Safety Concerns in a Pharmaceutical Manufacturing Process Using Dimethyl Sulfoxide (DMSO) as a Solvent

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ABSTRACT: During the process safety analysis of a fluoride displacement reaction, a highly exothermic event was observed when the reaction mixture was heated, which appears to be due to the decomposition of DMSO catalyzed by the HF byproduct from the displacement reaction. Although the T_{D24} for the decomposition is 42 °C above the reaction temperature and the synthesis reaction is mild, the consequences of the decomposition reaction are severe and could exceed the emergency venting capability of the reactor in the case of uncontrolled heating or an external fire, even at pilot plant scale. The use of several bases, cosolvents, and alternative solvents was investigated. Administrative safeguards, including temperature control system limits and removal of flammable solvents from the area, were identified to establish a basis of safety for a scale up to pilot scale. However, these safeguards would be impractical in a manufacturing facility. Eventually, an N-methyl-2-pyrrolidone (NMP)/tert-butyl methyl ether (MTBE) solvent system was identified, which provided an acceptable process while eliminating the use of DMSO and the associated decomposition reaction. This work shows some of the potential hazards that need to be investigated when using DMSO in a process. While DMSO alone can decompose near its boiling point, the effect of impurities, including byproducts of reactions, can lower the onset and increase the rate of this decomposition. Also, although this process falls into a Stoessel criticality index of 2, which is on the lower risk side of the scale, this case provides a good example where a low probability event needs to be investigated due to the severity of the consequences.

■ INTRODUCTION

Nucleophilic aromatic substitution of aryl fluorides is an important reaction for the preparation of custom chemicals and pharmaceutical intermediates. The reaction generally works best in polar aprotic solvents, and among these, DMSO is often the solvent of choice. High solubility for many compounds, in combination with its high boiling point, can make it a particularly attractive solvent widely used in organic syntheses. However, DMSO undergoes decomposition near its boiling point of 189 °C. This decomposition reaction is autocatalytic, which means that the reaction can accelerate very rapidly and that the onset temperature can be reduced by the thermal history of the solvent. Extended time at elevated temperatures can lead to the accumulation of the decomposition products that catalyze the reaction. In addition, the presence of other chemicals such as acids or bases can also reduce the onset temperature. A detailed process safety analysis and operational precautions were performed for DMSO distillation operations.[1] As noted by Lam and co-workers, DMSO-containing reaction mixtures can be more energetic and decompose at lower temperatures than pure DMSO.[2] The decomposition of DMSO has been identified as a process safety issue in multiple sources in the literature.[3] Incidents involving the decomposition of DMSO during chemical reactions and distillations have been reported, several of which have resulted in serious incidents, including fatalities.[4−6]

To safely scale up a batch chemical process using DMSO as solvent from lab scale to pilot plant operation, the thermal hazards associated with the process must be identified so that any necessary precautions can be taken. Screening the thermal stability of process samples, identifying potential runaway reactions, and measuring heats of reaction and gas generation are a few initial steps in evaluating thermal hazards.

The thermal stability of reactants, solvents, reaction mixture, and products is typically screened by calorimetric methods, such as DSC (differential screening calorimetry) or ARC (accelerating rate calorimetry). These tests can be used to identify the onset temperatures and the severity of exothermic events. The heat of reaction can be obtained using heat flow calorimetry, such as with the Omnical SuperCRC (Chemical Reactivity Calorimeter) or the Mettler-Toledo RC1. These tests provide the information to determine the adiabatic temperature rise (ATR) of a reaction. The adiabatic temperature rise provides a measure of the thermal potential of the synthesis (or desired) reaction. If cooling is lost after reaching the desired process temperature (T_p) and after charging the reactants, the temperature could increase by the ATR to the maximum temperature of the synthesis reaction (MTSR).

Secondary reactions, such as decomposition, could occur at elevated temperatures. Various instruments can be used to detect the onset temperature (T_{onset}) of these reactions. However, the onset temperature is dependent upon the sensitivity of the instrument used, and the secondary reaction may proceed below the detected onset temperature but at a rate below the detection limit of a given instrument. If the heat from this secondary reaction were not removed (adiabatic), the mixture would self-heat. As the temperature increases, the rate of the secondary reaction increases, eventually reaching a maximum rate. The time to reach this maximum rate is the TMRad. The temperature at which the TMRad is 24 h is defined as T_{D24}.

The concept of a Criticality Index, which allows the classification of potential runaway reaction scenarios, was developed by Stoessel[7] on the basis of the relative levels of the four temperatures: T_p, MTSR, T_{D24}, and the maximum technical temperature, which is the boiling point of solvent, T_b, in this case. (Note that, in a closed system, the boiling point of the solvent will be elevated to the boiling point at the maximum permissible pressure.) The criticality index rates the upset scenarios into five classes, ranging from the least critical (1) to most critical (5) as shown in Figure 1.
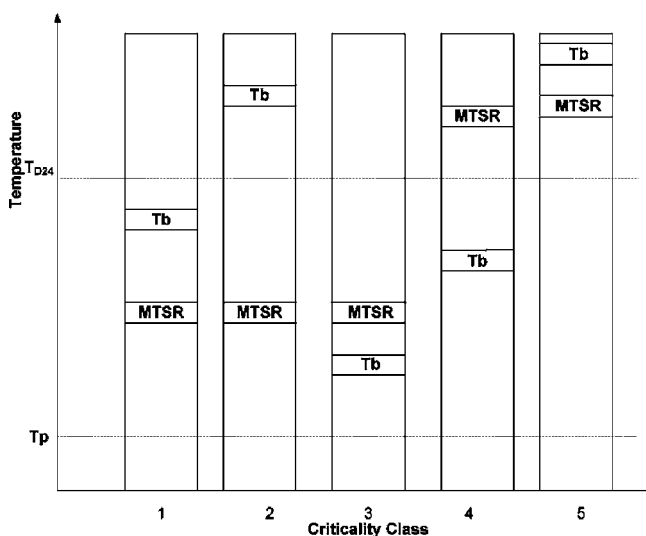

Figure 1. Criticality Classification of chemical processes.

Processes that fall into Criticality Classes 1, 2, and 3 do not have the thermal potential to reach the onset of the secondary reaction through self-heating. The difference in the three classes is the relative temperature of the boiling point. In the event of a heat accumulation condition, such as external heating, the boiling of the solvent can serve a protective role in a Class 1 process. The boiling of solvent can provide a barrier to reaching the onset of the decomposition reaction, even with external heating. In Class 2 processes, this protective barrier is lost as the boiling point of the solvent moves above T_{D24}. In this case, the decomposition reaction could be initiated by external heating without the benefit of evaporative cooling. In the case of a Class 3 process, the process has the energy to self-heat to the boiling point, which may lead to the potential for over-pressurization due to the vapor pressure of the solvent.

The desired reaction in Classes 4 and 5 has the thermal potential to self-heat to the decomposition onset temperature. Again, the difference in the classes is due to the boiling point of the solvent. In Class 4, the boiling of solvent can potentially provide a barrier to reaching the decomposition onset temperature. There are no inherent safe measures in Class 5, and these processes rely on engineering controls and procedures to be performed safely.

The Stoessel criticality classification is a useful tool in guiding a process safety engineer to specific scenarios and potential risk reducing measures. The primary focus of this tool is often on cooling failures, which has been a single failure scenario responsible for a number of process safety incidents. One recent example is the T2 Laboratories explosion in Jacksonville, FL.[8] However, this tool must be used in conjunction with an analysis

of the severity of less common, but still possible, scenarios, such as external heating.

Through the process safety analysis for scaling up a fluoride displacement reaction using DMSO as solvent, this work provides an example where the potential catastrophic exothermic decomposition of DMSO due to uncontrolled heating should not be neglected even for a reaction with a mild heat of reaction. To eliminate the source or to reduce the severity of the exothermic decomposition, an alternative solvent or a cosolvent should be pursued to replace DMSO or to reduce the amount of DMSO.

■ RESULTS AND DISCUSSION

A pharmaceutical intermediate is synthesized via a fluoride displacement similar to the reaction shown in the following scheme. The process temperature (T_p) for this reaction is 85 °C using DMSO as solvent.
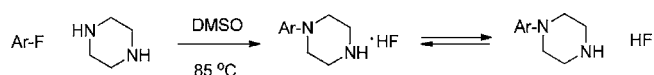
In order to scale up the synthesis into the pilot plant, a process safety analysis was conducted. The heat of reaction, measured with the Omnical SuperCRC, was used to calculate the MTSR during a loss of cooling event. In the test, after reaching thermal equilibrium at the reaction temperature (85 °C), DMSO was injected into the test cell containing the starting material and piperazine. The measured heat of reaction was −7917 J/mol aryl fluoride, corresponding to an ATR of 2 °C. The MTSR, calculated as the summation of the reaction temperature and the ATR, is 87 °C. The Omnical SuperCRC results are shown in Figure 2.
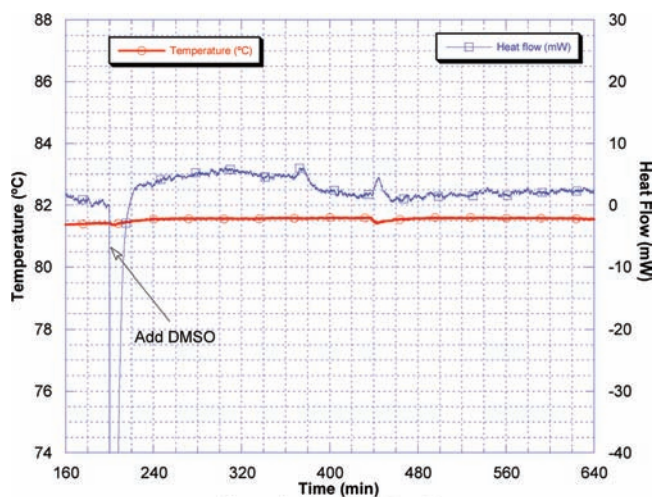

Figure 2. Omnical Results

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The thermal stabilities of the starting material aryl fluoride, piperazine, DMSO, and the product were screened via DSC testing. Decomposition temperatures are shown in Table 1. Although the tested pure DMSO onset temperature is 208 °C, slow decomposition at or above its boiling point (189 °C) has been reported.[4] The results are illustrated in Figure 3 and summarized in Table 1.

DSC testing indicated some exothermic events in the isolated reaction components. However, the test of the reaction mixture showed a highly exothermic event detected at 168 °C with over

Table 1. DSC Results

sample	onset temp of exotherm (°C)
starting material	194
dimethyl sulfoxide (DMSO)	208
piperazine	243
product	>275
reaction mixture	168

1100 J/g energy released. The observed heat flow fluctuations in the DSC screening tests at high temperatures are likely due to reflux in the glass ampules. On the basis of the results of these screening tests, further testing was warranted. To evaluate the onset temperature and monitor pressure effects, ARC was selected for additional thermal stability testing. A fresh reaction mixture was generated (with charges shown in Table 4 in the Experimental Section) and was tested with ARC using a titanium test cell.

Exothermic events were detected at 91 and 151 °C. Test results are shown in Figures 4−6. On the basis of its proximity to the process temperature, the exotherm at 91 °C is presumably due to the desired reaction. The pressure increase at this temperature is presumably the result of generation of the reaction byproduct, hydrogen fluoride. The second exotherm at 151 °C propagated into a runaway reaction in approximately 300 min, when a rapid temperature and pressure increase near 210 °C caused the test cell to burst. The recorded maximum pressure and pressure rise rate before the burst of the half-full test cell (rated over 100 bar) were 96 bara and 807 bar/min, respectively. The second exotherm was most likely due to the decomposition of the solvent, DMSO. It is known that, in the presence of acid, autocatalytic exothermic decomposition of DMSO can occur at temperatures well below its boiling point of 189 °C.[4] DSC tests (as shown in Table 3) indicate that the reaction byproduct (HF) can substantially reduce the onset temperature of DMSO
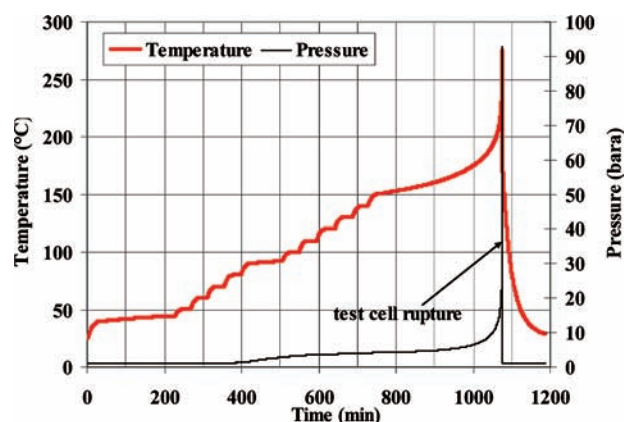

Figure 4. Reaction mixture ARC test temperature and pressure history.
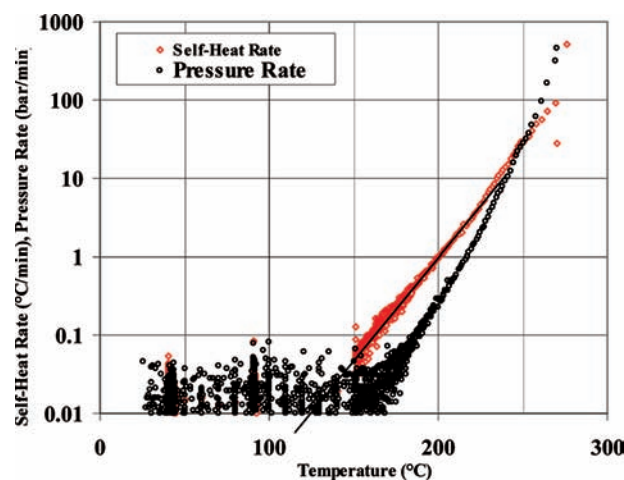

Figure 5. Reaction mixture ARC test self-heat and pressure rates.

decomposition. On the basis of the ARC data, the T_{D24} is ∼127 °C, as shown in Figure 7.

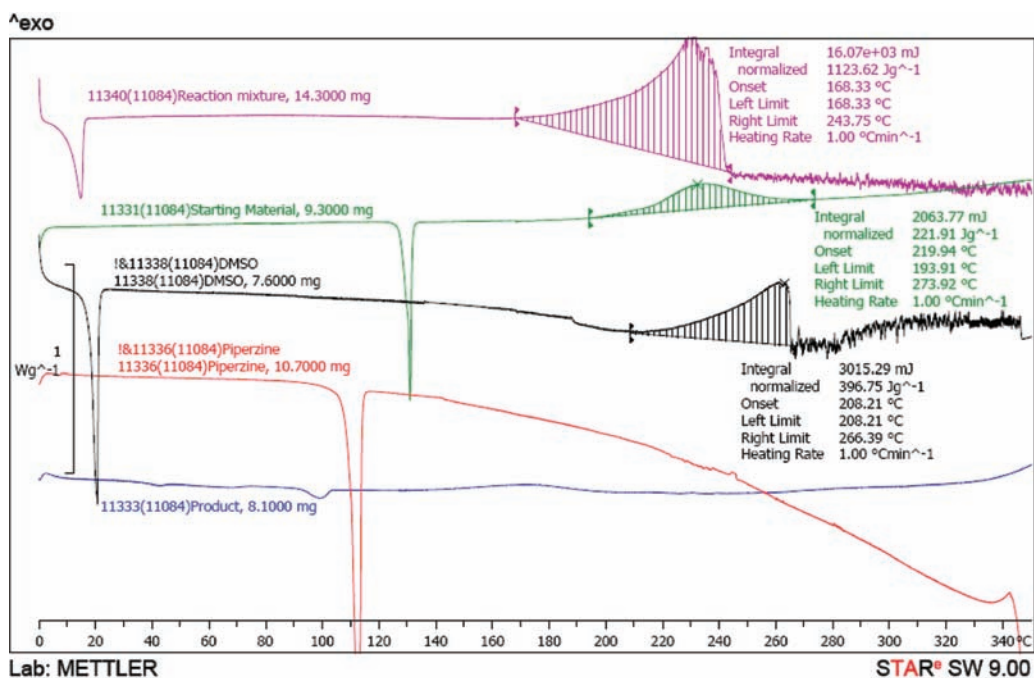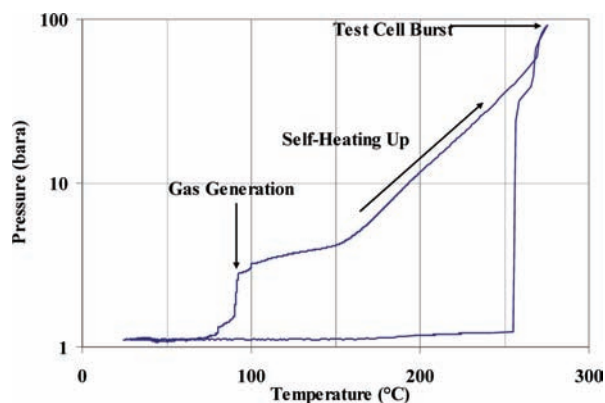**Figure 3.** DSC results.

Figure 6. Reaction mixture ARC test temperature/pressure relationship.
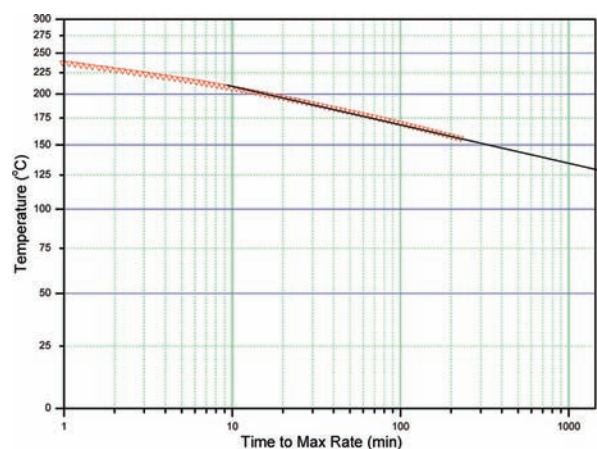

Figure 7. Reaction mixture ARC test raw data time to maximum rate.

On the basis of the testing and the four temperature levels required to determine the Criticality class, shown in Table 2,

Table 2. Relevant Process Temperatures for Safety Analysis

variable	temp (°C)
T_p	85
MTSR	87
T_b	189
T_{D24}	127

this process can be determined as a Criticality Class 2. In the event of a cooling failure, if the heat was generated by the desired reaction and not removed, the reactants could self-heat from T_p to MTSR (87 °C), as illustrated in the temperature profile for loss of heat removal (curves A–D) in Figure 8.

Since this process has a Criticality Class of 2, safety issues due to cooling failure are unlikely. However, cooling failure is only one of the scenarios to be investigated. As shown in temperature profiles C–F in Figure 8, during an uncontrolled heating event, i.e. temperature control failure or an external fire, the reaction temperature could increase to the onset temperature of the exothermic decomposition observed during ARC testing. Unlike a Class 1 process, there is no safety barrier posed by the boiling point of the solvent to prevent the reaction from reaching the onset of the decomposition reaction in an external heating scenario. Due to the severity of the decomposition, as demonstrated by the rupture of the half full ARC test cell, the consequences of an external heating scenario were investigated.
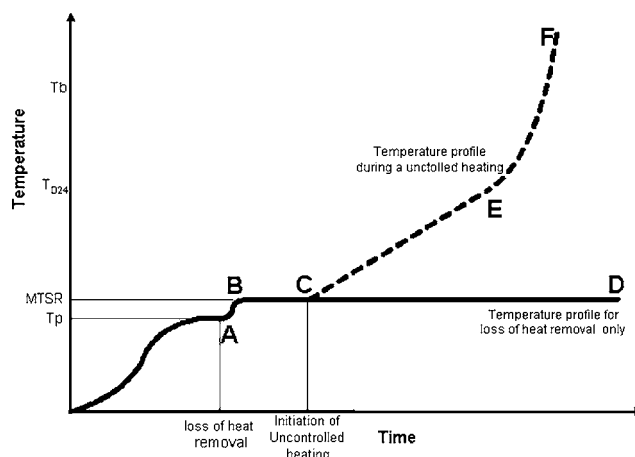

Figure 8. Temperature histories for loss of cooling and uncontrolled heating.

Ideally, the inherently best way to address the decomposition of DMSO would be to remove it from the process altogether. Alternative solvents with boiling points between 85 and 120 °C and with sufficient polarity were screened to replace DMSO. However, none of these solvents proved viable, due to either reactivity, solubility, or isolation and product recovery issues.

An alternative approach to reduce the severity of the decomposition was by introducing a cosolvent. By reducing the amount or decreasing the concentration of DMSO, the rate of decomposition could be reduced while providing additional mass to absorb the heat it produces. The use of a cosolvent with a lower boiling point also could act as a thermal barrier during an uncontrolled heating via evaporation and reducing the process to a Class 1. In the event of external heating, once the low boiling point cosolvent has been evaporated, the remaining DMSO may still proceed to decompose if a heat source still exists. Since the amount of DMSO is reduced, the severity is lower than that when running in neat DMSO. However, no suitable cosolvent was identified in time to meet the aggressive project timeline.

A third approach was to provide a scavenger for the byproduct of the reaction, HF, which is suspected in reducing the onset temperature of DMSO decomposition from 208 to 151 °C. Tests confirmed that the onset of decomposition for neat DMSO was reduced by 40 °C when HF was present (see Table 3). It was assumed that if an acid scavenger could be

Table 3. Additional DSC Results

sample	onset temp of exotherm (°C)
dimethyl sulfoxide (DMSO)	208
DMSO with 7% HF	169
DMSO with 4% HF and 12.3 equiv of piperazine	180
DMSO with product	212

found, the thermal stability of the reaction mixture and, therefore, the maximum temperature of safe operation could be increased. Since piperazine, a weak base used in excess in the reaction, failed to prevent the reduction of the onset temperature of DMSO decomposition, several stronger bases were screened. Sodium carbonate was selected, since satisfactory product quality and impurity profile could be obtained in lab experiments.

An ARC test of the reaction was then performed with excess sodium carbonate. Among the detected exothermic events, the exotherm at 140 °C ($dT/dt_{max} > 13$ °C/min, $dP/dt_{max} > 10$ bar/min) still resulted in a runaway reaction. The test was manually terminated at 29.7 barg prior to reaching the maximum rate to prevent the potential test cell rupture, so the actual runaway is more severe than that indicated in this test. The ARC test results are plotted in Figures 9 and 10.
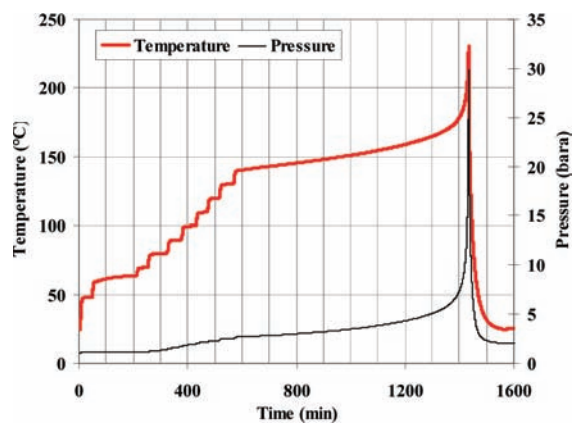

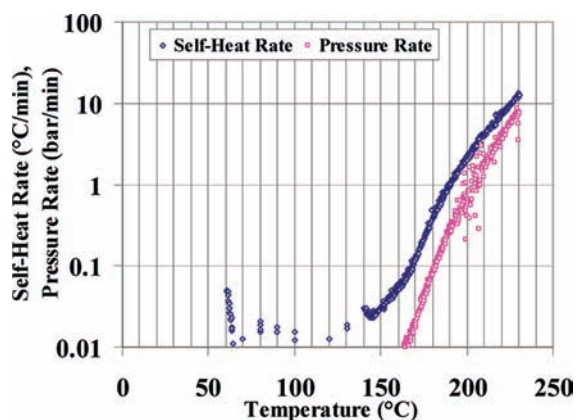**Figure 9.** Reaction mixture with Na_2CO_3 ARC test temperature and pressure history.

Figure 10. Reaction mixture with Na_2CO_3 ARC test self-heat and pressure rates.

The addition of sodium carbonate did not prevent or increase the onset temperature of the decomposition of DMSO. This was initially suspected to be the result of poor acid/base contact, since there is no mixing in the ARC test, leading to sodium carbonate accumulation at the bottom of the test cell.

Since mixing is available on the reactive system screening tool (RSST), and the data from the RSST test can be used for pressure relief calculations, the thermal stability of the reaction mixture with sodium carbonate was also tested using the RSST. An exothermic decomposition was detected at 200 °C in the RSST test. When the data was extrapolated back to the 0.02 °C/min self-heating rate, the sensitivity of the ARC, the onset temperature would be ~160 °C. The results indicate that, even with good mixing and good acid/base contact, the exothermic decomposition at a temperature lower than the DMSO boiling point is still possible. However, it may also indicate that the presence of a small amount of acid could initiate the autocatalytic

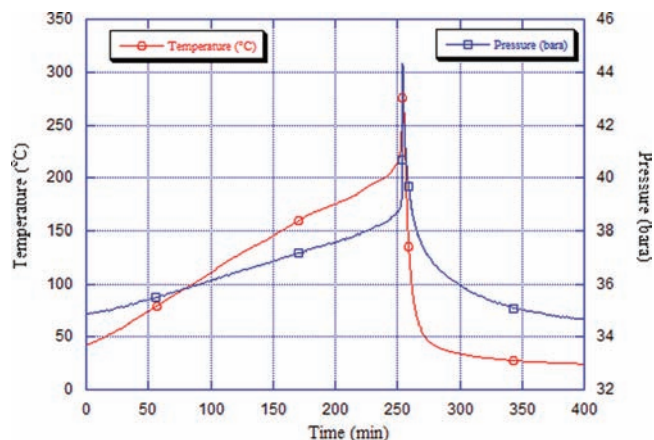decomposition of DMSO.[4] The RSST results are plotted in Figures 11 and 12.

Figure 11. RSST test temperature/pressure history (initial 33 barg back pressure).
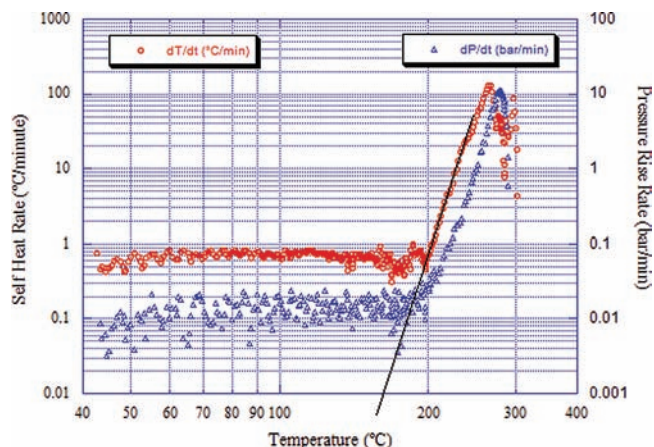

Figure 12. RSST test self heat rate and pressure rise rate vs temperature.

A satisfactory alternative solvent, cosolvent, or acid scavenger was not identified to eliminate or to sufficiently reduce the severity of the DMSO decomposition or to sufficiently increase the onset temperature. The next step was to evaluate the mitigation capabilities of the reactor for DMSO decomposition that could be taken to provide a basis of safety for the process. The primary mitigation system on the reactors is the emergency relief system. The required pressure relief ideal orifice area is calculated with the RSST method[9] for a gassy system.

A 0.33 m³ reactor with 6.9 barg design pressure in the pilot plant would be used for the reaction. The pressure relief device on this reactor is a 7.6 cm rupture disk set at 4.14 barg. The proposed batch charge (M_o) consists of 16 kg of aryl fluoride, 220 kg (200 L) of DMSO, 40 kg of piperazine, and 6 kg of sodium carbonate. In the RSST test, a 7.9 g sample (M_t) of the reaction mixture was charged. The maximum pressure rise rate (dP/dt)$_{max}$ in a 350 mL containment vessel was 11.1 bar/min. The calculated required pressure relief ideal orifice area with the RSST method as shown in the equation below at 4.5 barg

maximum pressure (P) is 0.024 m². The corresponding ideal orifice diameter is 19.6 cm

$$A = (3 \times 10^{-6}) \frac{M_o}{M_t} \frac{\left(\frac{dp}{dt}\right)_{max}}{P^{3/2}}$$

(units are in m², psi/min, psia).

Alternatively, the required pressure relief ideal orifice area for the gassy system can also be calculated using Leung's method.[10,11] The required ideal orifice area, if the reactor pressure is allowed to increase to 4.5 barg, is 0.019 m². The corresponding ideal orifice diameter is 18 cm. If the reactor pressure reaches 7.6 barg, the required orifice area is 0.0092 m², and the corresponding ideal orifice diameter is 10.8 cm. The 7.6 cm rupture disk on the reactor is too small to prevent the reactor pressure from increasing beyond the design pressure during the runaway reaction caused by uncontrolled heating. The required venting area could be reduced by running multiple batches, but due to the resulting low volumes and scheduling issues, this was not practical.

Without being able to identify a viable alternative solvent, an effective cosolvent system, or an acid scavenger to increase the thermal stability of the reaction mixture, and with insufficient protection from the emergency relief system, the options for safely running a process become limited. Due to the aggressive timeline of the project and an upcoming pilot plant campaign, restrictive administrative measures were identified to eliminate the possibility of external heating scenarios to allow the process to be run safely at pilot scale. To address a control system failure, the reactor temperature was limited to 50 °C below the onset temperature from the ARC test. Jacket heating would be automatically shut down should the reactor temperature exceed 90 °C. No flammable solvents were allowed in the process center to prevent a possible spill and external fire. Finally, in the low probability case of a widespread fire in the facility, quenching of the reactor with water or emergency dumping of the reactor contents would be considered. The first scale up to the pilot plant was successful and proceeded without incident.

Since the required safety measures were difficult to implement and may not be possible at larger scales, efforts to identify a safer alternative continued. After further investigation, a NMP/MTBE solvent system was identified as an alternative to replace DMSO with acceptable product quality, impurity profile, and efficient product isolation and recovery. As expected, the ARC test results of the reaction mixture with the new alternative cosolvent system confirmed that there is no exothermic decomposition up to 300 °C. The ARC results are shown in Figure 13.
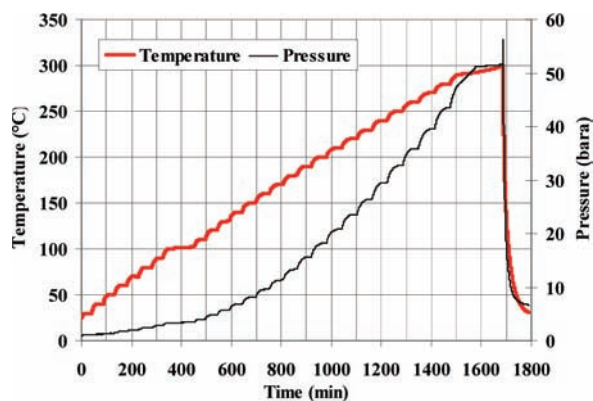
Figure 13. ARC test with NMP/MTBE as solvent temperature and pressure histories.

CONCLUSIONS

For a synthesis reaction using DMSO as solvent, there is a potential for a devastating decomposition in the case of reaction self-heating or external heating. DMSO can decompose exothermically near its boiling point, and the onset temperature of decomposition can be reduced significantly in mixtures, such as those containing contaminants, strong acids, or bases, or due to the thermal history of the DMSO. As noted in this case, as well as other sources, DMSO is a reactive solvent and requires careful evaluation for thermal stability issues when used in a process. Preventative measures such as removing or reducing the amount of DMSO from the process should be considered. In this study, although a set of conditions were identified to perform the reaction safely, these conditions would have been impractical at larger scales. Eventually, an inherently safer solution was identified using a NMP/MTBE alternative solvent system to replace DMSO, which produced an acceptable product while eliminating the thermal instability of the reaction mixture.

It is important to note that the Criticality Index is an immensely useful tool in process safety and in evaluating various upset scenarios. However, it must be used in conjunction with an evaluation of the severity of the consequences, along with other factors, such as gas generation. Due to the low ATR of the desired process in this case, the process falls into Criticality Class 2, which is classified on the "not critical" end of the scale. However, the consequences of an external heating scenario in this case could potentially be devastating.

EXPERIMENTAL SECTION

Equipment Used. Differential scanning calorimetry (DSC) was performed using a Mettler-Toledo DSC821e or DSC823e using sealed glass ampules with a capacity of approximately 50 μL. Accelerating rate calorimetry (ARC) was performed using a Thermal Hazard Technology esARC and either glass or titanium test cells. RSST was performed using a Fauske & Associates Reactive System Screening Tool. Heat of reaction testing was performed using an Omnical SuperCRC isothermal calorimeter.

General Procedure for DSC Testing. Samples were first loaded into and sealed in glass ampules and ramped in the DSC furnace from 0 °C to 300 °C or 350 °C at 1 °C/min

General Procedure for ARC Testing. The sample was loaded into a titanium pressure bomb, which was then inserted into the calorimeter. The temperature and pressure of the test were recorded. The sample was heated in heat—wait—search steps of 10 °C, starting at 30 °C. When self-heating was detected, the calorimeter maintained the airspace around the bomb at the same temperature as that of the sample and tracked the exotherm to 300 °C or until reaching a pressure of 80 bara.

ARC Test Charges. Charges for the fluoride displacement ARC test are shown in Table 4.

Table 4. Reaction ARC Test Charges

material	amount (g)
starting material	0.413
piperazine	0.513
DMSO	4.072

Charges for the fluoride displacement with the sodium carbonate ARC test are shown in Table 5.

Charges for the fluoride displacement with NMP/MTBE as solvent ARC test are shown in Table 6.

Table 5. Reaction with Na$_2$CO$_3$ ARC Test Charges

material	amount (g)
starting material	0.295
piperazine	0.706
DMSO	4.006
sodium carbonate	0.123

Table 6. Reaction with NMP/MTBE as Solvent ARC Test Charges

material	amount (g)
starting material	0.254
piperazine	0.613
NMP	0.783
MTBE	1.969

Procedure for RSST Testing. An open spherical glass test cell (~10 mL) was placed in a 350 mL containment vessel. The test cell was insulated and was equipped with an external heater, which compensates for heat losses and adds heat to initiate the runaway reaction if desired. Mixing was provided by a magnetic stir bar. The sample temperature and the containment pressure were recorded. The RSST test cell with charges shown in Table 7 was loaded into an RSST vessel. The RSST vessel was

Table 7. Reaction with Na$_2$CO$_3$ RSST Test Charges

material	amount (g)
starting material	0.450
piperazine	1.350
DMSO	6.470
sodium carbonate	0.185

pressurized with nitrogen to 33 barg. The sample was then heated at 1 °C/min to 300 °C.

Procedure for Heat of Reaction Testing. Two 15 mL glass test cells were used per test, one for the sample and the other for the reference. Mixing was provided by a magnetic stir bar. The test charges are shown in Table 8. The test cell with

Table 8. Reaction Omnical SuperCRC Test Charges

material	amount (g)
starting material	0.413
piperazine	0.525
DMSO	4.019

starting material and piperazine was inserted into the calorimeter block. Two syringes loaded with DMSO were inserted into the injection ports. After the system reached thermal equilibrium at 85 °C, the DMSO was manually added into the test cell.

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Notes
The authors declare no competing financial interest.

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