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Safety Assessment of Diels–Alder Reactions with Highly Reactive Acrylic Monomers

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Supporting Information

ABSTRACT: The Diels–Alder reactions of the diene (cyclohexa-1,5-dien-1-yloxy)trimethylsilane with either of the two dienophiles α-acetoxyacrylonitrile or α-chloroacrylonitrile pose severe safety hazards for scale-up. We report the systematic thermal hazard assessment of these Diels–Alder reactions and discuss their classification according to the Stoessel criticality diagram. Whereas the use of α-acetoxyacrylonitrile is not recommended, the reaction of the diene with α-chloroacrylonitrile can be scaled up when running the reaction in toluene in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and sodium bicarbonate.

INTRODUCTION

The bicyclic ketone **4** was required as an intermediate for the production of a clinical candidate at Actelion Pharmaceuticals Ltd. (Scheme 1). The first syntheses relied on the Diels–Alder reaction of the TMS-diene (cyclohexa-1,5-dien-1-yloxy)-trimethylsilane (**1**) with either of the two dienophiles, α-acetoxyacrylonitrile (**2**) and α-chloroacrylonitrile (**5**), to afford the Diels–Alder products **3** or **6**.[1] The high-temperature reaction of these polymerization-prone acrylic monomers presented a formidable challenge for a safe scale-up. In a study of 134 incidents from 1962 to 1987, polymerization accounted for the vast majority of runaway situations.[2] In addition to the exothermic decomposition potential of the acrylic monomers, controlling the heat of the reaction was of concern. Here, we present the process safety evaluation of both Diels–Alder reactions and assess the feasibility of a safe scale-up for each.[3] To the best of our knowledge, there is no detailed account of a safety assessment of a Diels–Alder reaction in batch mode. At the same time, this report shows the typical challenges process chemists are facing.[4] Often, a first synthetic route delivers enough material for preclinical studies, but safety concerns mandate alternative routes. A balanced approach is desired to meet stringent timelines without jeopardizing safety. Early recommendations for the maximum scale of a reaction are invaluable for an efficient route selection and should always be based on sound experimental data.

RESULTS AND DISCUSSION

α-Acetoxyacrylonitrile (2) as Dienophile. As part of the systematic safety evaluation, we first studied the distillation and the storage of **2** that is not commercially available on scales greater than 100 g. In addition, pertinent safety data were missing. Even when acrylic monomers are commercially available with a stabilizer (normally hydroquinone or 2,6-di-*tert*-butyl-4-methylphenol (BHT)),[5] physical operations such as distillation can remove the stabilizer; therefore, both types (stabilized and nonstabilized) must be tested. The thermal risk of the planned operation was assessed using both the severity and the probability of decomposition, following the method pioneered by Stoessel.[6] The time to maximum rate under adiabatic conditions (TMR_{ad}) is used as a measure of the probability, whereas the severity is derived from the decomposition energy, e.g. determined by differential scanning calorimetry (DSC) measurements. Thermal stability was studied by microthermal analysis in a dynamic DSC experiment (Figure 1). The acrylic monomer **2** had a high decomposition potential of −1530 kJ/kg, which corresponds to a calculated adiabatic temperature rise (ΔT_{ad}) of 900 K, using an estimated heat capacity of 1.7 kJ/(kg·K). Comparison of samples with and without stabilizer found that the main decomposition signal was not influenced by the presence of the stabilizer BHT (0.2% w/w). The severity of the decomposition of **2** was rated high; therefore, the TMR_{ad} was calculated.

In order to obtain TMR_{ad} values, the decomposition kinetics of stabilized **2** were studied in a series of isothermal DSC experiments at four different temperatures.[7] The maximum heat release rates, q_T, of the main decomposition could be interpreted in terms of a zero order reaction, which enabled the determination of the activation energy, E_a, by plotting the logarithm of the maximum heat release rate against $1/T$ (Arrhenius). The TMR_{ad} was then calculated for different safety-relevant temperatures with the activation energy and a reference heat release rate, q_{ref} (Table 1).

The thermal risk during distillation, assuming a wall temperature of 75 °C, was assessed as high (runaway within approximately 12 h after the cooling failure), and measures to improve safety had to be considered for a distillation under reduced pressure. The scale must be restricted to a few

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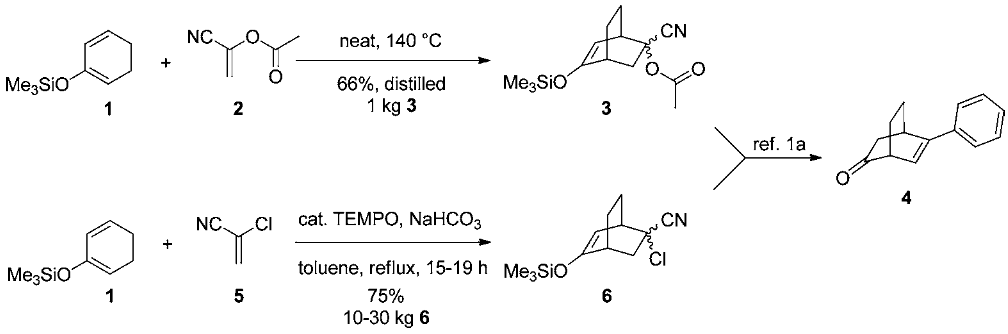
Scheme 1. Diels–Alder Reaction of TMS-diene 1, α-Acetoxyacrylonitrile (2), and α-Chloroacrylonitrile (5)



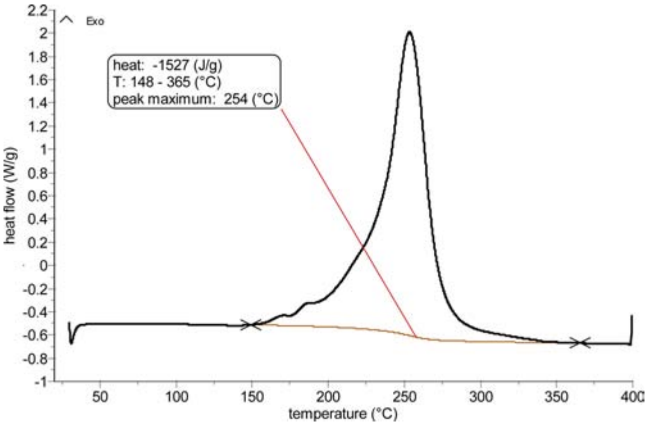


Figure 1. DSC trace of α-acetoxyacrylonitrile (**2**). The heat of decomposition Q_d = −1527 kJ/kg, corresponds to an equivalent of approximately 0.3 kg of trinitrotoluene (TNT).

Table 1. Kinetic Parameters of the Decomposition of 2

reference temperature T_{ref}	160 °C
reference heat release rate q_{ref} (at T_{ref})	57 W/kg
activation energy E_a	68 kJ/mol
decomposition uncritical below T_{D24}[a]	64 °C
decomposition critical above T_{D8}[a]	81 °C
TMR_{ad} at 75 °C (assessment temperature)	12 h

[a] T_{D24}, T_{D8}: temperatures at which TMR_{ad} is 24 and 8 h, respectively.

kilograms in an agitated glass vessel. This process cannot be considered adiabatic (there is substantial heat exchange with the surroundings), and in the case of an emergency (loss of vacuum or uncontrolled heating), the contents of the vessel could either be cooled or rapidly be dumped into a cooled vessel containing an inert solvent.

The thermal safety of the storage of **2** was assessed by the Frank–Kamenetskii approach.[8,6] On the basis of some approximations and the thermokinetic and physicochemical properties of **2**, the critical radius of a cylindrical container was calculated as a function of temperature (Supporting Information). α-Acetoxyacrylonitrile (**2**) was recommended to be stored in a vessel with a radius <0.25 m at a temperature <40 °C.

Batch Reaction of 1 and 2. The safety of the batch process with an equimolar mixture of **1** and **2** was studied using the concept of the cooling failure scenario. A classification based on the key parameters T_P (process temperature), T_{cf} (temperature after cooling failure), MTSR (maximum temperature of the synthesis reaction that could be reached after a cooling failure), TMR_{ad}, T_{D24}, and MTT (maximum temperature for technical reasons, often the boiling point) can be used to define the safety measures for this reaction.[6] A screening DSC measurement of the batch reaction showed three exothermic peaks (Figure 2).[9] Comparison with a thermogram of the reaction mixture after full conversion assigned the peak at 184 °C to the desired Diels–Alder reaction, whereas peaks at 310 and 334 °C were assigned to decomposition reactions of product **3**. Note that the desired reaction and the decomposition reaction overlap; that is, the decomposition reactions are already triggered within the temperature range of the desired reaction. In the case of partial conversion (unreacted **2** present), the decomposition of **2** has to be taken into account as well. A preliminary assessment of the cooling failure scenario showed that the desired reaction would trigger the decomposition and cause a runaway. Despite this assessment, it was decided to further develop the process and to define a maximum scale in order to fulfill early material requirements. This decision took into consideration the small batch volume (1–4 L flasks with substantial convection and heat flow to surroundings) that made an adiabatic scenario unlikely.

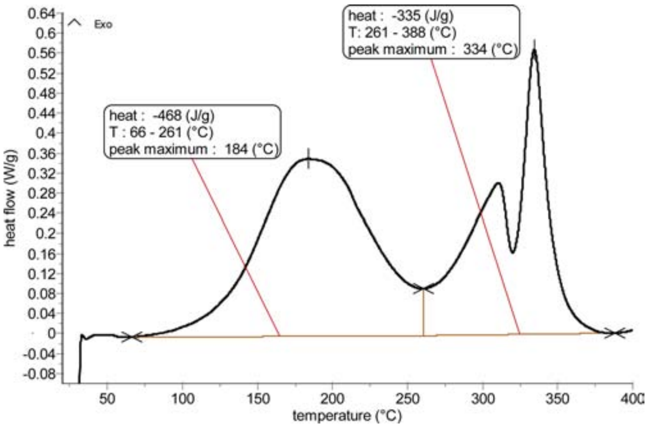


Figure 2. DSC trace of a mixture of **1** and **2** (1:1) at 4 K/min. Heat of desired reaction Q_r = −468 kJ/kg (68–261 °C); heat of decomposition Q_d = −335 kJ/kg (261–388 °C).

Investigation of the Diels–Alder reaction of **1** and **2** with a semipreparative Calvet calorimeter Setaram C80[10] revealed a small exotherm (−25 kJ/kg) after mixing both reagents at 25 °C (Supporting Information). We hypothesize that this exothermic signal indicates the formation of a charge-transfer complex between the diene **1** and **2**.[11] A further increase in temperature initiated the desired reaction (Figure 3). Due to the slower heating rate (0.7 K/min vs 4 K/min in the DSC)

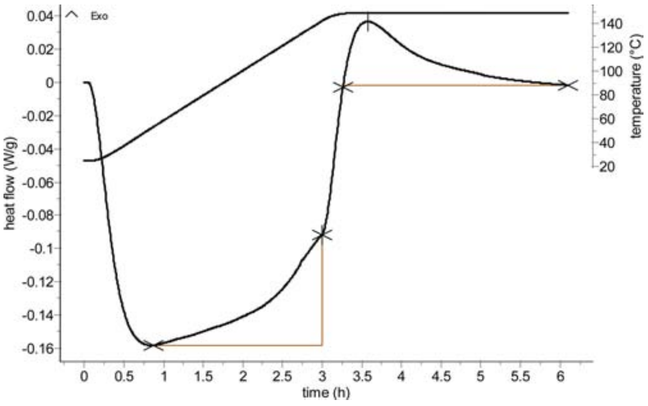


Figure 3. C80 trace of a mixture of **1** and **2** (1:1, 539 mg). Heat of reaction only indicative of $Q_r < -310$ kJ/kg (25−150 °C, 0−6 h).

and the isothermal phase after the temperature ramp, the decomposition signal was not detected by this technique.

Finally, the batch process was studied on a preparative scale (1:1 mixture of **1** and **2**, 213 g) in a reaction calorimeter where the reaction mass could be stirred (Figure 4). This study showed that the temperature which can be reached after a cooling failure (T_{cf}) passes its maximum at MTSR = 245 °C after 2.2 h. At this time, the batch temperature is 114 °C with a thermal conversion of 15%.

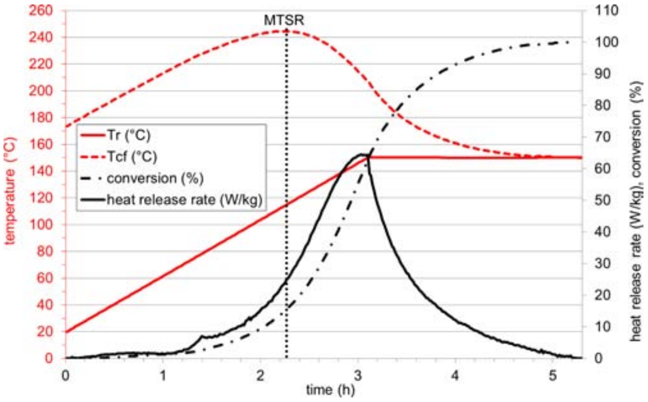


Figure 4. Reaction calorimetric data of the neat batch process of **1** and **2**. Heat rate: 0.7 K/min from 20−150 °C; then 2 h isothermal at 150 °C. The figure shows the reactor temperature T_r (°C), T_{cf} (°C), the thermal conversion (%), and the heat release rate (W/kg) as a function of time. Heat of reaction $Q_r = -308$ kJ/kg; MTSR = 245 °C.

The kinetics of the runaway of the final Diels−Alder reaction mass were modeled using the isoconversional method based on DSC scans at different heating rates.[12] Figure 5 shows the calculated adiabatic temperature course as a function of time for a starting temperature of 250 °C. This kinetics software (AKTS) predicts a TMR_{ad} of 40 min starting from 250 °C. The T_{D24} was calculated as 194 °C.

The Diels−Alder reaction of **1** with **2** is run in full-batch mode without a solvent barrier. At MTSR = 245 °C, decomposition would set in immediately, leading to a final temperature of >400 °C. The pivotal temperatures are summarized in Table 2 in increasing order, leading to a criticality index of 4. In such a situation, the safety of the process depends on the heat release rate of both the synthesis and the decomposition reaction at the MTT. Evaporative cooling or emergency pressure relief may serve as a safety barrier. However, if this technical measure fails, the secondary reaction will be triggered.

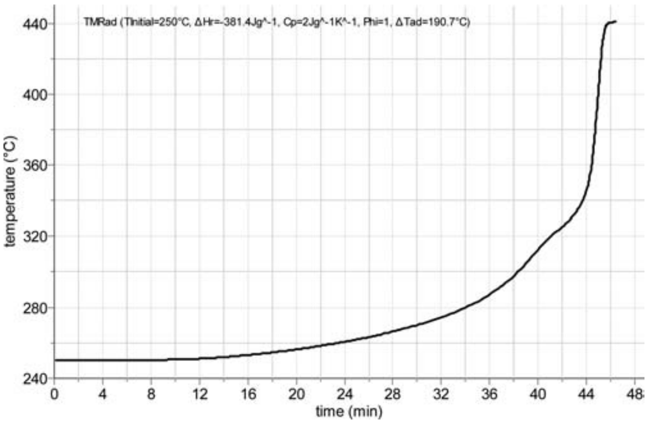
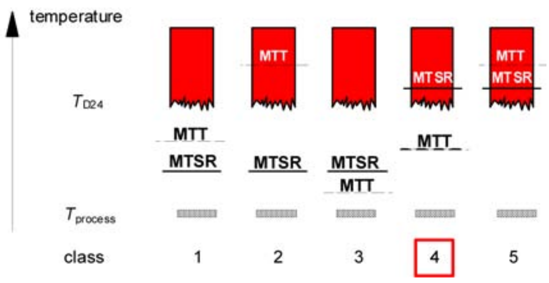


Figure 5. Simulation of the adiabatic runaway with AKTS software. The temperature course is shown as a function of time. $Q_r = -381$ kJ/kg was obtained from DSCs of the final Diels−Alder reaction mass and an estimated heat capacity of the reaction mass of 2 kJ/(kg·K).

Table 2. Characteristic Temperatures for the Neat Batch Reaction of 1 and 2 and Related Stoessel Diagram

T_P	MTT[13]	T_{D24}	MTSR
20–150 °C	173 °C	194 °C	245 °C



Semibatch Reaction of 1 and 2. As risk reduction by dilution with inert solvents only led to slow conversion or decomposition,[14] a special semibatch procedure, in which only a third of both reactants was initially charged at 25 °C, was chosen in order to reduce the overall runaway potential. Dosage of one reagent to the other is not advisable due to the thermal instability of each reagent. This initial mixture was heated to the reaction temperature (T_P = 140 °C) within 3 h, and the remaining reaction mass was fed into the reactor over 3 h at T_P (Figure 6). The MTSR was the same as in the batch process. However, the amount of reaction mass at the corresponding time is three times smaller. Albeit straightforward, this Diels−Alder process was not deemed scalable beyond a few kilograms. A further drawback of this reaction was the need to distill product **3** in order to obtain ketone **4** of acceptable quality.

α-Chloroacrylonitrile (5) as Dienophile. Further process research led to the choice of α-chloroacrylonitrile (**5**) instead of α-acetoxyacrylonitrile (**2**) as the dienophile and ketene equivalent.[1a] This time, the goal of process development was not the production of a few kilograms of **3** in the kilo lab, but pilot plant production on an approximately 100 kg scale to satisfy material requirements for clinical trials. The product **6** displayed in Scheme 1 was not isolated but transformed into a

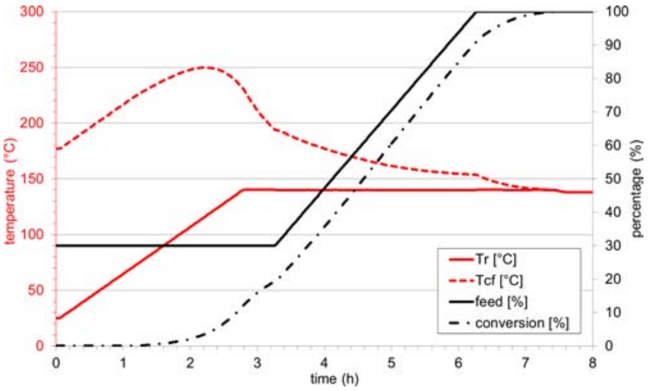


Figure 6. Reaction calorimetric data of the neat semibatch process of **1** and **2**. The figure shows the feed (%) in addition to the parameters of Figure 4. Heat of reaction Q_r = −304 kJ/kg; MTSR = 250 °C.

ketal with ethylene glycol after simple aqueous workup of the reaction mixture.[1a]

*Batch Reaction of **1** and **5** without Solvent.* We observed that some lots of α-chloroacrylonitrile (**5**) contained traces of anhydrous hydrochloric acid that might catalyze the polymerization of the reaction mixture. $NaHCO_3$ was therefore added as a pH buffer. As $NaHCO_3$ is not soluble in the reaction mass, unstirred samples consisted, therefore, of two phases: a clear upper phase and a slurry containing the $NaHCO_3$. DSC measurements of the two samples (with and without $NaHCO_3$) showed similar traces. Hence, it was concluded that $NaHCO_3$ did not interfere with the stability of the reaction mass. During the course of the process optimization, we found to our surprise that 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was the stabilizer best preventing polymerization of the reaction mixture containing **1** and **5**.[15] Therefore, all Diels−Alder reaction mixtures of **1** and **5** used in the following experiments contained $NaHCO_3$ (0.3 equiv) and TEMPO (0.01 equiv).[16]

Again, the reaction was first examined with DSC (Figure 7). The exothermic signal in the range from 64 to 197 °C was assigned to the desired Diels−Alder reaction. The measured reaction energy equaled −341 kJ/kg and corresponded to an adiabatic temperature rise of approximately 200 K, assuming a heat capacity of 1.7 kJ/(kg·K). When the Diels−Alder reaction is performed at 70 °C, the adiabatic end temperature is 270 °C, which triggers the decomposition. The peak corresponding to the Diels−Alder reaction (131 °C) was shifted to lower temperatures compared to the reaction with **2** (184 °C, cf. Figure 2). The reaction of **1** proceeds faster with **5** than with **2**; therefore, the reaction temperature is lower than in the reaction with **2**: this is a benefit, as this prevented premature decomposition of the Diels−Alder reagents at elevated temperatures. The enormous heat release rate of the decomposition of approximately −3300 W/kg was attributed to a polymerization of the reaction mixture. It is interesting to note that the undiluted reaction mixture (Figure 7) is reactive even at 5 °C. This becomes clear by comparing the DSC thermogram obtained with the above reaction mixture after storage at 5 °C for 4 h with the DSC thermogram shown in Figure 7 and with the DSC trace of the product **6** (Supporting Information).

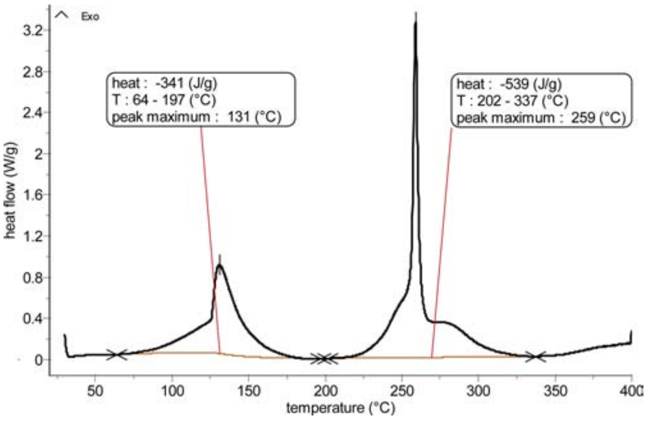


Figure 7. Screening DSC trace of a mixture of **1** and **5** (1.12 equiv of **5**, with 0.3 equiv of $NaHCO_3$, 0.01 equiv of TEMPO) at 4 K/min, recorded right after preparation of the mixture. Q_r = −341 kJ/kg (64−197 °C); Q_d = −539 kJ/kg (202−337 °C).

The results of the heat flow reaction calorimetry of the batch process (300 g of the above mixture, heated with a rate of 1 K/min from 20 to 65 °C and kept isothermally at 65 °C for 20 h; see Supporting Information) were similar to those obtained with **2** as the dienophile (cf. Figure 4). Again, the reaction heat was approximately −300 kJ/kg and the MTSR equaled 250 °C, at which temperature decomposition would set in immediately. The reaction was diluted with toluene to mitigate the adiabatic temperature rise (ΔT_{ad} = 201 K).

*Batch Reaction of **1** and **5** in Toluene.* The result of a diluted experiment in a heat-flow calorimeter is depicted in Figure 8. The same ratio of reagents was applied as depicted in Figure 7, but 2.2 L of toluene per 1 kg of reaction mass was used (332 mL of toluene, 150-g mixture of **1**, **5**, $NaHCO_3$, and TEMPO). As expected, the dilution of the reaction mass by a factor of 3 reduced the reaction heat by the same factor, and the MTSR equaled 132 °C compared to 250 °C in the undiluted case. In addition, the larger heat capacity (1716 vs 1650 J/(kg·K) in the undiluted case) was expected to shift the T_{D24} to higher temperatures.

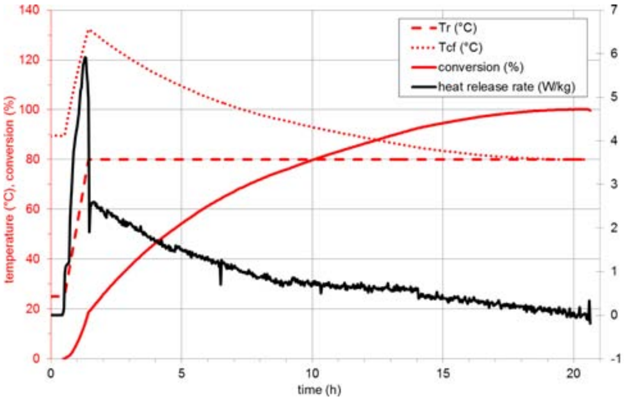
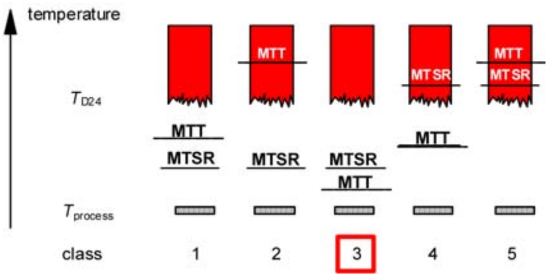


Figure 8. Reaction calorimetry of the diluted batch process with **5** at 80 °C (34% w/w in toluene). Reaction heat = −111 kJ/kg; MTSR = 132 °C.

To assess the probability of a runaway, the same method was used as for the study of the reaction mixture with **2**. The AKTS modeling of the kinetics of the decomposition was based on DSC traces with five different heating rates (Supporting Information). A decomposition energy of −346 kJ/kg was found corresponding to an adiabatic temperature rise of 204 K using an estimated heat capacity of 1.7 kJ/(kg·K). The thermokinetic modeling gave a T_{D24} of 162 °C. By arranging the four key temperatures in ascending order (Table 3), a criticality index of 3 was determined.

Table 3. Characteristic Temperatures for the Diluted Batch Reaction of 1 and 5 and Related Stoessel Diagram

T_P	MTT	MTSR	T_{D24}
25–80 °C	112 °C	132 °C	162 °C



According to the definition of the criticality index 3, the safety of this process is dependent on the heat release rate of the synthesis reaction at the boiling point. This means that the design of the reactor must allow for unhindered evaporation and condensation of the volatiles.

Hence, two questions must be addressed. First, is there enough toluene to limit the temperature of the mixture to the boiling point by evaporation? For this calculation (Supporting Information), the heat release rate of the desired reaction at the boiling point of toluene (112 °C) was conservatively estimated from the DSC of the mixture of starting materials (Figure 7) and has been corrected for the dilution of 34% w/w. In the case of a runaway reaction starting from 80 °C, 54 kJ/kg of the reaction energy of −111 kJ/kg is used to reach the boiling point. Even after evaporation of toluene, there is an ample amount of solvent left. At this temperature, the decomposition is very slow, and the reaction mass in the reactor can be considered as stable.

Second, is the flow rate of the resulting vapor stream compatible with the plant design? Following a very conservative approach, the reactor is equipped with an exhaust tube of only 0.03 m diameter. A calculation of the velocity of the toluene vapor through the exhaust pipe gives a value of 7.8 m/s that is acceptable (Supporting Information). To absorb the maximum evaporation power of 5.7 kW, a condenser heat exchange area of 0.12 m^2 is required, which is small compared to the typical sizes used at 100 kg scale (several square meters).

The diluted Diels–Alder reaction of **1** and **5** is deemed safe for a scale of 100 kg reaction mass in the reactor. An adiabatic situation in the worst case, i.e. at the end of the heat ramp, would result in a MTSR of 132 °C. The boiling of toluene starts already at 112 °C, acting as a thermal barrier. This Diels–Alder reaction was reproduced several times on 54–147 kg sized batches in a 200-L Hastelloy reactor, giving similar yields and purities.[17]

■ CONCLUSION

We have shown how a detailed risk assessment—one encompassing the determination of the severity and the probability of a runaway—has been essential for rapid route selection. Diels–Alder reactions of the TMS-diene **1** with two different dienophiles were chosen to produce the required quantities for the various stages of development. For each, thermokinetic and calorimetric measurements and modeling of the kinetics were performed to assess their feasibility for further scale-up. Accordingly, the safety risks are rated too high for a scale-up of the reaction with α-acetoxyacrylonitrile (**2**), although delivering 1-kg amounts was pivotal for an early start of the development of the downstream steps. However, the Diels–Alder reaction with α-chloroacrylonitrile as the dienophile in toluene in the presence of TEMPO and $NaHCO_3$ has been rated a viable method for batch sizes of approximately 100 kg in a standard pilot plant reactor. Whereas the reaction with **2**, which is not commercially available, required two distillations, i.e. for the purification of **2** and **3**, the Diels–Alder reaction with commercially available **5** gave product **6** of acceptable quality without requiring further purification. Indeed, 442 kg of TMS-diene **1** was safely processed in several batches through this Diels–Alder reaction and delivered material that was used for the production of clinical batches.

■ EXPERIMENTAL SECTION

Differential scanning calorimetry: DSC 821e robot-system (Mettler-Toledo). The samples were weighed under air in a gold plated high pressure steel crucible.[18] The kinetics were evaluated either based on isothermal measurements at different temperatures (Arrhenius) or based on measurements using different heating rates, followed by thermokinetic modeling with the AKTS software, as described in the text and delineated in the Supporting Information. A Calvet Setaram C80 semipreparative calorimeter was used, whereby the two reaction components were separately weighed in the two compartments of the mixing cell separated by a membrane that was perforated to start the reaction. Reaction calorimetry: reaction calorimeter RC-1 (Mettler-Toledo) with 1-L reactor, propeller stirrer, heated glass cover, and condenser. The dienes **1**[19] and α-acetoxyacrylonitrile (**2**)[20] were synthesized according to literature protocols and were distilled. α-Chloroacrylonitrile (**5**) was purchased from TCI (Lot No. L56PA FC, stabilized with hydroquinone). TEMPO was purchased from Fluka (No. 87903).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Isothermal DSC's, Arrhenius diagram, and Frank–Kamenetskii calculation for **2**. C80 thermogram of the mixing of **1** and **2** at 25 °C. RC-1 results of batch reaction of **1** and **5**. AKTS-modeling of the kinetics of the decomposition of the final reaction mass of **1** and **5**. DSC trace of **1** and **5**, measured after 4 h at 5 °C. Calculation of the required amount of toluene and vapor velocity for the reaction of **1** with **5**. DSC trace of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Estimated with bp (**2**) = 173 °C at 1027 mbar; bp (**1**) = 60 °C at 8 mbar.

(14) Footnote 32 in ref 1a.

(15) Typical stabilizers for such acrylic monomers are 2,6-di-*tert*-butyl-4-methylphenol (BHT), hydroquinone, and hydroquinone monomethyl ether. These proved to be inefficient in this mixture; that is, a precipitate was formed, indicative of polymerized **5**, see ref 1a.

(16) DSC experiments showed no influence of TEMPO or air on the stability of α-chloroacrylonitrile (**5**).

(17) When α-chloroacrylonitrile (**5**) was used that has been stored for a few months, polymeric residues were found in the vessel. It is recommended to only use fresh or distilled **5**.

(18) DSC measurements can give different results when measured under an inert gas blanket. See ref 9.

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