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Continuous Synthesis of an Intermediate of Quinolone Antibiotic Drug Using Static Mixers

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Abstract:

In-line static mixer technology was employed in a continuous synthesis of a pharmaceutical intermediate of new quinolone antibiotics. The reaction of interest is the protection of amine with *t*-Boc, and it is characterized by a fast rate and relatively high exothermicity. The heat generated from the reaction can alter the reaction pathway or destroy the structure of the products. Reaction kinetics were derived from a series of batch measurements of heat flows using an RC1 reaction calorimeter. Results showed that the heat generated from the reaction initiated a mechanism for byproduct formation, and efficient mixing and heat removal with the static mixer led to reduced byproduct formation and promoted a high yield. On the basis of the reaction kinetics, a simple plug-flow reactor model was developed for this system.

Introduction

Bulk manufacturing of active pharmaceutical ingredients or their intermediates covers a broad range of modern organic chemistry. Production of fine chemicals is generally carried out in batch processes because they are typically high value-added, small-volume products. Batch processes have many advantages over continuous processes, such as simplicity in operation, flexibility for various kinds of products, and so forth. However, they also have some disadvantages, such as: difficulties in precise control of the reaction temperature as the scale increases, the requirement for good mixing devices, and so forth.

Recently, the concept of process intensification has been applied to such processes for the improvement of product quality, throughput, and energy efficiency. According to Stankiewicz and Moulijn,[1] process intensification requires the development of unique apparatus and techniques. These, compared to those commonly used today, are expected to bring dramatic improvements in manufacturing and processing, substantially decreasing the equipment size/production-capacity ratio, energy consumption, or waste production, and ultimately resulting in less expensive, sustainable technologies. One of the benefits obtainable through process intensification can be the cost-effective improvement in heat and mass transfer. Replacement of a batch reaction with a continuous-process reaction using a plug-flow reactor equipped with an in-line static mixer is a good example of process intensification.

Static mixers are simple and versatile pieces of equipment commonly used for process intensification. They have good mixing characteristics, and since they have no moving parts, they can save capital and operating costs. Usually they are designed to disperse and mix two or more fluids in a short length of tube. Improved transport processes occurring in the static mixer such as flow division, radial eddying, flow constriction, and shear reversal eliminate the gradients in concentration, velocity, and temperature. One example of an effective static mixer application is found in the area of rapid, exothermic, multiple reactions[2−4] and in a recent publication on “intensified plug-flow reactor” for synthesis of a pharmaceutical intermediate.[5]

To scale-up a chemical reaction in a continuous process, it is important to measure kinetic data for the reaction desired. Reaction calorimetry is one of the tools for calculation of kinetic data through the measurement of reaction heat generated during the reaction. The measured heat flow is converted into reaction conversions, which are plotted against time to allow determination of a summary rate law. Although this method has some limitations for describing complex reaction mechanisms, the information drawn from such an analysis can provide reliable and valuable data for a first-order reaction model.

In this study, an addition reaction of *t*-Boc (*tert*-butoxy carbonyl) to an amine group in compound **1** to produce compound **2**, which is an intermediate for a new quinolone antibiotic drug, Factive, was investigated to determine optimum operating conditions for higher yields of compound **2** with a Kenics-type in-line static mixer.

Experimental Section

4-(*N*-*tert*-Butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one (**1**) was obtained from Korea Fine Chemical Co. (Korea). Potassium hydroxide (KOH) (85%, Junsei), isopropyl alcohol (99%, Aldrich), di-*tert*-butyl dicarbonate (97%, Sigma) were used without further purification.

1-(N-*tert*-Butoxycarbonyl)-4-(*N*-*tert*-butoxycarbonyl)-aminomethylene-pyrrolidin-3-one (2). 4-(*N*-*tert*-butoxycarbonyl)-4-aminomethylene-pyrrolidine-3-one (**1**) (61.6 g, 290 mmol) was dissolved in isopropyl alcohol (IPA) (338.4 g, 81.8% solution in water), then di-*tert*-butyl dicarbonate (*t*-Boc$_2$O) (76 g, 348 mmol) was added. In a batch reaction,

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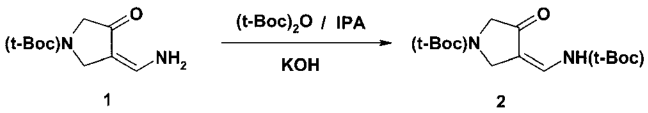

Figure 1. **Reaction scheme.**

the mixture was cooled or heated to the desired temperature. KOH (50% solution in water) was then added all at once to the mixture. This reaction requires proper mixing due to the immiscibility of aqueous KOH with *t*-Boc$_2$O in isopropyl alcohol. In the model reaction shown in Figure 1, aqueous KOH is used to deprotonate the amine, and *t*-Boc$_2$O is used for the protection of amine functionality.[6] Chromatography was carried out on a Waters 2690 HPLC system equipped with a Waters 996 photodiode array detector (Waters, MA). The Capcell-pak C18 (4.6 mm i.d. × 250 mm, particle size: 5 μm, Shiseido, Japan) HPLC column was used for the analysis. The mobile phase was prepared by mixing 500 mL of acetonitrile with 500 mL of water. All measurements were taken with a 1.2 mL/min mobile phase flow rate at a wavelength of 300 nm. Data integration was performed with Millennium software. For **2**: ^{1}H NMR (CDCl$_3$, δ, ppm) 10.10 (s, 1H), 7.30 (s, 1H), 4.40 (d, 2H), 3.95 (d, 2H), 1.55 (m, 18H). MS (FAB, *m*/*e*): 313 (M + H).

Reaction Calorimetry. The reaction was carried out in an RC1 reaction calorimeter (Mettler-Toledo) to study the reaction kinetics by measuring heat flows. The jacket temperature was controlled to maintain the reactor contents at the constant temperature of 0 °C. A propeller-type stirrer was used at 700 rpm in a 2-L AP01 glass reactor (Mettler-Toledo). The calorimeter can measure the heat of reaction and the rate of heat generation, the specific heat of reaction mass, and the overall heat-transfer coefficient. The measured heat flow was converted to degree of conversion as a function of time using the following relation:

$$X(t) = \frac{\int_0^t q_r \, dt}{\int_0^\infty q_r \, dt} \tag{1}$$

From the resulting conversion versus time plot the kinetic parameters were then calculated.[7] Pseudo-first-order rate constants were obtained from the heat generation rate data, since the changes in heat flow during the isothermal period are proportional to the changes in the reaction rate.[7,8]

Continuous Plug-Flow Reactor. Five straight tubes equipped with Kenics in-line static mixers were connected in series to serve as a continuous plug-flow reactor. Each reactor tube unit has 27 Kenics elements, and the tube dimensions are 19 cm in length and 3.3 mm in inner diameter (OD 3/16 in). A Kenics mixer is composed of a series of alternating right- or left-handed twisted mixing elements arranged axially within a tube. Each element is a plate with a 180° helical twist. The leading edge of each element is located 90° to the trailing edge of the preceding element. As the fluids pass through each element, they are divided by half since each successive element is offset by 90°. The series of alternating right- or left-handed helical structures improves radial mixing by giving the fluid element radial momentum, since the twisted structure directs the flow of material radially toward the tube walls and back to the center. This mixing eliminates radial gradients in temperature, velocity, and material composition.

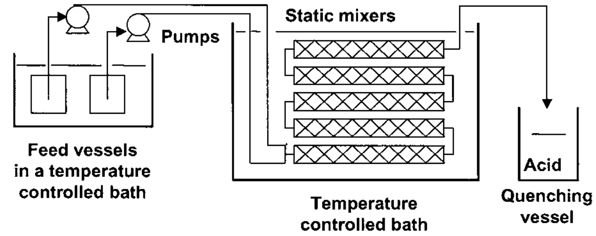

Figure 2. **Schematic diagram of the static mixer reactor.**

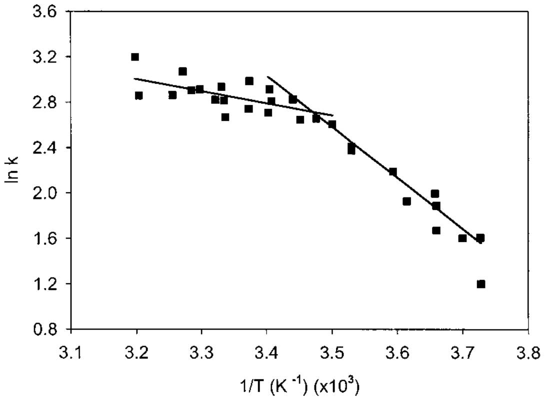

Figure 3. **Temperature dependency of the reaction rate.**

The reactor was immersed in a temperature-controlled bath as shown in Figure 2. Two peristaltic pumps, that is, Masterflex L/S tubing pumps equipped with an Easy-load pump head, were used to pump the two reactants with a total flow rate above 20 mL/min. Flows below 20 mL/min were controlled using diaphragm-type HPLC pumps. One feed consisted of compound 1 in IPA and *t*-Boc$_2$O as described above. The other feed was KOH (50% solution in water). The two feeds were pumped such that they mixed first in a union T-tube fitting (3/16 in o.d., Swagelok), which was directly connected to the static mixer, and then flowed through the reactor tube. The product mixture was discharged from the final reactor tube into acid quench, and samples were taken for HPLC analysis. Note that the two reactants were immiscible, which is another reason for the use of an in-line static mixer.

Results and Discussion

Reaction Kinetics. For the model reaction in Figure 1, the temperature dependence of the rate constants was studied in the range of −5 to 40 °C, under the assumption of a psseudo-first-order reaction with respect to the compound **1** as shown in eq 2. Figure 3 shows an Arrhenius plot for the *tert*-butoxycarbonylation reaction of amine group in the compound **1**. The data can be grouped into two groups when

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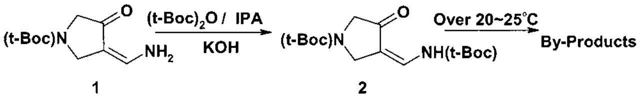

Figure 4. **Possible reaction scheme resulting from the kinetic study.**

the logarithm of the rate constant k is plotted against the inverse of temperature. With the boundary of 20−25 °C there is a clear distinction between the slopes of the two regression curves, which denotes a shift in the mechanism of the reaction. According to the literature,[9] the controlling mechanism can be shifted to a parallel or series path when the activation energy changes with temperature. As shown in Figure 3, the drop in activation energy with increasing reaction temperature indicates that the controlling mechanism has shifted to another elementary step in the series, leading to byproduct formation (Figure 4).[9] In batch experiments, byproducts increased rapidly when the reaction temperature exceeded 25 °C. The measured frequency factors and the activation energies for the production of **2** were 9.1×10^7 min^{-1} and 3.74×10^4 J/mol ($R^2 = 0.91$), respectively. For the byproduct formation steps, 6.6×10^2 min^{-1} and 8.82×10^3 J/mol ($R^2 = 0.49$) were observed.

The reaction is exothermic, of which the heat of reaction was −213.2 kJ/mol.[5] The adiabatic temperature rise was estimated to be 33 °C. This implies that the heat generated during the reaction is sufficient to raise the reaction temperature above 20 °C even if the initial temperature is below zero, which then could initiate the formation of byproducts. The enamine ketone and compound **2** will undergo base hydrolysis to produce the corresponding enol, and this can lead to the formation of uncharacterized oligomers. This tendency may become more pronounced as the reactor scale increases since temperature control becomes more difficult. It is well-known that the volume and the heat generated from an exothermic reaction increase as the cube of the reactor dimension, while the heat transfer through the external surface increases only as the square. A significant yield reduction caused by increased byproducts was observed when a commercial-scale batch production was performed.

Continuous Process. A Kenics static mixer reactor was employed to overcome the heat-transfer limitation of the batch reactor. The effects of residence time on product yield were investigated by changing the flow rate and reaction volume (Figure 5). The highest yield was achieved when the residence time was longer than 10 min or shorter than 10 s. A CFD (computational fluid dynamics) study on the Kenics mixer shows that effective chaotic mixing is achieved for creeping flow condition (i.e., longer residence time) and turbulent flow conditions (i.e., shorter residence time).[10] The study also shows an improper mixing in laminar flow for ranges near creeping flow conditions.[10] The experimental results shown in Figure 5 indicate that a high yield comparable to a maximum was achieved in the creeping flow region where the residence time was over 10 min. The yield of the reaction gradually falls as the residence time decreases, reaching a minimum. When the residence time is between 0.4 and 0.5 min, the reaction yield is very sensitive to the residence time. A possible explanation for this phenomenon is that the immiscible two-phase flow may not be dispersed well enough into each other in this flow regime, resulting in decreases in mass transfer and conversion of the reactant. When the residence time was less than 0.2 min, the yield reached 96% again. The best reaction yield could be achieved at the flow rate of 100 ± 40 mL/min in this experimental scale (residence time, 0.08−0.2 min).

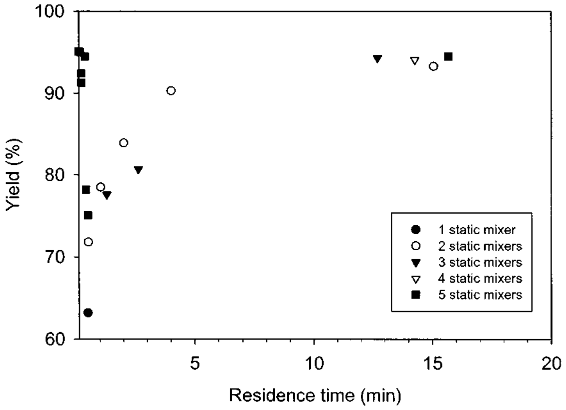

Figure 5. **Determination of the operating condition with the static mixer reactor.**

According to a study on residence time distribution for the Kenics static mixer, it is the number of elements of the Kenics static mixer that has the most significant effect on the mixing efficiency.[11] In this experiment, a total of 135 Kenics static mixer elements were used, which is sufficient to assume a radially flat profile in axial velocity, that is, a characteristic of plug flow.

Modelling. A simple plug-flow reactor model was applied to the Kenics static mixer reactor where the residence time is shorter than 0.2 min in Figure 5. The material and energy balances for a PFR can be described as follows:

$$r_A = k_1 C_{A0}(1 - X_A) \tag{2}$$

$$\frac{dX_A}{dz} = \frac{A}{F_{A0}}(-r_A) \tag{3}$$

$$\dot{m}C_P \frac{dT}{dz} = F_{A0}(-\Delta H)\frac{dX_A}{dz} - \pi U d_t (T - T_r) \tag{4}$$

$$k_1 = k_0 \exp\left(-\frac{E_a}{RT}\right) \tag{5}$$

Kinetic parameters, k_0 and E_a were calculated to be 9.1×10^7 min^{-1}, 3.74×10^4 J/mol respectively as discussed above. The heat capacity of reaction fluid was determined to be 2.6 J/g K using a RC1 reaction calorimeter. The overall heat-transfer coefficient, U was estimated by the following heat balance eq 6.

$$\dot{m}C_P(T_i - T_o) = UA(\Delta T_{m\,ln} - T_j) \tag{6}$$

The inlet and outlet temperatures were measured at steady

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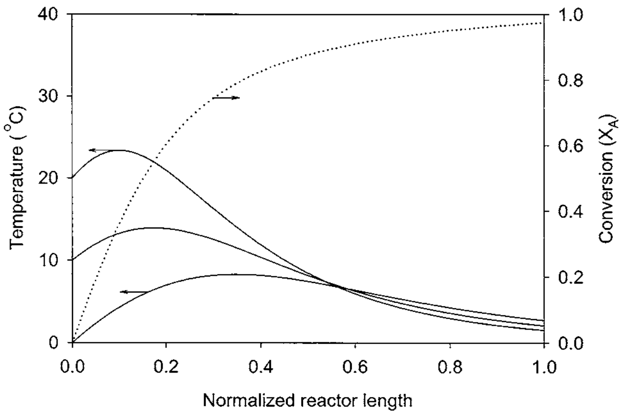

Figure 6. **Temperature profile in the static mixer reactor with various inlet temperatures. (—) Temperature profile in the static mixer for bath temperature = 0 °C. (···) Conversion (X_A) (yield equals conversion since the selectivity is 1); the reactor length was normalized on the basis of the total reactor length.**

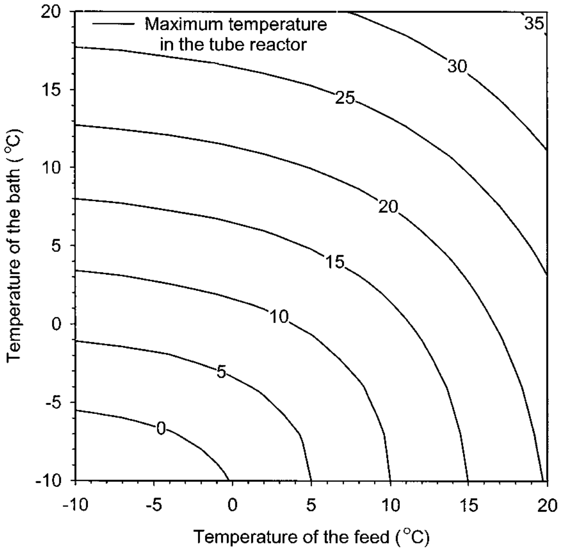

Figure 7. **Determination of a maximum temperature inside the static mixer reactor.**

state, while the flow rate of water and the heat-transfer unit temperature were 60 mL/min and 0 °C, respectively. In this experiment, the overall heat-transfer coefficient was 367 W/m^2 K.

The above PFR model can describe the evolution of the reactive mixture composition and the temperature profile along the reactor length. Figure 6 shows such an evolution, when the reactor wall temperature was set at 0 °C and the feed temperature was varied from 0 to 20 °C. The temperature profile shows that the maximum temperature develops closer to the reactor inlet, and the temperature rise from the initial feed temperature becomes smaller as the feed temperature increases. The former is because the higher feed temperature and higher concentration gradients promote the reaction rate, while the latter is due to the higher temperature difference between the feed and reactor wall.

To avoid the formation of byproducts, the feed temperature and the wall temperature of the static mixer should be determined to maintain the maximum temperature inside the static mixer below 25 °C. The maximum temperature inside the static mixer was predicted by the PFR model equation. Figure 7 shows a contour plot of a maximum temperature inside the static mixer as a function of the feed and bath temperatures. For example, an experiment was conducted with feed temperature and bath temperature of 20 and 0 °C, respectively, to achieve a maximum temperature of 23 °C from the contour plot shown in Figure 7. The model can be used as a tool for predicting the maximum temperature inside the static mixer reactor to prevent byproduct formation.

Conclusions

For a fast, exothermic reaction, the kinetics were analyzed using calorimetric measurements. The kinetic study revealed that byproducts were formed with a mode of series reaction when the reaction temperature increased over a certain value, 20−25 °C. The exothermic reaction behavior stimulated the use of a continuous plug-flow reactor equipped with Kenics in-line static mixers. On the basis of kinetic analysis and experiments using the continuous reactor, a simple model for a plug-flow reactor has been developed. The model produced a guideline for selecting bath and feed temperatures in order to control the reaction temperature. With this continuous reactor, a high yield of 97% was reached at a flow rate of 100 mL/min without byproducts, when the feed temperature and the mixer wall temperature were set at 20 and 0 °C, respectively.

NOMENCLATURE

A	cross sectional area (cm^2)
C	concentration (mol/ml)
C_P	specific heat capacity (J/g K)
d_t	tube outside diameter (cm)
E_a	activation energy (J/mol)
F_0 mole	flow rate (mole/min)
ΔH	heat of reaction (J/mol)
k	rate constant (min^{-1})
k_0	frequency factor (min^{-1})
$\dot{m}$	mass flow rate (g/min)
q_r	heat flow rate (W)
r_A	rate of reaction (mol/ml min)
T	temperature (K)
T_r	reactor wall temperature (K)
U	heat transfer coefficient (W/m^2 K)
X_A	fractional conversion of compound **1** (−)
z	reactor length (cm)

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