

DMSO Can Be More than a Solvent: Thermal Analysis of Its Chemical Interactions with Certain Chemicals at Different Process Stages

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Abstract:

During the process development of the product 6 via the route presented in Scheme 1, we encountered several safety issues that had to be resolved before moving these stages to production. In each case, the safety issues are related to the interaction of the solvent used, DMSO (dimethylsulphoxide, 3), with one of the other chemicals. Also in this case (Bollyn, *M. Org. Process Res. Dev.* 2005, 9, 982–996) we applied the runaway index as a guide to decide whether a process could be run at production scale. The combination of reaction calorimetry in the RC1 (Mettler Toledo's Reaction Calorimeter 1; <http://www.RXEFORUM.com>) and thermal analysis in the ARC (Accelerating Rate Calorimeter; <http://www.thermalhazard-technology.com>) was used in combination with the process parameters study to design process stages that were considered safe (enough) for production scale.

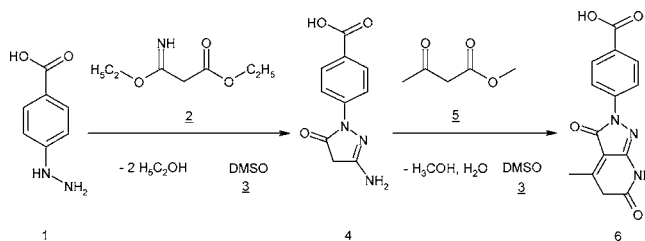
Introduction

As part of a process development project for a photographic active ingredient the conversion of 4-carboxyphenylhydrazine (1) with ethyl-3-ethoxy-3-iminopropionate (2) to benzoic acid, 4-(3-amino-4,5-dihydro-5-oxo-1H-pyrazol-1-yl) (4), and the further transformation with acetylacetic acid methylester (AAME) (5) to benzoic acid, 4-(1,3,5,6-tetrahydro-4-methyl-3,6-dioxo-2H-pyrazolo[3,4-b]pyridin-2-yl) (6) in DMSO as the main solvent was studied (Scheme 1). Even though the chemistry proved to be reproducible on scale-up and the required product quality could be achieved, changes had to be made to ensure intrinsic safety for the production processes.

In the European Union the Seveso II directive⁴ requires that the hazards of chemical processes are identified in order to control the risks and avoid major incidents. One of the common hazards of chemical reactions performed in a (semi-) batchwise process is a runaway resulting in a thermal explosion. It is imperative to have the appropriate experimental data to evaluate the risk of this possible event. Reaction and adiabatic calorimetry testing are the techniques used to acquire these data.

Batch and semi-batch processes can be classified into five types of runaway scenarios^{5,6} (Figure 1),⁷ depending on the

Scheme 1. General reaction scheme



relative position of the following parameters: process temperature (T_p), boiling temperature of the reaction mixture (T_b), maximum adiabatic temperature (MAT) for a batch process, maximum temperature of the synthesis reaction (MTSR; sometimes this is also called TCF, temperature in case of cooling failure) for semi-batch mode, and the temperature with a time to maximum rate of 24 h (TMR24 or $MaxT_{safe24}$ ⁸).

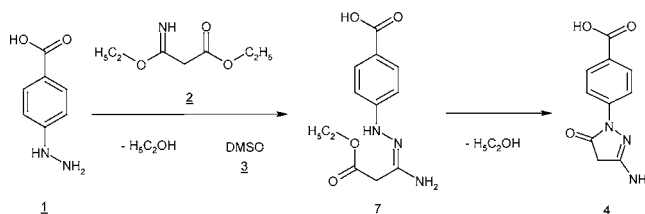
Process temperature and boiling point can quite easily be obtained, but MAT or MTSR should be calculated from calorimetric data (e.g., RC1) and $MaxT_{safe24}$ values come from adiabatic thermal stability testing (e.g., ARC).

This concept is used in the risk assessment of all our chemical processes. In this report we discuss the results of the study of the conversion of 1 to 4 and its transformation to 6.

Results and Discussion

Synthesis of 4. In the initial procedure for the synthesis of 4, 4-carboxyphenylhydrazine (1) is added as a solid to ethyl-3-ethoxy-3-iminopropionate (2) in a mixture of methanol and DMSO at 15 °C to form ethanol and an intermediate 7 (Scheme 2), which upon heating is cyclised to 4, with the elimination of a molecule of ethanol.

Scheme 2. Conversion of 1 to 4



Adding a solid to a reaction mixture is quite easy at lab scale because the quantities—and risks—are small. At

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(1) Bollyn, M. *Org. Process Res. Dev.* 2005, 9, 982–996.

(2) <http://www.RXEFORUM.com>.

(3) <http://www.thermalhazardtechnology.com>.

(4) <http://europa.eu/scadplus/leg/en/lvb/l21215.htm>.

(5) Gygax, R. *Chem. Eng. Sci.* 1988, 43, 1759–1771.

(6) Stoessel, F. *Chem. Eng. Prog.* 1993, 89, 1068–1075.

(7) Harsnet, *Thematic network on hazard assessment of highly reactive systems*; <http://www.harsnet.de>.

(8) We prefer to use the expression $MaxT_{safe24}$ rather than TMR24, because the physical meaning is a temperature, rather than a time.

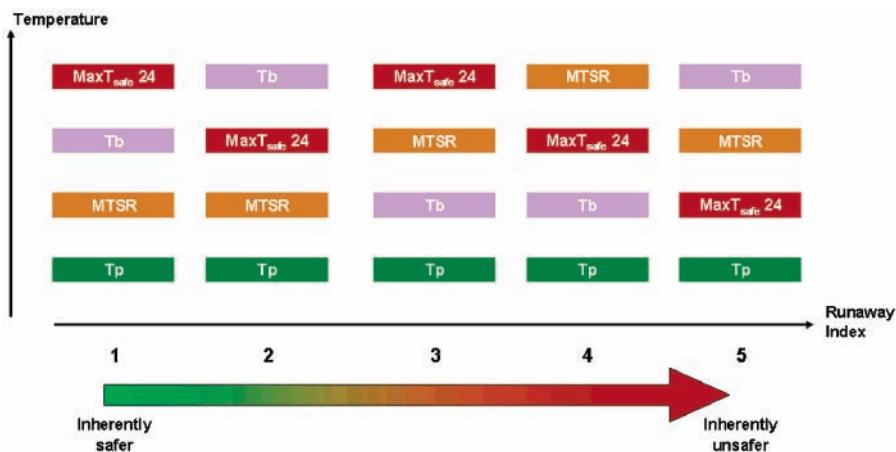
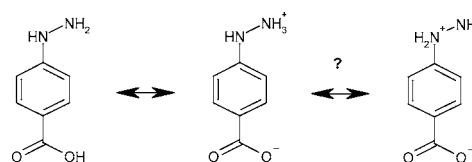


Figure 1. Classes of thermal runaway scenarios.

production scale this operation could involve several hundred kilograms that have to be transferred to the reactor. Since this type of chemical reaction is exothermic, it is required that feeding the solid is performed over a longer period to allow the control of the process temperature. In our flexible multipurpose and multiproduct production plant there are no fixed or mobile solid feed systems available, which means that that feeding would have to be done manually via the manway. Methanol has a flashpoint of 12 °C, and the physical meaning of this parameter is that above this temperature there are ignitable vapours in the headspace of the vessel at all times. These vapours could cause a fire in the reactor when air and an ignition source are present at the same time and place. This can be avoided by excluding the air and/or all possible ignition sources. In practice it is very difficult to keep a low oxygen content in a large reactor during charging it with solids over a long period (several hours). In a chemical production plant most ignition sources can be excluded, but the build-up of static charges and the discharge thereof are difficult to control at all times and especially on handling solid products. It mainly depends on the properties of the solid involved. 4-Carboxyphenylhydrazine has a low minimum ignition energy (MIE, 5–11 mJ) and a high specific resistivity ($>10^{12} \Omega \cdot \text{m}$) and thus can build up high electrostatic charges. It is clear that there is a safety issue when a large quantity of 4-carboxyphenylhydrazine is charged via the manway to a reactor containing substantial quantities of methanol at 15 °C. It is experimentally proven that methanol cannot be avoided in this process. One way to solve this problem could be to use a solids dosing system attached to the manway, which would allow maintaining a low oxygen concentration in the head space of the reactor. Another option would be to charge 4-carboxyphenylhydrazine in dissolved form to the reactor. This solution could be prepared in another vessel under safe conditions: charging the product to a dry and inert reactor, followed by the solvent. From the initial data it was already clear that the choice of solvent for 4-carboxyphenylhydrazine is limited to DMSO. The solubility in most other solvents is too low. The reason could be that this product is present in its zwitterion form (Scheme 3).

Scheme 3. Tautomeric forms of 1



Solubility tests indicated that 4-carboxyphenylhydrazine can be dissolved in DMSO up to a concentration of 310 g/l, but this requires heating to 45 °C to get the solution in an acceptable time.

Preparing a solution of a chemical is considered as a process stage, and the safety parameters should be established. 4-Carboxyphenylhydrazine is considered to be a thermally safe product up to a temperature of 140 °C based on DSC and ARC testing. A technical datasheet⁹ of DMSO mentions that it can be kept at 150 °C for 24 h with 0.1% purity loss and that its decomposition temperature is >190 °C; however, in the presence of some materials decompositions can occur at lower temperatures. It also states that DMSO is generally stable¹⁰ in neutral or basic conditions but that some strong bases should be used with great care and that some acids can cause a rapid decomposition.

The thermal stability of the mixture of 4-carboxyphenylhydrazine and DMSO was tested in the RADEX. The initial screening indicated that a violent decomposition occurred. The graph (Figure 2) shows the behaviour of dry and in DMSO-dissolved 4-carboxyphenylhydrazine. The RADEX tests generate data on the temperature difference between the test cell and a reference profile and also the pressure in the test cell. The temperature data indicate that the decomposition starts around 140 °C. It is clear that the red curve (dissolved) shows an additional peak—compared to the brown curve (dry)—starting at about 190 °C. The green curve (pressure, dissolved product) starts to deviate from the blue one (pressure, dry product) from 175 °C onwards and shows a strong peak at 235 °C. At the end of the test the dissolved product generates a 20 bar higher pressure in the test vial.

(9) <http://www.arkema-inc.com/literature/pdf/363.pdf>.

(10) The thermolytic degradation of DMSO to give acidic products which catalyse further decomposition has been discussed by Santusso, T.M. *Tetrahedron Lett.* **1974**, 4255–4258.

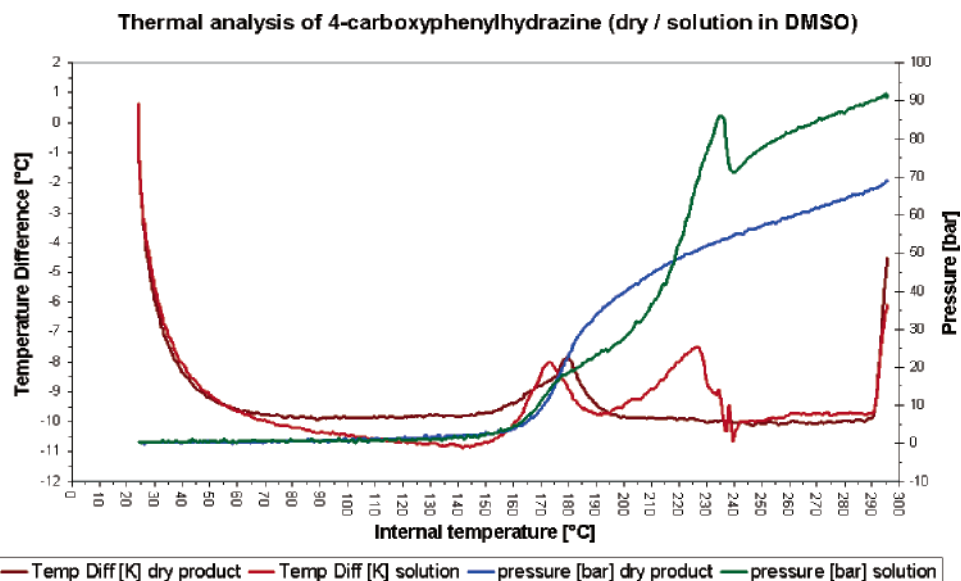


Figure 2. Temperature and pressure curves of dry and dissolved *1* (RADEX).

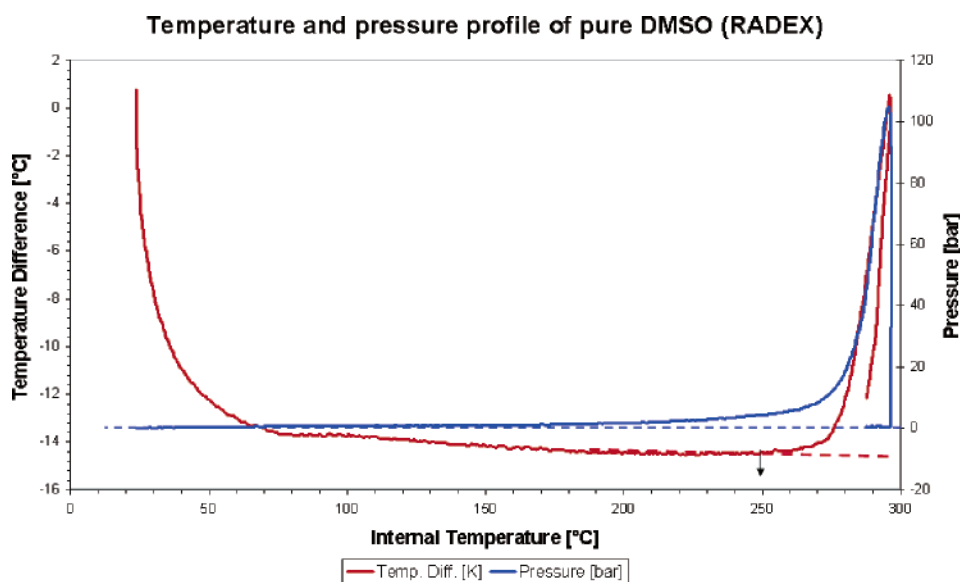


Figure 3. Temperature and pressure (*T,P*) curve of pure DMSO (RADEX).

Pure DMSO does not show any sign of exotherm or pressure generation in the temperature range from 50 to 190 °C under these conditions. From 250 °C on an exotherm sets in, and a high pressure (> 100 bar, the rupture disc is destroyed) is generated (Figure 3). This observation is in line with information found in the literature.^{10,11}

In the ARC the sample of dissolved *1* shows decomposition from 112 °C on, and about 500 min later an explosive temperature and pressure rise occurs at 175 °C (Figure 4). The pressure generation is so violent that the test cell is ruptured. A $MaxT_{safe}$ value of 90 °C is calculated from this experiment (Figure 5). The last recorded pressure value is 47 bar, but at that time the pressure rate was 66 bar/min (see Table 1 for a summary of the relevant ARC results).

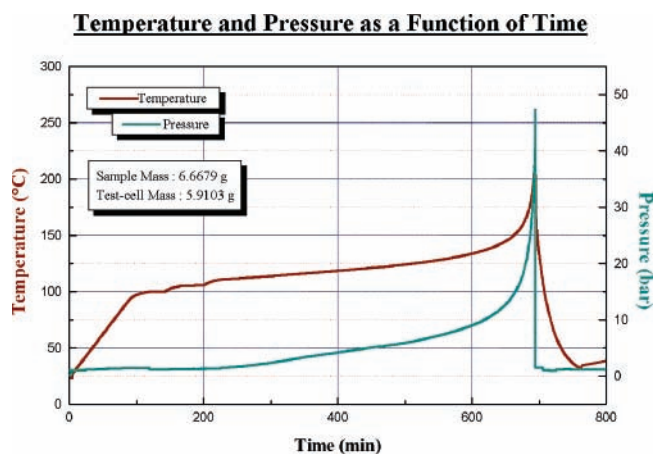


Figure 4. ARC: *T,P* graph of *1* dissolved in DMSO (31 wt %).

The test cell is known to resist pressures of over 100 bar, and still it was ruptured. Even the lid of the calorimeter was

(11) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann: Boston, Oxford, 1999; p 336. See also item 0917a in the CD-ROM version of this book. http://www.elsevier.com/wps/find/bookdescription.cws_home/676701/description#toc.

Raw Data Time to Maximum Rate

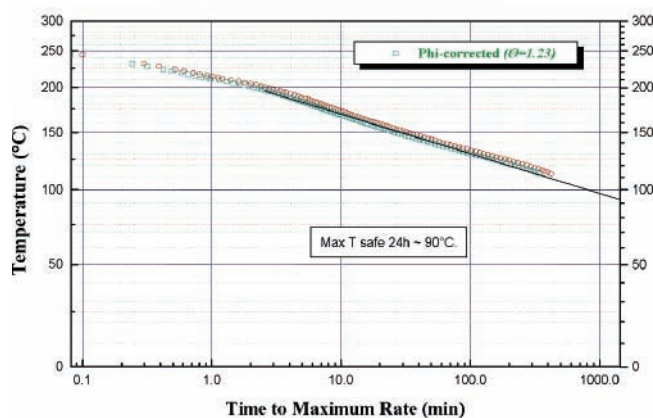


Figure 5. ARC: $MaxT_{safe24}$ graph of **1** dissolved in DMSO (31 wt %).

Table 1. Results of the ARC test of **1** dissolved in DMSO (31 wt %)

parameter	value	comments
onset T	112 °C	a surprising low value, considering that the dry product is stable up to 140 °C
T @ max rate	261 °C	this is the last recorded temperature before the test cell ruptured
max T rate	163 °C/min	a high rate, indicating an explosive decomposition
max P rate	66 bar/min	a high rate, indicating an explosive decomposition
$MaxT_{safe24}$	90 °C	calculated from the exotherm data, taking the dynamics into account
heat of reaction	366 J/g	this is a medium high reaction enthalpy, which is unexpected, considering the damage that occurred, but probably reflects only a fraction of the energy involved

lifted during the explosion. All these elements indicate that it must have been a violent decomposition.

The RADEX and ARC results indicate that there could be a scenario for a thermal explosion even for dissolving 4-carboxyphenylhydrazine in DMSO. The normal procedure is that the reactor is charged with the solid product and then the solvent; the mixture is then heated to 45 °C, stirred for 30 min, and finally cooled to 23 °C. In our production we normally use 5 bar steam to heat vessels. The vessel jacket is then at ± 140 °C. In case the temperature regulation system fails at the target temperature of 45 °C, the reaction mixture is heated up further. At 110 °C the decomposition would be initiated if the deviation would not be observed by the operator, and a thermal explosion would follow within a few hours. This problem can be avoided by using a vessel with “open steam” heating or one with a water circulation system. Both these systems have a physical limitation of heating up to only 100 °C, and the jacket temperature cannot exceed this value. At this temperature a $MaxT_{safe}$ of around 13 h is available in case the mixture were to be heated to this temperature.

Besides this measure the operators are also instructed to stay at the vessel during the whole operation of dissolving 4-carboxyphenylhydrazine and to charge cold water to the

reactor in case the temperature were to begin rising above 55 °C (loss of cooling scenario). This makes the starting material unusable for the reaction, but it would stop thermal explosion. The practical feasibility and the thermal consequences are established in RC1 experiments. It is known that mixing DMSO and water gives a temperature rise (-54 cal/g).¹² The mixing enthalpy of DMSO and water in the RC1 gives a value of -5.5 kJ/mol water or -295 kJ/kg water and an adiabatic temperature rise of ± 8 °C. Dosing water to a solution of **1** in DMSO yields a normal stirrable suspension. The presence of **1** in DMSO increases the mixing enthalpy with $\pm 10\%$.

The conversion of **1** and **2** to **4** is believed to proceed via the intermediate **7** (Scheme 2). It was already mentioned that the reaction is exothermic. The reaction heat and other safety parameters are obtained from a RC1 experiment in which a solution of **1** in DMSO is added to a solution of **2** in methanol at 15 °C over 2 h (Figures 6 and 7 and Table 2).

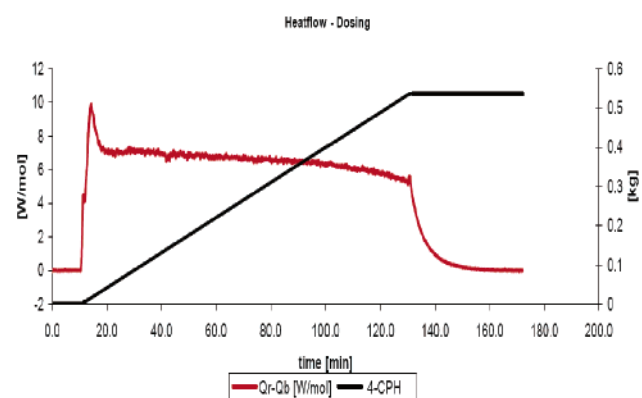


Figure 6. RC1 heatflow curve of **1** + **2** \rightarrow **7**.

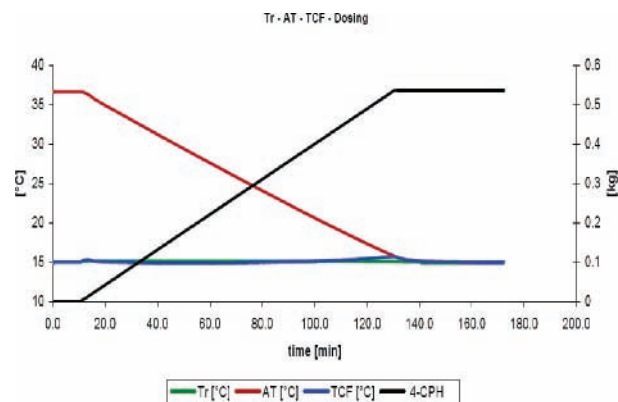


Figure 7. RC1 safety parameters of **1** + **2** \rightarrow **7**.

Table 2. Calorimetry results of **1** + **2** \rightarrow **7**

parameter	value	comments
Q_r	10 W/mol 7 W/mol	regarded as a low heatflow
ΔH	-49.14 kJ/mol	only a low exothermic reaction
MAT	37 °C	much lower than the boiling point of methanol, the lowest boiling solvent in this process
MTSR	15.7 °C	indicates an addition-limited process (TCF on the graph)
FHR	96%	nearly no accumulation; after 20 min of stirring the thermal conversion is complete

(12) <http://www.arkema-inc.com/literature/pdf/122.pdf>.

Temperature and Pressure as a Function of Time

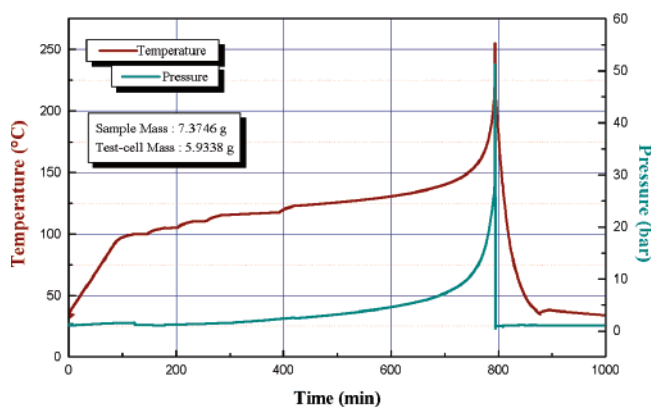


Figure 8. ARC: T,P graph of intermediate 7.

Raw Data Time to Maximum Rate

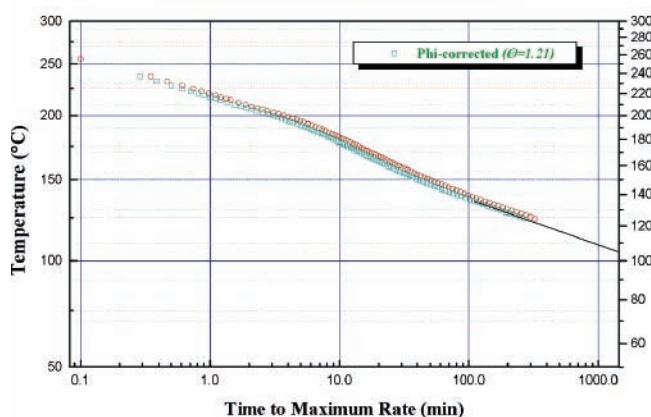


Figure 9. $MaxT_{safe24}$ graph of intermediate 7.

Table 3. Thermal stability data of intermediate 7

parameter	value	comments
onset T	124 °C	start of the exotherm
T @ max rate	259 °C	
max T rate	244 °C/min	a very high rate, indicating explosive character
max P rate	73 bar/min	a very high rate, indicating explosive character
$MaxT_{safe24}$	103 °C	13 °C higher than I in DMSO
heat of reaction	375 J/g	comparable to I in DMSO; due to the test cell rupture this value may be underestimated

A sample of the reaction mixture of 7 was tested in the ARC, and the results are shown in Figures 8 and 9 and Table 3. Also in this run the test cell was ruptured due to the high pressure generated. The exotherm starts at 124 °C, and 400 min later a sharp temperature and pressure rise at 200 °C indicate that the sample explodes. The highest recorded temperature is 259 °C, but there is no doubt that a much higher temperature has been attained during the decomposition since the temperature rate was 244 °C/min. The highest pressure recorded is 53 bar, but the pressure rate was 73 bar/min at that instant, and the test cell can hold a pressure of >100 bar. The behaviour of the sample at this stage is comparable with that of the solution of 4-carboxyphenyl-

hydrazine in DMSO. On the basis of this similarity, it can be assumed that this is also caused by a chemical interaction with DMSO.

Despite the low onset temperature and the violent decomposition, the runaway index (Figure 10) for this process stage is 1. This is due to the combination of low reaction enthalpy, high reaction rate (=low accumulation), and the boiling point of methanol, which is low compared to the $MaxT_{safe24}$ value. Even if we consider the worst case where the reagent is added all at once, the maximum attainable temperature of 37 °C is low enough to avoid reflux of methanol, and a runaway will not be initiated.

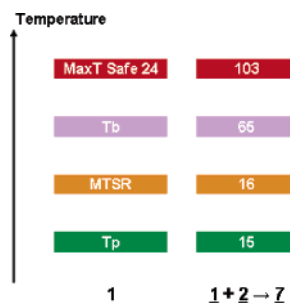


Figure 10. Runaway index for the reaction of $I + 2$.

The cyclisation of 7 to 4 needs a higher temperature to proceed smoothly. This means that the reaction mixture has to be heated and this requires that the runaway index (Figure 10) needs to be considered for this operation too. In case of a malfunction in a standard reactor during the heating, the reaction mixture would start to reflux at 65 °C, and methanol would boil off. From then on a physical barrier no longer exists to take the mixture into the runaway since the boiling point of DMSO is too high to be considered as a thermal buffer or physical barrier. By the time the mixture gets to this temperature, it is already decomposing. It is clear that measures have to be taken to avoid this. Also for this process stage it is obligatory to use a reactor with a hardware limitation on the jacket temperature: an “open steam” jacket or a water circulation system. This ensures that the reaction mixture can never be heated to the onset temperature. An additional recommendation is that water should be added to the reactor in case the reactor contents would start to reflux and the cooling would fail. This stage should never be run unattended.

The cyclisation reaction rate can be increased by neutralisation of 7 into its sodium salt. The explanation for this phenomenon is not obvious, but the experimental results are unambiguous. In practice the reaction mixture of 7 is heated to 45 °C, a 10% excess of concentrated NaOH solution is added over 2 h, and then the suspension is stirred for 20 h at 45 °C. As can be expected, the reaction of NaOH is fast and dosing controlled (see Figures 11 and 12 and Table 4). The observed heatflow and enthalpy include the mixing effects of water and DMSO. During the stirring period there is hardly any heatflow (but TLC analysis indicates that the long stirring time is required to complete the cyclisation).

The long stirring represents a considerable thermal stress; therefore, adiabatic calorimetry tests are run. The results (see Figures 13 and 14 and Table 5) indicate that this mixture is

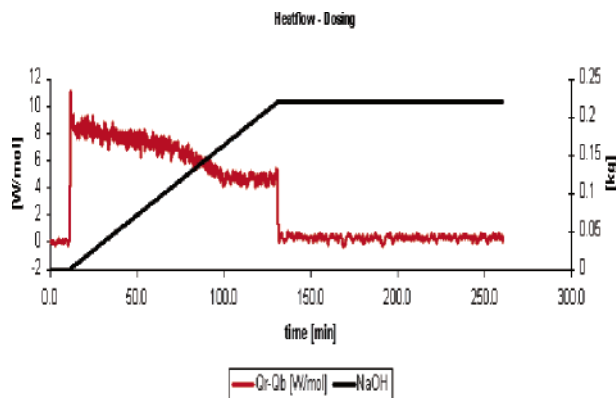


Figure 11. RC1 heatflow curve of 7 → 7 Na salt

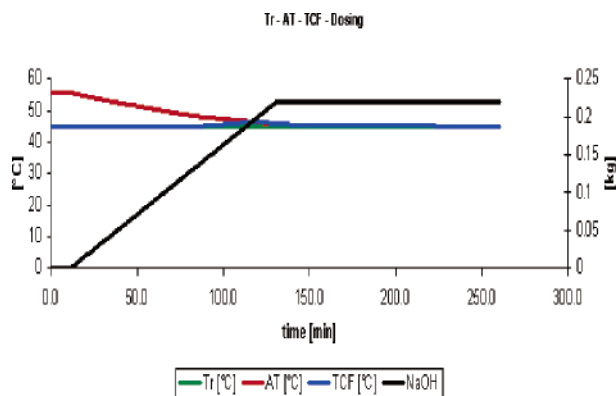


Figure 12. RC1 safety parameters of 7 → 7 Na salt

Table 4. Calorimetry results of 7 → 7 Na salt

parameter	value	comments
Q_r	9 W/mol → 4 W/mol	can be regarded as a low heatflow
ΔH	-37.1 kJ/mol	only a low exothermic reaction
MAT	56 °C	this temperature is still lower than the boiling point of methanol, the lowest boiling solvent in this process
MTSR	46.6 °C	indicates an addition limited process (TCF on the graph)
FHR	95%	nearly no accumulation; after 120 min of stirring the thermal conversion is complete

thermally stable. A series of two small decomposition exotherms are detected at ± 170 and ± 185 °C. The latter is the largest with a temperature rise to 230 °C. The $MaxT_{safe24}$ values are 152 and 162 °C, respectively.

The stability of this reaction mixture is also checked by heating samples over long periods. One sample was heated at 55 °C and another at 75 °C (in closed system to avoid evaporation of methanol) for 72 h. TLC analysis of the sample before and after the heating are identical, and no exotherm or pressure rise has been observed.

The neutralisation of 7 to its Na salt can be categorised as a runaway index 1 process (Figure 15). Even if NaOH would be added all at once, this would still be the case, since there is a thermal buffer of methanol. This neutralisation and long stirring can be regarded as safe, and there are no indications that a thermal runaway could occur.

Temperature and Pressure as a Function of Time

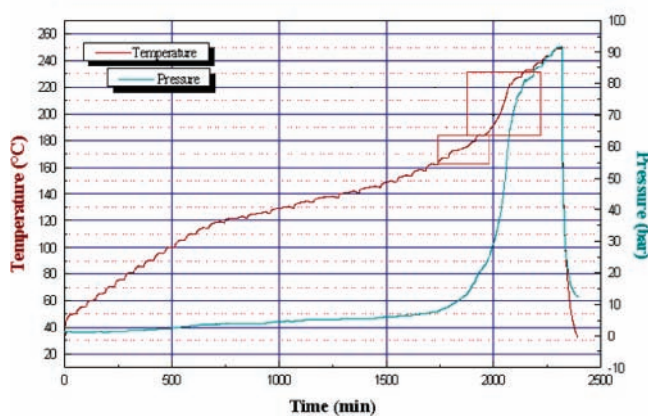


Figure 13. ARC: T,P graph of intermediate 7 Na salt

Raw Data Time to Maximum Rate

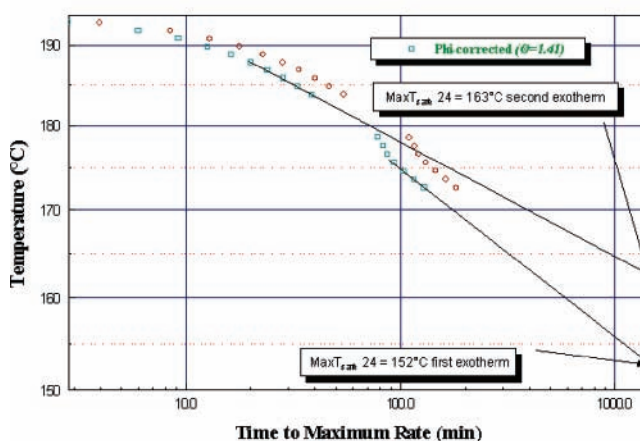


Figure 14. $MaxT_{safe24}$ graph of intermediate 7 Na salt

Table 5. Thermal stability data of 7 Na salt

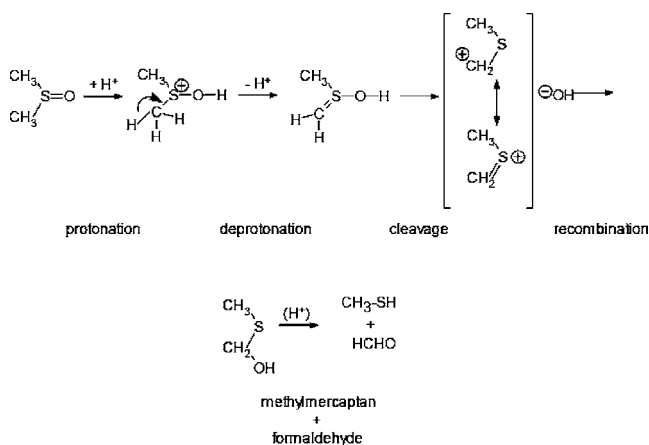
parameter	value	comments
onset T	172 °C	start of the first small exotherm
	183 °C	start of second, larger exotherm
T @ max rate	214 °C	this is during second exotherm
max T rate	0.59 °C/min	indicates slow temperature increase
max P rate	0.79 bar/min	indicates moderate pressure increase
$MaxT_{safe24}$	152 °C	first small exotherm
	162 °C	second and larger exotherm
heat of reaction	138 J/g	this is a low value

There is a remarkable difference in thermal stability of the product 7 and its sodium salt. From a chemical point of view this can be related to either the pH (slightly acidic to slightly basic) or the presence of water or a combination of both. It is mentioned in the literature that DMSO decomposes in acidic medium according to the mechanism represented in Scheme 4.¹³

The products 1 and 7 are only weak acids, but it seems that at higher temperature sufficient protons can be liberated to start the decomposition of DMSO. Since this process is autocatalytic, the thermal behaviour of the reaction mixtures

(13) <http://www.arkema-inc.com/literature/pdf/360.pdf>.

Scheme 4. Decomposition mechanism for DMSO in acidic medium



in DMSO could be explained. In addition to the DMSO decomposition, 1 and 7 could also start to decompose. From the experimental data it is clear that the DMSO effect is the largest (see Figure 2).

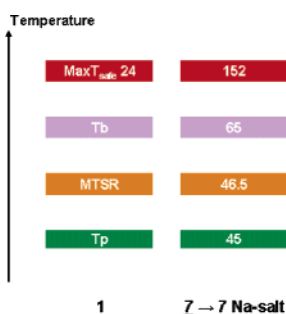


Figure 15. Runaway index for the reaction 7 → 7 Na salt.

After the cyclisation the product 4 is filtered, washed, and dried at 65 °C for 24 h. This imposes a thermal stress in the product, and it has to be tested that the product is stable enough under drying conditions. It is possible to remove DMSO to a level of <1 % during the workup, and a chemical interaction is not expected. A sample of the dry product was tested in the ARC after an initial screening in the RADEX. The RADEX results indicated that no exotherm occurred up to 200 °C, and therefore the ARC test starts at this temperature. On further heating a first small exotherm starts at 230 °C and stops at 270 °C. Between 270 and 300 °C (end of the test) no exotherm was observed anymore. During the exotherm a pressure rise from 10 to 40 bar is observed, and at the end of the test a residual pressure of 35 bar remains on the test cell, indicating that a noncondensable gas is formed (Figures 16 and 17 and Table 6). A MaxT_{safe} of 224 °C is calculated from the data of the small exotherm. The difference with the drying temperature is large enough to consider the drying operation as thermally safe.

Synthesis of 6. The original laboratory procedure for the synthesis of 6 consisted of mixing the reagents 4 and 5, with ammonium acetate as catalyst in DMSO, and heating to 110 °C, followed by stirring for 2 h, cooling to 45 °C, and diluting with methanol (Scheme 5).

Even before the information on the safety issues with the previous stage was available, it was clear that this process

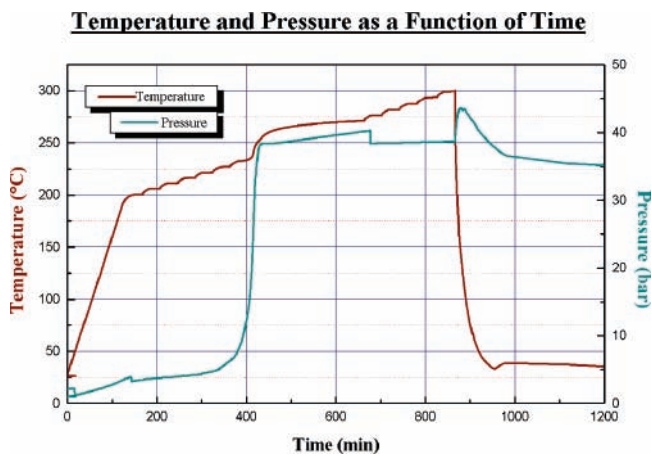


Figure 16. ARC: T,P graph of 4.

Raw Data Time to Maximum Rate

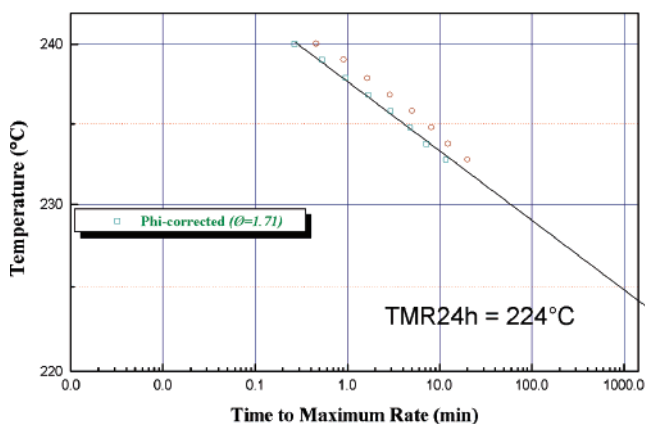


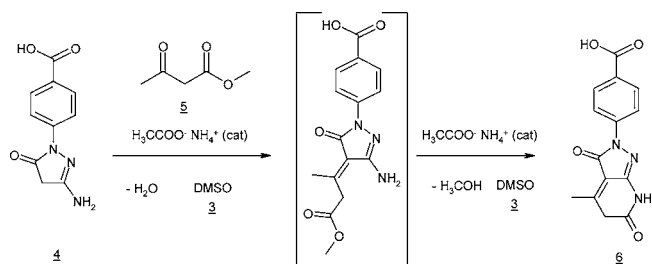
Figure 17. MaxT_{safe}-24 graph of 4.

Table 6. Thermal stability data dry 4

parameter	value	comments
onset temp	230 °C	
T @ max rate	241 °C	exotherm starts heavily but then subsides around 275 °C
max T rate	2.45 °C/min	this is a moderate rate
max P rate	2.4 bar/min	this is a moderate rate
MaxT _{safe} 24	224 °C	this value indicates that the product is quite stable on heating
heat of reaction	130 J/g	this is a low to moderate reaction enthalpy

could not be transferred to production without an in-depth study. Even on small scale and with careful heating there was an overshoot in the temperature of the reaction mixture. This indicates that there is some thermal accumulation. From earlier experiences with other cases it is known that it is

Scheme 5. Conversion of 4 to 6



difficult to get reliable calorimetry data for a batch-type process with a heat-up range of 20 to 110 °C, and therefore these data are not available. It took only a few tests to show that a semi-batch mode is possible and that feeding 5 to the mixture of the other reagents is a way to get control of the heat generation. In one of these test it is also shown that lowering the temperature to 102 °C combined with extending the stirring time to 4 h yields the same results. This means also that for this process we can use a reactor with a modified heating (“open steam” or water circulation) system which avoids overheating and an overshoot in the process temperature. In case of temperature control failure, the process temperature can never exceed 102 °C. However, a higher

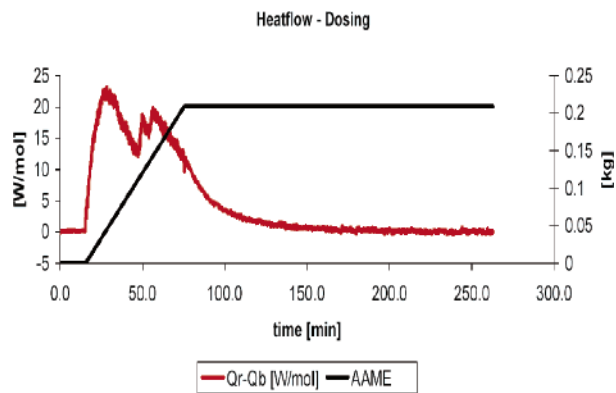


Figure 18. RC1 heatflow curve of 4 + 5 → 6.

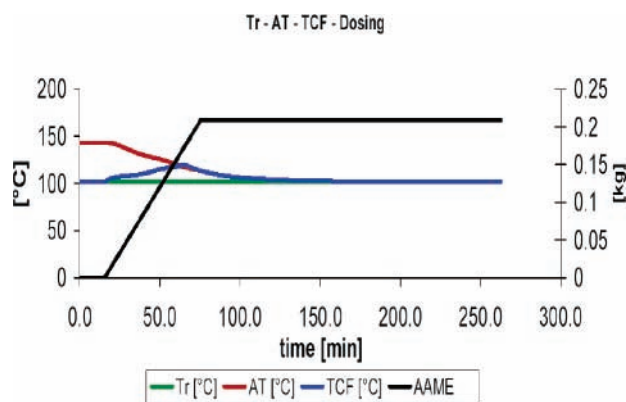


Figure 19. RC1 safety parameters of 4 + 5 → 6.

Table 7. Calorimetry results of 4 + 5 → 6

parameter	value	comments
Q_r	24 W/mol	this can be regarded as a moderate heatflow
ΔH	12 W/mol	at the end of the dosing
MAT	-75.1 kJ/mol	this is an average enthalpy value
	143.4 °C	this is one of the reasons this process should be run in semi-batch mode, especially in a high boiling solvent as DMSO
MTSR	119.9 °C	this indicates that there is some accumulation and that the cooling failure scenario should be considered carefully
FHR	79%	significant accumulation and a stirring time of 160 min is required to achieve full thermal conversion. TLC analysis of the reaction mixture indicates that 240 min is required for full chemical conversion

temperature is still possible due to reagent accumulation in case of cooling failure. A reaction calorimetry experiment at 102 °C with 20 mol % excess of 5 in the RC1 confirmed this and provided data on reaction enthalpy and accumulation as shown in Figures 18 and 19 and Table 7.

In the new procedure a mixture of 4 and ammonium acetate in DMSO would be heated to 102 °C. It is our standard procedure to test the thermal stability of the “first fill” of a process when this is heated in a reactor. In this case a screening test in RADEX indicated that there was a safety issue (Figure 20). The mixture showed exothermic behaviour (decomposition?) and strong pressure build-up. The onset of the exotherm is 135 °C with a maximum at 220 °C. From 180 °C the pressure starts to rise, and at 245 °C a pressure of 100 bar is attained at which the bursting disc breaks and protects the vial from rupture. If the “100 K-rule” were to be applied, the reaction mixture should be kept near room temperature to guarantee a safe condition, but this is not possible for the process. Further tests in the ARC provided more accurate data.

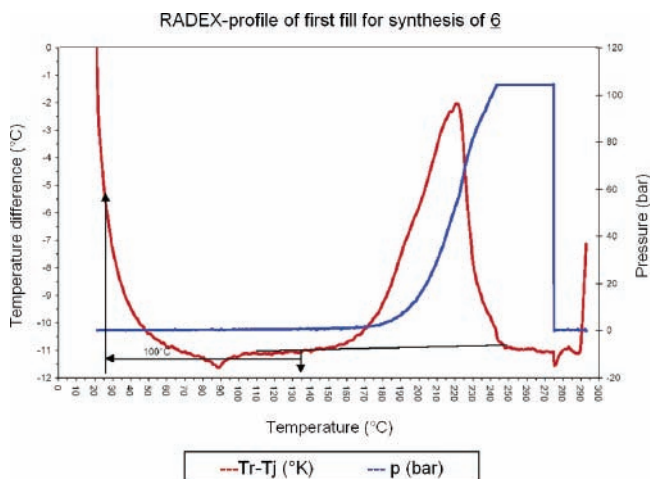


Figure 20. RADEX temperature and pressure curve of 4, ammonium acetate in DMSO.

The ARC results confirm the RADEX data: at 127 °C the exotherm sets in, and about 400 min later the temperature and pressure rise extremely fast (Figures 21 and 22 and Table 8). At this point the test was terminated manually to avoid rupture of the test cell and damage to the calorimeter. Since 4 is thermally stable ($MaxT_{safe-24} = 224$ °C), it can be assumed that the low stability of the first fill is due to a chemical interaction with DMSO. Also in this case there are proton donors that could start the decomposition according to Scheme 4.

The combination of the slow reaction at the chosen process temperature, the high boiling point of DMSO and the low $MaxT_{safe-24}$ value results in a runaway index 5 (Figure 23). This low $MaxT_{safe-24}$ value is a result of the low onset temperature and the short induction time (only 400 min). This type of process should not be transferred to production as such. The general recommendation is to redesign it. If this is not possible, additional safety interlocks and procedural measures should be implemented.

The first option is to test alternative solvents since it can be expected that these do not have a chemical interaction

Temperature and Pressure as a Function of Time

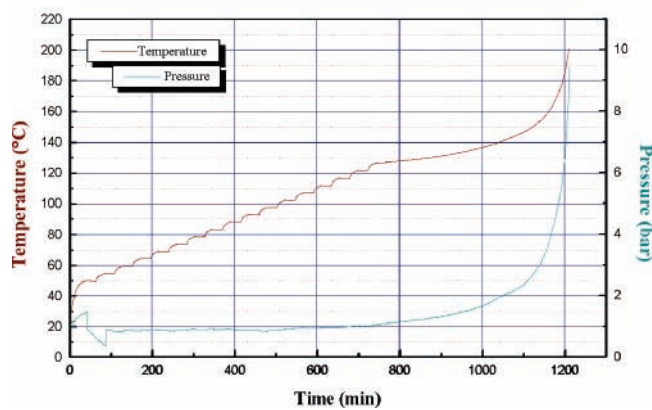


Figure 21. ARC: T,P graph of **4** and ammonium acetate in DMSO.

Raw Data Time to Maximum Rate

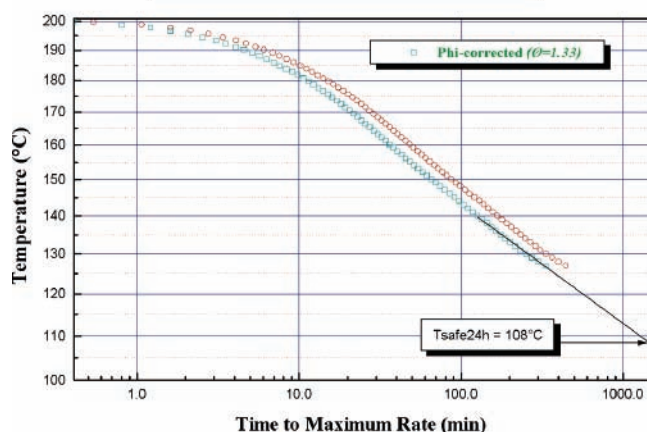


Figure 22. $MaxT_{safe24}$ graph of **4** and ammonium acetate in DMSO.

Table 8. Thermal stability data of **4** and ammonium acetate in DMSO

parameter	value	comments
onset T	127 °C	start of the exotherm
T @ max rate	201 °C	this figure has no value because the test was aborted manually
max T rate	2.213 °C/min	this is a high value and is probably underestimated because the test was aborted manually
max P rate	0.42 bar/min	this figure has no value because the test was aborted manually
$MaxT_{safe24}$	108 °C	this value can be considered as representative because it takes the most important part of the exotherm into account
heat of reaction	196 J/g	this figure has no value because the test was aborted manually

with the reagents involved. There is only a limited number of solvents available with a boiling point range of 100–130 °C or a sufficient polarity. None of the tested alternatives is suitable for this reaction. However, the RADEX results of the mixtures with **4** indicate that there is no chemical interaction with the reagent compared to that of DMSO. The decomposition behaviour is related to the presence of DMSO: when compared to other solvents like sulfolane, *N*-ethylpyrrolidone, and dimethylsulfone in the RADEX tests

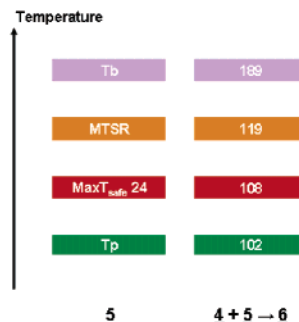


Figure 23. Runaway index for the reaction of **4 + 5** to **6**.

Thermal Analysis of *p*-carboxyphenylhydrazine in dipolar solvents

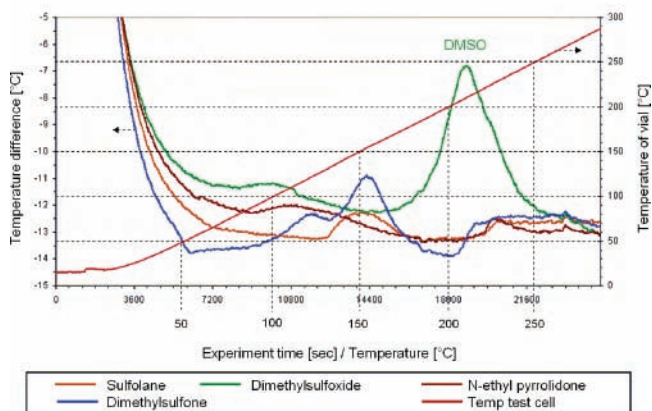


Figure 24. Temperature and pressure curves of **4 + 5** to **6** in different solvents (RADEX).

(Figure 24) DMSO shows the largest exotherm. Dimethylsulfone, a solid at room temperature that melts at 108 °C, was included in the test series because it is the molecule closest to DMSO.

The second option is to test mixtures of the candidates with DMSO in different ratios. A solvent with a boiling point in the range of 110 to 130 °C provides a thermal buffer that physically limits the temperature of the reaction mixture by reflux. It can also be expected that using less DMSO also makes the chemical interaction with the reagent less severe. The most successful combination proves to be a mixture of DMSO with 2-methoxypropanol (MP) in the range of 66/33 to 33/66 wt % and a ratio of 0.45 kg/mol. In the next phase the safety parameters of this 33/66 ratio (DMSO/MP) are tested in the RC1 (Figures 25 and 26 and Table 9). The reaction was run in a closed MP06 reactor to suppress the reflux of the methanol formed in the reaction.

The first fill for this reaction mixture is **4**, ammonium acetate, and MP in DMSO, and a sample of this is heated in the ARC to test its thermal stability (Figures 27, 28 and Table 10).

The modified process requires an extended stirring time of 10 h at 102 °C which can be regarded as a substantial thermal stress. To make sure that this would not impose an additional risk, a sample of the reaction mixture is prepared in situ in the ARC cell and then subjected to a heat–wait–seek sequence (Figure 29). The desired reaction starts at 75 °C and takes the sample temperature to nearly 100 °C (adiabatic temperature rise of ± 25 °C). On further heating the sample starts a decomposition exotherm around 150 °C

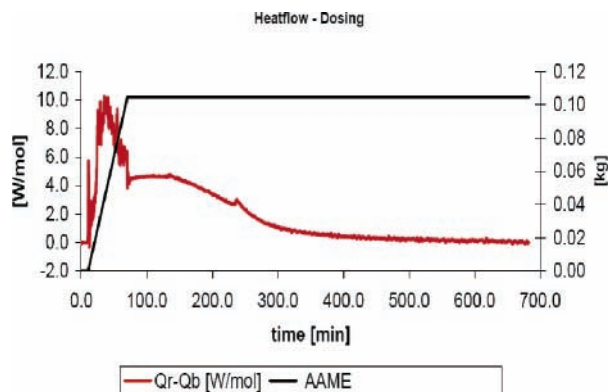


Figure 25. RC1 heatflow curve of 4 + 5 to 6 in DMSO/MP 33/66.

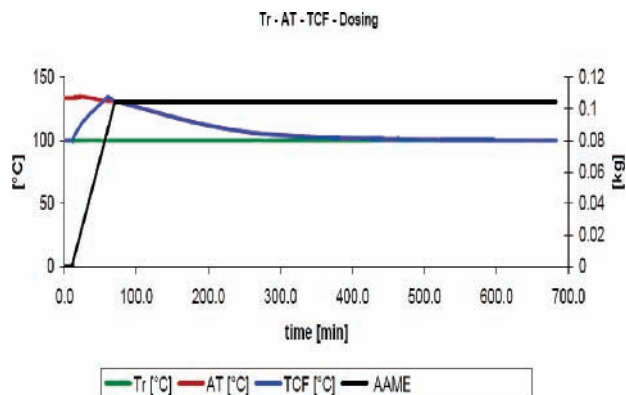


Figure 26. RC1 safety parameters of 4 + 5 to 6 in DMSO/MP 33/66.

Table 9. Calorimetry results of 4 + 5 in DMSO/MP 33/66

parameter	value	comments
Q_r	± 10 W/mol ± 5 W/mol	during the 1 h feed period during 3 h from the 10 h stirring period; the curve indicates that the reaction itself is slow
ΔH	-77.9 kJ/mol	total reaction enthalpy is comparable to the value obtained in pure DMSO
MAT	135 °C	result is 10 °C lower than in the pure DMSO experiment
MTSR	135 °C	value is 15 °C higher than in the pure DMSO experiment due to much higher accumulation
FHR	30%	indicates a high accumulation at the end of the feed period

which terminates around 200 °C after 700 min; up to 250 °C decomposition is no longer noticed. From the decomposition exotherm a $MaxT_{safe24}$ value of 136 °C (see Figure 30 and Table 11) is obtained which is close to the value of the first fill.

The $MaxT_{safe24}$ is determined by numerical transformation of the temperature data recorded during the exotherm and then graphical extrapolation of results to 1440 min in the temperature-TMR24 plot. This procedure takes the dynamics of the decomposition into account and is therefore closer to the real-life situation than just taking the onset temperature. It is recommended to have a safety margin of 20 °C between $MaxT_{safe24}$ and MTSR or MAT. This is not the case in this

Temperature and Pressure as a Function of Time

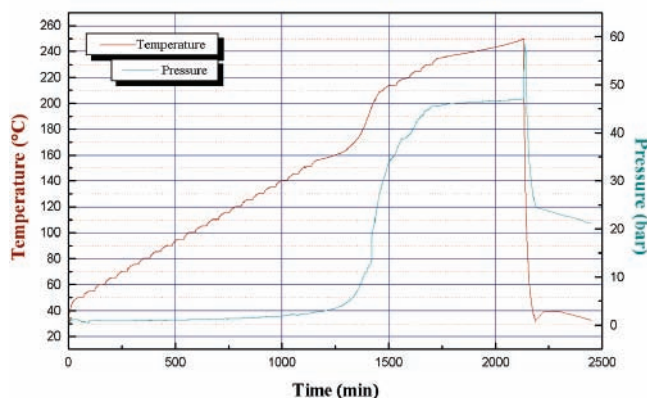


Figure 27. ARC: T,P graph of 4 + 5 to 6 in DMSO/MP 33/66.

Raw Data Time to Maximum Rate

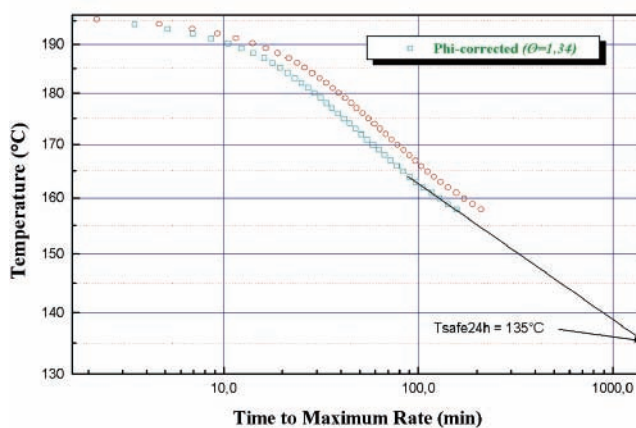


Figure 28. $MaxT_{safe24}$ graph of 4 + 5 to 6 in DMSO/MP 33/66.

Table 10. Thermal stability data of 4, ammonium acetate, and MP in DMSO

parameter	value	comments
onset temp	157 °C	onset temperature is 30 °C higher than in pure DMSO, indicating that there is less chemical interaction. A second exotherm starts around 235 °C but is not further considered
$T @ \text{max rate}$	196 °C	this value is comparable to the experiment in pure DMSO; it is important to note that the exotherm subsides at 217 °C and a new series of heat–wait–seek is started; adiabatic temperature rise of 60 °C is still considerable
max T rate	0.46 °C/min	moderate value
max P rate	0.31 bar/min	pressure rate is low, and also the 45 bar that is attained after the first exotherm is lower than in pure DMSO
$MaxT_{safe24}$	135 °C	17 °C rise in $MaxT_{safe24}$ value also indicates a less severe chemical interaction (less DMSO in the reaction mixture)
heat of reaction	105 J/g	this is a low enthalpy value (less DMSO in the reaction mixture)

process. In our concept for the modification we assume that MP acts as a thermal buffer and inhibits the temperature rise. To confirm the $MaxT_{safe24}$ value, a sample of the reaction

Temperature and Pressure as a Function of Time

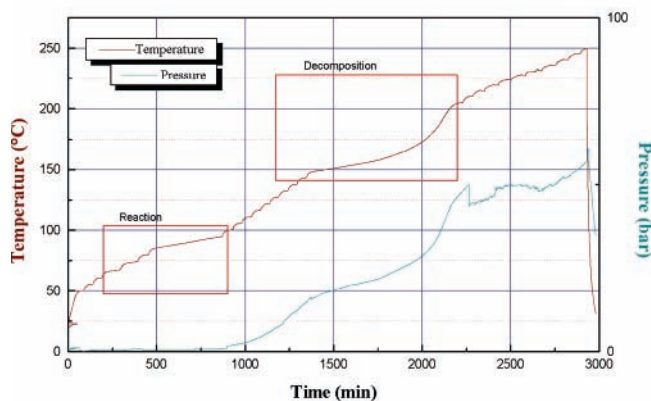


Figure 29. ARC: T,P graph of 4 + 5 to 6 in DMSO/MP 33/66 reaction in ARC test cell.

Raw Data Time to Maximum Rate

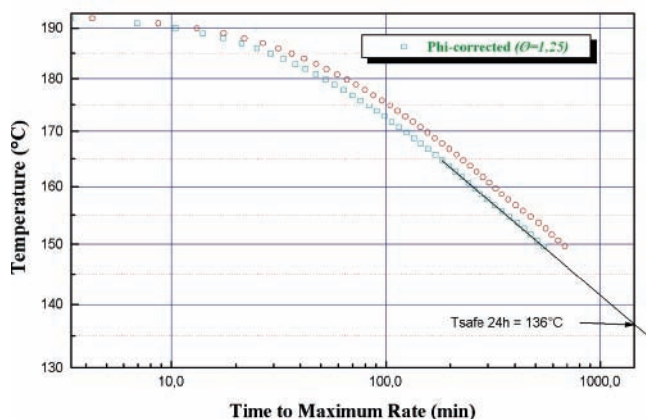


Figure 30. $MaxT_{safe24}$ graph of 4 + 5 to 6 in DMSO/MP 33/66 reaction in ARC test cell.

Table 11. Thermal stability data of 4 + 5 to 6 in DMSO/MP 33/66 reaction in ARC test cell

parameter	value	comments
onset temp	149.6 °C	onset is about 7 °C lower than for the “first fill”, without methyl acetoacetate comparable to the result of the first fill
temp @ max rate	193 °C	comparable to the result of the first fill
max T rate	0.236 °C/min	low to moderate value
max P rate	0.14 bar/min	low value
$MaxT_{safe24}$	136 °C	this value is close to the result of the first fill
heat of reaction	137 J/g	comparable to the result of the first fill

mixture was put in a closed ARC cell over a long period at 120 °C in adiabatic mode (without a heat–wait–seek profile imposed). Over a period of 2700 min (45 h) a slow temperature rise to 150 °C is observed (Figure 31). From this data a $MaxT_{safe24}$ of 137 °C is calculated. This confirms that even when the cooling effect of the evaporation of MP is not taken into account it takes 45 h before the reaction mixture self-heats to the onset temperature of the decomposition.

From the RC1 and ARC data the runaway index for the modified process is generated. The runaway index for the modified process is 3 although $MaxT_{safe24}$ and MTSR are

Temperature and Pressure as a Function of Time

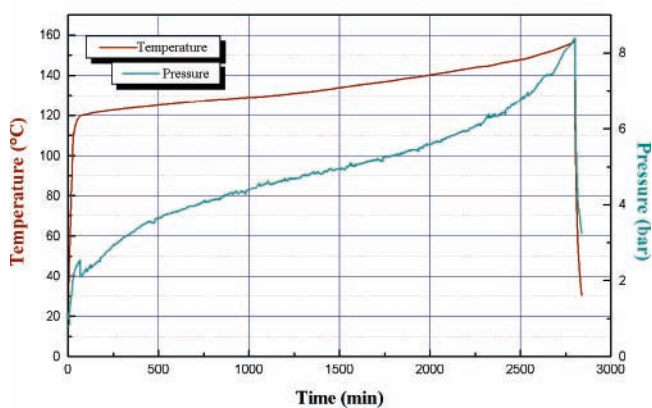


Figure 31. ARC: T,P graph of 4 + 5 to 6 in DMSO/MP: adiabatic test over 2700 min.

close and it might be argued that it would be safer to attribute a runaway index 4 (Figure 32). Nevertheless, this is considered to be an improvement over the original process since there is a thermal buffer at 120 °C. Only 24% of the MP can be evaporated by the accumulated energy. Since the process is slow (probably due to low solubility or dissolution rate of the starting material), no sudden heat release is expected to happen.

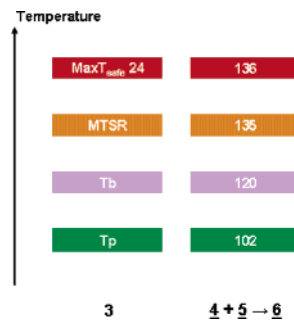


Figure 32. Runaway index for the modified process of 4 + 5 to 6.

The high accumulation and the resulting high value of MTSR are still points of concern. One way of reducing the accumulation is to accommodate the feed rate to the apparent reaction rate. The influence of a longer feed time can be estimated by running an additional RC1 experiment. The reaction is run with a feed time of 5 h in a closed MP06 reactor to avoid reflux of the methanol formed in the chemical transformation (Figures 33 and 34 and Table 12).

It is clear that extending the feed time causes less accumulation and improves the process safety parameters. In Figure 35 the thermal conversion curves of both experiments are plotted versus the feed of AMME, and this shows that there is less accumulation with the longer feed time.

The new calorimetry data can be combined with the previous ARC data to generate the appropriate runaway index (Figure 36). The process with the extended feed time has a runaway index of 1 because the MSTR value has dropped below the T_b . By extending the feed time the accumulation can be reduced. Because of the uncertainty on the different values, care should be taken on extrapolation of this process to production scale. The process parameters should only be

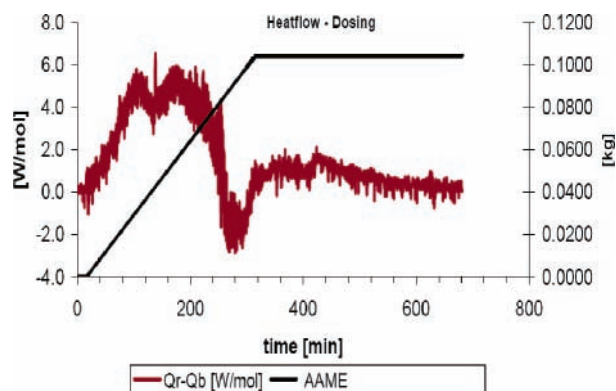


Figure 33. RC1 heatflow curve 4 + 5 to 6 with 300 min feed time.

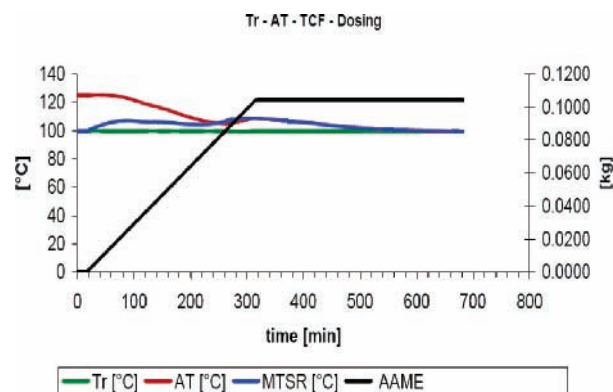


Figure 34. RC1 safety parameters 4 + 5 to 6 with 300 min feed time.

Table 12. Calorimetry results of 4 + 5 in DMSO/MP 33/66 with 300 min feed time

parameter	value	comments
Q_r	± 5 W/mol	reaction slowly builds up this heatflow over a period of 1 h
	-2 W/mol	during the last hour of dosing (=the excess of AAME)– the reaction becomes endothermic
	± 1.5 W/mol	during most of the stirring time a low exotherm is observed
ΔH	-64.02 kJ/mol	this is 15 kJ/mol lower than the other experiment and is the result of the endothermic phase near the end of the feed
MAT	125 °C	MAT is lower due to the lower overall reaction enthalpy
MTSR	108 °C	MTSR is lower due to lower accumulation (25% compared to 70%) and lower overall reaction enthalpy
FHR	75%	thermal accumulation is much lower at the end of the extended feed

changed after careful consideration and after new tests results indicate that it is still safe enough.

After the cyclisation the product 6 is filtered, washed, and dried at 50 to 60 °C for 36 h. This imposes a thermal stress in the product, and it has to be tested that the product is stable enough under drying conditions. It is possible to remove DMSO to a level of <1 % during the workup, and a chemical interaction is not expected. A sample of the dry product is tested in the ARC after an initial screening in the RADEX (Figures 37 and 38). On heating, an endotherm is

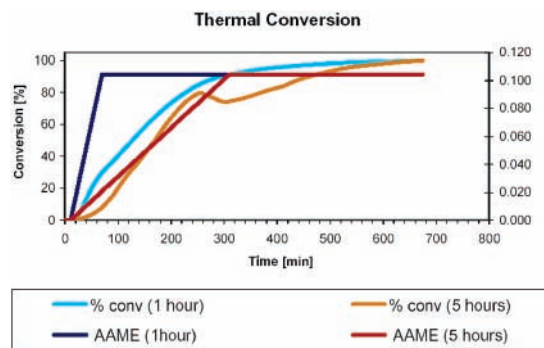


Figure 35. Comparison of thermal conversion with different feed times.

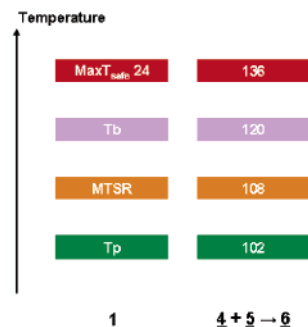


Figure 36. Runaway index for the modified process of 4 + 5 to 6 with extended feed time.

observed at ± 78 °C which extends over 100 °C, and an exotherm starts at 285 °C and proceeds to 300 °C (end of the test). During the ARC test no exotherm is observed until 250 °C. Furthermore, only a small pressure rise to 4 bar is observed, and at the end of the test a residual pressure of 2 bar remains on the test cell, indicating that a small amount of noncondensable gas is formed. Since there is no exotherm, no $MaxT_{safe24}$ can be calculated. The difference from the onset with the drying temperature is large enough to consider the drying operation as thermally safe.

RADEX-profile of dry product 6

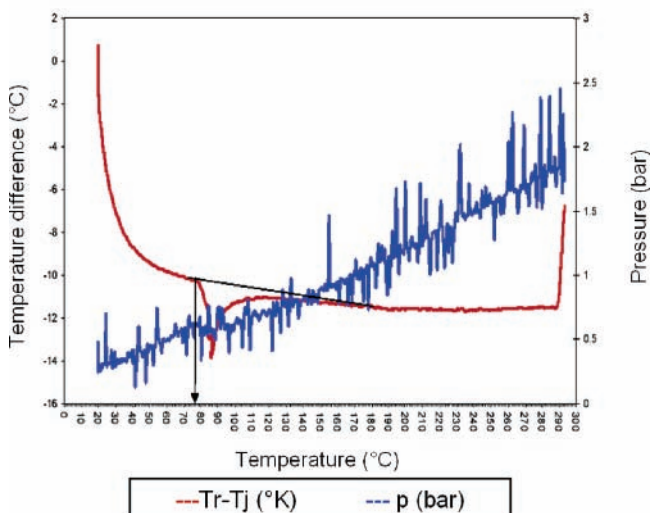


Figure 37. RADEX: T,P graph 6.

Temperature and Pressure as a Function of Time

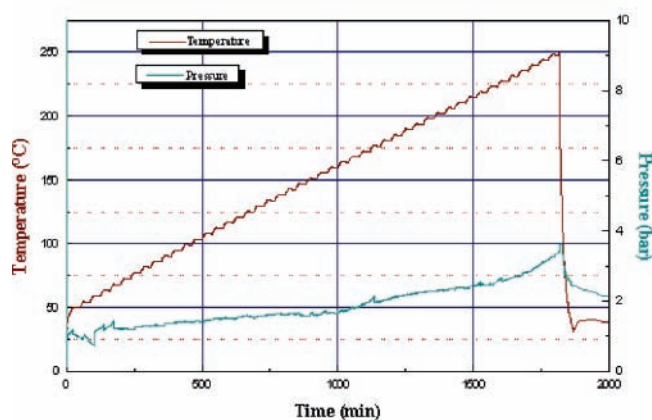


Figure 38. ARC: T,P graph 6.

Conclusions

From this study of the reaction calorimetry and thermal stability of the indicated process stages, the following conclusions can be drawn with respect to the thermal hazards (other process hazards are not within the scope of this discussion). DMSO is more than a solvent: there is a chemical interaction with the other products. In our processes DMSO is selected because of its dissolving power for the products. By comparing the thermal behaviour of the products neat and in contact with other solvents we have been able to show that the apparent lower thermal stability comes from a chemical reaction of the products and DMSO. Since this occurs in the temperature region of 100 to 150 °C required for the processes it has a serious influence on the process safety parameters. There is experimental evidence that the decomposition comes from DMSO itself and is induced by the acidity of the products involved.

The concept of the runaway index is a useful approach to look at the thermal process hazards and consider what is acceptable for transfer to production. It should be applied to the various process stages where heating is applied or exothermicity is observed.

For the synthesis of **4** the process had to be changed because the dosing of the solid poses a potential fire hazard. In the modified process the solid is dissolved and added as a solution. Because there is a chemical interaction between **1** and DMSO the jacket temperature of the reactor is limited to 102 °C, the dissolution temperature is kept at 45 °C, and in case of deviation water should be added to cool the mixture and prevent further heating and reaction. The same measures are applicable to formation of the intermediate **7** and the process conditions for the cyclisation. This process has a runaway index 1 despite the low $MaxT_{safe24}$ of 103 °C because of the low process temperature, high reaction rate (low accumulation and MTSR close to T_p) and the intermediate boiling temperature of the methanol present. The conversion of **7** to **4** proceeds best in slightly basic conditions (Na salt of **7**), and the stability of the reaction mixture is much better than before the neutralisation. This supports the explanation that the exotherm comes from the decomposition of DMSO in contact with the products.

For the synthesis of **6** the initial batch process is transformed in a semi-batch procedure. Although the process temperature is limited to 102 °C, the low $MaxT_{safe24}$ value—a result of the chemical interaction of the reagent with DMSO—causes a runaway index of 5 which requires a process modification. By reducing the amount of DMSO and substituting it with MP it is possible to obtain the same chemical yield and quality with a runaway index 3. The presence of MP with a boiling point of 120 °C provides a large thermal buffer that inhibits the rise of temperature. With a 1 h feed time for AAME this process exhibits a large accumulation of the dosed reagent which leads to a MTSR value close to the $MaxT_{safe24}$. An extended feed time of 5 h reduces the accumulation substantially. This lowers the MTSR value, and as a consequence the runaway index shifts from 3 to 1.

In addition to the process modifications it is important that the recommended reactors are used. To avoid using the thermal buffer as a “basis of safety” it is imperative that the jacket temperature is limited to 102 °C; this can be achieved by using a water circulation system or “open steam” (1 bar).

Experimental Section

Equipment. For the reaction calorimetry a Mettler Toledo RC1 with a standard AP01 or MP06 reactor with anchor stirrer was used in combination with the WinRC V7.11 (SR6) software. Prominent pumps with PTFE head and PTFE tubing were used for the dosing from a Mettler balance. The quickcal option is used for the calibrations in the AP01. Data files are exported to Microsoft Excel 97 for further calculations and charting. Heatflow data include the dosing term correction.

Adiabatic calorimetry experiments are run in an EuroARC from Thermal Hazard Technology with EuroARC software V1.1, and ARCCal (based on Origin 3.53) is used for data processing and charting. Sensitivity threshold was set to 0.02 °C/min. Onset temperatures mentioned are not ϕ -factor corrected. The $MaxT_{safe24}$ values are obtained from the ϕ -factor corrected datapoints.

Thermal stability testing was also done using the Systag RADEX instrument, with 3-mL Hastelloy or Stainless steel vials.

DMSO from Atochem/Arkemi supplied in 200-L drums was for the synthesis and tests. This grade is $\geq 99.5\%$ pure (GC), contains $\leq 0.2\%$ water, and has an acid value of ≤ 0.04 mg KOH/g

Experiments. RC1 (AP01) Synthesis of **4.** **1** (228 g, 1.50 mol) and **3**, DMSO (503 g) are charged to the reactor, thermostated at the 45 °C for 10 min, and cooled to 23 °C. **2** (1.75 mol) in methanol (415 g) is generated in situ from its HCl salt (353 g, 1.8 mol) by neutralisation with 30% sodium methylate (316 g, 1.75 mol) in methanol at 15 °C over 2 h. The solution of **1** in DMSO is added to the solution of **2** at 15 °C over 2 h. The reaction mixture is heated to 45 °C, and the NaOH solution (220 g @ 30%, 1.65 mol) is added over 2 h and stirred for 20 h (cyclisation). Then the HCl solution (198 g @ 37%, 2 mol) is added at 45 °C over 1 h to pH 4.5. The suspension is cooled to room temperature,

filtered, washed with water and methanol, and dried at 65 °C for 24 h. In general, a yield of $\pm 85\%$ is obtained.

RC1 (MP06) Synthesis of 6. 4 (164 g, 0.75 mol), DMSO (113 g), MP (226 g), and ammonium acetate (11.6 g, 0.15 mol) are charged to the reactor and thermostated at 100–102 °C. 5 (AAME, 104.5 g, 0.90 mol) is added to the reactor over 1 (or 5) h, and the mixture is stirred for 10 (or 6) h at 100–102 °C. After cooling to room temperature the suspension is filtered and washed with DMSO/methanol and methanol. The isolated product is dried at 50 to 60 °C for 36 h. In general, a yield of $\pm 85\%$ is obtained.

ARC Tests. A sample of 3 to 6 g of the reaction mixture was transferred with a pipet to a preweighed test cell. This was mounted in the calorimeter and fastened. After closing the instrument the initial data is entered and the heat–wait–seek temperature program is started. At the end of the test

the data are transferred to the ARCCal software package, and the sample is collected as chemical waste.

Products. 1: CASRN619-67-0

2: CASRN27317-59-5

3: CASRN67-68-5

4: CASRN56957-32-5

5: CASRN105-45-3

6: CASRN190380-26-8

7: no CASRN

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