Organic Process Research & Development **1998**, *2,* 382–392

A Calorimetric Investigation To Safely Scale-Up a Curtius Rearrangement of Acryloyl Azide

David J. am Ende,* Keith M. DeVries, Pamela J. Clifford, and Steven J. Brenek

*Central Research Division, Process Research & Development, Pfizer Inc., Eastern Point Road,
Groton, Connecticut 06340*

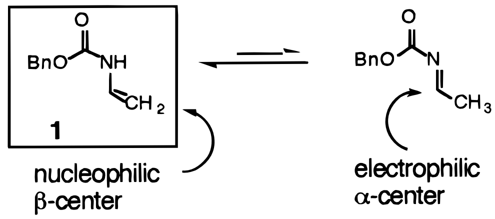
Abstract:

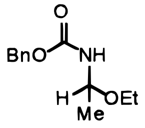
***N*-Vinyl-*O*-benzyl urethane was prepared for use as a starting material in a multistep synthesis of a drug candidate. After unsuccessful attempts to employ non-Curtius options to prepare this intermediate, we decided to assess the thermodynamic and kinetic parameters of the acyl azide Curtius rearrangement and trapping of the intermediate isocyanate. (Prepared in analogy to the literature method of Hegedus et al.: Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* 1989, *54*, 4649−4653.) Reaction calorimetry was utilized to show that the rate of the Curtius rearrangement was completely dose-rate controlled, and that under carefully defined conditions this reaction could be safely performed on limited scale. In addition to addressing the thermal hazard issues, profiling the reaction with reaction calorimetry and interfaced technologies resulted in significant process improvements.**

Introduction

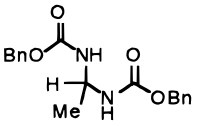
N-Vinyl urethanes and amides, as exemplified by *N*-vinyl-*O*-benzyl urethane (**1**), are very reactive intermediates, both being electrophilic at the α carbon[1] and nucleophilic at the *β* center.[2] This equilibrium (Scheme 1) lies almost exclusively toward **1**. The *N*-vinyl compounds are often masked as the *N*-acyl-*N*,*O*-acetal **2** or the corresponding biscarbamate **3**. The *N*-acyl-*N*,*O*-acetals represented by **2** have been prepared by electrochemical oxidation of the corresponding amides or urethanes[3] as well as by oxidative decarboxylation of the corresponding *N*-protected amino acids.[4] The biscarbamates **3** are prepared by acid-catalyzed exchange of the corresponding primary carbamate with an aldehyde.[5] Due to cost and safety concerns, we initially attempted to prepare **1** by acid-catalyzed exchange between acetaldehyde diethyl ketal and *O*-benzyl urethane followed by loss of ethanol to provide the *N*-vinyl derivative (Scheme 2). Although we were able to obtain small amounts of **2**, the major product which was the result of further disproportionation was the biscarbamate **3**. In Scheme 2, DCE and TsOH refer to dichloroethane and para-toluene sulphonic acid, respectively.

Scheme 1



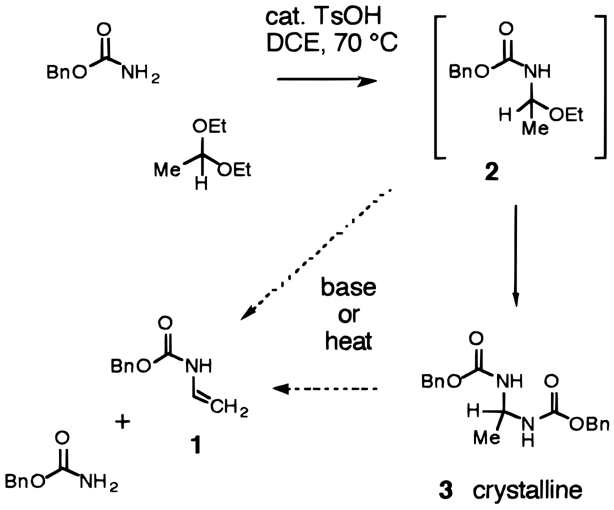


2



3

Scheme 2



All attempts to “crack” **2** or **3** with heat or base to prepare pure **1** were unsuccessful. The stability of the *N*-vinyl derivatives increases with the degree of substitution on the nitrogen as well as the degree of branching on the nitrogen substituents. Thus, **1** is quite unstable due to its lack of substitution. In addition, attempts to use either **2** or **3** to

---

* To whom correspondence should be addressed: Pfizer, Inc., Process R&D, Bldg. 156, Box 5, Eastern Point Rd., Groton, CT 06340. Phone 860-441-6504. Fax 860-441-5445. E-mail david_j_amende@groton.pfizer.com.

[1] For example, see: (a) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16−21. (b) Weinreb, S. M. *Heterocycles* 1979, *12*, 949−975. (c) Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* **1973**, *95*, 5273−5280. (d) Shono, T.; Kise, N.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231−234. (e) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795−3798.

[2] For example, see: (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* 1982, *104*, 6697−6703. (b) Katrizky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 3993−4001.

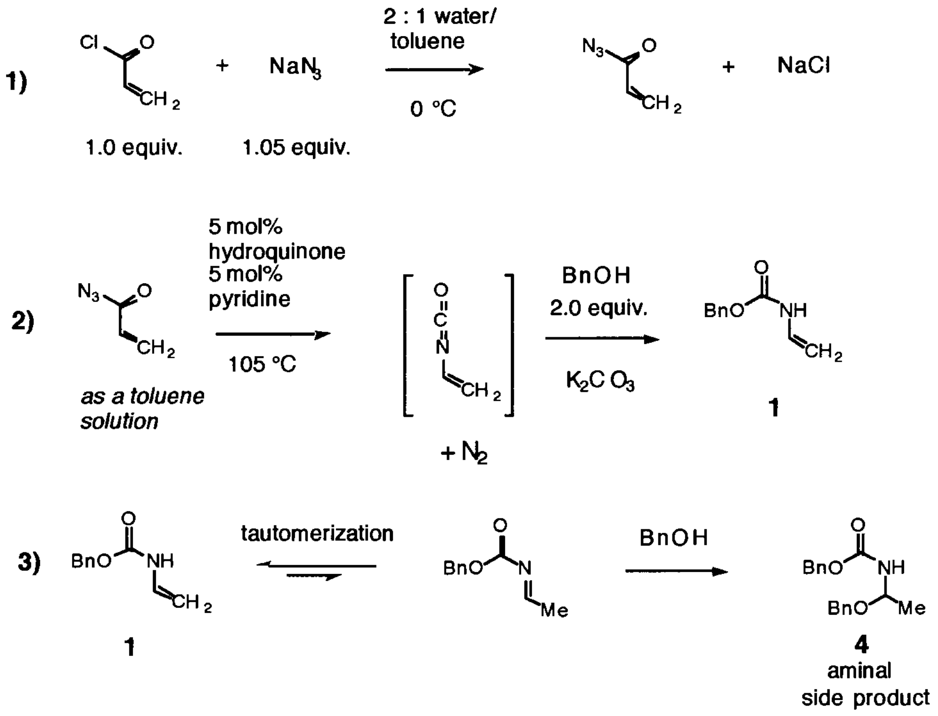
[3] See refs 1d and 2a and references therein.

[4] Harding, K. E.; Liu, L. T.; Farrar, D. G. *Synth. Commun.* **1991**, *21*, 1409−1417.

[5] For example, see: (a) Giger, R.; Ben-Ishai, D. *Isr. J. Chem.* **1967**, *5*, 253−259. (b) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

10.1021/op970115w CCC: $15.00

Scheme 3



Run:	BnOH equiv:	K_2CO_3:	Addition time:	Post heat time:	Selectivity ratio, Desired:aminal
1	1.0	no	2.5 hours	3.0 hours	0.8:1.0
2	2.0	yes	3.0 hours	3.0 hours	3.0:1.0
3	2.0	yes	1.0 hour	1.0 hour	15.0:1.0

generate **1** in situ for the subsequent reaction gave inferior results.

The preferred method in the literature for preparing compound **1** was that reported by Hegedus et al.[6] Curtius chemistry involves potentially serious reaction hazards associated with the use of sodium azide, the formation of an acryloyl azide, and the isocyanate intermediate. The following discussion describes our assessment of the Curtius rearrangement (Scheme 3, step 2) using the Mettler RC-1 reaction calorimeter with interfaced technologies. Thermodynamic and kinetic data obtained from this assessment permitted us to safely scale-up the reaction.

Discussion

Chemistry. The initial step (eq 1, Scheme 3) was formation of the acryloyl azide from acryloyl chloride, using a slight modification of the literature procedure. To determine the point of reaction completion, a pilot reaction was carried out in toluene-d_8 and D_2O. Aliquots of the reaction mixture, sampled by ^{1}H NMR, showed that the reaction was complete in 2 h. After workup,[7] the toluene solution was shown to be stable for days with storage at 5 °C.

The hazard associated with this reaction is due to the thermally unstable azide solution. The acryloyl azide has a heat of formation of $+230$ J/mol (calculated from CHETAH) and, as will be discussed later, can decompose at low temperatures to liberate an equivalent of nitrogen gas and vinyl isocyanate. Positive heats of formation provide an indication for potential thermal instability. Further, a potential pressure hazard exists when handling the azide due to its propensity to release gas and heat. The thermal stability issue was minimized by preparing and storing the azide solution at 0 °C and then using it as a stock solution in toluene in the Curtius chemistry. *As a safety precaution, this azide should not be isolated from solution, as it could be dangerously explosive!* DSC, Radex, and ARC tests were performed to characterize the acryloyl azide−toluene solution. The results describing the onset temperature, decompositions energy, and gas evolution regarding the thermal stability of the azide are discussed in the Thermal Analysis section. The azide−toluene solution is reacted with benzyl alcohol (BnOH) in the Curtius rearrangement to produce **1**, the desired urethane. Three reaction calorimetry (RC-1) experiments were performed for the Curtius rearrangement which involved the addition of acrylolyl azide to benzyl alcohol shown in eq 2 of Scheme 3. The selectivity results from each run are shown at the bottom of Scheme 3. For the RC-1 runs, we prepared the acryloyl azide from 100 mL of acryloyl chloride as the stoichiometric limiting reagent

---

(6) Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649−4653.

(7) In analogy to the literature preparation, we did one sodium carbonate wash followed by four water washes. We did not do the silver nitrate test since the chloride ion in the tap water complicated this assay.

according to eq 1 of Scheme 3.

The Curtius rearrangement is shown in eq 2 of Scheme 3 which involves the formation of the vinyl isocyanate from the acryloyl azide and in situ trapping with benzyl alcohol using a small amount of pyridine and hydroquinone. The literature procedure called for adding the acryloyl azide solution to 105 °C benzyl alcohol. On larger scale, we saw varying amounts of the aminal side product **4** (eq 3, Scheme 3). The amount of aminal byproduct formed decreased with increasing number of aqueous washes of the acryloyl azide starting material. However, in place of numerous water washes, we found that, by adding finely ground potassium carbonate to the reaction mixture, this side product was greatly minimized, as shown by the results of runs 1 and 2. The formation of the undesired *O*-benzyl aminal (**4**) is an acid-catalyzed process, and the potassium carbonate served to neutralize any acid which was present.[8]

Initially it was assumed that using a stoichiometric amount of benzyl alcohol (1.0 equiv) would minimize the amount of undesired **4** that was formed. Analysis of the headspace by GC/MS, however, showed that, toward the end of the azide addition of run 1, the rate of vinyl isocyanate being liberated as a gas increased substantially (see off-gas rate and composition section).[9,10] This observation is consistent with a change in selectivity from successful in situ trapping of the isocyanate by the benzyl alcohol during the early stages of the addition to unsuccessful trapping and release of the vinyl isocyanate toward the end of the addition. Evidently, toward the end of the addition, there was not enough benzyl alcohol remaining for trapping of the isocyanate, as it had been consumed to produced the undesired aminal, which consumes 2 equiv of the benzyl alcohol. The addition of potassium carbonate allowed us to increase the amount of benzyl alcohol to 2.0 equiv without increasing the formation of **4**. This greatly reduced the amount of vinyl isocyanate being lost in the headspace.[11]

The final parameter which we observed to reduce the amount of **4** formed was the reaction hold time. Even in the presence of potassium carbonate, if the azide addition and subsequent hold times were long, formation of **4** became an issue. With an addition time of 60 min[12] and no hold time, the selectivity improved significantly, with a ratio of ~15:1 of the desired urethane relative to the undesired aminal (i.e., **1**:**4** in Scheme 3, run 3).[13]

The RC1 showed that the desired reaction was completely dose-rate controlled, with the gas evolution and heat liberation ending immediately upon the completion of the dose. This and the FTIR results (see FTIR results section) assured us that no acyl azide accumulated over the course of the addition and that by cooling the reaction immediately after the azide was added, the formation of **4** was minimized.

Calorimetric Principle. In general, heat flow calorimetry is accomplished by way of an energy balance around the reaction calorimeter. This enables the determination of the net heat flow produced from the reactor as a result of a combination of reagents or other thermal events. Mathematically, the energy balance around the reactor is described by eq 1 for a semibatch reaction under nonrefluxing conditions:

$$q_{r}(t) = UA(T_{r} - T_{j}) + m_{r}Cp_{r}\frac{dT_{r}}{dt} + \frac{dm_{dose}}{dt}Cp_{dose}(T_{r} - T_{dose}) \quad (1)$$

where $q(t)$ is measured in watts. Through controlled temperature ramping and the use of a calibration heater, the reaction calorimeter returns a heat capacity (Cp_{r}) and heat transfer coefficient (U) for the initial and final reactor contents.[14] During a semibatch reaction, the energy balance must also account for the sensible heat of the feed, which is the last term of eq 1. This term is zero for a purely batch reaction or when $T_{r} = T_{dose}$.

To obtain the total heat liberated for a reaction or thermal event occurring over an interval of time, the integral of eq 1 must be computed over the reaction limits according to the following equation:

$$\Delta H_{total} = \int_{0}^{t_{f}} q_{r}(t)\, dt \quad (2)$$

whereΔH_{total} is the net heat liberated over the time interval between zero and some final time, t_{f}.

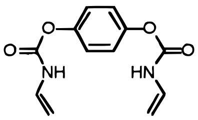
The adiabatic temperature rise calculation provides an estimate for the final temperature that could be reached if the exothermic energy went to raising the temperature of the desired reaction. This calculation obviously assumes that no undesired reactions are encountered along the way. There are different levels of sophistication for calculating adiabatic temperature rise. For example, the temporal dependencies of heat capacity, Cp, and reaction mass, m_{rxn}, with extent of reaction can be considered in its description.[15] A simpler

---

(8) The original literature report has pyridine in it, presumably to neutralize any acid which may be generated. Pydidine·HCl, however, can also serve as an acid catalyst.

(9) Vinyl isocyanate has been reported in the literature to boil at 38.5 °C. We strongly recommend the use of a scrubber. See: Konig, K.-H.: Reitel, C.; Mangold, D.; Feuerhead, K.-H.; Oeser, H.-G. *AIChE J.* **1979**, *18*, 319−320.

(10) We also saw varying amounts of the bis-carbamate shown below as a solid, which precipitated from the reaction mixture. This is consistent with no benzyl alcohol being present at the end of the addition due to the formation of **4**, and the isocyanate being lost as a gas or being trapped by the hydroquinone stabilizer. ^{1}H NMR (400 MHz, $CDCl_3 + CD_3OD$): δ 7.15 (s, 4H), 6.55 (dd, J = 15.9 and 8.9 Hz, 2H), 4.63 (d, J = 15.9 Hz, 2H), 4.28 (d, J = 8.9 Hz, 2H).



(11) The other three gases observed by GC/MS were nitrogen, carbon dioxide, and acetaldehyde. The carbon dioxide is a result of the potassium carbonate used, and the *N*-vinyl portion of compound **1** is a latent source of acetaldehyde.

(12) Caution: this reaction is very exothermic. Very efficient cooling and internal temperature control are necessary for this rate of addition.

(13) ^{1}H NMR ratio.

(14) Specifically, during the temperature ramp, the heat flow, $q_{r}(t)$, is zero, while the temperature rise, dT_{r}/dt, remains a constant. During the action of the precision heater, $q_{r}(t)$ is known while dT_{r}/dt is zero. As a result, two equations in two unknowns are solved simultaneously to solve for both the heat transfer coefficent, U, and the heat capacity of the reactor contents, Cp_{r}. This sequence is usually performed before and after the thermal events so that a linear interpolation can be calculated throughout the course of the reaction.

(15) Landau, R. N.; Cutro, R. S. *Chem. Eng. Prog.* **1993**, 66−71.

Table 1. **Comparison of thermal data obtained from selected instrumentation for the decomposition of the acryloyl azide solution (the solution was 36% acryloyl azide in toluene)**

test	ΔH (J/g of soln)	ΔH (J/g of azide)	onset temp (°C)	moles of gas per mole of azide	TMR at onset (h)
DSC[a] (4 °C/min)	−731	−2031 (−197 kJ/mol)	40		
	−282	−783 (−76 kJ/mol)	190		
ARC ($\Phi = 1.74$)	−482	−1340 (−130 kJ/mol)	27 ($\Delta T_{ad} = 157$)	0.7	11
Radex	−	−	50−60	1	
CHETAH[b]	−776	−2144 (−208 kJ/mol)			

[a] Two exotherms were observed; see Figure 1. [b] Gas-phase heats of formation values were used to estimate the heat of reaction. No Benson group for the carbonyl in O=C=N was available but was approximated as C=O−(2N).

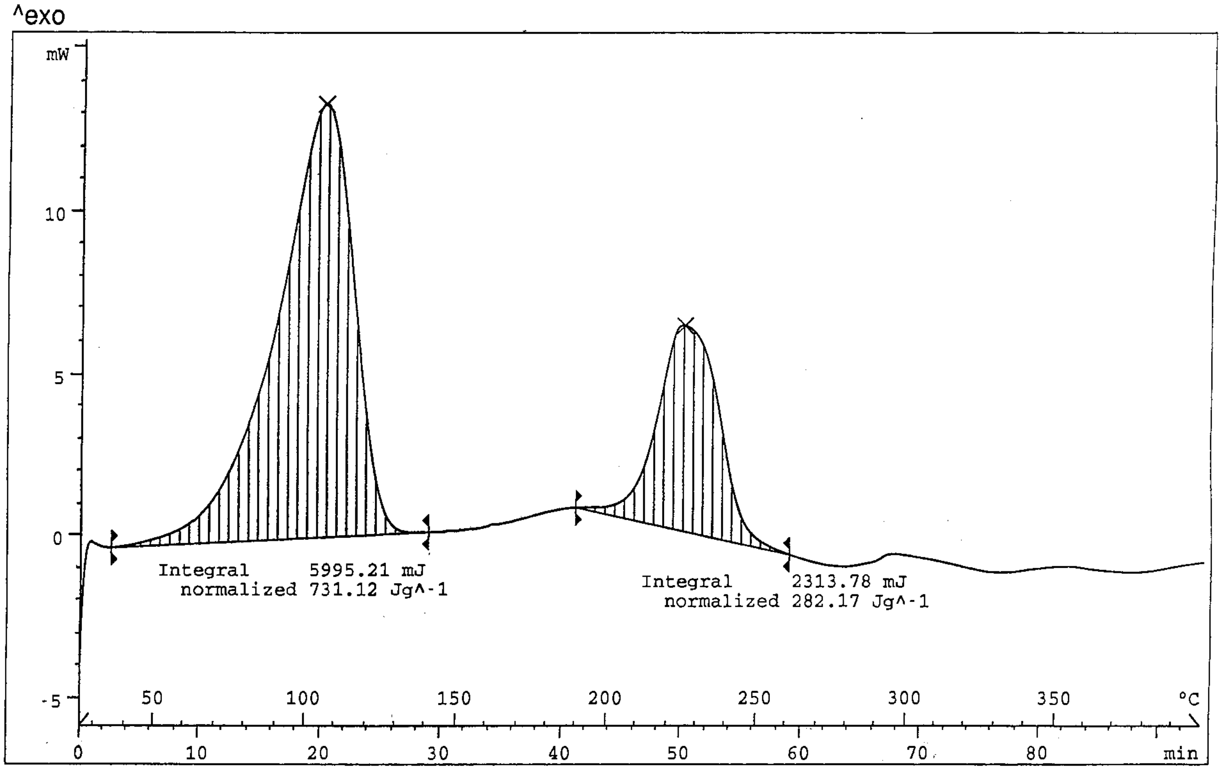


Figure 1. **DSC scan of a 36% solution of acryloyl azide in toluene. The initial decomposition exotherm (731 J/g) is presumably due to the formation of nitrogen and vinyl isocyanate. The sample size was 8.2 mg, with a scan rate of 4 °C/min using gold-plated stainless steel crucible. Onset of the first exotherm was shown to be less than 50 °C.**

form is the one shown in eq 3:

$$T_{\text{adiabatic}} = T_{\text{rxn}} + \frac{\Delta H_{\text{rxn}} n}{Cp(m_{\text{rxn}})} \tag{3}$$

where ΔH_{rxn} and n have units of kilojoules per mole and moles, respectively, and Cp is the heat capacity of the reaction mass. The adiabatic temperature rise is useful in evaluating whether potential decomposition reactions could be reached during a thermal runaway.

Thermal Analysis. ***Caution:*** *In general, carbamoyl azides are explosive compounds. Investigators considering work with these compounds should consult the literature and take proper precautions.*[16,17]

Thermal analysis was performed for both the acryloyl azide solution (in toluene) and the isolated reaction products **1** and **4** to examine their thermal stability. The thermal analysis data for the azide solution are listed in Table 1. Based on the DSC measurement using a scan rate of 4 °C/min, the energy associated with the acryloyl azide decomposition was measured to be −731 J/g of solution (or −2031 J/g of azide = −197 kJ/mol of azide), with an onset occurring in the neighborhood of 40 °C (see Figure 1). A secondary exotherm was observed from the DSC at higher temperatures but was of lower energy (−282 J/g of solution).[18]

Analysis of the Radex data (Figure 2) revealed that the observed pressure rise corresponded closely to the volume of nitrogen that was expected from the stoichiometry.[19] The number of moles of gas calculated from the pressure rise

---

(16) Bretherick's Reactive Chemical Hazards Database, Butterworth-Heinemann Ltd., 1996, warns that azides of low molecular weight (more than 25% nitrogen) should not be isolated from solution, as the concentrated material is likely to be dangerously explosive and the concentration of such solutions should be kept to <10%. Failure to ensure that solutions are free of residual acyl azide before distillation or heat treatment has led to a violent explosion.

(17) See also: Lieber, E.; Minnus, R.; Rao, C. *Chem. Rev.* **1965**, *65*, 377−384.

(18) DSCs were obtained using sealed gold-plated stainless steel crucibles rated to 2000 psi.

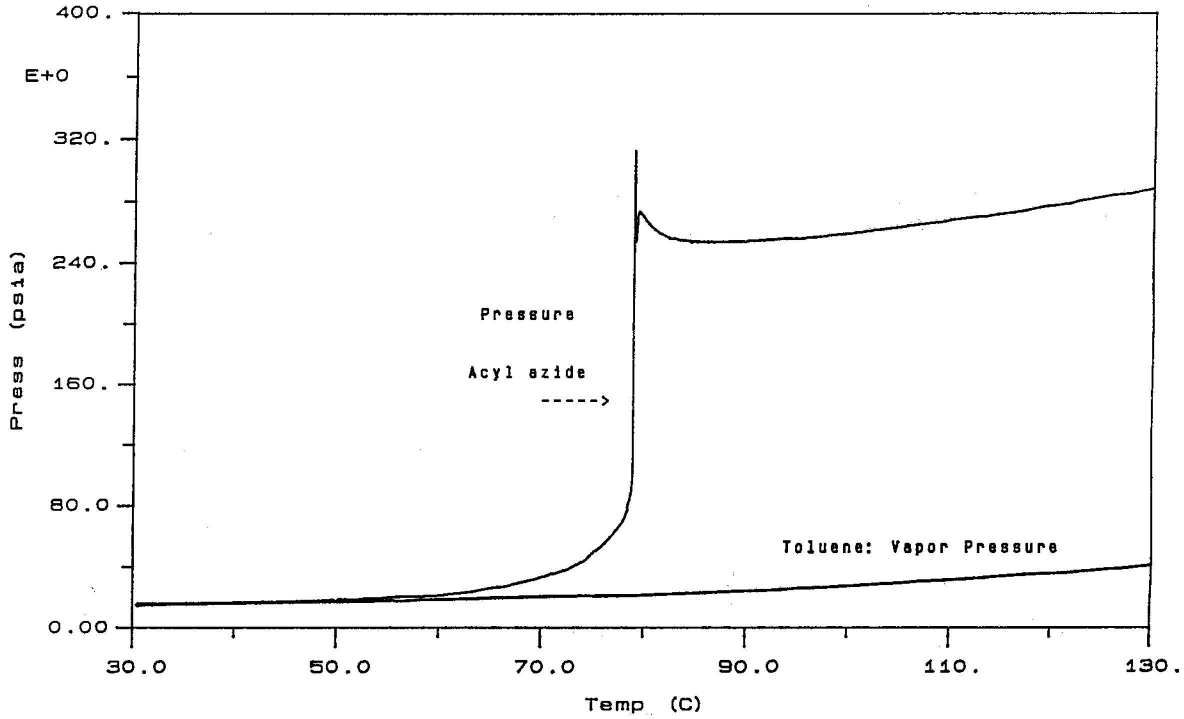


Figure 2. **Pressure profile obtained from Radex experiment of a 36% solution of acryloyl azide in toluene. The rise in pressure closely corresponds to that predicted for 1 stoichiometric equiv of nitrogen liberated. The vapor pressure of toluene over the same temperature range is shown for reference. The sample size was 0.660 g of solution with a scan rate of 2 °C/min.**

was equivalent to 1 mol of nitrogen per mole of azide. These data suggest that the stoichiometry of the initial exotherm shown in Figure 1 represented the formation of the isocyanate with the liberation of nitrogen. As a check of the hypothesis of the first exotherm, CHETAH[20] was used to estimate the heat of reaction for acryloyl azide decomposing to 1 mol of nitrogen and 1 mol of vinyl isocyanate. In this exercise, CHETAH returned a gas-phase heat of reaction (of decomposition) of −2144 J/g of azide (−208 kJ/mol), while the DSC measured an energy of −2031 J/g of azide (−197 kJ/mol); thus, very good agreement was obtained.[21] The second exotherm shown in the DSC scan of Figure 1 was presumed to be that of the decomposition of vinyl isocyanate.

Accelerating rate calorimetry (ARC), which is an adiabatic experiment, was performed to establish a more sensitive self-heat temperature for the azide solution. The ARC returned a self-heat (onset) temperature of 27 °C when corrected for the Φ factor (in this case, Φ was 1.74).[22] The self-heat data are shown in Figure 3 which exhibit rates exceeding 100 °C/min. The Φ-corrected onset temperature is obtained by extrapolation of the self-heat rate curve until it intersects with the Φ-corrected instrument sensitivity obtained by dividing 0.02 °C/min by 1.74 (0.0115 °C/min). The temperature at which these lines intersect is the corrected onset temperature, which is shown graphically in Figure 3. Time to maximum rate (TMR) data are shown in Figure 4 which, when extrapolated to room temperature, 25 °C, indicate a TMR of about 11 h. The data shown in Figure 4 have been corrected for Φ factor. For example, under adiabatic conditions and initially held at 25 °C, it would take approximately 11 h for the acryloyl azide solution to

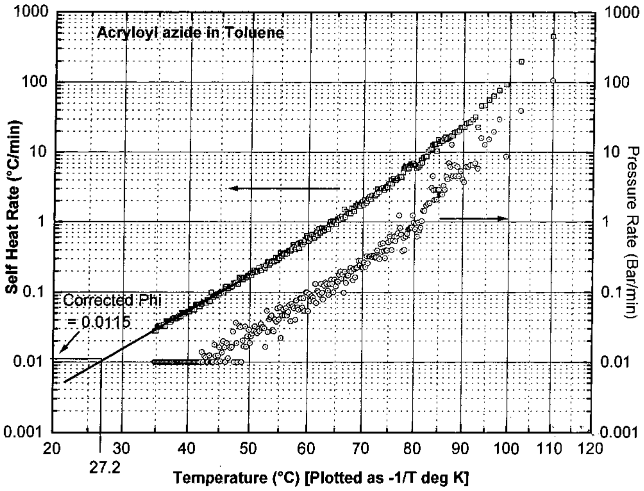


Figure 3. **Accelerating rate calorimetry (ARC), self-heat rate vs temperature plot for a 36% acryloyl azide in toluene solution. Data were obtained in a 6.1 g thin-walled (0.02 in.) titatium bomb loaded with 2.48 g of sample, resulting in a Φ of 1.74 with a heat step of 5 °C and sensitivity of 0.02 °C/min. The Φ-adjusted slope sensitivity was 0.0115 °C/min. As shown above, the extrapolated self-heat curve results in an onset for self-heating at 27.2 °C.**

---

(19) 0.26 g (0.0027 mol) of acyl azide was present in the toluene with an approximate headspace of 5 mL. The stoichiometry was 1 mol of N_2 per mole of azide. At 80 °C, this corresponded to a change in pressure of about 230 psi above the vapor pressure of toluene at 80 °C in Figure 2.

(20) CHETAH version 7.0 is the ASTM computer program for chemical thermodynamic and energy release evaluation (NIST special database 16).

(21) $H_{f(gas)}$ of the acryloyl azide was computed with CHETAH to be +55.1 kcal/mol. The ΔH_f(gas) for the vinyl isocyanate was computed to be +5.4 kcal/mol. ΔH_f(gas) for N_2 is zero. $(+5.4 - 55.1)$ kcal/mol × 4.18 J/cal × (mol/97 g) = −2144 J/g azide.

(22) The Φ factor is the ratio of the combined thermal capacity (*mCp*) of the sample and container to that of the sample; thus, Φ of 1.0 implies that the thermal capacity of the container is negligible relative to the sample. Φ = 1 + (*mCp* bomb/*mCp* sample).

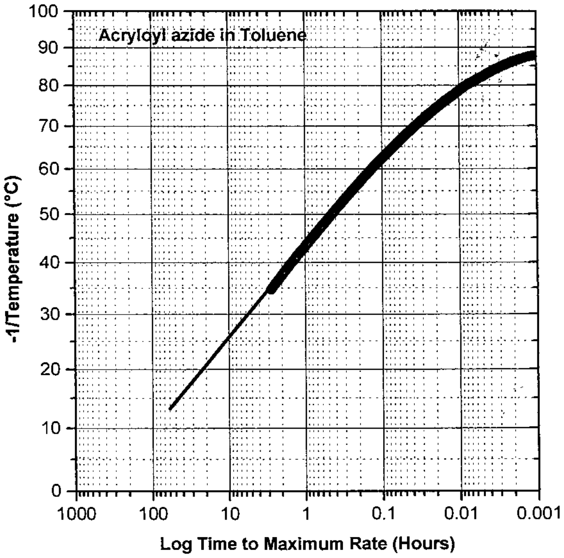


Figure 4. **ARC time to maximum rate (TMR) curve attained from the data shown in Figure 3 for 35% acrylolyl azide in toluene. The TMR curve has been corrected for Φ. As seen from the curve, a TMR of about 3 h at 34 °C is obtained, and, if extrapolated, a TMR of approximately 11 h is predicted for 36% acyrloyl azide solution at 25 °C under adiabatic conditions. Extrapolations such as this should, in general, be confirmed with isothermal (adiabatic) experiments for confirmation as the mechanism for decomposition may change at lower temperatures.**

thermally run away to its maximum rate. The following equation describes how TMR is corrected for the Φ factor:

$$\mathrm{TMR}\ (T, {}^{\circ}\mathrm{C}) = \Phi(t_{\mathrm{TMR}} - t_T) \qquad (4)$$

where $(t_{\mathrm{TMR}} - t_T)$ is the elapsed time between some temperature, T, and the maximum rate, TMR. Figure 4 was obtained by multiplying the raw TMR data by the Φ factor of 1.74. The ARC experiment resulted in an adiabatic temperature rise of 157 °C. When corrected for Φ and estimating a heat capacity for the azide solution, the heat of decomposition reaction from the ARC was calculated to be −1340 J/g of azide (−130 kJ/mol). This value is thought to be low because the self-heat rate exceeded 100 °C/min and, consequently, resulted in a loss of adiabaticity in the sample container. Thus, the true adiabatic temperature probably was not reached.

Based on the thermal analysis, the propensity for the acryloyl azide to liberate nitrogen, and the fact that it was considered "plosive"[23] by CHETAH, solutions of this material should be consumed relatively quickly after their preparation. The acryloyl azide certainly poses a pressure hazard, and storage containers must be adequately vented to allow for the escape of nitrogen. The rate of nitrogen liberation, resulting from decomposition of the azide, is highly dependent on temperature. The rate is significantly reduced at temperatures below 25 °C but is not entirely suppressed, thus the need for adequate venting. Based on the ARC data, the activation energy for the azide decomposition was calculated to be +102 kJ/mol of azide using the initial portion of the self-heat rate data shown in Figure 3.

DSC scan of the products **1** and **4** and of the reaction mixture upon completion of the Curtius rearrangement showed no exotherms. This finding was important for assessing the safety of the overall process because it confined the safety issues to the thermal stability of the acryloyl azide feed and to controlling the rate of conversion in the reactor. Furthermore, in an adequately vented vessel under ambient to subambient temperatures, the acryloyl azide solution (in toluene) can be safely handled and transferred from a charge tank to the reaction vessel. It was also learned by DSC tests that decomposed azide solutions no longer pose thermal stability or pressure hazards.

Reaction Calorimetry Results. Isothermal reaction calorimetry (RC-1) provided the instantaneous heat flow data measured during the Curtius rearrangement reactions. The azide−toluene solution was dosed for 2.5 h in run 1 and for 3.0 h in run 2. The heat flow profiles for runs 1 and 2 are shown in Figure 5. The measured exotherm from the RC-1 energy balance was −202 and −203 kJ/mol of azide for runs 1 and 2, respectively. The energy balance is as follows:

$$\Delta H_{\mathrm{reaction}} = Q_{\mathrm{RC-1\ measured}} + Q_{\mathrm{dose}} + Q_{\mathrm{gas\ evolution}} + Q_{\mathrm{loss}} \qquad (5)$$

$$Q_{\mathrm{RC-1\ measured}} = -202\ \mathrm{kJ/mol\ of\ azide}$$

$$Q_{\mathrm{dose}} = mCp\Delta T = -42\ \mathrm{kJ/mol\ of\ azide}$$

$$Q_{\mathrm{gas\ evolution}} \approx 0$$

$$Q_{\mathrm{losses}} \approx 0$$

The heat of reaction for the Curtius rearrangement is the sum of several terms shown in eq 5. The first term, $Q_{\mathrm{RC-1\ measured}}$, is the heat flow measured by the RC-1, which includes the heat removed through the jacket and any heat consumed to raise the temperature of the reactor contents. To calculate the heat of reaction, Q_{dose} must be included to account for the sensible heat of the feed. The loss of nitrogen has a slight cooling effect as it escapes the reactor but is assumed to be a relatively minor contribution, as it is not a latent heat. Variant heat losses can occur from the reactor lid, especially during nonisothermal operation. However, under isothermal conditions, as was the case here, heat losses from the reactor tend to have a less significant effect on the measured heat flow. This is a result of the ability of the calorimeter to remove the exothermic heat through the cooling jacket while maintaining isothermal conditions. Summing the significant contributions, the heat of reaction was measured to be −244 kJ/mol of azide. Most of this reaction heat can be attributed to the decomposition of the azide to release vinyl isocyanate and nitrogen, which was measured by DSC to be about −197 kJ/mol for the initial exotherm. The coupling of the vinyl isocyanate with the benzyl alcohol would presumably make up the difference, contributing approximately −44 kJ/mol. Calculations using CHETAH to estimate ΔH_{rxn} of the desired reaction gave −353 kJ/mol for the gas-phase and −192 kJ/mol for the liquid-phase reaction. The latter is in fairly good agreement

---

[23] A "plosive" determination implies that the material is expected to decompose with violence.

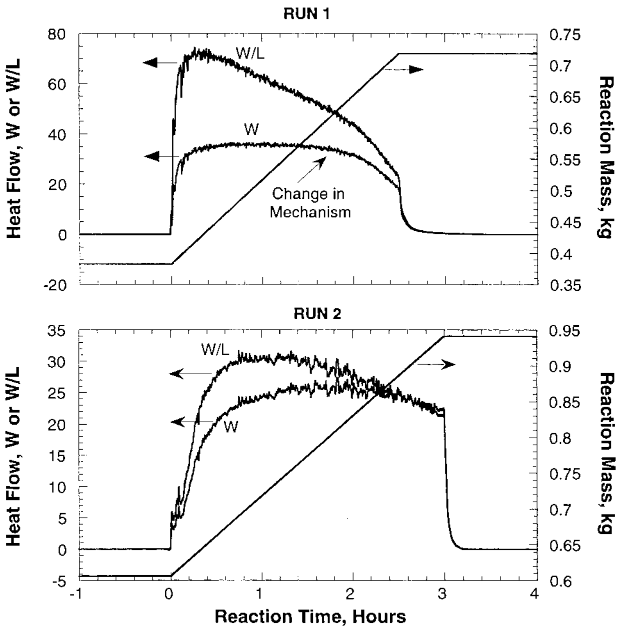


Figure 5. **Heat flow profiles of Curtius rearrangement for runs 1 (top) and 2 (bottom). The acryloyl azide is added to the reactor linearly and is the stoichiometric limiting reagent. It is apparent from run 1 that a change in mechanism occurred at about 2 h into the addition in which the vinyl isocyanate was no longer being trapped. With the increase in benzyl alcohol and the addition of carbonate in run 2, the trapping efficiency was further improved. Run 3 (not shown) was further improved with a shorter add time and immediate cooling after the addition of azide was complete.**

with experimental results and was estimated on the basis the summation of terms shown in eq 6:

$$\Delta H_{\mathrm{rxn}}(\mathrm{liquid}) = (\Delta H_{\mathrm{f}},\mathrm{urethane} - \Delta H_{\mathrm{vap}},\mathrm{urethane} + \Delta H_{\mathrm{f}},\mathrm{N}_2) - (\Delta H_{\mathrm{f}},\mathrm{azide} - \Delta H_{\mathrm{vap}},\mathrm{azide} + \Delta H_{\mathrm{f}},\mathrm{BnOH} - \Delta H_{\mathrm{vap}},\mathrm{BnOH}) \quad (6)$$

where ΔH_{f} is the gas-phase heat of formation and ΔH_{vap} is the latent heat of vaporization. It was assumed that ΔH_{vap},urethane and ΔH_{vap},azide were approximately on the same order of magnitude and cancel each other. Thus, $\Delta H_{\mathrm{rxn}}(\mathrm{liquid}) = \Delta H_{\mathrm{rxn}}(\mathrm{gas}) - \Delta H_{\mathrm{vap}}$,BnOH, where ΔH_{vap},BnOH is referenced to be +161 kJ/mol. Thus, given the approximations made in the theoretical CHETAH calculation, the estimate was found to be fairly reasonable compared to the RC-1 experimental result (−192 vs −244 kJ/mol).

The adiabatic temperature rise calculated for the Curtius rearrangement was 142 °C. This is interpreted for the desired reaction such that there is sufficient exothermic energy to raise the temperature of the reaction mixture above the processing temperature by 142 °C in a purely adiabatic system. This calculation does not recognize whether secondary exotherms are encountered along the way, however. In this particular process, no thermal activity remains based on DSC, once the azide has been added at 105 °C and the urethane has been formed.

The reaction of acryloyl azide with benzyl alcohol was dose-rate controlled. This was based on the observation at the end of the azide addition which indicated that the heat flow and off-gas flow rate immediately subsided. Thus, if there were a cooling failure, simply stopping the feed would stop the exothermic event because there is no significant accumulation of reagent. Dose-rate control refers to the reaction rate being controlled by the rate of addition. For this reason, rate constants are not reported here.

Heat flow profiles for dose-rate controlled reactions tend to have square wave heat flow profiles. As a result, longer addition times have lower maximum heat flows because the energy is being spread over a longer period of time. In run 1, for instance, the addition time was 2.5 h, and the maximum heat flow was measured to be about 70 W/L. When the add time was increased to 3 h (run 2), the maximum heat flow dropped to about 32 W/L, as can be seen in Figure 5. Table 2 clarifies the conditions of each RC-1 experiment. Run 2, for example, used 2 equiv of benzyl alcohol and thus had a much larger initial volume than run 1, which reduced the heat flow per unit volume. Run 3 had an add time of about 1 h, but calorimetry was not obtained so as to eliminate postreaction heating needed for calibrations and heat capacity measurements. The estimated heat flow for run 3 with a 1 h add time was 100 W/L.[24] The cooling needed to remove 100 W/L without refluxing is significant and would probably pose difficulties on scale.[25] In this case, however, the reaction temperature is within 5−10 °C of reflux or the boiling point of toluene (110 °C), which acted as a barrier to temperature rise, tempering the reaction mass as heat of vaporization and preventing further temperature rise. (Clearly this will not be the case, and the temperature will rise if the reactor is sealed rather than vented to atmosphere.) As a result of reflux, higher heat loads such as that calculated for run 3 (100 W/L) are feasible.

A thermal mass flow meter in combination with GC/MS was used during the RC-1 experiments to measure the rate of off-gas evolution. The two curves shown in Figure 6 represent the rate of nitrogen and other gaseous byproducts evolved during the Curtius rearrangement. In the upper curve of Figure 6 (run 1), it is evident that the off-gas rate increased as the reaction progressed. This was shown to be due to acetaldehyde and vinyl isocyanate being released in larger fraction as the reaction progressed. It was presumed that BnOH had been entirely consumed by side reaction (Scheme 3, eq 3), with the urethane forming the undesired aminal. When BnOH is no longer present, the vinyl isocyanate cannot be trapped and thus is liberated as a gas through the condenser. To address this problem, a second equivalent of benzyl alcohol and potassium carbonate was added in run 2 to more efficiently trap the vinyl isocyanate and to minimize the formation of the aminal **4** side product. The increased trapping efficiency which resulted from this modification was evident in the off-gas profile of run 2 (Figure 6), as shown

---

(24) In this case, the maximum heat flow was estimated from the following equation: $(Q_{\mathrm{max}}/\mathrm{volume}) = (\Delta H/t_{\mathrm{add}})/\mathrm{volume} = (243\ \mathrm{kJ}/3600\ \mathrm{s}/0.67\ \mathrm{L}) \times 1000\ \mathrm{J/kJ} = 100\ \mathrm{W/L}$. This assumes a constant heat flow, or $q(t) = Q_{\mathrm{max}} = \Delta H/t_{\mathrm{add}}$, which is an approximation for dose-rate controlled reactions (i.e., square-wave heat flow profiles).

(25) Knowledge of the heat transfer coefficient and heat transfer area for the large scale reactor would allow for a calculational check of the ΔT across the jacket. Then a determination of feasibility for a given addition rate could be made.

Table 2. **Conditions of reaction calorimetry experiments (all three experiments were performed at 105 °C in RC-1)**

	run 1	run 2	run 3
azide−toluene solution (36% acryloyl azide) (1.23 mol of azide)	335 g	335 g	335 g
benzyl alcohol	1 equiv (134 g)	2 equiv (268 g)	2 equiv (268 g)
toluene	242 g	242 g	242 g
hydroquinone	6 g	6 g	6 g
pyridine	6 g	6 g	6 g
potassium carbonate	0 g	85 g	85 g
total mass	388 g	607 g	607 g
initial	723 g	942 g	942 g
final			
add time for dosing the azide solution	2.5 h	3.0 h	1.0 h
hold time at 100 °C after the dosing	3 h	3 h	1 h
calorimetry measurements	yes	yes	no
measured heat of reaction without Q_{dose}	−202 kJ/mol	−203 kJ/mol	
measured heat of reaction with Q_{dose}	−244 kJ/mol	−245 kJ/mol	
maximum heat flow	70 W/L	32 W/L	100 W/L (calcd)

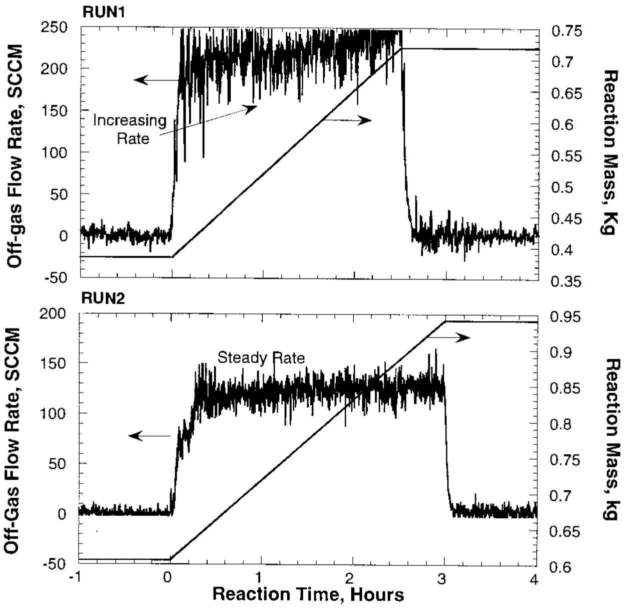


Figure 6. **Off-gas evolution curves measured from runs 1 (top) and 2 (bottom) using a thermal mass flow meter. The profiles were consistent with the interpretation of the change in mechanism observed in the heat flow data in Figure 3. In run 1, not only was nitrogen being liberated, but also vinyl isocyanate was liberated through the condenser in increasing fashion instead of being trapped to produce the urethane. In run 2, it is apparent that the off-gas remained more constant throughout the addition, which suggests that vinyl isocyanate was not being liberated in significant quantities.**

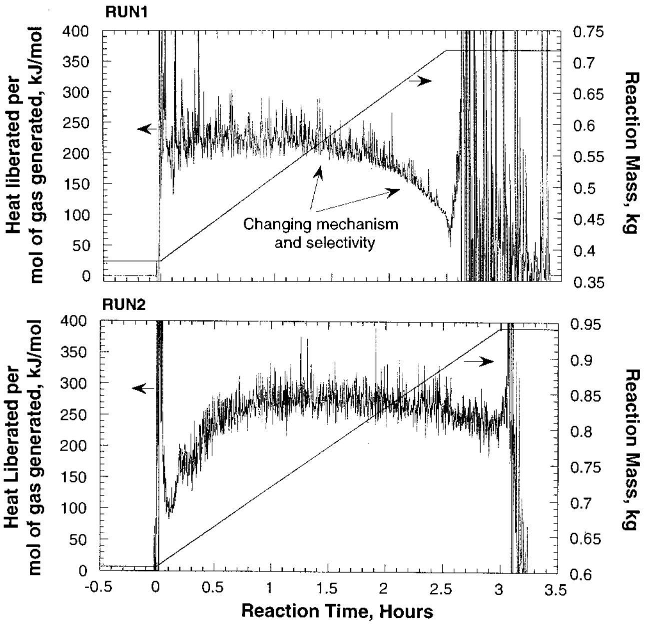


Figure 7. **Instantaneous heat of Curtius rearrangement per mole of gas liberated as a function of time. This plot was derived by dividing the heat flow profiles shown in Figure 5 with the gas flow profiles shown in Figure 6.**

by less vinyl isocyanate or other gases being produced.

Instantaneous heat of Curtius rearrangement per mole of gas liberated is shown in Figure 7 and was obtained by dividing the heat flow profiles shown in Figure 5 with the gas flow data of Figure 6. Notice in run 1 (Figure 7) that the heat per mole of liberated gas initiates near 224 kJ/mol but quickly tapers off toward the end of the addition. This is consistent with less trapping and increased rate of gas liberation (both N_2 and vinyl isocyanate), which tend to reduce the heat per volume of gas liberated in run 1. Essentially, only nitrogen was liberated in run 2 due to more efficient trapping of the vinyl isocyanate resulting in increased selectivity while the heat per mole of gas was fairly steady at 250 kJ/mol of gas.

FTIR spectra obtained for the azide in toluene feed solution showed a strong band absorbing at 2135 cm^{-1}, which corresponds to the azide $R{-}N_3$ resonance structure. During the Curtius rearrangement, this band was not apparent during the reaction profile.[26] This is significant as it indicated qualitatively that no accumulation of the azide occurred during the reaction. Further evidence of this was observed from the RC-1 and mass flow meter profile where, at the end of the azide addition, the heat flow and off-gas signals return to zero, indicating no further reaction. FTIR profiles of characteristic bands for the desired product also provided

---

(26) ASI's DiComp probe is a composite of Zn/Se and diamond crystal with a region of low energy in the 1900−2100 cm^{-1} range. Nevertheless, the azide functional group was clearly visible in the acyl azide in toluene spectrum.

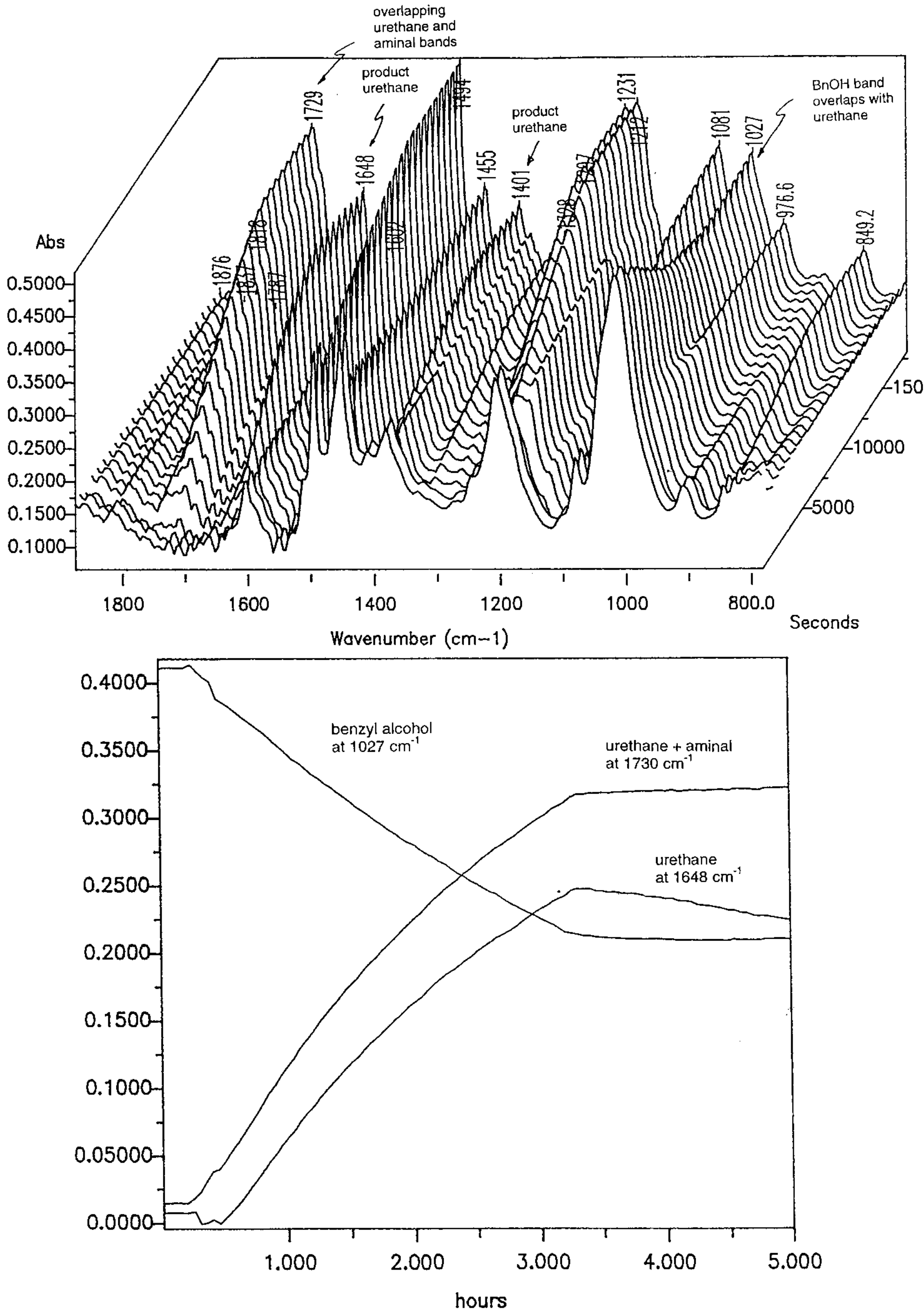


Figure 8. **FTIR spectra (above) of Curtius rearrangement reaction (in situ) in run 2. A wavenumber of 1648 cm^{-1} can be assigned to a characteristic peak of product 1. No unique peak was observed for the aminal byproduct 4, but wavenumber 1730 cm^{-1} included absorbance for both 1 and 4. Wavenumber 1027 cm^{-1} can be assigned to benzyl alcohol but with some overlap with 1. Temporal profiles of assigned wavenumbers are also shown in the lower plot.**

valuable information. Figure 8 shows that the product urethane **1** band at 1648 cm^{-1} reached a maximum before it declined, while a band characteristic of both product **1** and aminal **4** reached a maximum and then leveled off (1730 cm^{-1}). No unique peak was observed for the aminal byproduct **4**. Wavenumber 1027 cm^{-1} was assigned to benzyl alcohol but with slight overlap with **1**. Taking the difference between the temporal profiles of 1648 and 1730 cm^{-1}, it followed that the formation of **1** reached a maximum at the end of the addition and that the undesired aminal side product **4** continued to be produced with prolonged heating. This observation was consistent with calorimetry and yield results. Namely, the longer add times and excessive heating caused **1** to react further with remaining BnOH to form the undesired aminal **4**. This undesired reaction was supressed by faster add times and rapid cool-downs following the azide addition. The improvement is noted by the selectivity of run 3 (Scheme 3), with a 15:1 desired urethane relative to undesired aminal ratio.

Conclusion

Run 3 was carried out with a total addition time of 1 h and in the presence of potassium carbonate and 2 equiv of benzyl alcohol. Under these conditions, the ratio of product to aminal was ~15:1. The extra equivalent of benzyl alcohol and other process changes essentially eliminated the amount of vinyl isocyanate being lost in the headspace. The amount of undesired aminal formed was also shown to be minimized with a short addition time, cooling immediately upon completion of the addition, as well as the presence of potassium carbonate to serve as an acid scavenger.

The stoichiometric limiting reagent of the Curtius rearrangement was the acryloyl azide, which was established to be thermally unstable at temperatures below the synthesis temperature. However, as we learned from this investigation, the mechanism for thermal decomposition of the acyl azide (and liberation of N_2) was also the desired reaction for the trapping reaction of the Curtius rearrangement, albeit under carefully controlled conditions. Viewed another way, the desired reaction (Curtius and trapping) involves a controlled decomposition of the acyl azide, as it is introduced into the reactor held at 105 °C to generate the vinyl isocyanate which immediately reacts with the benzyl alcohol. Because the final reaction products and byproducts were thermally stable and the desired reaction was dose-rate controlled, the safe operation of the process focused primarily on the storage and handling of the acyl azide solution. Because the azide in toluene solution poses a thermal and pressure hazard, it is recommended that the inventory of this solution be minimized and solutions be consumed quickly after preparation and that, if stored, they be maintained at ambient temperatures or below and that they be properly vented to allow for the escape of nitrogen. Further, vent-sizing experiments should be performed for the vessel feed tank and reactor to prevent overpressurization under potential worst case scenarios.

The reaction calorimetry revealed that the rate of reaction and the associated exotherm were strictly dependent on the rate of azide addition. The combined technologies utilized in this investigation greatly increased our understanding of the process and accelerated the delivery of the safety assessment to our proposed vendor.

Combination of reaction calorimetry and thermal analysis with the interfaced technologies (FTIR, GC/MS, and thermal mass flow meters) resulted in the following:

(i) increased clarity and understanding of the reaction mechanisms;

(ii) confidence that the process could be safely scaled up;

(iii) a significant increase in the selectivity and yield of the desired urethane; and

(iv) a savings of 2−4 months of development time while on critical path.

The acryloyl process was transferred to a vendor where it was safely scaled to produce **1**, *N*-vinyl-*O*-benzyl urethane.

Experimental Section

Reagents. Acryloyl chloride was 96% pure and used as received from Aldrich. Benzyl alcohol was 99.8% anhydrous and used as received from Aldrich. Potassium carbonate from J. T. Baker was finely ground with a mortar and pestle. Toluene from Fisher (certified ACS) was used as received. All other reagents (pyridine, hydroquinone, and sodium azide) were also used as received.

Acryloyl Azide. Following a slight modification of the literature preparation of compound **1**, acryloyl azide was prepared by dropwise addition of 100 mL of acryloyl chloride (1.23 mol, 1.0 equiv) dissolved in 150 mL of toluene to 83.8 g of sodium azide (1.29 mol, 1.05 equiv) dissolved in 300 mL of water[27] at a rate to keep the temperature <0 °C. This reaction was fairly exothermic, and the addition was done over an hour using an ice/acetone cooling bath. The mixture was *vigorously* stirred at 0 °C for 3 h.[28] The final pH was ~8. An additional 100 mL of toluene was then added to give a better separation of the organic and aqueous layers. The layers were separated, and the organic layer was washed with 100 mL of 10% sodium carbonate. This was followed by 4 × 100 mL water[29] washes and 2 × 100 mL brine washes, and then the toluene solution containing the acyl azide was filtered through 50 g of sodium sulfate to provide a clear solution. This solution was stored at 5 °C overnight.[30]

^{1}H NMR (400 MHz, toluene-d_8): δ 6.48−6.54 (m, 1H), 6.10−6.19 (m, 1H), 5.91−5.98 (m, 1H).

***N*-Vinyl-*O*-benzyl Urethane (1).** The toluene solution of the acyl azide was added dropwise to a 100 °C mixture of 256 mL of benzyl alcohol (2.46 mol, 2.0 equiv), 6.1 g of hydroquinone (0.055 mol, 0.045 equiv), 6.0 mL of anhydrous pyridine (0.074 mol, 0.060 equiv), 85.0 g of potassium carbonate (0.62 mol, 0.5 equiv), and 250 mL of toluene.[31] *This reaction is very exothermic, and nitrogen is liberated!* The nitrogen evolution subsided immediately upon competion of the addition. After the potassium carbonate was filtered off, the reaction mixture was concentrated in vacuo to remove toluene and some of the benzyl alcohol. The residue could be further purified by fractional distillation, according to Hegedus,[32] or purified by silica gel chromatography.[33] The final product is a crystalline solid which melts at 43−44 °C. Our Discovery group routinely obtained 150 g of clean product (69% of theory).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.41 (m, 5H), 6.65−6.77 (m, 1H), 6.49 (bs, 1H), 5.12 (s, 2H), 4.41−4.52 (m,1H), 4.28−4.32 (m, 1H). TLC (silica gel, 80:20 hexane/ethyl acetate): R_f 0.40. HPLC (2400:1600:8:4 water/acetonitrile/triethylamine/acetic acid, 4.6 × 150 mm C_8 Zorbax, 210 nm, 1 mL/min): $t_r = 8.3$ min.

Aminal Side Product 4. For characterization puroposes, a purified sample of **4** was obtained by flash chromatography using the system previously described.

---

(27) The original preparation used distilled water. We used Groton city water with no noticeable difference.

(28) If the reaction was allowed to warm to room temperature and then stir overnight, some decomposition of the azide was observed.

(29) Due the presence of chloride in the tap water used, we did not do the silver nitrate test described by Hegedus.

(30) A solution of the acyl azide in toluene-d_8 was shown to be stable under these storage conditions. If the solution is stored at room temperature, some nitrogen pressure is observed. The solution may get cloudy after overnight storage.

(31) The original procedure did not add additional toluene here. We saw a more controlled addition/exotherm with this modification.

(32) This requires a very efficient vacuum source, or else the longer contact times on larger scale for the material in the pot results in some decomposition. Bp 120 °C at 0.5 mmHg.

(33) 10 g of silica gel/1 g of product theory. Gradient of hexane to 97.5:2.5 hexane/ethyl acetate. Conditions courtesy of G. T. Magnus-Aryitey, C. J. Mularski, and R. T. Wester.

^{1}H NMR (300 MHz, CD_3CN): δ 7.29−7.40 (m, 10H), 6.13 (bs, 1H), 5.01−5.17 (m, 3H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.45 (d, $J = 11.8$ Hz, 1H), 1.31 (d, $J = 6.0$ Hz, 3H). TLC (silica gel, 80:20 hexane/ethyl acetate): R_f 0.35. HPLC (2400:1600:8:4 water/acetonitrile/triethylamine/acetic acid, 4.6 × 150 mm C_8 Zorbax, 210 nm, 1 mL/min): $t_r = 24.2$ min. (The *N*-vinyl compound has a 1.9 times higher absorbance than the aminal at this wavelength.)

Instrumentation. To investigate the preparation of **1** (*N*-vinyl-*O*-benzyl urethane), the Curtius reactions were performed in a fully automated reaction calorimeter (Mettler RC-1) equipped with a 1 L (MP-10) glass reactor and thermostated stainless steel head. Stirring was accomplished with a stainless steel anchor impeller. The acyl azide in toluene solution was pumped to the reactor at a linear rate using a control loop between the RC-1 computer and an analytical balance. An Applied Systems (ReactIR 1000) reaction analysis system was utilized to collect in situ compositional (FTIR) data. FTIR spectra were collected using a diamond-Zn/Se composite (DiComp) attenuated total reflectance (ATR) sampling probe inserted into the RC-1. Off-gas flow rates were measured with an Omega FMA-1800 series thermal mass flow meter, while off-gas compositional data were measured with a Hewlett-Packard 6890 gas chromatograph with mass-selective detector (MSD) equipped with automatic sampling valves. Thermal analysis was performed using DSC (Mettler 821e), Radex-Solo (Astra Scientific), and accelerating rate calorimetry (ARC, Columbia Scientific) instruments.

Nomenclature

A: heat transfer area, m^2
$q_r(t)$: instantaneous heat transfer, W or J/s
m_r: reaction mass, kg
dm_{dose}/dt: addition rate of dosed material, kg/s
Cp_{dose}: heat capacity of added material, J/(kg K)
ΔH_{rxn}: molar heat of reaction, kJ/mol
ΔH_{total}: total enthalpy of thermal event, kJ/kg
t: time, s
$T_{adiabatic}$: adiabatic temperature rise, °C
T_{dose}: temperature of added (dosed) material, °C
T_r: reaction temperature, °C
T_j: temperature of reactor jacket, °C
TMR: time to maximum rate, h
U: heat transfer coefficent, W/(m^2 K)
V: volume of raction mass, L

Received for review September 1, 1997.

OP970115W