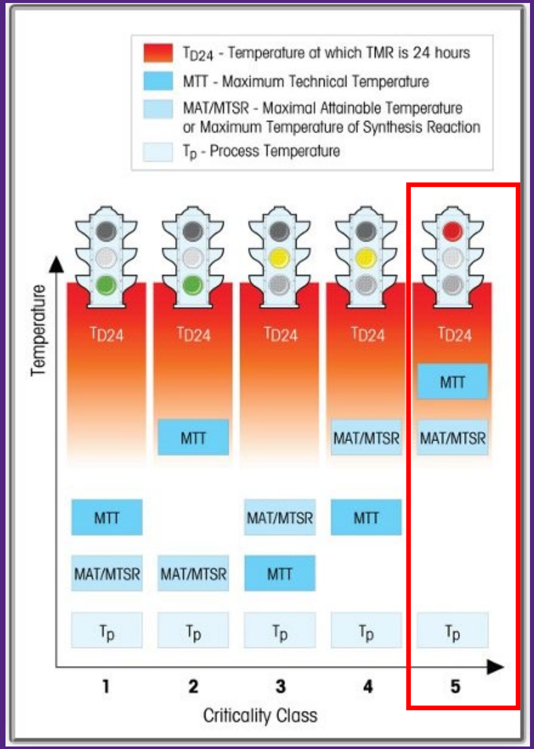
<u>Process Safety Testing Plan:</u>

1. Thermal stability of:
   - ✓ Starting material
   - ✓ **THDB**
   - ✓ 4,4’-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ **Starting material in DMF**
   - ✓ Stating material and 4,4’-bipyridine in DMF
   - ✓ **THDB in DMF**
   - ✓ **THDB and 4,4’bipyridine in DMF**
   - ✓ End of reaction
3. **Heat of Reaction**

Risk: High, Medium, or Low

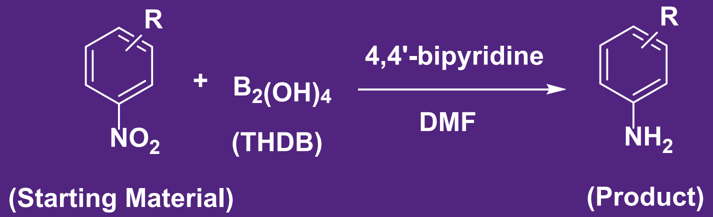


(Starting Material) (Product)



Stoessel Class 5

Conclusions



Process Safety Testing Plan:

1. Thermal stability of:
   - ✓ Starting material
   - ✓ **THDB**
   - ✓ 4,4'-bipyridine
   - ✓ Product
2. Thermal stability of reaction mixtures
   - ✓ **Starting material in DMF**
   - ✓ Stating material and 4,4'-bipyridine in DMF
   - ✓ **THDB in DMF**
   - ✓ **THDB and 4,4'bipyridine in DMF**
   - ✓ End of reaction
3. **Heat of Reaction**

Risk: High, Medium, or Low

Conclusions: In its current state, this process is unsuitable to scale up. Additional development work is required, or an alternative method must be utilized.

Questions??