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Kinetics for Scale-Up of a One-Pot Pathway to 5-(3-Fluorophenyl)-2,4-dihydro-2,4-dimethyl-3*H*-1,2,4-triazole-3-thione Using a Hybrid Model of Parallel and Consecutive Reactions

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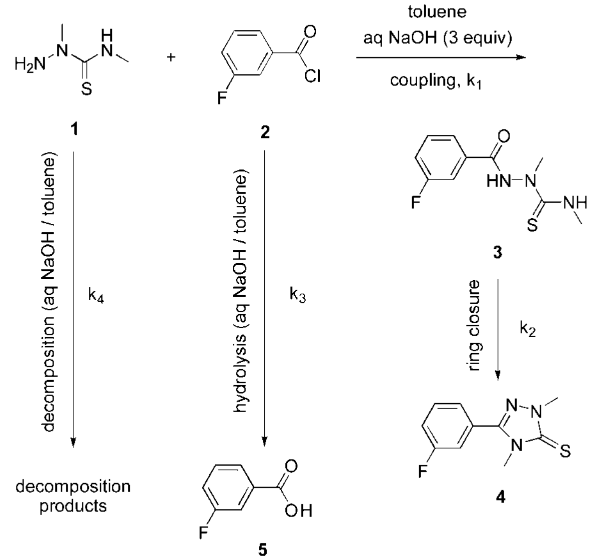
Abstract:

Kinetic results are reported for the one-pot reaction of 2,4-dimethylthiosemicarbazide (1) and 3-fluorobenzoyl chloride (2) to the unisolated benzamide intermediate (3), and on to the ring-closed product, 5-(3-fluorophenyl)-2,4-dihydro-2,4-dimethyl-3*H*-1,2,4-triazole-3-thione (4). The sensitivity of the synthetic route to competing side reactions was examined by studying the kinetics of each reaction step. A first-order kinetic Model of the hybrid consecutive and parallel reaction scheme was developed and fit to experimental data. The Model was extended to address potential mixing concerns resulting from the formation of the insoluble intermediate 3 upon scale-up where a more concentrated reaction would be used. Scale-up of the product drug substance from laboratory to 50-gal scale was successfully completed using this recently developed one-pot pathway.

Introduction

The reaction product 5-(3-fluorophenyl)-2,4-dihydro-2,4-dimethyl-3*H*-1,2,4-triazole-3-thione (**4**) was an early stage pharmaceutical evaluated by Hoechst Marion Roussel for the treatment of depression[1] and for memory enhancement in treating Alzheimer's disease.[2] The reaction of 2,4-dimethylthiosemicarbazide (**1**) and 3-fluorobenzoyl chloride (**2**) to ultimately produce the drug product can be run in one reaction pot.[3] As shown in Scheme 1, this pathway involves two consecutive reactions, first the coupling reaction to form the unisolated benzamide (**3**) and then the ring-closure reaction to product. Using aqueous caustic as base, **1** and **2** can be coupled by a Schotten–Baumann procedure, and sodium hydroxide also catalyzes the ring-closure reaction of **3** to **4**. Toluene as the solvent helps to prevent hydrolysis of acid chloride **2** and also solubilizes the product for a simple isolation. Byproduct salt and any hydrolysis product (sodium 3-fluorobenzoate) are decanted in the aqueous layer. The product in toluene can be crystallized directly or from other suitable solvents such as 2-propanol.

Scheme 1



With scale-up, heat-up and cool-down cycles and reactant addition times often increase as a result of jacket and mechanical limitations in larger equipment. Amine **1** was shown to decompose in aqueous caustic, and hydrolysis of **2** was sometimes >30% during development of the one-pot process. Also, intermediate **3** is nearly insoluble in this reaction system. Previous routes that isolate **3** have produced very fine crystals. Dilute concentrations were necessary to make a mobile slurry, e.g., 1 g of **3** in 25 mL of toluene. To ensure an understanding of the competing chemistry, the rates of these reactions, as well as those of the principal reaction pathway, were sought as illustrated in Scheme 1. Rather than a rigorous study to determine rate constants, the desired outcome was to give a reliable estimate of the relative reaction rates. Elaborate sampling and quenching methods were not used. Moreover, the two-phase system is complex and will likely be dependent upon vessel geometry, impeller design, etc., which dictate mixing flow, droplet size, and the like.[4] Instead of configuring a small, well-mixed apparatus, as is often used in a detailed kinetic study, a conventional jacketed straight-wall reactor was used to simulate the 50-gal scale-up vessel.

Results and Discussion

1. Initial Conditions for the One-Pot Reaction. Exploratory reactions found that **4** could be produced in good yield by the following procedure: charge **1**, toluene, and aqueous caustic and heat to about 80 °C; continuously add **2** over 30–60 min; after complete addition, hold at 80 °C for 60 min before

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(1) Kane, J. M.; Miller, F.P. U.S. Patent 4,912,095, March 27, 1990.

(2) Miller, J. A. U.S. Patent 5,100,906, March 31, 1992.

(3) Stolz-Dunn, S. K.; Louks, D. H.; Puga, Y. M.; Goralski, C. T. U.S. Patent 5,723,624, March 3, 1998.

(4) Zhang, J.; Atherton, J. H.; Unwin, P. R. Acid chloride hydrolysis kinetics are valid only for the specific agitation conditons used. *Langmuir* **2004**, *20*, 1864.

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Table 1. **Typical laboratory reaction recipe to prepare 4 by the one-pot procedure**

component	amount	molar ratio
1	27.8 g	0.96
toluene	465 mL	
20% NaOH	114 mL	
(NaOH)	(27.8 g)	2.87
(H_2O)	(111.1 g)	25.5
2	38.4 g	≡1

cooling to about 50 °C to begin the phase separation. A typical recipe is shown in Table 1.

The decomposition of **1**, the hydrolysis of **2**, and ring-closure reaction of **3** to **4** were evaluated in separate experiments. More dilute conditions were used to control reaction exotherms, and lower temperatures were used to slow the reactions to a measurable rate. In order to determine rates for the overall reaction scheme, all components were charged and the reaction was started. The rate-limited reaction, by continuously adding acid chloride **2**, was examined later.

Results show that the reactions are generally first-order. Of most interest is the rate of acid chloride **2** hydrolysis (k_3) versus the desired route to intermediate **3** and product **4** (k_1 and k_2). This part thus represents the hybrid of parallel reactions (**2** → **3** and **2** → **5**) with the consecutive reaction of one of the products to another (**3** → **4**). Although the individual first-order reaction paths are both commonly found in the literature,[5–7] the "hybrid" is not. A reaction model was derived that solves for all four component concentrations (**2**, **5**, **3**, and **4**) versus time, given the three rate constants and the initial concentration of **2**.

2. Hydrolysis of 3-Fluorobenzoyl Chloride (2). A warm toluene solution of acid chloride **2** was added to 1 N NaOH and agitated to measure the rate of hydrolysis at 41 °C. The molar ratios of (**2**:NaOH:H_2O) were (1:2.96:165). By analyzing for the amount of **2** remaining in the toluene layer (LC as the methyl ester), the disappearance over time was easily found. Because salt is a byproduct, this conveniently allowed another way to follow the reaction. The inorganic chloride concentration in the aqueous layer was measured by ion chromatography in mg/mL solution. By assuming a constant volume of the aqueous layer, the total amount of chloride produced can be determined. Subtracting the initial molar amount of **2** charged from the salt produced during the course of the reaction gives the amount of unreacted **2**. This should closely resemble the profile found previously by direct LC analysis. The two reaction profiles are very similar as shown in Figure 1.

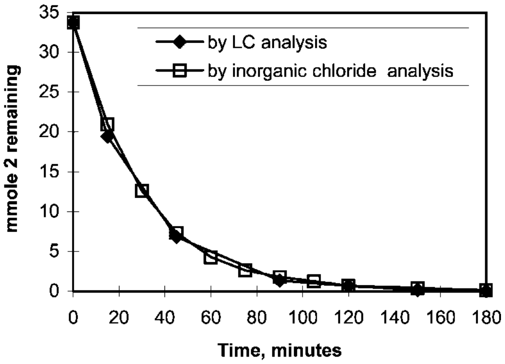

Figure 1. **Hydrolysis of 2, at 41 °C in aqueous caustic/toluene by two analytical procedures.**

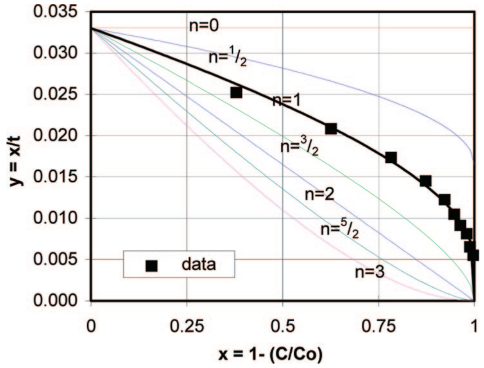

Figure 2. **Determination of reaction order for the hydrolysis reaction of 2, from inorganic chloride analyses in Figure 1 (after Holleran[7]).**

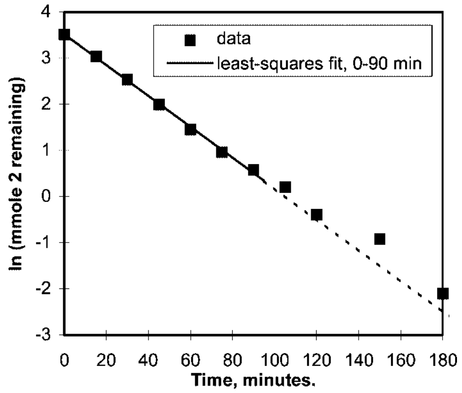

Figure 3. **Determination of first-order rate constant for the hydrolysis of 2, at 41 °c in aqueous caustic/toluene, using inorganic chloride data.**

Because the kinetic order was unknown, the method of Holleran[8] was used, whereby a graphic plot of $y = x/t$ versus $x = 1 - (c/c_0)$ gives a shape that is characteristic of the reaction order (x is the fraction of reactant consumed, where c is the concentration at time t and c_0 is the initial concentration). The x,y plot for a first-order reaction will be linear and sloping downward for the first third of the reaction. Then, it will exhibit a sharp curvature late in the reaction and will converge to (0,1). As shown in Figure 2, the shape was indicative of a first-order reaction. The contrasting shapes of curves, representative of other reaction orders, are also shown.

The classical method of plotting ln(mol **2** remaining) versus time and evaluating the linear slope $= -k_3$, can certainly be employed since the order $n = 1$ is established. This was done for the more frequent analyses from inorganic chloride (Figure 1), with the result in Figure 3. Samples taken late in the reaction are expected to be more prone to error: the small molar amount of unreacted **2** was calculated as c_0 (initial moles of **2** charged) $- c_{Cl}$ (moles of chloride at time t). By ion chromatography, this difference gives large percentage errors with small fluctuations in c_{Cl} (e.g., at $t =$ "∞", by the experimental analysis, c_{Cl} may

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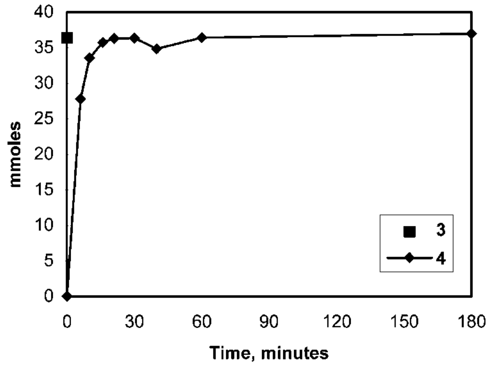

Figure 4. **Ring-closure reaction of 3 to 4, at 41 °C in aqueous caustic/toluene.**

not exactly equal c_0). Therefore, in Figure 3, the rate constant $k_3 = 0.0334$ min^{-1} was determined using data from samples at 0–90 min reaction time. Alternately, using the direct LC analysis for the amount of **2** remaining, the rate constant at 0–180 min was $k_3 = 0.0356$ min^{-1}.

Finding the hydrolysis reaction to be pseudo-first-order is not surprising, as reactions of this type in a large molar excess of water are often so. The effect of NaOH and H_2O concentrations upon the hydrolysis rate could be determined later, if needed.

3. Ring-Closure Reaction of Intermediate Benzamide 3 to Product 4. The reaction was run at approximately the concentration that would be expected midway through the coupling reaction: 2.5 equiv of NaOH and 0.5 equiv of byproduct salt in the aqueous/toluene solvent system. Benzamide **3** is a fine solid that is nearly insoluble in both phases, so its dissolution may limit the kinetic rate. The reaction began as a stirred slurry at 41 °C using the molar ratios (**3**:NaOH:H_2O:NaCl) = (1:2.32:166:0.48). Obtaining a respresentative sample of the multiphase reaction mixture to determine the amount of nearly insoluble **3** remaining in the reaction vessel by LC is a difficult task. Instead, the reaction was followed by analyzing for **4** formed in the toluene layer, since the product is essentially insoluble in the aqueous layer and yields are nearly quantitative. The reaction profile is shown in Figure 4. Both phases became clear of solids after 30 min, visually indicating high conversion of the insoluble reactant **3**. By LC, the amount of **4** formed after complete reaction (at 180 min) was 37.0 mmol, whereas the total amount of **3** charged to the reaction was 36.5 mmol. The reaction fits first-order kinetics, as a plot of ln(mmol **3** unreacted) versus time, derived from the formation rate of product, gave a straight line for the majority of the reaction.

Figure 5 shows the linear least-squares line, giving $k_2 = 0.255$ min^{-1}.

4. Decomposition of 2,4-Dimethylthiosemicarbazide (1). A 0.76 wt % solution of **1** in toluene was stable when held at 80 °C for 48 h. Rotary evaporation yielded the near quantitative recovery of solid, and LC analysis showed high assay. In the presence of aqueous caustic, however, decomposition occurred. Amine **1** was heated and stirred under nitrogen, in a two-phase system of 2.93% aqueous caustic and a half-volume of toluene. Initial samples from two experiments, at 50 and 80 °C, showed that about 92% of **1** resided in the aqueous layer. The molar ratios used in both experiments were (**1**:NaOH:H_2O) = (1:2.94:219). Samples of each phase were taken at timed intervals, and analysis by LC quantified the amount of **1** remaining. By summing the individual layer analyses at a given time, the total amount of decomposition was found. Figure 6 shows the total decomposition rate at both temperatures. After an initial “induction period”, the rate increased, but then slowed sometime after 480 min. The decomposition products are unknown but could reach some meta-stable equilibrium as the end point. Over the 120- to 480-min interval, the decomposition rates at 50 and 80 °C were 4.7% and 6.1% per hour. Thus, the rate at 80 °C was only 1.3 times the rate at 50 °C. Although the data do not fit well to a first-order reaction, the decomposition at 50 °C, about 0.001 min^{-1} (k_4), is at least an order of magnitude slower than the others that were determined in this study. Still, care must be taken to prevent prolonged heating of **1** in aqueous caustic before starting the coupling reaction.

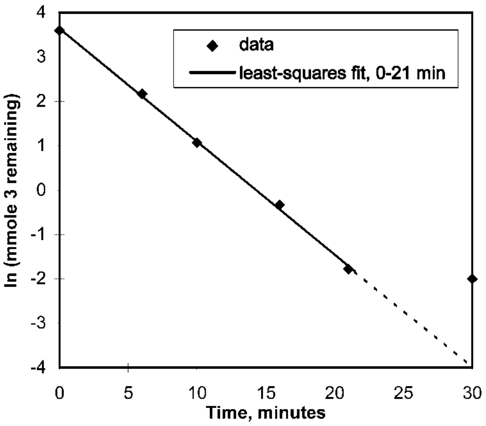

Figure 5. **Determination of the first-order rate constant for the ring-closure reaction of 3 to 4, at 41 °C in aqueous caustic/toluene.**

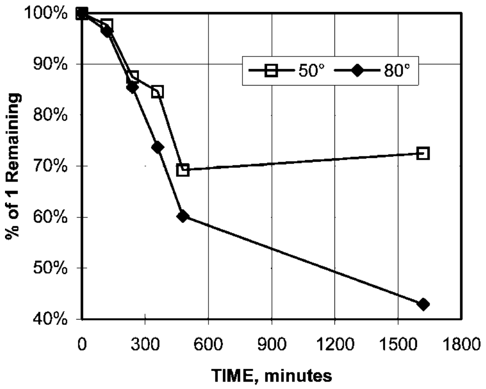

Figure 6. **Decomposition of 1, at 50 and 80 °C in aqueous caustic/toluene.**

5. First-Order Kinetic Model for the Hybrid Parallel and Consecutive Reaction Scheme. Of the principal and competing reactions studied so far, the decomposition of **1** is nearly insignificant in comparison to the other rates. This makes the coupling and competing hydrolysis of acid chloride **2** and the ring-closure reaction of **3** to **4** the primary interest in Scheme 1 for these first-order or pseudo-first-order reactions. This route is the combination of parallel reactions, with consecutive reaction of one of the products to a new product. For this Model, the concentration versus time profile is derived for the four components of Scheme 1.

The time-dependent solution for the concentrations of **2** and **4** are readily obtained from the differential equations of the parallel reaction.[6] (To avoid confusion with numerals, compounds **2**, **3**, **4**, and **5** in Scheme 1 are designated as A, B, C, and D, respectively.)

The time-dependent concentrations of A and D are

$$[\mathrm{A}] = A_0 \quad \mathrm{e}^{-(k_1+k_3)t} \tag{1}$$

$$[\mathrm{D}] = \mathrm{D}_0 + \frac{k_3 A_0}{k_1 + k_3}(1 - \mathrm{e}^{-(k_1+k_3)t}) \tag{2}$$

The time-dependent concentration of B is

$$\frac{\mathrm{d}B}{\mathrm{d}t} = k_1 A - k_2 B \tag{3}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = k_1 A_0 \quad \mathrm{e}^{-(k_1+k_3)t} - k_2 B \tag{4}$$

This equation was solved by introducing the integrating factor,

$$\rho = \mathrm{e}^{\int P dt}, \quad P = k_2 \tag{5}$$

By multiplying each side of the dB/dt equation by ρ, the solution can be found as

$$[\mathrm{B}] = \frac{k_1 A_0}{k_2 - (k_1 + k_3)} \quad \mathrm{e}^{-(k_1+k_3)t} + K \ \mathrm{e}^{-k_2 t} \tag{6}$$

where K is the constant of integration. This constant can be defined by specifying the initial conditions, at $t = 0$, $B = 0$ (i.e., $B_0 = 0$). This yields the solution as:

$$[\mathrm{B}] = \frac{k_1 A_0}{k_2 - (k_1 + k_3)}(\mathrm{e}^{-(k_1+k_3)t} - \mathrm{e}^{-k_2 t}) \tag{7}$$

By the conservation of mass, the concentration of C can be found by difference:

$$[\mathrm{C}] = C_0 + A_0 + D_0 - [\mathrm{A}] - [\mathrm{B}] - [\mathrm{D}] \tag{8}$$

$$[\mathrm{C}] = C_0 + A_0 \left\{ (1 - \mathrm{e}^{-(k_1+k_3)t}) \left(1 - \frac{k_3}{k_1 + k_3} \right) - (\mathrm{e}^{-(k_1+K_3)t} - \mathrm{e}^{-k_2 t}) \left(\frac{k_1}{k_2 - (k_1 + k_3)} \right) \right\} \tag{9}$$

The four concentrations versus time can easily be plotted in a personal computer's spreadsheet by specifying initial concentrations and the three rate constants, and choosing appropriate time intervals. By changing any of the rate constants in the Model, instant visual feedback is obtained by graphing the predicted reaction profile versus the experimental data. Other useful equations from the Model include:

time at maximum [B]:

$$t_{\max[\mathrm{B}]} = \frac{\ln\left(\frac{k_2}{k_1 + k_3}\right)}{k_2 - (k_1 + k_3)} \tag{10}$$

if $(2k_1 + k_3) > k_2$, then [A] = [B] at

$$t_{[\mathrm{A}]=[\mathrm{B}]} = \frac{\ln\left(\frac{-k_1}{k_2 - 2k_1 - k_3}\right)}{k_2 - (k_1 + k_3)} \tag{11}$$

6. Kinetics of the One-Pot Pathway to 4. The one-pot process was run by adding a solution of **2** in toluene to a slurry of **1** in 1 N NaOH at about 41 °C. See Table 2 for the amounts added. By analyzing both the aqueous and toluene layers, the amounts of **2**, **4**, and **5** were determined. The product layer was quite clean by LC, with only three small unknown peaks totaling about 1 area %. The amount of insoluble intermediate **3** was determined indirectly by [**3**] = [total inorganic chloride] – [**5**] – [**4**]. From the rate of disappearance of acid chloride **2**, the first-order rate constant $k = (k_1 + k_3)$ could be determined as $k = 0.129$ min^{-1}, shown in Figure 7. Alternately, the formation rate of **5** gave $k = 0.119$ min^{-1} by evaluating the slope of ln(**2**$_{\text{final}}$ – **2**) versus time over the 0–21 min interval. Salt as the unreactive byproduct of both coupling and hydrolysis of **2** allows one to determine the formation rate of **3**, irrespective of the ring-closure reaction. Because **5** was determined and total salt was known, the total amount of **3** produced by coupling is [**3**] = [total inorganic chloride] – [**5**]. Plotting ln(**3**$_{\text{final}}$ – **3**) versus time at 0–21 min gave $k = 0.134$ min^{-1}. The variation in k values are likely a reflection of the different analytical determinations.

Since the ring-closure reaction went cleanly to completion, the final ratio of (**4**/**5**) gives the ratio of (k_1/k_3) = (22.9 mmol/10.7 mmol) = 2.14.[9] From $(k_1 + k_3) = 0.129$ min^{-1} and $(k_1/k_3) = 2.14$, solving yields $k_1 = 0.0879$ min^{-1} and $k_3 = 0.0411$ min^{-1}. Using the previously determined value of $k_2 = 0.26$ min^{-1}, the reaction profile by the kinetic Model can be overlaid onto the actual data. Figure 8 shows a reasonable fit. A better fit was obtained with k_1, k_2, k_3 = 0.11, 0.26, 0.05 min^{-1}, respectively. Inferences from the Model aid our understanding of the one-pot pathway:

- The reaction is essentially complete after 60 min at 41 °C. The common practice of adding **2** over 30–60 min and holding for another 60 min at 80 °C certainly ensures completion. Reactions at >40 °C are only necessary in more concentrated systems, where higher temperatures can ensure solubility of the product in the toluene layer and byproducts (especially **5**) in the aqueous layer. Fortunately, little product decomposition has been observed at 80 °C, and decomposition of **1** is manageable.

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[9] A similar reaction at 41 °C (sampled less frequently) gave [**4**/**5**]$_{240\text{nm}}$ = (27.9 mmol/5.62 mmol) = 4.96. From the disappearance of **2** over 15–45 m, the approximate rate constants were $k = 0.11$ min^{-1}, $k_1 = 0.092$ min^{-1}, and $k_3 = 0.018$ min^{-1}. This lower amount of hydrolysis was more typical of exploratory reactions. Experiments in a round-bottomed flask at 70–80 °C gave yields of 74–83% of **4** to the toluene layer when using 3 equiv of 1 N NaOH. This implies (k_1/k_3) = 2.9–4.9, assuming all yield loss was from hydrolysis of **2**. When using 3 equiv of 20% NaOH, yields were 94–95%, suggesting (k_1/k_3) = 16–19.

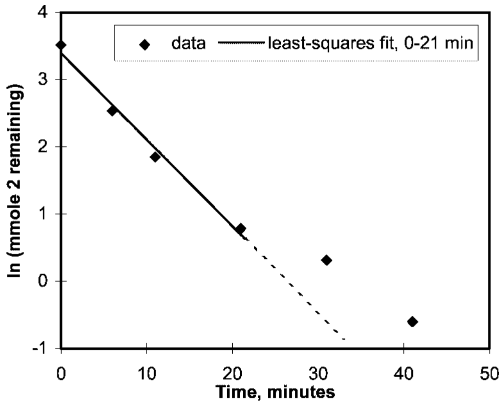

Figure 7. **Determination of the first-order rate constant $k = (k_1 + k_3)$ from the one-pot reaction at 41 °C in aqueous caustic/ toluene.**

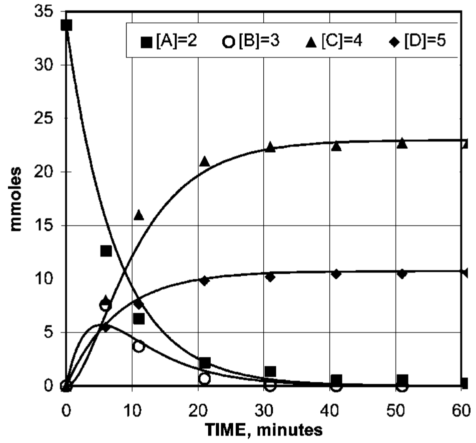

Figure 8. **One-Pot reaction to 4, at 41 °C in aqueous caustic/ toluene: overlay of kinetic model (lines) and experimental data (symbols).**

Table 2. **Laboratory reaction recipe for the kinetic evaluation of the one-pot procedure to prepare 4**

component	amount	molar ratio
1	4.02 g	1.00
toluene	400 mL	
1N NaOH	100 mL	
(NaOH)	(4.0 g)	2.96
(H_2O)	(100.1 g)	165
2	5.35 g	≡1

- The ring-closure reaction is over twice as fast as the coupling reaction, so substantial amounts of the insoluble intermediate **3** never build up. The Model shows that the maximum concentration of **3** is about 25% of the eventual total of product **4**. This assures that a heavy slurry in the two-phase liquid will never be present which allows the use of more concentrated reaction mixtures.[10] The original process, employing two consecutive reactions, was necessarily more dilute because a stoichiometric amount of fine, insoluble **3**, with its associated agitation problems, is present at the end of the first reaction.
- When the one-pot pathway is run at higher reactant loading, the reaction starts with a slurry of undissolved **1**. From $t_{\max[B]}$ in the Model, the maximum concentration of the insoluble intermediate occurs after about half of **2** has been reacted. With the maximum of 25% of **3** formed (solids), this again implies that a heavy slurry is not likely, but instead the reaction will become more dilute in solids as it proceeds.

Table 3. **Laboratory reaction recipe for the concentrated, rate-limited one-pot procedure to prepare 4**

component	amount	molar ratio
1	28.7 g	0.98
toluene	465 mL	
20% NaOH	138.8 g	
(NaOH)	(27.8 g)	2.84
(H_2O)	(111.0 g)	25.2
2	38.8g	≡1

7. Rate-Limited Kinetics (Continuous Addition of 2) for the One-Pot Pathway to 4. In practice, the one-pot pathway is run more concentrated at a higher temperature, with continuous addition of **2** over about 30 min. A compromise temperature of about 60 °C was chosen, half-way between the kinetic model experiment and the typical 80 °C reaction temperature. Table 3 shows the reaction charge. The liquids (except **2**) were preheated and poured to the jacketed straight wall reactor at 60 °C. **1** was added, and the contents were stirred for 20 min before continuously adding **2** over 27 min to initiate reaction. At 400 rpm, large aqueous layer droplets and undissolved solids of **1** were dispersed throughout the toluene phase. The reaction temperature was about 60–61 °C, although the initial exotherm[11] after 10 min raised the temperature to 62.5 °C, and overcompensation of cooling gave a minimum temperature of 57.5 °C, 20 min later. By sampling at 10 min intervals, the combined aqueous/toluene layer mass balance gives the reaction profile in Figure 9a and b. Note that the reaction proceeded in high yield to **4**, with much less hydrolysis of **2**. The ratio of **4**/**5** at 85 min was (227 mmol/10.9 mmol) = 20.8 and was typical for reactions charged with 3 equiv of 20% NaOH (see ref 9). Acid chloride **2** appeared to react as fast as it was added, because only a trace (about 0.1 mmol) was detected by LC in the 30- and 40-min samples. By changing to a linear addition rate of **2**, formation of products from **2** now follow a pseudo-zero-order mode. Over the first half of the reaction, however, a first-order plot of ln(mmol unreacted **2**) versus time can be approximated by a straight-line fit. Thus, reacting at the linear feed rate over the first half of the reaction would suggest that the apparent first-order rate constant is about 0.05 min^{-1}. See Figure 10.

We re-emphasize that $k = 0.05\ \text{min}^{-1}$ is a fictitious rate constant, which allows the first-order kinetic model to approximate the zero-order linear addition rate of **2** over the first half of the reaction. It is dependent upon the feed rate. The constant ($k = 0.05\ \text{min}^{-1}$) shows that the addition rate at 61 °C is much slower than the intrinsic first-order rate, estimated at $k \approx 0.52\ \text{min}^{-1}$ (by the rule-of-thumb doubling of the reaction

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(10) As mentioned, the relative kinetic rates are dependent upon agitation (droplet size, etc.) and mass transfer rates (particle size, dissolution rates, etc.).

(11) The heat of reaction for the coupling and neutralization (Scheme 11) was estimated as moderately exothermic (about −60 kcal/mol). The ring-closure reaction was estimated as mildly exothermic (about −2 kcal/mol). Calculated results were obtained using the computer program CHETAH, which predicts heats of reaction in the gaseous phase, and by data from analogous reactions.

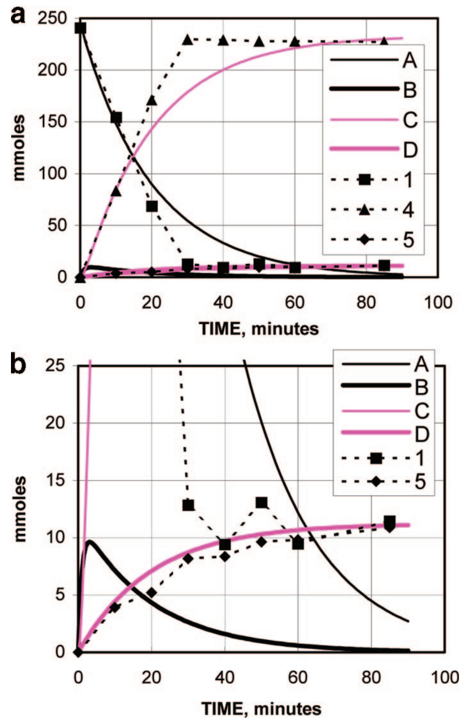

Figure 9. **(a) Rate-limited one-pot reaction at about 61 °C in aqueous caustic/toluene. Overlay of kinetic model (solid lines estimating the first half of the reaction, where compounds 2, 3, 4 and 5 are designated as A, B, C and D, respectively) and experimental data (dashed lines and symbols). (b) Expanded scale.**

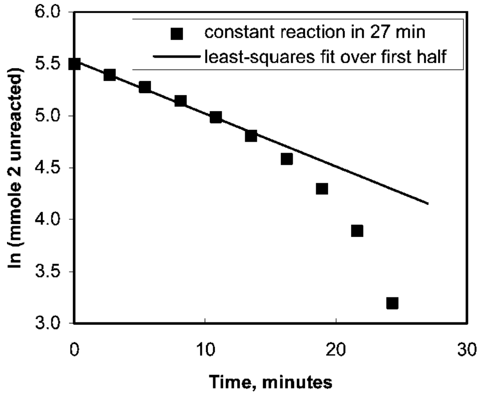

Figure 10. **Deviation from first-order kinetics for the one-pot reaction with a linear feed rate of 2.**

rate for each 10 °C increase, $k_{(61\,°C)} \approx 4 \times k_{(41\,°C)} = 4 \times 0.13 = 0.52\ \text{min}^{-1}$). Zero-order kinetics will govern, and **2** will react nearly as fast as it is added. Conversely, if **2** had been added in only 2 min instead of 27 min, the fictitious first-order rate constant would be calculated as $k = 0.65\ \text{min}^{-1}$, which suggests that first-order kinetics may be dominating (i.e., **2** is being added faster than it can react).

With these reservations, the first-order kinetic model can still be used as a predictive tool in estimating component concentrations at 0–50% conversion. The kinetic rate of the ring-closure reaction is unaffected by the addition rate of **2** and should be faster than the 0.26 min^{-1} rate at 41 °C (e.g., the rule-of-thumb doubling for each 10 °C increase). By approximating these rate constants as $k_2 = 4 \times 0.26 = 1.04\ \text{min}^{-1}$, $k = 0.05\ \text{min}^{-1}$, and $k_1/k_3 = 20.8$, the model should approximate the first half of the reaction and lag behind for the remainder. This determination (the model assumes that all of **2** was initially added and reacts at the given rate) is shown in Figure 9a. One point that the model clearly illustrates is that by continuously adding **2**, the maximum amount of intermediate **3** formed is substantially less, shown in Figure 9b, and occurs after only about 15% of **1** has reacted. The coupling reaction produces **3** at a slow rate (by the limited addition rate of **2**), while the ring-closure reaction is relatively fast. The maximum intermediate amount is only 4% of the eventual total of **4** formed.

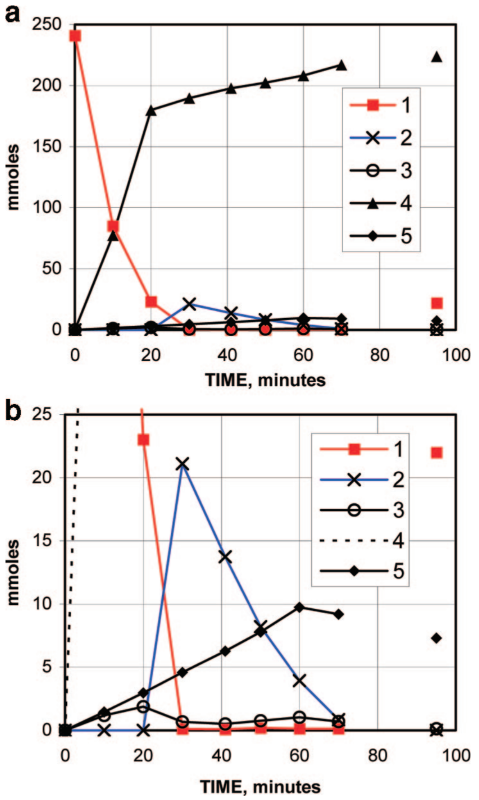

Figure 11. **(a) Rate-limited one-pot reaction with poor agitation, at about 60–65 °C in aqueous caustic/toluene: combined aqueous/toluene layer analyses (neglects solids at wall, 10–70 min). (b) Expanded scale.**

8. Rate-Limited Kinetics (Continuous Addition of 2) for the One-Pot Pathway to 4 under Conditions of Poor Mixing. The reaction in Part 7 (same feed amounts as Table 3) was repeated, but intentionally with poor agitation by reducing the stirring rate from 400 to 200 rpm. Before adding **2**, the interface between the swirling bottom aqueous layer and the top toluene layer was evident. Most of the undissolved **1** lies just above the liquid interface, although some fines were suspended to make a weak slurry throughout the toluene layer. Six minutes after starting the addition of **2** (dropwise addition to the toluene layer), the temperature had increased to 65 °C and solids coated the vessel wall of the toluene layer. After about 20 min, the acid chloride **2** feed pump malfunctioned after adding three-fourths of the charge. The remaining one-fourth was added all at once at about 23 min. The vessel was sampled at 10 min intervals for 70 min. Because the solids still coated the wall in the toluene layer after 90 min, the contents were then well mixed at 400 rpm before ending the experiment 5 min later. Figure 11a and b shows the reaction profile. A

Table 4. **Comparison of well-mixed and poorly mixed reactions for the one-pot pathway to 4**

	from Figure 9		from Figure 10	
mixing	good	good	poor	good
sample after	60 min	85 min	70 min	95 min
% yield to **4**[a]	93.9	94.3	90.0	92.9
% **5** formed[b]	4.0	4.5	3.8	3.0
ratio [**4**/**5**]	23.2	20.8	23.6	30.7

[a] Mol % based on **1** charged. [b] Mol % based on **2** charged.

Table 5. **Pilot Plant reaction recipe for the concentrated, rate-limited one-pot procedure to prepare 4**

component	amount	molar ratio
1	5.44 kg	0.99
Toluene	91.6 L	
18.6% NaOH		
(NaOH)	(5.44 kg)	2.94
(H_2O)	(23.9 kg)	28.6
2	7.35 kg	≡1

good yield of **4** was still produced, 90.0% of the theoretical amount (at 70 min). Note also over the 30- to 70-min interval the slow disappearance of **2** and formation of **4** and **5**. Solids taken from the wall at the 10-min sample were dried and indicated a composition of about 24 wt % **1**, 31 wt % **3**, 7.3 wt % **4**, 6 wt % unknowns, and perhaps 32 wt % salt (by difference from 100% LC accountability).

The following scenario may explain the results. Coupling of **1** and **2** occurred in the upper toluene layer to form insoluble intermediate **3** and byproduct salt or perhaps also hydrochloride salts. Amine **1** is apparently basic enough itself such that caustic is not even needed to cause coupling. The reaction products and some soluble **1** in the toluene layer then formed a rind on the cold vessel wall as the reaction exotherm warmed the toluene layer. Contact of the solid intermediate **3** with the aqueous layer allowed the ring-closure reaction to proceed, except for intermediate coating the wall. The last 12% of product (over 30–70 min) was formed slowly, perhaps limited by dissolution of **1** off the vessel wall or by transfer across the aqueous/toluene layer interface. By increasing agitation at the end, contact of the rind with the aqueous layer allowed dissolution of the salt and contact of **3** with caustic for the transformation to **4**. Table 4 compares this reaction to the previous well-mixed one.

The uncatalyzed coupling reaction (without NaOH added) was verified by reacting **1** and **2** in toluene/water at about 80 °C.[12] The solids from the reaction were filtered and found to be composed of 99.0% of **3**, 0.50% of **1**, and 0.46% of **4**. The overall yield to **3** was 78%.

9. Scale-Up of the One-Pot Pathway to 4 in 50-gal Equipment. The one-pot process was run in our Pilot Plant, in a 50-gal vessel using the concentrated recipe in Table 5. Sampling of the toluene layer revealed that yields to **4** were about 92–95% and indicated $k_1/k_3 = 16–25$. The toluene layer was vacuum distilled to remove most of the solvent. 2-Propanol was added, and the product was crystallized, yielding 24.5 kg from three batches in 80.2% overall isolated yield from **1**, the limiting reagent. See Table 6. The low isolated yield of batch 1 was attributed to poor execution of the phase separation, wherein some of the product toluene layer was discarded with the aqueous layer.

Experimental Section

The following raw materials were used in the kinetic studies: amine **1** was supplied by Hoechst Marion Roussel and was the same material used in the Pilot Plant campaign. However, the decomposition study of **1** used freshly synthesized material. Acid chloride **2** was also material used in the Pilot Plant campaign, manufactured by Hoechst. Benzamide **3** was produced in-house, and purity by LC was >99.5 area %, with 0.1 area % **4**. For molar calculations, a 100% assay was assumed for all materials. Other common reagents included toluene (Fisher Scientific, ACS grade), 0.995–1.005 N NaOH (Fisher Scientific, certified), and 20% NaOH (Red Bird Service, reagent grade).

General Kinetic Study Procedure. A nominal 1-L jacketed straight-wall reactor with a bottom drain valve was most often used for the kinetic experiments. The vessel i.d. was about 3.9 in., and the height from the bottom to the ground glass joint was about 5.5 in. The openings in the vessel head, near the perimeter and 120° apart, were fitted with a thermowell, a 0.5-in.-wide baffle, and a Claisen adapter to a nitrogen purge and a condenser. The agitator consisted of a three-tiered configuration of four-bladed impellers, 2.5 in. in diameter. The bottom two were pitched 45° to pump downward, while the top impeller blades were mounted flush for radial flow. The unagitated volume required to successively submerge each impeller was 50, 330, and 500 mL. For experiments with a constant addition of **2**, a piston pump with 0.125-in. o.d. poly(tetrafluoroethylene) tubing was used. The tubing was routed through the condenser opening and gave a dropwise addition to the liquid surface. An immersion heater with a built-in pump circulated "constant-temperature" water from a 7-L insulated reservoir, through the vessel jacket, and back to the reservoir.

The most common sampling procedure involved removing the thermowell and withdrawing about 5–8 mL of the agitated reaction mixture with a pipet to a sample vial. Vials and pipets were taken from an oven at about the temperature of the study. Upon momentary phase separation in the vial, portions of each layer were removed to separate vials. Methanol was immediately added to the toluene layer sample to convert unreacted **2** to its methyl ester for LC analysis. Further dilution with mobile phase (acetonitrile/water/2 M sodium dihydrogen phosphate = 25.0/72.5/2.5, v/v/v) and LC injection were done as soon as practical for analysis on a Supelcosil LC-18-DP column (Supelco, Inc.). A gradient elution profile was used, and known compounds were standardized by an external standard method. Aqueous layers were analyzed by LC and ion chromatography.

The study for the decomposition of **1** used a 500-mL flask, heated with a mantle and mixed with a magnetic stirring bar. The flask was equipped with a thermometer, condenser, and nitrogen bubbler.

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(12) To a mixture of 3.70 g of **1**, 62 mL of toluene, and 15 mL of deionized water in a stirred, 100-mL flask was added 5.1 g of **2** over 10 min at 80–88 °C. After 2.2 h at about 80 °C, the mixture was cooled and filtered. The solids were washed with 2-propanol and dried to give 5.9 g of fine, white crystals.

Table 6. **Scale-up of the one-pot procedure in a 50-gal vessel**

			4	
batch	molar ratio [**4**/**5**] after reaction	% yield of **4** (from **1**) in toluene layer	isolated (dry product), kg	% isolated yield (from **1**) of **4**
1	24.6	95.0	7.38	72.4[a]
2	15.6	91.8	8.66	85.0
3	23.0	94.1	8.48	83.2

[a] Approximately 82%, when corrected for product loss during phase cut.

General Scale-Up Procedure. The reaction and crystallization were conducted in a jacketed 50-gal glass-lined vessel using reactant loading as in Table 5. The vessel was baffled with a radial-flow (retreat-curve) impeller located near the bottom and had demonstrated good mixing of toluene/water phases. The general procedure involved adding toluene and **1**, heating to 50 °C, followed by the addition of the caustic solution and heating to 80 °C. Acid chloride **2** was added over about 45 min at 78–84 °C, and the contents were held at about 80 °C for another 60 min. The contents were cooled to 50 °C and sampled. The bottom aqueous layer was decanted, and the remaining organic layer was washed with water (40 kg) and decanted. The washed toluene layer was vacuum distilled to remove most of the solvent, 2-propanol was added, and the product was dissolved and polish filtered at 70–75 °C. Product **4** was crystallized by cooling, centrifuged, washed, and dried, producing a total of 24.5 kg from three batches in 80.2% overall isolated yield from **1**. See Table 6.

Conclusion

A kinetic model for the combination of consecutive and parallel first-order reactions was developed to provide a fundamental understanding of component concentrations with time. Experimental data were generated to investigate the relative importance of each reaction pathway in Scheme 1. Because the system is multiphase, the kinetic model can not be extrapolated to systems where the agitation results in defferent interfacial areas from those used in this study.

The k_4 decomposition rate is at least an order of magnitude smaller than k_1 and k_3, so loss of **1** during reaction is not a great concern. The ratio of the undesired hydrolysis of **2** to coupling (k_3/k_1) was affected by caustic strength. The amount of **5** was reduced from 17% to 32% (based upon **2** fed) to 4–5% by using 20% NaOH instead of 3.8% NaOH. The rate of the ring-closure reaction (k_2) is more than twice as fast as the coupling reaction (k_1), and this prevents significant quantities of the insoluble intermediate **3** from being present. The maximum amount of **3**, about 25% in a batch reaction, occurs after about half of **2** has been reacted. In practice, the reaction is run more concentrated at 80 °C, with the continuous addition of **2** to control the reaction exotherm as it reacts almost instantaneously. The added benefit of this procedure is that whereas k_1 is kinetically limited by the reactant feed rate, k_2 is not. Though **3** is not easily quantified under reaction conditions, the model predicts that this reduces the amount of insoluble benzamide **3** even more and belies concern for poor agitation from thick slurries. Under conditions of poor mixing, the reaction products can form a rind on the vessel wall, causing potential loss of cooling capacity. The one-pot procedure was successfully scaled up in a 50-gal vessel to yield **4** in >92% yield. After crystallization, three batches produced 24.5 kg of product **4** in 80% overall yield from **1**.

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