Safe Scale-Up of a Hydrazine Condensation by the Addition of a Base

Zhe Wang,* Steven M. Richter, Jorge Gandarilla, Albert W. Kruger, and Michael J. Rozema

Process Research and Development, AbbVie Inc., 1 North Waukegan Road, North Chicago, Illinois 60064, United States

S *Supporting Information*

ABSTRACT: Herein we describe an observation where an exothermic event encountered during the safety evaluation of the scale-up of the synthesis of 4-chloro-1H-indazol-3-amine was mitigated upon the addition of a base. The 100 °C adiabatic temperature rise was attributed to the hydrazine condensation reaction, which could cause the batch to self-heat beyond the onset temperature of the exothermic decomposition of the reaction mass. Switching from 1-methyl-2-pyrrolidinone to a lower-boiling-point solvent was explored, but that alone did not guarantee the safe operation in the event cooling is lost. The reaction byproduct, HCl, was identified as a possible cause for the decreasing onset temperature of hydrazine monohydrate. The addition of a base to the reaction mixture increased the onset temperature and decreased the severity of the observed decomposition of the reaction mass. By the introduction of sodium acetate as a base in combination with a lower-boiling-point solvent, safe operating conditions for the process were identified. This base-stabilizing effect has been observed with other hydrazine condensation reactions in our laboratory.

■ INTRODUCTION

The condensation reaction between 2,6-dichlorobenzonitrile and hydrazine was initially optimized using 1-methyl-2-pyrrolidinone (NMP) to generate our target intermediate 4-chloro-1H-indazol-3-amine (**1**, chloroaminoindazole). As shown in Scheme 1, two reaction pathways were postulated.

Scheme 1. Chloroaminoindazole Formation
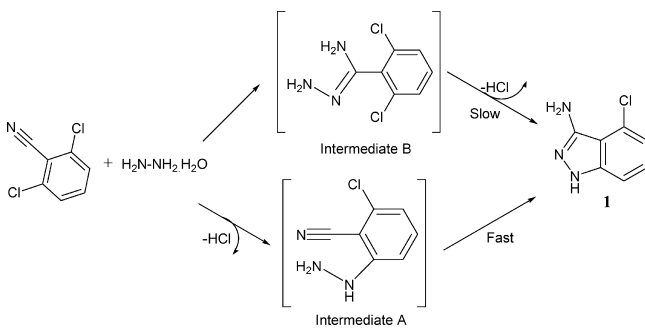
Under the optimized reaction conditions, the formation of intermediate A was favored, and its conversion to product was fast.[1] By comparison, path B required excess hydrazine, and intermediate B was converted to the product only after extended reaction times. The chloroaminoindazole product/intermediate B ratio at the end of the reaction was approximately 20:1. The safety evaluation findings were summarized in the discussion of process development of ABT-869 by Kruger et al.[1] Details of the process safety evaluation are discussed in this work.

Hydrazine is toxic, and the 8 h time-weighted exposure limit is 0.1 ppm. Personal exposure to hydrazine through skin contact, ingestion, and inhalation should be minimized.[2] Hydrazine is flammable over a very wide range, from 4.7% to 100% in air. Once ignited, hydrazine can burn by exothermic decomposition in the absence of air or another oxidant.[3] Water

solutions of hydrazine containing >40 mol % hydrazine are also flammable.[4]

In order for a process to be scaled up in a pilot plant, a process safety evaluation is typically performed. This usually comprises measuring heats of reaction, determining the propensity for gas generation, screening the thermal stabilities of process intermediates and reaction mixtures, and identifying potential runaway reactions.

In the case of chloroaminoindazole, the thermal stabilities of reactants, solvents, reaction mixtures, intermediates, and products were screened by calorimetric methods to identify the onset temperatures and the severity of exothermic events. The heat of reaction, measured with heat flow calorimetry, was used to determine the adiabatic temperature rise (ATR) of the reaction. The ATR provides a measure of the thermal potential of the desired reaction. If cooling is lost at the process temperature (T_p), the temperature could increase by the ATR to the maximum temperature of the synthesis reaction (MTSR). Secondary reactions such as exothermic decompositions can occur if the MTSR is higher than their onset temperature. Various instruments can be used to detect the onset temperature (T_{onset}). The onset temperature of a reaction is dependent upon the sensitivity of the instrument used, and a reaction may proceed below the detected onset temperature, but at a rate below the detection limit of the instrument. Insufficient removal of the heat from an exothermic reaction can cause the reaction mass to uncontrollably self-heat. As the temperature increases, the rate of the reaction increases, eventually reaching a maximum rate. The temperature at which this time to reach the maximum rate is 24 h is defined as T_{D24}. The criticality index introduced by Stoessel[5] allows the classification of potential runaway reaction scenarios based on

the relative levels of T_p, MTSR, T_{D24}, and a maximum technical temperature, which is frequently the boiling point of solvent, T_b. The criticality index categorizes the upset scenarios into five classes ranging from the least critical (1) to the most critical (5), as shown in Figure 1. The processes in classes 1 to 3 do
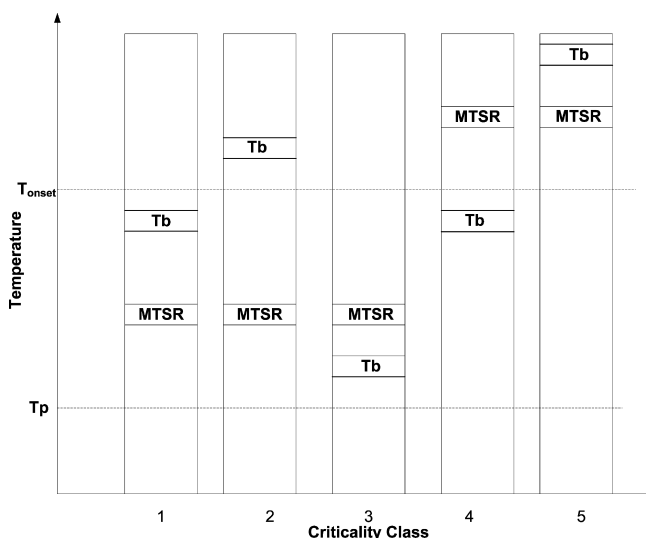

Figure 1. Criticality classification of chemical processes.

not have the thermal potential to reach the onset of the secondary reaction through self-heating alone. The processes in classes 4 and 5 have the thermal potential to self-heat to the decomposition onset temperature.

■ RESULTS AND DISCUSSION

The heat of reaction was measured with a Mettler-Toledo reaction calorimeter (RC1) to calculate the MTSR during a loss of cooling event. In the test, after thermal equilibrium was reached at the reaction temperature (110 °C), hydrazine monohydrate was added over a period of 30 min into the reactor containing the 2,6-dichlorobenzonitrile starting material and NMP (with the charges shown in Table 9 in the Experimental Section). The measured heat of reaction was −237 kJ/mol of 2,6-dichlorobenzonitrile, and the corresponding ATR was 100 °C. The MTSR, calculated as summation of the process temperature and ATR, was 210 °C. The RC1 results are shown in Figure 2.
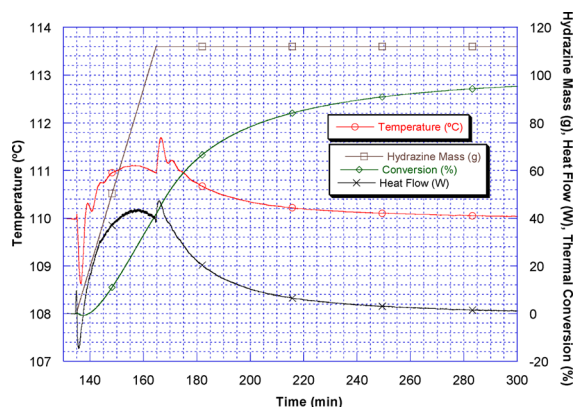

Figure 2. RC1 results for hydrazine condensation.

To attempt to identify the source of the exotherm, the thermal stabilities of the starting material, reaction mixture, and product were screened using a differential scanning calorimeter (DSC). No exothermic event was detected in the isolated starting material or product. As displayed in Figure 3, the DSC analysis of the reaction mixture showed exothermic events from 87 to 202 °C and above 215 °C.
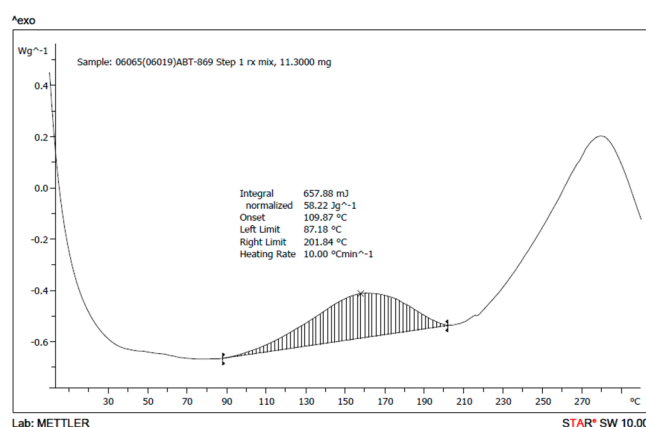

Figure 3. DSC results for the fresh NMP reaction mixture.

On the basis of the process temperature of 110 °C, the exothermic event detected from 87 to 202 °C was most likely due to the desired reaction. The RC1 and DSC results indicated that the ATR of the reaction was sufficient to increase the temperature of the reaction mass to near the onset temperature of the second and more energetic exothermic decomposition. These observations caused us to perform a thorough investigation of the energetics of the system. Additional thermal stability testing using the more sensitive accelerating rate calorimeter (ARC) was conducted in order to obtain a more accurate onset temperature and monitor pressure effects. A fresh reaction mixture (with the charges shown in Table 5 in the Experimental Section) was tested with the ARC, and the results are summarized in Table 1 and shown in Figures 4, 5, and 6.

Table 1. ARC Test Results for the Fresh Reaction Mixture

range of exotherm (°C)	estimated ATR (°C)[a]
45−120	116
130−210	160
>280	>30

[a]Corrected for thermal inertia, ϕ = 1.78.

Exothermic events were detected at 45, 130, and 280 °C, which were in line with the DSC results. Since the ARC is more sensitive than the DSC in detecting exothermic events, the first exothermic event was detected at 45−120 °C and is presumably due to the desired reaction. Exothermic decomposition occurred during the event at 130 °C, as indicated by the noncondensable gas generation accompanying the second exotherm. Because of the complexity of the decomposition, as indicated by the multiple peaks in the self-heating rate, the determination of T_{D24} was not attempted for this secondary reaction, and T_{onset} was used for the safety analysis instead.

Since the MTSR is 210 °C, the heat generated by the desired reaction can increase the temperature to the second exotherm if excess heat is not removed. Using a high-boiling-point solvent
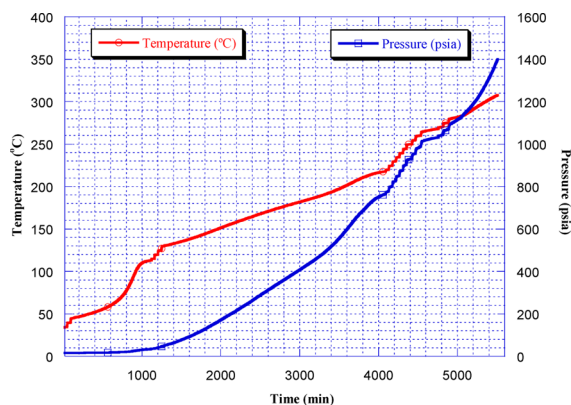
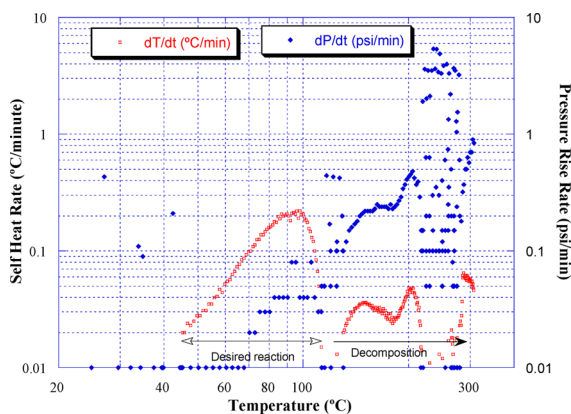**Figure 4.** Reaction mixture (NMP): ARC test temperature and pressure history.

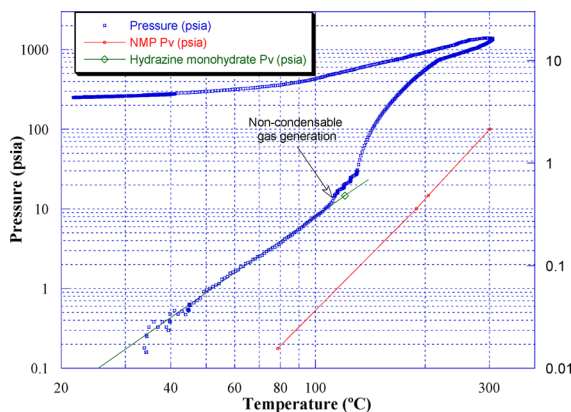**Figure 5.** Reaction mixture (NMP): ARC test temperature and pressure rise rates.

Figure 6. Reaction mixture (NMP): ARC test temperature and pressure (corrected for pad gas).

Figure 7. Reaction mixture (NMP): VSP2 test temperature and pressure history.
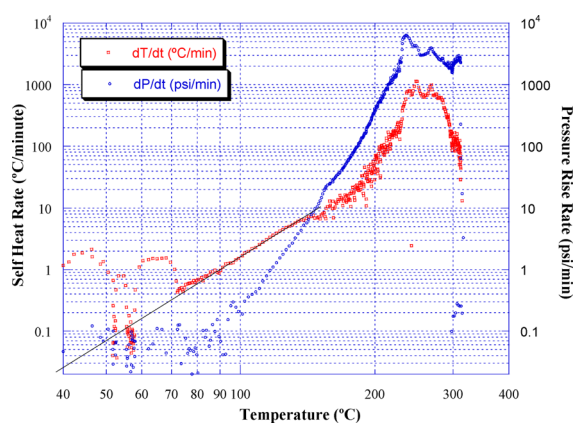
Figure 8. Reaction mixture (NMP): VSP2 test temperature and pressure rise rates.

such as NMP places this reaction in criticality class 5, with enough thermal potential to reach the exothermic decomposition and no thermal barrier to overcome.[5]

The reaction was observed to become organic−aqueous biphasic as the reaction proceeds. To examine agitated conditions, a thermal stability test was performed using the Vent Sizing Package 2 (VSP2) and a closed test cell (with the charges shown in Table 6 in the Experimental Section). In addition to the availability of agitation, this low-thermal-inertia calorimeter provides a more realistic simulation of how the
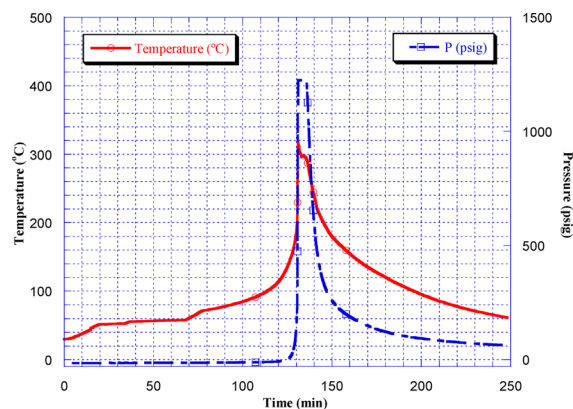
runaway would proceed at larger scales. The results are shown in Figures 7 and 8.

An exothermic event, presumably due to the desired hydrazine condensation reaction, was detected at 70 °C. Extrapolation of the data to the ARC detection sensitivity of 0.02 °C/min gave a temperature of ∼40 °C, in agreement with the onset temperature observed in ARC testing. The event led to violent exothermic decomposition. The maximum temperature and pressure for the half-full test cell were 316 °C and >1250 psig, respectively. The recorded maximum temperature and pressure rates exceeded 1150 °C/min and 6400 psi/min, respectively.

At 202 °C, the boiling point of NMP, the reaction was in the process of running away with the self-heat rate of 65 °C/min. Relying on solvent evaporative cooling to remove the reaction heat at such a high reaction rate was not considered practical. The reaction did not proceed to practical levels at lower temperatures, and thus, reducing reaction temperature was not an option.

In an effort to take advantage of energy removal via evaporative cooling, solvents with boiling points near the reaction temperature were screened. The intent of this effort was that in the event of loss of cooling or uncontrolled heating, the energy generated by the reaction could be removed via evaporation of the solvent while maintaining a lower reaction rate. Adding this thermal barrier would reduce the criticality class from 5 to 4. Pyridine, with a boiling point of 115 °C, was identified as the most favorable alternative solvent to NMP in

terms of yield, selectivity, and reactivity to test the hypothesis. The reaction using pyridine was examined using VSP2 (with the charges shown in Table 7 in the Experimental Section). A sufficient amount of solvent was charged to remove the generated heat of the desired reaction by evaporative cooling. The test cell was vented to atmospheric pressure to test whether this barrier could prevent the reaction mass from reaching the onset temperature of exothermic decomposition. The vented vapor was condensed and collected on a balance. The results are shown in Figures 9 and 10.
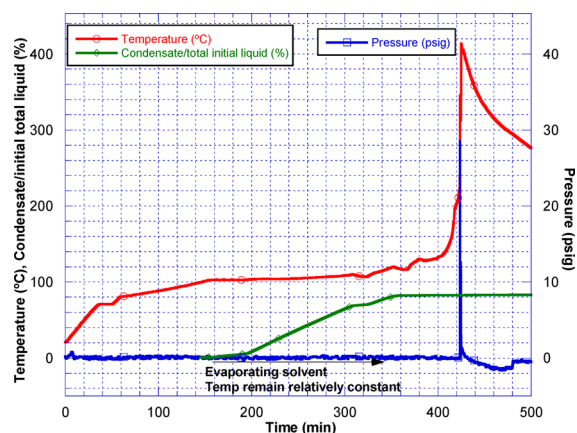

Figure 9. Reaction mixture (pyridine) vented to ambient: VSP2 test temperature, pressure, and collected condensate history.
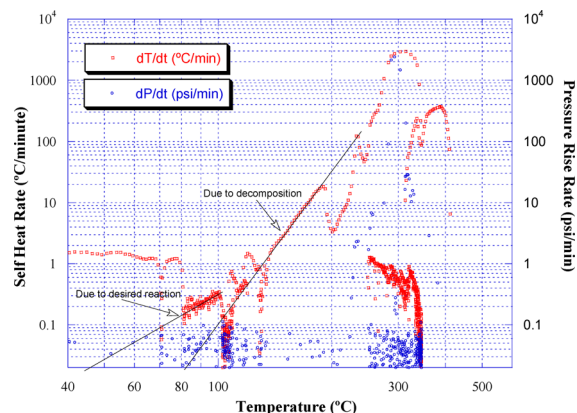

Figure 10. Reaction mixture (pyridine) vented to ambient: VSP2 test temperature and pressure rise rates.

After evaporation of most of the solvent, exothermic decomposition still occurred and resulted in temperature and pressure excursions with magnitudes of 100 °C and 30 psi, respectively. The maximum observed temperature and pressure rise rates were 3000 °C/min and 2500 psi/min, respectively. The onset temperature of the exothermic decomposition was 83 °C, as determined by extrapolating the self-heat rate to 0.02 °C/min. This indicated that the vaporization of solvent alone did not provide an adequate barrier to prevent reaching the decomposition. However, because of the partial safety benefit it offered, pyridine was still preferred over NMP and therefore used in the further investigation.

To identify the source of the exothermic decomposition, a series of thermal stability tests using the DSC were performed. As shown in Figure 11, no exotherms were observed up to 300 °C in the starting material and product. Since HCl was
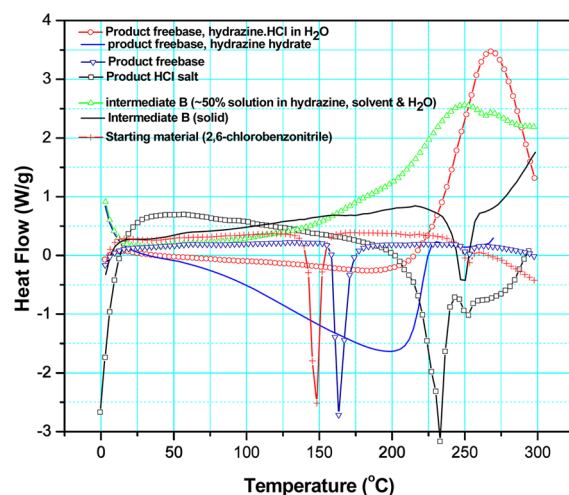

Figure 11. DSC results for the reaction components.

generated during the reaction, the effects of HCl on the thermal stability of the product as well on hydrazine were examined. The HCl salt of the product was stable up to 280 °C. The hydrazine hydrochloride and hydrazine dihydrochloride salts were both stable up to >250 °C (see Figure 12). When the
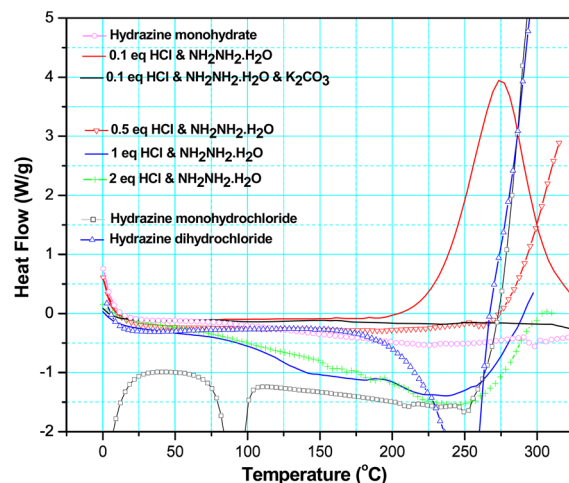

Figure 12. DSC results showing the effect of HCl and K_2CO_3 on the thermal stability of hydrazine monohydrate.

product was exposed to hydrazine hydrochloride or hydrazine hydrate, the thermal stability was reduced, but the onset temperatures were still approximately 200 °C, which is significantly higher than the onset observed in the reaction mixture. Although the isolated crystalline intermediate B was thermally stable up to 260 °C, the solution containing 50% intermediate B in hydrazine, solvent, and water showed an exothermic event at 70 °C.

DSC results for the reaction mixtures sampled at different stages of the reaction are shown in Table 2. The reaction mixture did not exhibit any significant exotherm after addition of 27% of the hydrazine charge. Reaction mixture samples taken at the completion of hydrazine monohydrate addition and 2, 3, and 6 h after the addition exhibited exothermic decomposition at temperatures as low as 120 °C.

Since the reaction is biphasic, DSC testing was also conducted for samples taken from the aqueous and organic phases 3 and 6 h after hydrazine monohydrate addition. The

Table 2. DSC Results for the Reaction Mixture (Pyridine as Solvent, Addition of Hydrazine at 110 °C)[a]

	sample	ΔH (J/g)	range of exotherm (°C)
reaction mixture	after adding 27% of the hydrazine	endothermic	105−150
	after adding all of the hydrazine	−1590	120−276
	2 h after adding hydrazine	−1243	120−254
	3 h after adding hydrazine	−1384	155−281
	6 h after adding hydrazine	−651	131−278
solid obtained by concentrating the reaction mixture (6 h after adding hydrazine)		−835	138−253

[a]Plots showing the DSC results are provided in the Supporting Information.

results are shown in Table 3. The organic portions of the reaction mixture did not exhibit any exothermic events. The

Table 3. DSC Results for Aqueous and Organic Samples of the Reaction Mixture (Pyridine as Solvent)[a]

	sample	ΔH (J/g)	range of exotherm (°C)
organic layer	3 h after adding hydrazine	stable	up to 255
	6 h after adding hydrazine	stable	up to 220
aqueous layer	3 h after adding hydrazine	−2036	134−284
	3 h after adding hydrazine, retested 2 days later	−1977	134−281
	6 h after adding hydrazine	−2081	119−270
	6 h after adding hydrazine, retested 2 days later	−1879	140−275
	6 h after adding hydrazine, retested 2 days later and filtered with 2 micron filter paper	−2088	126−280
solid	concentrated from organic layer (6 h after adding hydrazine)	−874	121−295
	concentrated from aqueous layer (6 h after adding hydrazine)	exothermic	>90

[a]Plots showing the DSC results are provided in the Supporting Information.

solid obtained by concentrating the organic phase taken at 6 h exhibited a mild exotherm starting at ∼120 °C. All of the aqueous portions of the reaction mixture, even samples retested 2 days later, exhibited strong exothermic decompositions at temperatures as low as 119 °C. Through HPLC analysis and mass balance, it was concluded that the aqueous layer consisted of hydrazine, hydrazine hydrochloride, and the formed intermediate B.

In a process safety review of a similar process using an aryl fluoride, this thermal instability of the reaction mixture was not observed. In the case of the aryl fluoride, a base was added to prevent etching of glassware by the HF byproduct. The possibility that the presence of this base may also have affected the thermal stability of the reaction mixture led us to explore the effect of adding a base to the aryl chloride reaction.

Since the only reaction component identified in the aqueous phase in significant concentration was hydrazine, its thermal stability in the presence of HCl and base was studied with DSC. No significant exothermic event was observed for hydrazine monohydrate up to 300 °C. During the hydrazine condensation reaction, 0.1 molar equiv of HCl relative to hydrazine is generated as a byproduct of the reaction. After addition of this

amount of HCl to hydrazine monohydrate, an energetic exothermic event with onset temperature near 180 °C was observed. Upon introduction of a base, K_2CO_3, this exothermic event was eliminated. It seems that the presence of HCl significantly reduces the thermal stability of hydrazine monohydrate. However, the introduction of a base improved (or restored) the thermal stability of the mixture after exposure to HCl.

Interestingly, increasing the HCl concentration to 0.5, 1, or 2 equiv had a smaller effect on the thermal stability. In these cases, the onset temperature of exothermic decomposition was reduced only to ∼250 °C, similar to the onset temperature of hydrazine monohydrochloride. DSC results for the effect of HCl on hydrazine monohydrate are presented in Figure 12.

Since intermediate B was also identified in the aqueous phase, its thermal stability and the influences of adding hydrazine monohydrate and a base on the thermal stability were also investigated by DSC testing. As shown in Figure 13,
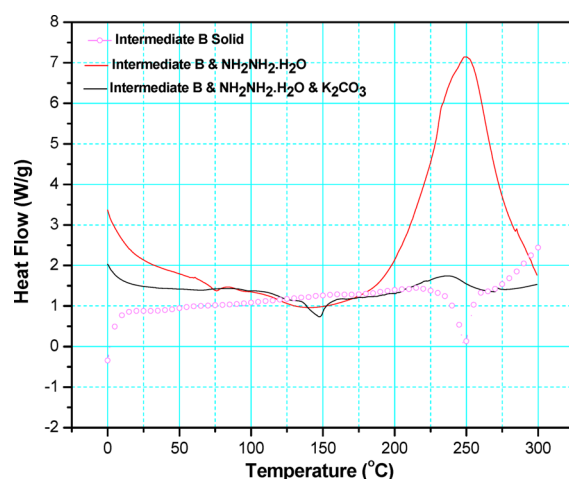
Figure 13. DSC results showing the effect of hydrazine monohydrate and K_2CO_3 on the thermal stability of intermediate B.

no exothermic event was detected in the intermediate B solid up to 260 °C. After addition of hydrazine monohydrate, an exothermic event with an onset temperature near 150 °C was detected. By the further introduction of a base, K_2CO_3, the severity of the exothermic event was reduced to 5% of the case without the base. It was suspected that with hydrazine monohydrate, the dissolved intermediate B underwent the cyclization reaction to form the product and to generate HCl. This process would accelerate with increasing temperature during the DSC testing. The generated HCl reduces the thermal stability of hydrazine monohydrate.

The effect of the addition of base additives to the reaction mixture on the onset temperature of exothermic decomposition was also evaluated. On the basis of DSC testing, the aqueous layers of reaction mixtures using KOAc, NaOAc, K_2CO_3, or Na_2CO_3 as the base exhibited no significant exotherms up to 300 °C. The onset temperatures of the exotherms observed with K_2HPO_4 and $NaHCO_3$ were below 300 °C but were still much higher than without base. Organic bases also had a stabilizing effect but were less effective than the inorganic bases screened. The results are summarized in Table 4. The DSC results showing the effect of sodium acetate on the stability of the reaction mixture aqueous layer are shown in Figure 14.

Table 4. DSC Results for Samples of the Aqueous Layer of the Reaction Mixture in Screening of Bases (in Pyridine)

| base used in the reaction	T_{onset} (°C)
potassium carbonate	>300
potassium acetate	>300
sodium carbonate	>300
sodium acetate	>300
(solid concentrated from aq layer with potassium phosphate tribasic)	270
potassium phosphate dibasic	255
potassium phosphate tribasic	250
sodium bicarbonate	210
sodium phosphate dibasic heptahydrate	210
triethylamine	205
potassium bycarbonate	205
N-methylmorpholine	200
no added base	120

Results using other bases can be found in the Supporting Information.
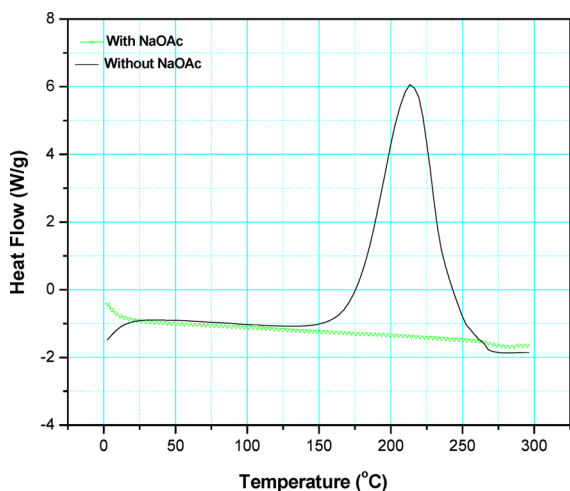
Figure 14. DSC results showing the effect of NaOAc on the aqueous sample of the reaction mixture.

Introducing a base such as KOAc, NaOAc, K_2CO_3, or Na_2CO_3 into the reaction mixture effectively increased the onset temperature of decomposition to above 300 °C. A weak base was preferred in order to minimize the dimerization of product and potential hydrolysis of the nitrile starting material to the amide. NaOAc was considered to be favorable in the scale-up because of its high solubility and effectiveness in increasing the thermal stability of the reaction while delivering product of good quality.

A closed-cell VSP2 test on the reaction using pyridine as the solvent and NaOAc as the base (with the charges shown in Table 8 in the Experimental Section) was performed to verify whether the heat generation from the hydrazine condensation reaction would lead to an exothermic decomposition. The initial exotherm due to the hydrazine condensation reaction brought the temperature to 140 °C under adiabatic conditions with corresponding vapor pressure at about 50 psig. A second exotherm was detected at 200 °C during the subsequent heat−wait−search step. It is also noted that the exothermic

decomposition detected at 200 °C did not cause a pressure excursion. The results are shown in Figures 15 and 16.
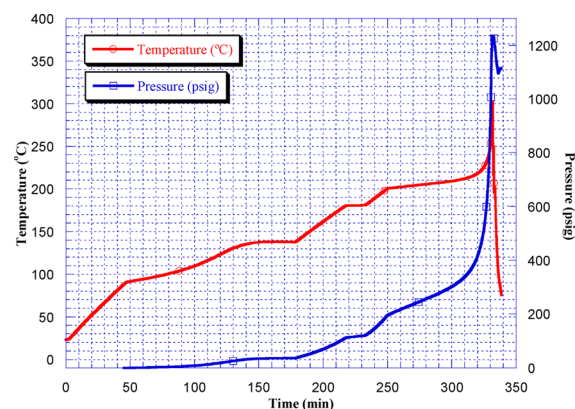
Figure 15. Reaction mixture with NaOAc: VSP2 test temperature and pressure history.
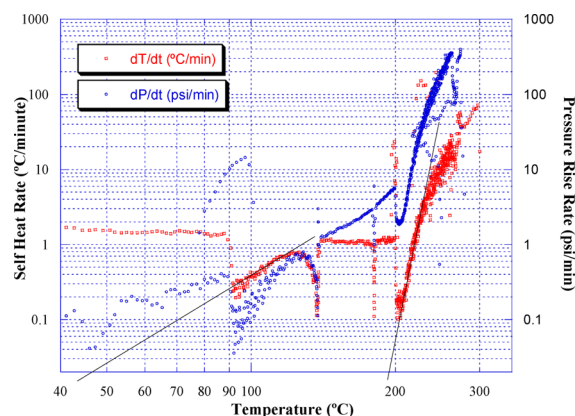
Figure 16. Reaction mixture with NaOAc: VSP2 test temperature and pressure rise rates.

With the updated safety procedures in place, namely, adding sodium acetate as a base, using pyridine as the solvent, and including sufficient venting, the hydrazine condensation process was safely and successfully scaled-up into multikilogram pilot plant runs. Taking these measures increases the onset temperature of the decomposition reaction, changing the criticality classification from 5 to 3. The severity of the decomposition reaction is also reduced.

■ **CONCLUSION**

The synthesis of 4-chloro-1H-indazol-3-amine via the hydrazine condensation reaction at 110 °C in NMP was determined to be unsafe to scale up because, in the event of a loss of cooling, the heat of reaction could heat the reaction above the onset temperature of violent exothermic decomposition of the reaction mass. Employing a low-boiling-point solvent alone would not guarantee a safe operation. The aqueous phase of the biphasic reaction mixture was identified as being the source of the unstable components (potentially a combination of hydrazine, hydrazine hydrochloride, and intermediate B.) The thermal stability of hydrazine monohydrate and therefore of the reaction mixture appears to be reduced by the presence of HCl. In fact, 0.1 equiv of HCl in hydrazine monohydrate was enough to lower the onset temperature of decomposition from >300 °C to around 180 °C. Introduction of a base (sodium acetate) in

combination with a low-boiling-point solvent (pyridine) reduced the criticality classification from class 5 (no inherent safeguards to prevent decomposition) to class 3 (sufficient thermal potential to reach the boiling point of the solvent but not enough to reach the onset of the decomposition) by enhancing the thermal stability of the reaction mass. After safe operating conditions for the hydrazine condensation reaction for a loss of cooling upset contingency were identified, the process was successfully scaled up in pilot plant runs.

Although we cannot disclose structures, the base stabilization effect has proven effective in other hydrazine condensation processes examined in our laboratory. In all instances, indazole entities were prepared with either hydrazine or methylhydrazine as the nucleophile. With respect to the S_NAr reaction, our observations include bromo, fluoro, and chloro displacements followed by condensation on a ketone, aldehyde, or nitrile. Invariably in every case, the exothermic degradation stage was reached, and addition of base postponed the onset temperature of the decomposition.

■ EXPERIMENTAL SECTION

Equipment Used. Differential scanning calorimetry was performed using a Mettler-Toledo DSC821e or DSC823e calorimeter and sealed glass ampules. Accelerating rate calorimetry was performed using a Columbia Scientific ARC and either glass or titanium test cells. VSP2 testing was performed using Fauske & Associates Vent Sizing Package 2. Heat of reaction testing was performed using a Mettler-Toledo reaction calorimeter (RC1) or an Omnical SuperCRC isothermal calorimeter.

General Procedure for DSC Testing. Samples were first loaded into and sealed in glass ampules with a capacity of approximately 50 μL and ramped in the DSC furnace from 0 to 300 °C at 10 °C/min.

General Procedure for ARC Testing. The sample was loaded into a pressure bomb made of titanium or glass with a capacity of 10 mL. The temperature and pressure of the test were recorded. The bomb was inserted into the calorimeter and 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 adiabatic condition and tracked the exotherm to 300 °C or until a pressure of 1200 psia was reached.

ARC Test Charges. Charges for the reaction using NMP as the solvent for the ARC test are shown in Table 5.

Table 5. Test Charges for the Reaction Using NMP as the Solvent in the ARC Test

material	amount (g)
2,6-dichlorobenzonitrile	0.8131
1-methyl-2-pyrrolidinone	2.4706
hydrazine monohydrate	0.9706

General Procedure for VSP2 Testing. A closed cylindrical stainless steel test cell (∼120 mL) was placed in a 4 L containment vessel. The test cell was enclosed by a test heater, a layer of insulation, and a guard heater, which in turn was enclosed by thermal insulation. Mixing was provided by a magnetic stir bar. The sample temperature and pressure as well as the containment pressure were recorded. The VSP2 test cell with the charges shown in the following tables was loaded into the VSP2 vessel and heated in heat−wait−search steps. When

self-heating was detected, the calorimeter maintained adiabatic conditions by offsetting heat losses through the guard heater and tracked the exotherm to the temperature or pressure limits defined for the test.

Test Charges for the Reaction Using NMP as the Solvent in the Closed-Cell VSP2 Test. Charges for VSP2 test using NMP as the solvent are shown in Table 6.

Table 6. Test Charges for the Reaction Using NMP as the Solvent for the Closed-Cell VSP2 Test[a]

material	amount (g)
2,6-dichlorobenzonitrile	10.43
1-methyl-2-pyrrolidinone	32.05
hydrazine monohydrate	12.50

[a]Thermal inertia ϕ = 1.25.

Test Charges for the Reaction Using Pyridine as the Solvent in the Open-Cell VSP2 Test with Venting to Ambient. Charges for the vented VSP2 test using pyridine as the solvent are shown in Table 7. The test cell was equipped

Table 7. VSP2 Test Charges Using Pyridine as the Solvent with Venting to Ambient

material	amount (g)
2,6-dichlorobenzonitrile	7.07
pyridine	35.93
hydrazine monohydrate	22.14

with two thermocouples, one located ∼1/4″ from the bottom and the other located near the bottom closer to the outer test cell wall. The test cell was vented through a 1/16″ line. The condensate was collected in a flask located on a balance. The vent valve was opened, and the condensate mass was measured during the test. The heat−wait−search steps were performed from 60 °C. An exothermic event was detected at 80 °C.

Test Charges for the Reaction Using Pyridine as the Solvent and NaOAc as the Base in the Closed-Cell VSP2 Test. Charges for the VSP2 test using pyridine as the solvent and NaOAc as the base are shown in Table 8. The heat−wait−search steps were performed from 70 °C. The exothermic event detected at 80 °C heated the reaction to 140 °C. The heat−wait−search was restarted with 20 °C steps.

Table 8. VSP2 Test Charges Using Pyridine as the Solvent and NaOAc as the Base

material	amount (g)
2,6-dichlorobenzonitrile	6.04
pyridine	28.34
sodium acetate	3.35
hydrazine monohydrate	18.40

Procedure for Heat of Reaction Measurement Using RC1 with NMP as the Solvent at 110 °C. A 1 L reactor was used for the testing. Mixing was provided by a mechanical stirrer. The test charges are shown in Table 9. The reactor with 2,6-dichlorobenzonitrile and NMP was heated to 110 °C. After the system reached thermal equilibrium at 110 °C and a calibration was performed, hydrazine monohydrate was added in 30 min.

Table 9. RC1 Reaction Test Charges

material	amount (g)
2,6-dichlorobenzonitrile	96.9
1-methyl-2-pyrrolidinone	298.1
hydrazine monohydrate	112.0

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

DSC results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Zhe.Wang@abbvie.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Kruger, A. W.; Rozema, M. J.; Chu-Kung, A.; Gandarilla, J.; Haight, A. R.; Kotecki, B. J.; Richter, S. M.; Schwartz, A. M.; Wang, Z. *Org. Process Res. Dev.* **2009**, *13*, 1419−1425.

(2) Simpson, D. K. 22nd Department of Defense Explosives Safety Seminar, 1985.

(3) Troyan, J. E. *Ind. Eng. Chem.* **1953**, *45*, 2608−2612.

(4) Kuethe, J. T.; Childers, K. G.; Peng, Z.; Journet, M.; Humphrey, G. R.; Vickery, T.; Bachert, D.; Lam, T. T. *Org. Process Res. Dev.* **2009**, *13*, 576−580.

(5) Stoessel, F. *Thermal Safety of Chemical Processes: Risk Assessment and Process Design*; Wiley-VCH: Weinheim, Germany, 2008.