Kinetic Study of the Microflow Synthesis of 4-Hydroxyquinoline in Supercritical Ethanol

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Abstract

Supercritical ethanol was used as a solvent for the thermal cyclization of ethyl 3-(phenylimino)-butanoate to 2-methyl-4-hydroxyquinoline; the reaction is of great importance in pharmaceutical and color industries but conventionally needs specific solvents with high boiling points. The mechanism and the kinetics were studied with a microreactor by measuring the yield of the product at various temperatures up to 350 °C. The reaction in ethanol completed in 27 s at 350 °C and 10.0 MPa giving the quinoline in 97% GC yield, although it required higher temperature than that in acetonitrile. The results were explained by the mechanism consisting of the two steps: (i) a reversible elimination of ethanol from the reactant yielding ketene intermediate followed by (ii) an irreversible ring closure into the quinoline. On the basis of the reaction mechanism, the rate constant and the activation energy were determined from the yield-time profiles measured at temperatures of 300 to 350 °C and a constant ethanol density of 0.11 g cm⁻³. The kinetic analysis revealed that the overall reaction is controlled by a pseudo-first-order rate constant. The activation energy was determined to be 204 ± 2 kJ mol⁻¹, which was close to that calculated by density functional theory (187 kJ mol⁻¹).

Keywords: supercritical alcohol; the Conrad-Limpach thermal cyclization; high-temperature and high-pressure microreactor; pseudo-first-order rate constant; activation energy; density functional theory (DFT) calculation

1. Introduction

4-Hydroxyquinolines are important building blocks for the productions of pharmaceuticals and color chemicals, e.g., mefloquine antimalarials and quinacridone pigments [1-3]. The quinoline ring structure is usually synthesized by the Conrad-Limpach reaction illustrated in Fig. 1 [4]. A condensation of aniline **1** with ethyl acetoacetate **2** provides ethyl 3-(phenylimino)butanoate **3** [5] and the thermal cyclization of **3** gives 4-hydroxyquinoline **4** with an elimination of an equimolar amount of ethanol [6]. However, the thermal cyclization needs very high temperature above 250 °C and thus conventionally requires (i) specific solvents with high boiling points such as diphenyl ether and (ii) long heat-up time to reach the reaction temperature, often leading to undesired side reactions [7]. In the present study, we use supercritical ethanol ($T_c = 241$ °C, $P_c = 6.1$ MPa, and $\rho_c = 0.276$ g cm⁻³) as an alternative solvent for the thermal cyclization and elucidate the reaction mechanism and kinetics using a microreactor.

Microreactor designed for the high-temperature and high-pressure solvent is a powerful tool in controlling the thermal reactions [8-13]. High-pressure condition allows us to use common solvents above their normal boiling points, thereby extending the choices of solvent and temperature; e.g., sub- and supercritical water [14-17] and alcohols [18-20] have been used as environmentally benign alternative solvents for many organic reactions. Microtube reactor enables a rapid heating of the reactant solution to the high reaction temperature and a precise control of the reaction time by changing the reactor length. Recently, Lengyel, et al. applied a microreactor to the Conrad-Limpach thermal cyclization and performed the reaction in supercritical tetrahydrofuran (THF; $T_c = 267$ °C and $P_c = 5.1$ MPa) [21]. They reported that the reaction in THF completed within 45 s at 360 – 370 °C and 13.0 MPa giving the target quinoline in 92% isolated yield.

Here we try the thermal cyclization in supercritical ethanol. The use of ethanol as the solvent is apparently inappropriate because the reaction involves an elimination of ethanol from the reactant. The elimination of ethanol may be hindered by the surrounding abundant ethanol. In fact, several papers

suggest that ethanol should be removed from the reactor, although it is difficult for the closed-vessel reactions, in order to avoid the equilibrium shift toward the reactant [22-24]. We show, however, that the reaction can provide a complete conversion within 27 s even in supercritical ethanol at 350 °C and an almost quantitative yield of the target quinoline. The surprising result is explained by the reaction mechanism assuming that the elimination of ethanol is reversible but is followed by an irreversible ring closure. We further demonstrate that the reaction in supercritical ethanol offers a clean and simple reaction system suited not only for easy solvent recycling but also for detailed kinetic analysis and reaction control.

In this paper, the thermal cyclization in ethanol is studied over a wide range of temperature from the subcritical to the supercritical conditions and is compared with that in acetonitrile to clarify the reaction mechanism. The kinetic analysis is also carried out on the basis of the reaction mechanism. The yield-time profile is systematically investigated at various temperatures of 300 to 350 °C and a fixed ethanol density. We show that the overall reaction kinetics is controlled simply by a pseudo-first-order rate constant with an activation energy. **The activation energy experimentally determined is compared with that calculated by density functional theory to support the mechanistic and kinetic analyses.**

2. Experimental and computational methods

2.1. Reagents

The two solvents, acetonitrile (Wako, 99.5%) and ethanol (Wako, 99.5%), were used as purchased. The reactant of the thermal cyclization, ethyl 3-(phenylimino)butanoate **3**, was synthesized according to the literature procedure [5] by the condensation of aniline **1** (Wako, 99%) with ethyl acetoacetate **2** (Wako, 98%) in the presence of acetic acid (Wako, 99.7%) as an acid catalyst and was identified by GC-MS analysis (m/z = 205, 160, 144, 132, 118, and 77) using an authentic sample (Avocado, 97%). The crude **3** was purified by evaporating the remaining **1**, **2**, acetic acid, and water at

120 °C under reduced pressure in a vacuum oven (Yamato DP33) until the GC purity exceeded 99%. The purified **3** was dissolved in the solvent at the concentration of 50 mmol dm⁻³ and was used as the reactant solution of the microflow experiment. 2-Methyl-4-hydroxyquinoline **4** (Aldrich, 98.5%) was used as an authentic sample to identify the main product of the microflow reaction by GC-MS analysis (m/z = 159 and 130).

2.2. Apparatus

A schematic diagram of the high-temperature and high-pressure microreactor is shown in Fig. 2a. The reactant solution was dispensed with an HPLC pump A (Shodex DS-4) at a constant flow rate of 0.50 cm³ min⁻¹ and was rapidly heated to the reaction temperature by mixing with preheated solvent. The mixing was performed in a low-dead-volume T-shaped micromixer (Swagelok SS-1F0-3GC, 0.3 mm i.d.). The solvent was supplied from another HPLC pump B at a constant flow rate of 2.0 cm³ min⁻¹ and was heated by a preheater. The preheater was composed of a cartridge heater (Hakko HLD1404, 3/8 inch o.d., 130 mm length, 25 Ω) and a SUS316 stainless steel tube (1/16 inch o.d., 0.5 mm i.d., 2.7 m length) coiled around the heater.

The heated solution passed through a microtube reactor made of SUS316 stainless steel (1/16 inch o.d., 1.0 mm i.d., 2.0 to 10.0 m length). The temperature of the solution entering into the reactor and that exiting from the reactor were monitored with the two sheathed thermocouples (Chino, 1/16 inch o.d.) T1 and T2, respectively. Each thermocouple was installed in an originally designed low-dead-volume tee (Taiatsu Techno), as described in Fig. 2b, to form a flow-through temperature probe unit. The micromixer, the microreactor, and the temperature probe units were heated in a thermostated GC oven (Shimadzu GC-8A). The temperatures of the solution, T1 and T2, were controlled to the reaction temperature (150 to 350 °C) within a deviation of 1 °C by adjusting the temperature of the preheater T3 and that of the GC oven T4.

After a given residence time, the solution was rapidly cooled down in a double-tube water cooler to quench the reaction and then was depressurized through a back-pressure regulator (JASCO, 880-81). The pressure of the reactant solution and that of the pure solvent were monitored by strain gauges P1 and P2 (Kyowa Electronics Instruments, PG-500KU), respectively. The pressure of the solution after the reaction was measured by a pressure gauge P3 attached to the back-pressure regulator. The pressures were controlled to the target pressure (8.2 to 10.0 MPa) within a deviation of 0.1 MPa. Stop valves SV1 to SV3 were used for the leak tests of the pumps A and B and the microreactor, respectively. The temperatures T1 to T4 and the pressures P1 to P3 were recorded with a data logger (Agilent 34970A).

The effluent was analyzed with a GC-MS/FID (Agilent, GC-6890) equipped with an HP-5 column (30 m length, 0.25 mm i.d., 0.25 μm film thickness) to determine the yields of the products. The carrier gas was helium and the flow rate was 30 cm s^{-1} . The temperature of the GC inlet was set at 200 $^{\circ}\text{C}$, because at higher temperature a part of **3** underwent the thermal cyclization in the GC inlet. The temperature of the column oven was initially fixed at 70 $^{\circ}\text{C}$ for 1 min and then was increased up to 300 $^{\circ}\text{C}$ with a constant slope of 10 $^{\circ}\text{C min}^{-1}$. The GC analysis were performed 3 times for each experimental condition and the relative error in the determined yield was typically within 3%.

2.3. Reaction conditions

Here we performed the two types of experiment: In the first experiment, we changed the solvent and the temperature at a constant pressure (isobaric condition) to clarify the reaction mechanism. In the second experiment, we changed the reaction time and the temperature at a constant density of solvent ethanol (isochoric condition) to study the reaction kinetics.

2.3.1. Solvent and temperature effects

In the first experiment, we compared the reaction in sub- and supercritical ethanol with that in acetonitrile at various temperatures. The temperature was changed from 150 to 350 $^{\circ}\text{C}$ at a constant

pressure of 10.0 MPa and the reactor length was fixed at 10.0 m. The reaction time t , i.e., the residence time of the solution in the microtube reactor, is given by

$$t = \frac{V}{v_0} \cdot \frac{\rho}{\rho_0} . \quad (1)$$

V is the internal volume of the reactor from the micromixer to the cooler and was determined by measuring the weight of water required to fill the reactor. V was 8.1 cm³ when the reactor length was 10.0 m. v_0 is the sum of the flow rate of the reactant solution (0.5 cm³ min⁻¹) and that of the pure solvent (2.0 cm³ min⁻¹) at ambient temperature. ρ is the solvent density at the reaction temperature and ρ_0 is that at ambient temperature. We should note that the increase in the temperature under the isobaric condition causes a marked decrease in the solvent density ρ , resulting in a decrease in the residence time t of the solution in the microreactor.

For ethanol, the density ρ was calculated from the equation of state [25]. Fig. 3a shows the temperature dependence of the ethanol density under the isobaric condition of 10.0 MPa. The ethanol density decreased from 0.67 to 0.11 g cm⁻³ with the temperature increase from 150 °C to 350 °C. In proportion to the decrease in the density ρ , the residence time t was shortened from 164 to 27 s.

For acetonitrile, no literature equation of state was available in the high-temperature region studied here. **This prevents us from carrying out a precise kinetic analysis of the reaction in supercritical acetonitrile.** We can expect, however, that the residence time of acetonitrile would be comparable to that of ethanol, because the critical point of acetonitrile ($T_C = 272$ °C and $P_C = 4.9$ MPa) is not so far from that of ethanol ($T_C = 241$ °C and $P_C = 6.1$ MPa).

2.3.2. Kinetic analysis

In the second experiment, the yield was measured as a function of the reaction time t in supercritical ethanol at various temperatures. The temperature was changed from 300 to 350 °C at a constant ethanol density of 0.11 g cm⁻³. The constant ethanol density (i.e., the constant ethanol molarity) simplifies the kinetic analysis of the reaction, as discussed in detail in Sec. 3.2. To keep the isochoric

condition, the pressure was adjusted to the value obtained by the equation of state [25], as shown in Fig. 3b, from 8.2 MPa at 300 °C to 10.0 MPa at 350 °C. The reaction time t was varied from 6.0 to 27 s by changing the reactor length from 2.0 to 10.0 m, where the reactor volume V ranged from 1.8 to 8.1 cm³.

2.4. Density functional theory (DFT) calculations

The corresponding DFT calculations were performed to determine the optimized geometries and energies of the reactant, the product, the intermediates, and the transition states. The DFT calculations were performed at the B3LYP level in conjunction with the 6-31G(d,p) basis set using the Gaussian 09 package [26]. Solvent effect was neglected here because the dielectric constant of supercritical ethanol is low enough ($\epsilon \sim 1.1$) at the low density ($\rho = 0.11 \text{ g cm}^{-3}$), as explained in detail in Supplementary data S1. The transition-state structures were characterized by one imaginary frequency. Intrinsic reaction coordinate (IRC) calculations were carried out on the transition states to ensure that they connect the corresponding reactants and products. The relative energies with respect to the reactant **3** were calculated including the zero-point vibrational energy corrections and the thermal corrections at 350 °C and 10.0 MPa.

3. Results and Discussions

3.1. Solvent and temperature effects

Before going to discuss the kinetics, we investigate the solvent and temperature effects on the thermal cyclization to clarify the reaction mechanism. In Fig. 4a and 4b, the yields of the reactant and products are compared between the two solvents, acetonitrile and ethanol, respectively, at various temperatures from 150 to 350 °C. The yield of the reactant **3** denotes here the ratio of the concentration of **3** in the solution after the reaction to that before the reaction.

In acetonitrile, the reactant **3** started to react at 200 °C, giving the target product **4** and a by-product **5**. The yield of **4** monotonically increased with increasing temperature, despite the decrease in the reaction time under the isobaric condition, as explained in Sec. 2.3.1. At 275 °C, the reactant **3** was

completely consumed to provide the target quinoline **4** in 94% GC yield. The quinoline yield showed a further gradual increase up to 97% with increasing temperature to 350 °C as a result of the decrease in the yield of the by-product **5**. The temperature dependence is consistent with the Lengyel's microflow work on this reaction in supercritical THF [21]. The authors reported that the highest quinoline yield (92% isolated yield) was obtained at the highest temperature studied (360 – 370 °C).

The by-product **5** was identified as 2-(phenylimino)propane, as depicted in Fig. 4c, by GC-MS analysis (m/z = 133, 118, and 77). We confirmed that the same compound was obtained by the acid-catalyzed condensation of aniline **1** with acetone **9** shown in Fig. 5. The by-product **5** is generated probably by the thermal decarboxylation of the carboxylic acid **6** shown in Fig. 4c [27] and the carboxylic acid **6** is considered to be formed from the reactant ester **3** and water involved in the solvent as an impurity. In fact, when 0.5 wt% water was added in the reactant solution, the yield of the by-product **5** increased markedly from 8 to 51% at 250 °C.

In ethanol, by contrast, the reaction occurred only above 275 °C, requiring higher temperature than that in acetonitrile. This is because the solvent ethanol hinders the elimination of ethanol from the reactant by accelerating the reverse reaction owing to the very high concentration of ethanol. With increasing temperature up to 350 °C, however, the reactant **3** was completely consumed to provide the target quinoline **4** in 97% GC yield. No equilibrium was observed between **3** and **4** despite the presence of the reversible elimination of ethanol. To elucidate the reason why, we examined the reactivity of **4** in supercritical ethanol. Ethanol solution of **4** was heated in the microflow reactor under the same condition as shown in Fig. 3a. In the effluent, **4** was collected as supplied without any reaction. The chemical stability of **4** indicates that the product quinoline **4** is not involved in the equilibrium of the elimination of ethanol.

The experimental results can be explained by the reaction mechanism described in Fig. 4c. The thermal cyclization consists of the two processes: (i) a reversible elimination of ethanol and (ii) a subsequent irreversible ring closure [4, 22, 24]. The elimination of ethanol from the reactant ethyl ester

3 provides ketene intermediate **7** [28, 29]. A part of the ketene **7** reacts with the surrounding ethanol to regenerate the reactant **3**. The reverse reaction occurs more frequently at higher concentration of ethanol, resulting in the lower conversion of **3** in ethanol than that in acetonitrile. The other part of the ketene intermediate **7** undergoes a pericyclic reaction to form 4a*H*-quinolone **8**, and is finally transformed to 4-hydroxyquinoline **4** via a keto-enol tautomerization. The ring closure is irreversible. This is why the reaction gave complete conversion even in supercritical ethanol, although it involves the reversible elimination of ethanol. The reaction mechanism is considered to be slightly affected by the difference in the solvent polarity between supercritical ethanol and acetonitrile, because the dielectric constants ϵ of the supercritical solvents at the low densities are much lower than those at the ambient condition, e.g., $\epsilon \sim 1.1$ for supercritical ethanol at 350 °C and 0.11 g cm⁻³, as shown in Supplementary data S1. We should note, however, that the hydrogen bonding ability of ethanol may have a catalytic effect on the reaction mechanism, especially on the elimination of ethanol.

The thermal cyclization in supercritical ethanol offered several advantages over those in conventional solvents such as diphenyl ether [6] and that in supercritical THF [21]. The clean and simple reaction system allowed easy solvent separation and recycling. The solvent ethanol in the effluent was separated from the product simply by evaporation owing to the boiling point much lower than diphenyl ether. The product quinoline in the solid residue was purified only by washing with cyclohexane into white powder. The melting point of the product (236 °C) determined with a differential scanning calorimetry system (Shimadzu DSC-60) was in good agreement with the literature value (234 to 236 °C) [6]. When ethanol was used as the solvent, the evaporation gave pure ethanol ready for the solvent recycling; otherwise the solvent (e.g., THF) is contaminated with the ethanol generated by the reaction, requiring distillation before the recycling. In addition, ethanol is environmentally benign and rather harmless. This is desirable especially for the pharmaceutical industries. The solvent ethanol also simplifies the kinetic analysis and the reaction control, as demonstrated in the next section.

In this paper, the production scale was limited to 0.2 g h^{-1} by our aim for the precise kinetic analysis. Dilute reactant solution was mixed with preheated solvent to realize the rapid heating to the reaction temperature. For industrial purpose, however, scaling up of the reaction can be attained, e.g., by increasing the reactant concentration as well as the flow rate and by eliminating the solvent mixing for the rapid heating. Simple heating through the tube wall negligibly decreased the product selectivity, because in supercritical ethanol the by-product **5** is slightly produced at lower temperatures during the heating, as shown in Fig. 4b. In fact, the production scale was increased to 10 g h^{-1} , when the reactant solution at higher concentration (0.05 to 0.25 mol dm^{-3}) was provided at increased flow rate (0.5 to $5.0 \text{ cm}^3 \text{ min}^{-1}$) and was reacted without the mixing through the elongated microtube (10 to 20 m). The continuous microflow synthesis of the target product with high selectivity provides a great advantage over the batch process; the latter needs long waiting time for heating and cooling of the reactor.

3.2. Kinetic analysis

On the basis of the reaction mechanism elucidated above, we make a kinetic analysis of the thermal cyclization in supercritical ethanol. Here we determine the rate constant k and the activation energy E_a for the overall reaction from the yield-time profiles at various temperatures. We further discuss how the kinetic properties for the overall reaction are related to the rate constants k_i and the activation energies E_{ai} for the elementary reactions involved therein.

3.2.1. Rate constant

In Fig. 6a, the yield of the remaining reactant **3** is plotted as a function of the reaction time at various temperatures from 300 to $350 \text{ }^\circ\text{C}$ and a constant ethanol density of 0.11 g cm^{-3} . It should be noted that the total yield of the reactant **3** and the product **4** was larger than 97% at every experimental condition. The yield of the by-product **5** was lower than 3% and other by-products were not detected. The yield of **3** showed an exponential decrease with the reaction time at every temperature and the decrease was more rapid at higher temperature. The exponential decrease indicates that the reaction is

controlled by a pseudo-first-order kinetics with an overall rate constant k . The overall rate constant k was determined from the least-squares fit of the yield-time profile to the exponential decay function, as shown by the solid lines in Fig. 6a. The value of k is summarized in Table 1 as a function of the temperature. The overall rate constant k increased by 30 times from 0.0063 to 0.191 s⁻¹ with the temperature increase from 300 to 350 °C.

Let us explain the pseudo-first-order kinetics on the basis of the reaction mechanism. Since the ketene intermediate **7** is highly reactive, we can apply a steady-state approximation to **7** as

$$\frac{d[\mathbf{7}]}{dt} = k_1[\mathbf{3}] - k_2[\text{EtOH}][\mathbf{7}] - k_3[\mathbf{7}] \cong 0, \quad (2)$$

where $[\mathbf{X}]$ denotes the molarity of the chemical species $\mathbf{X}$. $[\text{EtOH}]$ is the molarity of ethanol and was 2.4 mol dm⁻³ when the methanol density was 0.11 g cm⁻³. k_1 is the first-order rate constant for the elimination of ethanol from **3** to **7**, k_2 is the second-order rate constant for the addition of ethanol from **7** to **3**, and k_3 is the first-order rate constant for the ring closure from **7** to **4**, as illustrated in Fig. 6c. Other reactions were neglected here because of their small contributions (< 3%). Eq. (2) relates the molarity of **7** to that of **3** as

$$[\mathbf{7}] \cong \frac{k_1[\mathbf{3}]}{k_2[\text{EtOH}] + k_3}. \quad (3)$$

Thus the time derivative of the molarity of **3** is given by

$$\begin{aligned} -\frac{d[\mathbf{3}]}{dt} &= k_1[\mathbf{3}] - k_2[\text{EtOH}][\mathbf{7}] \\ &\cong \frac{k_1 k_3}{k_2[\text{EtOH}] + k_3} [\mathbf{3}]. \end{aligned} \quad (4)$$

The differential equation indicates that the reaction is controlled by the pseudo-first-order kinetics, in agreement with the experimental result. The molarity of **3** varies with the reaction time t as

$$[\mathbf{3}] \cong [\mathbf{3}]_0 \cdot \exp\left(-\frac{k_1 k_3}{k_2 [\text{EtOH}] + k_3} \cdot t\right), \quad (5)$$

where $[\mathbf{3}]_0$ denotes the initial molarity of $\mathbf{3}$ at $t = 0$. Hence the rate constant k for the overall reaction is related to those for the elementary reactions as

$$k \cong \frac{k_1 k_3}{k_2 [\text{EtOH}] + k_3}. \quad (6)$$

Here we should note that $[\text{EtOH}]$ in Eq. (6) was negligibly changed during the reaction in our experiment using ethanol as the solvent, because the molarity of the ethanol generated from the reactant ($\leq 50 \text{ mmol dm}^{-3}$) was much smaller than that of the solvent ethanol (2.4 mol dm^{-3}). We should also note that $[\text{EtOH}]$ is independent of the temperature in our isochoric experiment. The constant $[\text{EtOH}]$ in Eq. (6) simplifies the analysis of the activation energy in the next section.

3.2.2. Activation energy

Fig. 6b shows the Arrhenius plot of the overall rate constant k . The logarithm of the rate constant k has a good linearity to the reciprocal of the absolute temperature T , commonly referred to as the Arrhenius behavior. From the slope, the activation energy was determined to be $E_a = 204 \pm 2 \text{ kJ mol}^{-1}$. The corresponding pre-exponential factor A was $2.5 \times 10^{16} \text{ s}^{-1}$.

The Arrhenius behavior of k is apparently inconsistent with the expression in Eq. (6), because the denominator has the two temperature-dependent terms, $k_2 [\text{EtOH}]$ and k_3 . We can assume, however, that $k_2 [\text{EtOH}]$ was much larger than k_3 , i.e., the addition of ethanol onto the ketene intermediate was dominant over the ring closure, because of the high molarity of the solvent ethanol. Under the approximation of $k_2 [\text{EtOH}] \gg k_3$, Eq. (6) is transformed into

$$k = \frac{k_1 k_3}{k_2 [\text{EtOH}] + k_3} \cong \frac{k_1 k_3}{k_2 [\text{EtOH}]}$$

$$= \frac{A_1 A_3}{A_2 [\text{EtOH}]} \cdot \exp\left(-\frac{E_{a1} - E_{a2} + E_{a3}}{RT}\right), \quad (7)$$

where A_i and E_{a_i} ($i = 1$ to 3) are the pre-exponential factors and the activation energies, respectively, of the elementary reaction rate constant k_i . R is the gas constant. Since $[\text{EtOH}]$ was independent of the temperature under the isochoric condition, Eq. (7) means that the overall rate constant k shows the Arrhenius behavior in agreement with the result in Fig. 6b. The pre-exponential factor A and the activation energy E_a for the overall reaction are related to those for the elementary reactions as

$$A \cong \frac{A_1 A_3}{A_2 [\text{EtOH}]} \quad (8)$$

and
$$E_a \cong E_{a1} - E_{a2} + E_{a3}. \quad (9)$$

Eq. (9) suggests that the pre-exponential factor A is inversely proportional to the ethanol molarity $[\text{EtOH}]$ or the ethanol density ρ . Eq. (9) reveals also that the overall activation energy E_a determined above is equal to the internal energy difference between the reactant **3** and the transition state **TS₂** of the ring closure, as illustrated in Fig. 6c.

The energy profile along the reaction obtained by the DFT calculation is described in Fig. 7a. The energy difference between the reactant **3** and the transition state **TS₂** was 187.4 kJ mol⁻¹. This is close to the overall activation energy E_a experimentally determined (204 kJ mol⁻¹) with the underestimation of 8%. The energy barrier for the ring closure of **7** was as low as 58.9 kJ mol⁻¹. This is in accordance with the DFT calculation by Cantillo, et al. [10] on the ring closure of a similar imidoyleketene intermediate, whose energy barrier was reported to be 62.5 kJ mol⁻¹. In contrast, the energy barrier for the thermal elimination of ethanol from **3** was very high (269.5 kJ mol⁻¹) due to the four-membered ring structure of the transition state **TS₁**. The DFT calculation suggests an alternative pathway energetically favorable via an enamine tautomer of the reactant **3'**. The alternative route has a

much lower barrier ($132.1 \text{ kJ mol}^{-1}$) owing to the six-membered ring structure of the transition state TS_1' . The optimized geometries of the transition states TS_1 , TS_2 , and TS_1' are shown in Fig. 7b to 7d, respectively.

4. Conclusions

The present study on the Conrad-Limpach thermal cyclization in supercritical ethanol using the microreactor provided the following conclusions on the reaction mechanism and the kinetics:

- The reaction in supercritical ethanol was found to complete within 27 s at 350°C and 10.0 MPa giving the target quinoline in 97% GC yield, although it required higher temperature than that in acetonitrile. The solvent and temperature effects on the reaction revealed that the thermal cyclization consists of the two steps: (i) a reversible thermal elimination of ethanol from the reactant yielding ketene intermediate and (ii) the subsequent irreversible ring closure into the target quinoline.
- The overall kinetics was described simply by a pseudo-first-order rate constant k . The temperature dependence of k under the isochoric condition was expressed by an activation energy of $E_a = 204 \pm 2 \text{ kJ mol}^{-1}$. The overall rate constant and the activation energy were theoretically related to those of the elementary reactions on the basis of the reaction mechanism. The value of E_a agreed well with that obtained by the DFT calculation (187 kJ mol^{-1}).

In addition, the use of supercritical ethanol as the reaction medium offered a clean and simple process enabling easy solvent separation and recycling. The kinetic insight will facilitate the design and control of the reaction process in the high-temperature and high-pressure medium.

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References

- [1] R.H. Reitsema, The chemistry of 4-hydroxyquinolines, *Chem. Rev.*, 43 (1948) 43-68.
- [2] M. Foley, L. Tilley, Quinoline antimalarials: Mechanisms of action and resistance and prospects for new agents, *Pharmacol. Ther.*, 79 (1998) 55-87.
- [3] H. Zollinger, *Color Chemistry. Syntheses, Properties, and Applications of Organic Dyes and Pigments*, 3rd. ed., Wiley-VCH, Weinheim, 2003.
- [4] T.T. Curran, Conrad-Limpach reaction, in: J.J. Li (Ed.) *Name Reactions in Heterocyclic Chemistry*, Wiley-Interscience, Hoboken, 2005, pp. 398-406.
- [5] G.A. Reynolds, C.R. Hauser, Ethyl β -anilinocrotonate, *Organic Syntheses*, 29 (1949) 42-43.
- [6] G.A. Reynolds, C.R. Hauser, 2-Methyl-4-hydroxyquinoline, *Organic Syntheses*, 29 (1949) 70-71.
- [7] J.C. Brouet, S. Gu, N.P. Peet, J.D. Williams, Survey of solvents for the Conrad-Limpach synthesis of 4-hydroxyquinolones, *Synth. Commun.*, 39 (2009) 1563-1569.
- [8] T. Razzaq, T.N. Glasnov, C.O. Kappe, Continuous-flow microreactor chemistry under high-temperature/pressure conditions, *Eur. J. Org. Chem.*, (2009) 1321-1325.
- [9] J. Wegner, S. Ceylan, A. Kirschning, Flow chemistry - A key enabling technology for (multistep) organic synthesis, *Adv. Synth. Catal.*, 354 (2012) 17-57.
- [10] D. Cantillo, H. Sheibani, C.O. Kappe, Flash flow pyrolysis: Mimicking flash vacuum pyrolysis in a high-temperature/high-pressure liquid-phase microreactor environment, *J. Org. Chem.*, 77 (2012) 2463-2473.
- [11] V. Hessel, D. Kralisch, N. Kockmann, T. Noel, Q. Wang, Novel process windows for enabling, accelerating, and uplifting flow chemistry, *ChemSusChem*, 6 (2013) 746-789.
- [12] B. Gutmann, D. Cantillo, C.O. Kappe, Continuous-flow technology - A tool for the safe manufacturing of active pharmaceutical ingredients, *Angew. Chem.-Int. Edit.*, 54 (2015) 6688-6728.
- [13] C. Wiles, P. Watts, Recent advances in micro reaction technology, *Chem. Commun.*, 47 (2011) 6512-6535.

- [14] P.E. Savage, Organic chemical reactions in supercritical water, *Chem. Rev.*, 99 (1999) 603-621.
- [15] T. Fujii, R. Hayashi, S. Kawasaki, A. Suzuki, Y. Oshima, Effects of pressure on decomposition of formic acid in sub- and super-critical water, *J. Supercrit. Fluids*, 71 (2012) 114-119.
- [16] D.A. Cantero, M.D. Bermejo, M.J. Cocero, Kinetic analysis of cellulose depolymerization reactions in near critical water, *J. Supercrit. Fluids*, 75 (2013) 48-57.
- [17] G. Akgul, A. Kruse, Hydrothermal disproportionation of formaldehyde at subcritical conditions, *J. Supercrit. Fluids*, 73 (2013) 43-50.
- [18] J. Lu, E.C. Boughner, C.L. Liotta, C.A. Eckert, Nearcritical and supercritical ethanol as a benign solvent: Polarity and hydrogen-bonding, *Fluid Phase Equilib.*, 198 (2002) 37-49.
- [19] A. Yermakova, A.M. Chibiryayev, I.V. Kozhevnikov, V.I. Anikeev, The kinetics of thermal isomerization of β -pinene and a mixture of β - and α -pinenes in supercritical ethanol, *J. Supercrit. Fluids*, 45 (2008) 74-79.
- [20] O. Farobie, Y. Matsumura, A comparative study of biodiesel production using methanol, ethanol, and tert-butyl methyl ether (MTBE) under supercritical conditions, *Bioresour. Technol.*, 191 (2015) 306-311.
- [21] L. Lengyel, T.Z. Nagy, G. Sipos, R. Jones, G. Dorman, L. Urge, F. Darvas, Highly efficient thermal cyclization reactions of alkylidene esters in continuous flow to give aromatic/heteroaromatic derivatives, *Tetrahedron Lett.*, 53 (2012) 738-743.
- [22] A. Stadler, S. Pichler, G. Horeis, C.O. Kappe, Microwave-enhanced reactions under open and closed vessel conditions. A case study, *Tetrahedron*, 58 (2002) 3177-3183.
- [23] C.O. Kappe, Controlled microwave heating in modern organic synthesis, *Angew. Chem.-Int. Edit.*, 43 (2004) 6250-6284.
- [24] T.D. White, C.A. Alt, K.P. Cole, J.M. Groh, M.D. Johnson, R.D. Miller, How to convert a walk-in hood into a manufacturing facility: Demonstration of a continuous, high-temperature cyclization to process solids in flow, *Org. Process Res. Dev.*, 18 (2014) 1482-1491.

- [25] J.A. Schroeder, S.G. Penoncello, J.S. Schroeder, A fundamental equation of state for ethanol, *J. Phys. Chem. Ref. Data*, 43 (2014) 043102.
- [26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M.J. Bearpark, J. Heyd, E.N. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A.P. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N.J. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, *Gaussian 09, Revision A.02*, in, Gaussian, Inc., Wallingford, CT, USA, 2009.
- [27] T.B. Brill, P.E. Savage, Kinetics and mechanisms of hydrothermal organic reactions, in: D.A. Palmer, R. Fernandez-Prini, A.H. Harvey (Eds.) *Aqueous Systems at Elevated Temperatures and Pressures: Physical Chemistry in Water, Steam and Hydrothermal Solutions*, Elsevier/Academic Press, Amsterdam, 2004, pp. 643-675.
- [28] H. Briehl, A. Lukosch, C. Wentrup, Reactive nitrogenous molecules from Meldrum's acid-derivatives, pyrrole-2,3-diones, and isoxazolones, *J. Org. Chem.*, 49 (1984) 2772-2779.
- [29] S.Y. Ham, D.M. Birney, Imidoylketene: An ab initio study of its conformations and reactions, *J. Org. Chem.*, 61 (1996) 3962-3968.

Table 1. The pseudo-first-order rate constant k for the thermal cyclization of **3** to **4** in supercritical ethanol as a function of the temperature at a constant ethanol density of 0.11 g cm^{-3} .

Temperature (°C)	Rate constant, k (s^{-1})
300	0.0063 ± 0.0003
310	0.0124 ± 0.0003
320	0.027 ± 0.001
330	0.053 ± 0.001
340	0.102 ± 0.001
350	0.191 ± 0.002

Figure captions

Fig. 1. Conrad-Limpach reaction for the synthesis of 2-methyl-4-hydroxyquinoline **4**.

Fig. 2. (a) Schematic diagram of the high-temperature and high-pressure microreactor designed for the kinetic analysis. T_1 to T_4 : thermocouples; P_1 to P_3 : pressure gauges; SV_1 to SV_3 : stop valves. (b) Cross section of the flow-through temperature probe unit.

Fig. 3. Experimental conditions: (a) Change in the density of ethanol ρ calculated from the equation of state [25] as a function of the temperature at a constant pressure of 10.0 MPa and that in the residence time t of ethanol in the microreactor with the internal volume of 8.1 cm^3 . ρ_0 : the density of ethanol at 25°C and 10.0 MPa. T_C : the critical temperature of ethanol. (b) Change in the pressure of ethanol calculated from the equation of state [25] as a function of the temperature at a constant density of 0.11 g cm^{-3} .

Fig. 4. (a) Yields of the reactant **3**, the target product **4**, and the by-product **5**, and their total yield **3+4+5** in acetonitrile and (b) those in ethanol as functions of the reaction temperature at a constant pressure of 10.0 MPa. (c) Plausible reaction pathway for the thermal cyclization of **3** to **4** and that for the side reaction to **5**.

Fig. 5. Synthetic route of 2-(phenylimino)propane **5** at ambient condition. The product **5** was used for the identification of the by-product of the reactions of ethyl 3-(phenylimino)butanoate **3** in supercritical acetonitrile and ethanol shown in Figs. 4a and 4b by GC-MS analysis.

Fig. 6. (a) Yield of the reactant **3** in supercritical ethanol as a function of the reaction time t at various temperatures and a constant ethanol density of 0.11 g cm^{-3} . The lines are the exponential decay fits to the yield-time profiles with a pseudo-first-order rate constant k . (b) Logarithm of the rate constant k plotted against the reciprocal of the absolute temperature T . The line is the Arrhenius fit to the data with an overall activation energy of E_a . (c) Diagram of the rate constants k_i and the activation energies $E_{a,i}$.

for the elementary reactions involved in the thermal cyclization. [EtOH]: the molarity of ethanol. TS₁ and TS₂: the transition states.

Fig. 7. (a) Energy profile of the thermal cyclization from **3** to **4** obtained by the DFT calculations. The blue line shows an alternative pathway for the thermal elimination of ethanol via the enamine tautomer **3'** and the transition state TS_{1'} with a six-membered ring structure. (b-d) Optimized geometries of the transition states (b) TS₁, (c) TS₂, and (d) TS_{1'}.

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Graphical Abstract