A Consecutive Microreactor System for the Synthesis of Caprolactam with High Selectivity

Kai Wang, Jisong Zhang, Chen Zheng, Chen Dong, Yangcheng Lu, and Guangsheng Luo
The State Key Laboratory of Chemical Engineering, Dept. of Chemical Engineering, Tsinghua University, Beijing 100084, China

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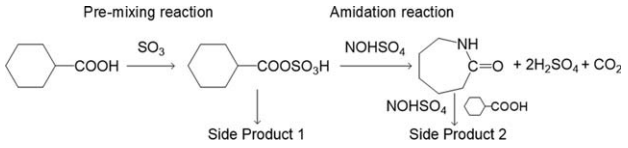
A microreactor system containing two consecutive microreactors and a stirred vessel was developed for the improvement of selectivity of caprolactam (CPL) synthesis. The first microreactor was used to conduct the reaction of cyclohexanecarboxylic acid and oleum, and 97% selectivity for the intermediate product, named mixed anhydride, was obtained. The mixed anhydride then quickly reacted with nitroso-sulfuric acid in the second microreactor, and the reaction was completed in the vessel, where CPL selectivity reached 93.9%, a much higher value than that achieved either in a control experiment with a batch reactor or in industrial process. The advantage of microreactors is that they can provide high-quality mixed anhydride and can mix it quickly with the nitroso-sulfuric acid prior to reaction in the vessel reactor, which, from an engineering standpoint, gives better performance than the traditional syringe-fed method that is common in chemical synthesis. © 2015 American Institute of Chemical Engineers *AIChE J*, 61: 1959–1967, 2015
Keywords: microreactor, selectivity, caprolactam, cyclohexanecarboxylic acid

Introduction

As the monomer of nylon 6, ε-caprolactam (CPL) is a commercially important chemical product.[1] Among the methods of CPL synthesis, the SNIA Viscosa process[2] is an important route using toluene as the raw material, and differs from the cyclohexanone oxime Beckmann Rearrangement route[3,4] that uses benzene as the source material. The manufacturing process in the SNIA route has several steps, including toluene oxidation, benzoic acid hydrogenation, cyclohexanecarboxylic acid (CCA)–oleum premixing, and mixed anhydride amidation, as well as the subsequent neutralization, extraction, and distillation processes. Of these steps, the premixing and amidation reactions using CCA as the main reactant are the core of the process. These typically fast, consecutive, and strongly exothermal processes have serious side reactions, which are common concerns in many organic syntheses.[5] Although the chemistry of this reaction is relatively well established, a selectivity enhancement study remains a worthwhile exercise from the chemical engineering standpoint, because according to the data of a Chinese Company, the CPL selectivity is usually lower than 90% in the industrial process using consecutive continuous stirred-tank reactors (CSTRs).

Microreactors are effective tools for increasing the yields and selectivity of chemical reactions, especially for fast and exothermal reactions.[6,7] In earlier studies, researchers have found that enhancements of mixing and mass-transfer performance in microreactors are effective ways to prohibit side product formation, in both consecutive and parallel reactions, using kinetic differences.[8] A famous work on the Friedel–Crafts aminoalkylation reaction reported by Nagaki et al. is a good example,[9] where a 92% main-product yield was obtained in a splitting–recombination type microreactor. Good temperature control based on small-scale reaction channels is also important. Microchannels with a specific surface area of larger than 1000 m^2/m^3 have proved to be effective heat exchangers in fluorination and nitration reactions.[10,11] In recent years, the potential of microreactors has been further developed. Microreactors have been operated at relatively higher temperatures and pressures, such as subcritical and supercritical states,[4,12] where the mixing and heat-/mass-transfer rates, as well as the reagent solubility can be significantly improved. The cyclohexane oxidation reaction, reported by Leclerc et al., showed that conditions of temperature and pressure in excess of 200°C and 25 bar, respectively, were safely handled in a Pyrex-silicon microreactor using pure oxygen in an explosive environment.[13] A good selectivity of 88% was obtained for the desired products, at a high productivity of 2.84 mol/L/h. Finally, but very importantly, the coupling of multistep reactions is very effective for obtaining high selectivity, and can be easily realized using microreactors. There have been some examples in recent years, such as the microreactor system reported by Noël et al. to conduct a Suzuki–Miyaura cross-coupling reaction.[14] The system contained a tubular microreactor, a microfluidic extractor, and a small packed-bed reactor. The experiment obtained high yields of biaryls, from 83 to 99%. Another example of a continuously integrated microreactor system was developed by Herath et al. for the synthesis of imidazo[1,2-a]pyridine-2-carboxamides.[15] A multistep synthesis without intermediate isolation was enabled by

Correspondence concerning this article should be addressed to K. Wang at kaiwang@tsinghua.edu.cn or G. S. Luo at gsluo@tsinghua.edu.cn.



Scheme 1. Caprolactam synthesis from cyclohexanecarboxylic acid.

consecutive microreactors, and a yield of 46% was achieved as opposed to the 16% yield in a batch reactor system.

In our studies, a tubular microreactor has been developed to conduct the premixing of CCA and oleum.[16] A selectivity higher than 97% for the mixed anhydride (AS), the intermediate product of CPL synthesis was obtained using the mass-transfer enhancing effect of a liquid–liquid reacting system containing microdroplets with an average diameter of 60 μm.[17,18] Although the side reactions in premixing reaction are temperature-sensitive, the system temperature was successfully raised to 90°C under adiabatic operating conditions,[17] much higher than the 30°C temperature of industrial processes. In this article, a further study on the consecutive CPL synthesis including both premixing and amidation reactions is reported. To realize high CPL selectivity, a consecutive microreactor system was developed, meeting the requirements for reactant mixing and temperature control. The selectivity enhancement principle and the advantage of the consecutive microreactor system were demonstrated by comparing the performance of this microreactor system to that of the batch reactors of the control experiments.

CPL Synthesis Reaction

The reactions for the synthesis of CPL from CCA are shown in Scheme 1.[19] There are two main reactions: the premixing reaction between CCA and oleum that forms a mixed anhydride,[20] and the amidation reaction between the mixed anhydride and nitroso-sulfuric acid that forms the desired CPL, with sulfuric acid and carbon dioxide as by-products.[21] Both reactions have consecutive side reactions. The CPL selectivity (S_{CPL}) in this process is defined as the molar ratio of CPL formed to reacted CCA.

Figure 1a gives some details of the premixing reaction. It is a multiphase reaction, as CCA is usually dissolved in a liquid alkane (*n*-hexane is the most frequently used) working as the continuous phase. Oleum is dispersed to droplets, and the reaction starts with the mass transfer of CCA from the continuous phase to the dispersed phase. Two main reactions take place in the droplets: first, a proton exchange between CCA and sulfuric acid, and second, the mixed anhydride formation from sulfur trioxide.[22] The mixed anhydride is the intermediate product required. The main reactions are ultrafast and exothermal, with enthalpies of -13.9 kJ/mol-H_2SO_4 for the proton exchange reaction ($\Delta_r H_p$) and -50.4 kJ/mol-SO_3 for the mixed anhydride formation reaction ($\Delta_r H_m$).[22,23] These reactions are usually written as reversible reactions in the literature,[2,24] but are almost irreversible in our experiment, as excess CCA ($N_{CCA} > 2.5\ N_{SO3}$) was used, and the equilibrium constants are large ($K_p = 19.4$–8.4 from 20 to 70°C for the proton exchange reaction, and $K_m \approx 10^4 K_p$ for the mixed anhydride formation reaction).[16,17] Irreversible side reactions convert the mixed anhydride to undesirable sulfonic acids, such as α-sulfo CCA and benzensulfonic acid,[23] which are simplified to Side Product 1 in this article.

The side reactions of the premixing reaction are relatively slow, but are temperature-sensitive.[17,23] Exploiting the kinetic difference between main and side reactions has proved to be an effective method to obtain high selectivity of the mixed anhydride.[16] Considering that the main reactions are mass-transfer-controlled, microdroplets were used to enhance the mass-transfer rate of CCA. Figure 1b depicts the microdroplets in our microreactor. The average droplet diameter was about 60 μm, and the mass-transfer coefficient, $k_c a$, ranged from 1.6 to 5.7 s^{-1} in this microdispersed liquid/liquid system, according to the results of our experiment.[17] A mixed anhydride selectively of higher than 97% was obtained, with 100% oleum conversion at product temperatures ranging from 50 to 90°C. As conversion of the mixed anhydride to Side Product 1 by the side reactions continues, it is best to commence the subsequent amidation reaction as soon as possible after completion of the premixing reaction.

In the amidation reaction, the nitroso-sulfuric acid solution (72–75 wt % $NOHSO_4$ in sulfuric acid) is added to the reacting system as the second dispersed phase. Once the droplets of the mixed anhydride and nitroso-sulfuric acid fuse together, CPL formation commences, as shown in Figure 2. According to this reaction mechanism, a CO_2 molecule is formed in the generation of a CPL molecule, and this is released into the continuous phase. To conduct the amidation reaction successfully, the system temperature should be higher than 60°C, otherwise the reaction cannot be initiated, and crystals of CCA and nitroso-sulfuric acid will appear in the system, quickly blocking the small channels of the microreactor. Thus, the reactant solution should be preheated during operation, either by an external heat source or by utilizing the reaction enthalpy of the premixing reaction. Using the premixing reaction enthalpy is energy-efficient, but the

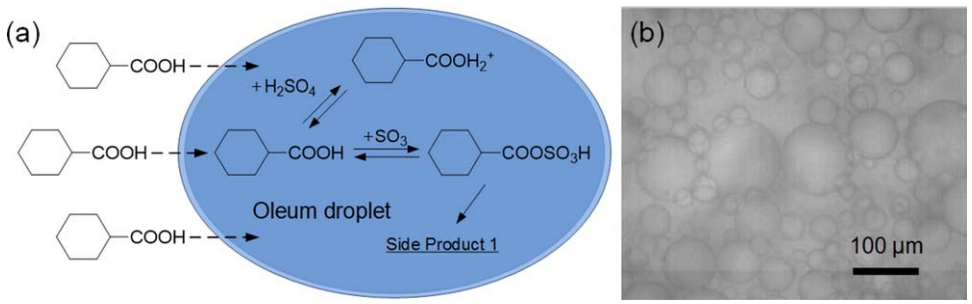


Figure 1. The premixing reaction and droplets in the tubular microreactor.

(a) A schematic of the premixing reaction process; (b) a microscope picture of sulfuric acid droplets flowing out of the micromixer. 98% sulfuric acid, used in this cold state experiment to replace dangerous oleum, and 66 wt % CCA hexane solution were used as the continuous phase. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

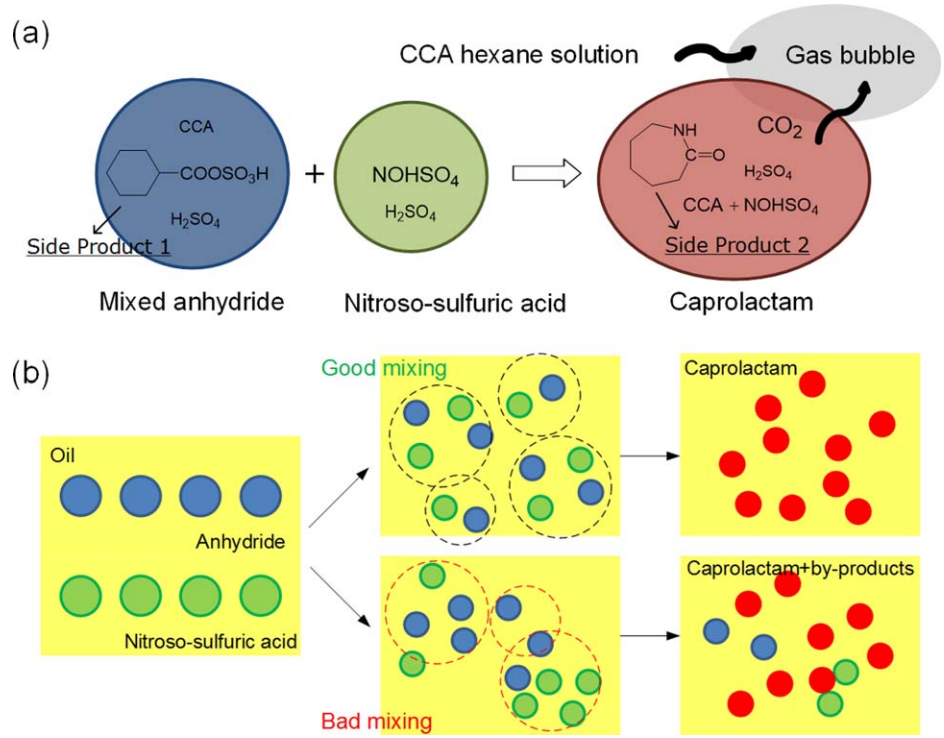


Figure 2. The amidation reaction and selectivity enhancement principle.

(a) A schematic of the amidation reaction process; (b) a schematic of the effect of droplet mixing on CPL selectivity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

operating condition of the premixing reaction must be designed to match the temperature of the mixed anhydride and the initiation temperature of the amidation reaction. The amidation reaction is rapid, and the reaction time in an industrial process is usually controlled at 15 min. It is also a strongly exothermal reaction, with an enthalpy ($\Delta_r H_n$) of about -316 kJ/mol-$NOHSO_4$. This large amount of heat is mainly removed by boiling hexane in the continuous phase.

CPL can further react with CCA and nitroso-sulfuric acid, forming cyclohexamide, which is labeled Side Product 2 in this article. Figure 2b shows the key requirement for high CPL selectivity. It is important to have good mixing of the droplets of the mixed anhydride and nitroso-sulfuric acid to avoid local excess of reactants, as excess mixed anhydride can be converted to Side Product 1, and excess nitroso-sulfuric acid can further consume CPL. The rapid consumption of nitroso-sulfuric acid and mixed anhydride is important, as they can lead to side reactions. However, the fast mixing of two dispersed phases is difficult in a common batch reactor, as the density of nitroso-sulfuric acid solution (1993 kg/m^3) is different from the densities of mixed anhydride droplets (800–900 kg/m^3) and the continuous phase (650–750 kg/m^3). The heavy nitroso-sulfuric acid solution is hard to break-up, and according to our observations, always spreads out over the vessel bottom. Addition of the nitroso-sulfuric acid solution by syringe is helpful for droplet dispersion and reactant mixing. However, this feed method is empirical and hard to scale-up for industrial application. Nevertheless, a microreactor can provide an environment to enhance nitroso-sulfuric acid solution dispersion and mixing with mixed anhydride under the negligible gravity condition at a micrometric scale. It will become an important component of organic synthesis devices.

Method and Setup

Consecutive microreactor system

Based on the above analysis, a consecutive microreactor system has been designed to carry out the CPL synthesis reaction in this study, as shown in Figure 3. To obtain a high selectivity for mixed anhydride formation, the premixing reaction is conducted adiabatically in a microreactor (top center of the schematic diagram in Figure 3) using reaction enthalpy to heat the reagents. The microreactor consists of a microsieve mixer and a delayed loop made from 316-L stainless steel. The micromixer is designed to generate oleum droplets, and is comprised of a mixing channel (10 mm $\times$ 1 mm $\times$ 0.5 mm, in Figure 3 colored orange, and then red after mixing), a distribution chamber of the dispersed phase (0.22 mL), and three microsieve pores (diameter of 0.4 mm). The inner diameter of the delayed loop (Loop 1 in Figure 3) is 1 mm and the length is 0.6 mm. The inlet temperatures of the CCA solution and oleum are controlled by preheating the tubes in a water bath (Bath 1). The microreactor is almost completely insulated from the environment by thick NBR-PVC rubber foam. Pt-100 sensors are placed on the inlet tubes and at the end of the delayed loop to monitor temperature variation.

The amidation microreactor is directly connected to the premixing microreactor. A preheating system (Bath 2) is used to increase the temperature of nitroso-sulfuric acid solution to 70°C. The construction of the second microsieve mixer is the same as that of the first, but it is used to generate nitroso-sulfuric acid droplets in the continuous hexane phase and cause them commence mixing with the mixed anhydride droplets. The micromixer is followed by a 3-mm inner diameter delayed loop (Loop 2) to provide a mixing

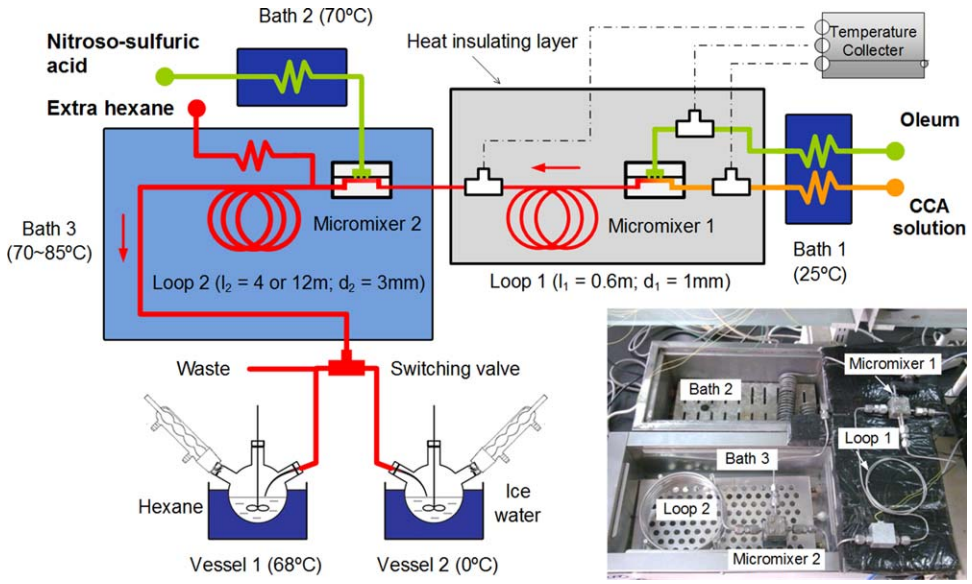


Figure 3. Schematic and photograph of the consecutive microreactor system.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

time. The length of Loop 2 in most experiments was 4 m; although a 12-m delayed loop containing an extra inlet for hexane was also tested. The amidation microreactor (the microsieve mixer and delayed loop) is placed in a water bath (Bath 3) to control its temperature between 70 and 85°C. As the amidation reaction starts in this microreactor, the bath temperature is also deemed the initiation temperature of amidation reaction. A large amount of hexane will be vaporized during the reaction. The process is not entirely completed in the microreactor due to the extreme volumetric flow rate. A glass vessel (Vessel 1, 500 mL) with a Teflon agitator and a condenser is used as the final reactor to complete the reaction. Its initial temperature is controlled at the boiling temperature of hexane (68°C) with a small water bath. The condenser was used to condense hexane vapor. Toevaluate the mixed anhydride conversion in the second microreactor, another stirred vessel (Vessel 2, 500 mL) in an ice-water bath is used to quench the reacting solution from the microreactor with ice water.

Operation and analysis

The performance of the premixing microreactor was first tested. A solution of 61.5 wt % CCA in hexane, and oleum containing 64.2 wt % SO_3 were used as the reactants. These were pumped into the first microreactor by metering position pumps (Beijing Satellite Co.). It is necessary to inject the CCA solution first, to avoid fast carbonization by local excessive oleum. In the second microreactor, cold water (10–15°C) was fed from the inlet of nitroso-sulfuric acid to quench the premixing reaction. Product samples were collected at the microreactor outlet. As the mixed anhydride is very hard to detect with common analysis equipment,[16] the oleum conversion was monitored by the temperature rise of the working system, which was calculated by the following equations

$$q_r = \int_{T^{in}}^{T^{out}} Q_{oil}\rho_{oil}\left[x_{CCA}Cp_{CCA} + (1-x_{CCA})Cp_{C_6H_{14}}\right]dT + Q_{oleum}\rho_{oleum}Cp_{oleum}dT \quad (1)$$

$$\Phi_{oleum} = \frac{q_r}{Q_{oleum}\rho_{oleum}\left[x_{SO_3}\Delta_r H_m/M_{SO_3} + (1-x_{SO_3})\Delta_r H_p/M_{H_2SO_4}\right]} \times 100\% \quad (2)$$

Here, q_r is the flux of heat released; Φ_{oleum} is the oleum conversion calculated from the heat balance; T^{in} and T^{out} are inlet and outlet temperatures; Q_{oil} and Q_{oleum} are two-phase volumetric flow rates; ρ_{oil} and ρ_{oleum} are the densities of the CCA solution and oleum; x_{CCA} is the mass fraction of CCA in oil; x_{SO3} is the mass fraction of SO_3 in oleum; Cp_{CCA}, $Cp_{C_6H_{14}}$, and Cp_{oleum} are the heat capacities of CCA, hexane, and oleum; M_{SO_3} and $M_{H_2SO_4}$ are the molecular weights of SO_3 and H_2SO_4. The selectivity of mixed anhydride formation was analyzed from the quenching product, in which the protonated CCA and the mixed anhydride had been converted back to CCA, but that converted to the side products was not detected. Therefore, the selectivity of mixed anhydride at nearly 100% oleum conversion was calculated by

$$S_{AS} = \frac{Q_{oil}\rho_{oil}\left(x_{CCA} - x_{CCA}^{oil}\right)/M_{CCA}}{Q_{oleum}\rho_{oleum}x_{SO_3}/M_{SO_3}} \times 100\% \quad (3)$$

where x_{CCA}^{oil} is the mass fraction of CCA in the oil phase after hydrolyzation (CCA is insoluble in diluted acid), and M_{CCA} is the molecular weight of CCA (128.17 g/mol). All of the physical properties of the working system are listed in Table 1.

In the amidation reaction experiment, 50.9–61.5 wt % CCA hexane solution and 63.6–65.7 wt % SO_3 oleum were used to conduct the premixing reaction in the first microreactor. The nitroso-sulfuric acid solution containing 72.8–74.3 wt % $NOHSO_4$ was fed to the second microreactor by the position pumps (Beijing Satellite Co.). The feed sequence was CCA solution followed by oleum, followed by nitroso-sulfuric acid solution, but in the experiment with a 12-m Loop 2, extra hexane was earlier fed from the extra inlet to prevent complete boil-off of the solvent. The reacting solution out of Loop 2 was discarded until the flow and system temperature had stabilized. When the system had been stable

Table 1. Physical Properties of the Working System

	ρ (kg/m^3)	μ (mPa s)	Cp [kJ/(kg °C)]
CCA	$390x_{CCA} + 607$ (25°C)[a]	0.63–0.78 (25°C, 50% $< x_{CCA} <$ 66%)[a]	$1.67 + 0.0069T$ ($20 < T < 100$°C)
n-hexane			$2.16 + 0.0043T$ ($20 < T < 68$°C)
Oleum	1994 (25°C)	39.2 (25°C)	$1.82 + 0.0025T$ ($20 < T < 100$°C)
$NOHSO_4$ solution	1993 (70°C)	13.1 (70°C)	1.37 (70°C)

[a]The density and viscosity of a CCA *n*-hexane solution.

for more than 5 min, the effluent solution from the amidation microreactor was switched to Vessel 1, which contained 100 g hexane at 68°C. The feed time of less than 60.5 s was carefully recorded to calculate the amount of reactants. The feed of fluids was then halted. In the next 15 min, the reaction was implemented in Vessel 1. After the completion of the reaction, the vessel was allowed to cool naturally to room temperature. The product solution was then carefully hydrolyzed with ice water. To evaluate the reaction performance in the microreactor, a separate experiment was performed in which the reacting solutions out of Loop 2 were fed to a quenching vessel (Vessel 2), where 100 g ice water was prestored. The experimental condition was the same as above, but only the mixed anhydride conversion was studied.

During the experiment, the reactant space-time in the microreactor, the length of Loop 2, the molar ratio of mixed anhydride to nitroso-sulfuric acid, Bath 3 temperature, and the agitator speed in Vessel 1 were varied to show their effects on the mixed anhydride conversion and CPL selectivity. Equation 4 was used to calculate the mixed anhydride conversion based on the consumption of CCA. (The generation of the small amount of Side Product 1 in the premixing microreactor was neglected.)

$$\Phi_{AS} = \frac{\left(Q_{oil}\rho_{oil}x_{CCA}t - m_{oil}x_{CCA}^{oil}\right)/M_{CCA}}{\Phi_{oleum}Q_{oleum}\rho_{oleum}x_{SO_3}t/M_{SO_3}} \times 100\% \qquad (4)$$

where t is the vessel feed time and m_{oil} is the weight of oil after hydrolyzation. As the CPL was dissolved in both the oil and water phases, Eq. 5 was used to calculate its selectivity

$$S_{CPL} = \frac{\left(m_{oil}x_{CPL}^{oil} + m_{water}x_{CPL}^{water}\right)/M_{CPL}}{\left(Q_{oil}\rho_{oil}x_{CCA}t - m_{oil}x_{CCA}^{oil}\right)/M_{CCA}} \times 100\% \qquad (5)$$

where the x_{CPL}^{oil} and x_{CPL}^{water} are the mass fractions of CPL in the two phases, m_{water} is the weight of the water phase, and M_{CPL} is the molecular weight of CPL (113.16 g/mol). The mass fractions of CCA and CPL in the oil phase were measured by a gas chromatography (Agilent 6890) and the mass fraction of CPL in the water phase was measured by a high performance liquid chromatography (Agilent 1100). To confirm the results, a validation of the mass balance before and after reaction was performed. Comparing the mass data from the residential liquid in Vessel 1 or 2 after hydrolyzation and the feed liquids including reactant solutions, extra hexane, and water, the mass loss ratio was less than 2%, which can be attributed to the mass loss of CO_2.

In addition, control experiments with a batch reactor were made in Vessel 1. To confirm that reactants are well mixed by the consecutive amidation microreactor, the main purpose this work, the mixed anhydride was also provided by the premixing microreactor for the control experiments and the amidation microreactor was removed. Two control group experiments were performed. The first was a batch experiment with prefed nitroso-sulfuric acid (13.0 g) and hexane (100 g) in the vessel. The second was a batch experiment, using syringe fed nitroso-sulfuric acid (13.1 g). In the first control experiment, the reaction started as the mixed anhydride was fed into the vessel and the loading amount was controlled by the vessel feed time (45.6 s). In the second control experiment, the nitroso-sulfuric acid was introduced using a syringe immediately after the feed of mixed anhydride was completed. The feeding time of nitroso-sulfuric acid solution was 15 min, and the inner diameter of the syringe needle was only 0.5 mm. Both control experiments were finished in 20 min.

Results and Discussion

Results of the premixing reaction

As the performance of the premixing reaction in our tubular microreactor has been sufficiently studied in our previous

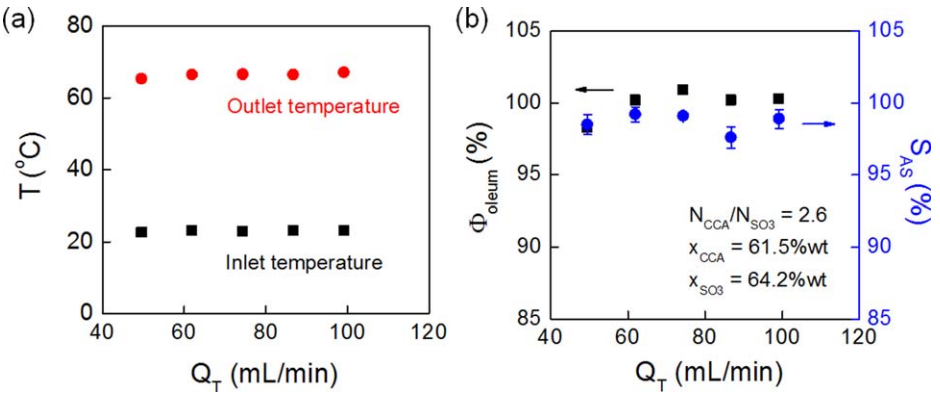


Figure 4. Local temperature in the premixing microreactor and reaction performances.

(a) The temperature of micromixer inlets and delayed loop outlet. The temperature of CCA solution and oleum was almost the same. (b) The oleum conversion and mixed anhydride selectivity with the variation of total flow rate of CCA solution and oleum. $Q_T = Q_{oil} + Q_{oleum}$. The experimental details are $x_{CCA} = 61.5$ wt %; $x_{SO_3} = 64.2$ wt %; $Q_{oil} = 40$–80 mL/min, $Q_{oleum} = 4.0$–8.0 mL/min. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

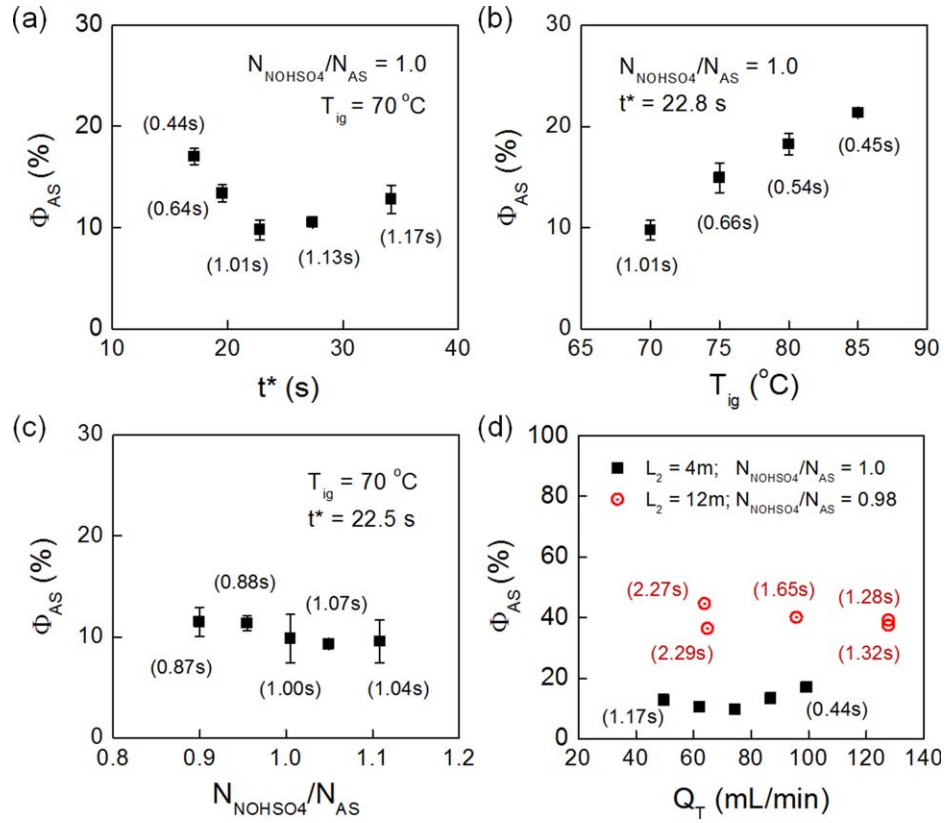


Figure 5. Mixed anhydride conversion in the amidation microreactor.

(a) The effect of space-time. The experimental details were $x_{CCA} = 61.5$ wt %, $x_{SO_3} = 64.2$ wt %, $x_{NOHSO_4} = 74.3$ wt %, $Q_{oil} = 40$–80 mL/min, $Q_{oleum} = 4.0$–8.0 mL/min, $Q_{NOHSO_4} = 5.6$–11.2 mL/min, $T_{ig} = 70°C$, $L_2 = 4$ m. (b) The effect of reactor bath temperature. The details were $x_{CCA} = 61.5$ wt%, $x_{SO_3} = 64.2$ wt %, $x_{NOHSO_4} = 74.3$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 8.4$ mL/min, $T_{ig} = 70$–85°C, $L_2 = 4$ m. (c) The effect of molar ratio of nitroso-sulfuric acid to mixed anhydride. The details were $x_{CCA} = 60.4$ wt %, $x_{SO_3} = 63.6$ wt %, $x_{NOHSO_4} = 72.8$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 7.7$–9.4 mL/min, $T_{ig} = 70°C$, $L_2 = 4$ m. (d) The effect of loop length. The details were the same as (a) for the 4-m loop experiment and the details for the experiment of 12-m loop were $x_{CCA} = 50.9$ wt %, $x_{SO_3} = 65.7$ wt %, $x_{NOHSO_4} = 73.1$ wt %, $Q_{oil} = 20$–40 mL/min, $Q_{oleum} = 1.7$–3.4 mL/min, $Q_{NOHSO_4} = 2.5$–5.0 mL/min, $T_{ig} = 70°C$. 40–80 mL/min extra hexane was added from the entrance of Loop 2 to prevent the complete vaporization of hexane in the microreactor. Its volumetric flow rate was considered in calculating the space-time and residence time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

works,[16,17] the operating conditions in the premixing microreactor were varied only to provide a good design and to ensure a high conversion and selectivity. The results are displayed in Figure 4. Based on the heat capacity of all reactants, the volumetric ratio of oil to oleum was fixed at 10, allowing a temperature rise in the reacting system from 23 to 66°C. (Some heat loss occurred from the pipes exiting Bath 1.) The corresponding conversions of oleum were almost 100%, showing that the reactant residence time in Loop 1 (0.83–1.65 s) was sufficient to complete the premixing reaction. At all conditions, the mixed anhydride selectivity was larger than 97%, demonstrating good process control. The effects of CCA concentration and molar ratio of CCA to sulfur trioxide were not tested in this study, because the operating conditions had previously been optimized. The results in this experiment provide important evidence that the reaction enthalpy of premixing reaction can be used to initiate the amidation reaction with high selectivity of mixed anhydride.

Conversion of mixed anhydride in the microreactor

In the second microreactor, the amidation reaction was rapidly initiated. We found that the reacting solution sprayed out at the outlet pipe of delay Loop 2, as a large amount of gas was generated in the microreactor. The mixed anhydride conversions at different operating conditions in the amidation microreactor are given in Figure 5. In Figure 5a, the space-time in the microreactor (t^*), defined as the ratio of the reactor volume to the total volumetric flow rate entering the reactor, is used to show the condition of reactant feeding

$$t^* = V_{Loop2}/(Q_{oil} + Q_{oleum} + Q_{nitroso}) \tag{6}$$

The mixed anhydride conversion in the 4-m delay loop ranges between 10 and 18% at varying space-time. As t^* is increased from its lowest value of 17.1 s, the conversion initially falls to a minimum at $t^* = 22.8$ s. With a further increase in the space-time, the conversion changes little. As a large amount of hexane and CO_2 gas was generated in the loop tube, the actual residence time of reactants in the microreactor was much shorter than the space-time. Values of residence time τ (s), given as bracketed numbers in Figure 5, were evaluated by Eq. 7

$$\tau = V_{Loop2}/(Q_{oil} + Q_{oleum} + Q_{nitroso} + Q_{CO_2} + Q_{vapor}) \tag{7}$$

The average volumetric flow rate of the gas phase ($Q_{CO_2} + Q_{vapor}$) in Eq. 7 was evaluated by applying the ideal

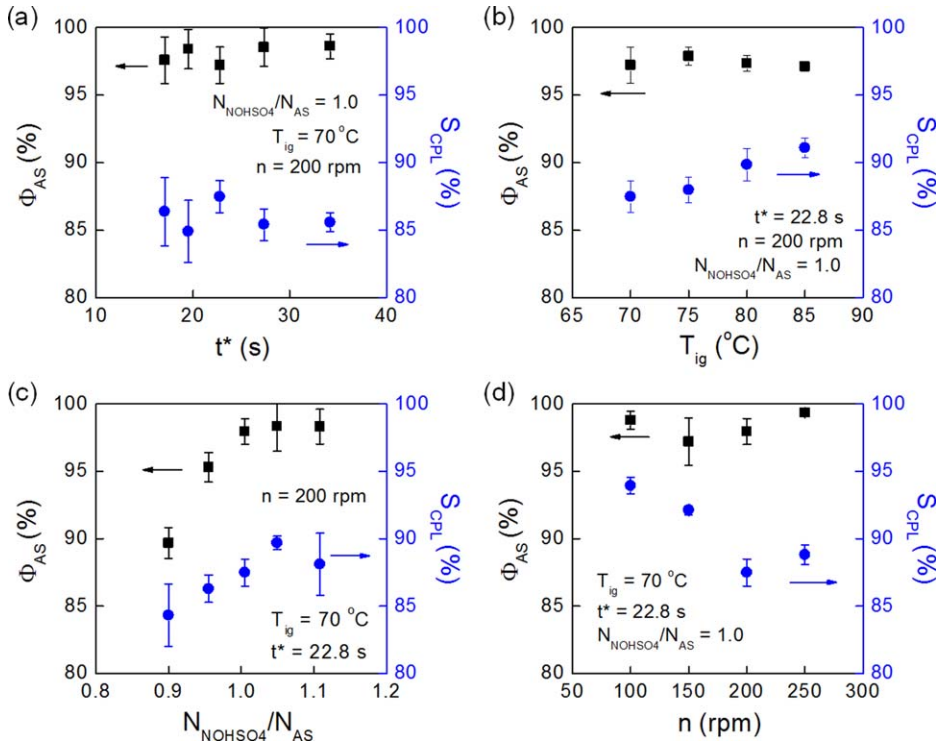


Figure 6. Mixed anhydride conversion and CPL selectivity in the whole system.

(a) The effect of space-time. The details were $x_{CCA} = 61.5$ wt %, $x_{SO_3} = 64.2$ wt %, $x_{NOHSO_4} = 74.3$ wt %, $Q_{oil} = 40$–80 mL/min, $Q_{oleum} = 4.0$–8.0 mL/min, $Q_{NOHSO_4} = 5.6$–11.2 mL/min, $T_{ig} = 70$°C, $L_2 = 4$ m, $n = 200$ rpm. (b) The effect of reactor bath temperature. The details were $x_{CCA} = 61.5$ wt %, $x_{SO_3} = 64.2$ wt %, $x_{NOHSO_4} = 74.3$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 8.4$ mL/min, $T_{ig} = 70$–85°C, $L_2 = 4$ m, $n = 200$ rpm. (c) The effect of molar ratio of nitroso-sulfuric acid to mixed anhydride. The details were $x_{CCA} = 60.4$ wt %, $x_{SO_3} = 63.6$ wt %, $x_{NOHSO_4} = 72.8$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 7.7$–9.4 mL/min, $T_{ig} = 70$°C, $L_2 = 4$ m, $n = 200$ rpm. (d) The effect of agitation. The details were $x_{CCA} = 60.4$ wt %, $x_{SO_3} = 63.6$ wt %, $x_{NOHSO_4} = 72.8$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 8.5$ mL/min, $T_{ig} = 70$°C, $L_2 = 4$ m, $n = 100$–250 rpm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

gas law to the CO_2-hexane mixture, assuming a 1/2 outlet conversion of mixed anhydride as the average value along the tube

$$Q_{CO_2} + Q_{vapor} \approx \frac{\Phi_{AS} S_{AS}}{2} (1 + \Delta_r H_n / r) \frac{Q_{oleum} \rho_{oleum} x_{SO_3}}{M_{SO_3}} \frac{RT_b}{p} \tag{8}$$

where r is the vaporization enthalpy of hexane (28.89 kJ/mol), T_b is the boiling point of hexane (341.2 K) that reflects the gas temperature, and p is the pressure at the reactor exit (101 kPa). The shorter residence time caused by the higher gas flow rate did not reduce the mixed anhydride conversion at t^* lower than 22.8 s, for the better mixing performance in microreactor at higher flow rate.[17] Another effective method to increase the mixed anhydride conversion is raising the temperature. As shown in Figure 5b, with the temperature in water Bath 3, labeled by T_{ig}, increases from 70 to 85°C, the mixed anhydride conversion increases from 10 to 22%. Thus, it is possible to increase the reaction rate using a high initiation temperature. The effect of the molar ratio of nitroso-sulfuric acid to mixed anhydride has little effect on the conversion, as shown in Figure 6c. Considering the stoichiometry of reactants, this molar ratio was not varied over a wider range. To understand the conversion of mixed anhydride at longer residence time, the 12-m delayed loop was tested in the experiment, and the conversion increased to 40%, as shown in Figure 5d. The residence time in the 12-m loop is lower than 2.3 s, much shorter than the reaction time in the vessel reactor. This result shows that the reaction rate was much higher in the microreactor, which might be because the actual temperature of the reacting dispersed phase was much higher than the boiling temperature of hexane with inadequate heat exchange between fluids. More gases were formed (4.3–7.5 L/min) in this experiment, and with consideration of operational safety, the 12-m loop was not used in the following experiment.

Selectivity of CPL

According to the reaction mechanism shown in Figure 2, good mixing of the reactants and fast consumption of the nitroso-sulfuric acid and mixed anhydride are the key factors for achieving high CPL selectivity. Figure 6 shows the final conversion of mixed anhydride and CPL selectivity in the microreactor system. At all the experimental conditions except those with a nitroso-sulfuric acid deficiency ($N_{NOHSO_4}/N_{AS} < 1$ in Figure 6c), the conversions of mixed anhydride are larger than 97%, showing that the reaction was almost completed in the vessel reactor. The effect of space-time in the amidation microreactor on the selectivity is not obvious, as shown by Figure 6a. The reason is that the reaction takes place predominantly in the vessel reactor, and the main contribution of microreactor is to provide good reactant mixing. The results of the temperature variation experiment show that selectivity increases slightly as the initiation temperature increases from 70 to 85°C. This phenomenon is interesting, as high temperature is often proposed to

Table 2. Performance Comparison Between Different Reactors

	N_{NOHSO_4}/N_{AS}	T_{ig} (°C)	n (rpm)	Φ_{AS}(%)	S_{CPL} (%)
Consecutive microreactor system in this work	1.00	70	150	97.2	92.1
	1.00	70	100	98.8	93.9
Prefed batch reactor	1.00	68	150	100	84.6
Syringe fed batch reactor	1.01	68	150	99.3	94.2

The other details in this table were $x_{CCA} = 60.4$ wt %, $x_{SO_3} = 63.6$ wt %, or 64.1 wt %, $x_{NOHSO_4} = 72.8$ wt %, $Q_{oil} = 60$ mL/min, $Q_{oleum} = 6.0$ mL/min, $Q_{NOHSO_4} = 8.5$ mL/min, $L_2 = 4$ m.

increase the rate of side reactions.[23] However, the variation of the mixed anhydride conversion in the amidation microreactor suggests that the main reaction was accelerated at higher initiation temperature. As the rapid consumption of nitroso-sulfuric acid and mixed anhydride was achieved, while control of the side reactions was maintained, the selectivity was increased. The selectivity data in Figure 6c show a maximum value at a molar ratio of nitroso-sulfuric acid to mixed anhydride of 1.05. This result is reasonable, as nitroso-sulfuric acid is also involved in the side reaction to form Side Product 2 and a slight excess of nitroso-sulfuric acid is helpful for mixed anhydride conversion. However, the ratio 1.05 is not an optimal value, as all the selectivity data in Figure 6c are lower than 90%, meaning that a substantial fraction of the mixed anhydride is converted to Side Product 1. To achieve a selectivity of close to 100%, this molar ratio should strictly be equal to 1.0.

Figure 6d displays the most interesting aspect of these results. In fact, the higher selectivity at weaker agitation was an entirely unexpected observation. As a high agitator speed promotes good heat exchange, most experiments were conducted at $n = 200$ rpm, and we found that selectivity did not increase at higher values of n. However, a selectivity of 93.9% was obtained at the lowest agitator rate of 100 rpm. This behavior can be explained by a similar effect to that of the microreactor bath temperature. As the reactant mixing was completed in the microreactor, the main effect of the agitator was to enhance heat exchange between the dispersed and continuous phases. The relatively high temperature of the reacting dispersed phase at lower agitation increased the reaction rate and realized rapid reactant consumption. This inhibited side reactions, in the same manner as the reaction enhancement process using extreme temperature and pressure.[6,7] As the majority of the reaction was conducted in the vessel reactor, the selectivity enhancement effect in Figure 6d is more obvious than the results showed in Figure 6b. For this strongly exothermal reaction, an important prerequisite to realize this high temperature enhancement strategy is the thorough mixing of reactants before they enter the reaction vessel. Without the microreactor, the low agitator speed will strongly impair the dispersion of nitroso-sulfuric acid and affect its mixing with mixed anhydride, as shown in Table 2.

Table 2 shows the comparison between the microreactor and control experiments. At almost the same operating condition, the batch reactor with prefed nitroso-sulfuric acid gave a selectivity of only 84.6%, a lower value than at all conditions in the consecutive microreactor system. In the other control experiment, a CPL selectivity of 94.2% was obtained in the same batch reactor with syringe-fed nitroso-sulfuric acid, which confirms the importance of reactant mixing in this process. The microsieve mixer has the same function as the syringe needle in dispersing nitroso-sulfuric acid, but it operates continuously. The CPL selectivity of 93.9% in the microreactor system is also much higher than the value in most industrial processes, which have nine consecutive CSTRs that are replicated by the batch fed vessel reactor in the laboratory experiment.

Conclusion

In summary, a consecutive microreactor system was designed for the highly selective synthesis of CPL from CCA. With the fast, consecutive, and strongly exothermal reactions of the chemical system, the main benefits of the microreactor system were to enable rapid mixing of the mixed anhydride and nitroso-sulfuric acid reactants, and enhancement of their consumption with controllable temperature increase. Mixed anhydride conversion of higher than 97%, and CPL selectivity close to 94% were obtained based on this selectivity enhancement principle. The selectivity enhancement effect was not observed in the common batch reactor experiment, for which selectivity was only 84.6%. The microreactor in a continuously working configuration also displays a better performance than the syringe fed method in operating the chemical synthesis process. Considering the high efficiency and reasonable energy application in this consecutive microreactor system, its optimization and scale-up[25] will be further considered in our work.

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Notation

AS = mixed anhydride
CCA = cyclohexanecarboxylic acid
CPL = caprolactam
Cp_i = heat capacity of reagent, kJ/kg°C (i refers to CCA, oleum, C_6H_{14}, and $NOHSO_4$ solution)
d_i = inner diameter of the delayed loop, mm (i refers to Loop 1 and Loop 2)
K_m = equilibrium constant of AS formation reaction
K_p = equilibrium constant of CCA protonation reaction
L_i = length of the delayed loop, m (i refers to Loop 1 and Loop 2)
M_i = molecular weight of reagent, kg/mol (i refers to CCA, SO_3, H_2SO_2, $NOHSO_4$, and CPL)
N_i = molar flow rate of reactant, mol/s (i refers to CCA, SO_3, and $NOHSO_4$)
n = agitator speed, rpm
N_i = molar flow rates mol/s (i refers to AS, CCA, SO_3, and $NOHSO_4$)
Q_i = volumetric flow rates, m^3/s (i refers to oil, oleum, nitroso-sulfuric acid solution, CO_2, and C_6H_{14} vapor)
Q_T = total volumetric flow rates of reactant solution, m^3/s
q_r = heat flux of released in the premixing reaction, W
r = vaporization enthalpy of hexane, kJ/mol
S_i = selectivity, % (i refers to AS and CPL)

T_b = boiling point of hexane, °C
T^i = local temperature, °C (i refers to inlet and outlet)
T_{ig} = temperature of amidation microreactor water bath, °C
t = vessel fed time, s
t^* = space-time in microreactor, s
x_i^j = mass fraction of reagent, wt % (i refers to CCA, SO_3, $NOHSO_4$, and CPL; j refers to oil and water phases)
$\Delta_r H_m$ = reaction enthalpy of mixed anhydride formation reaction, kJ/mol SO_3
$\Delta_r H_n$ = reaction enthalpy of amidation reaction, kJ/mol $NOHSO_4$
$\Delta_r H_p$ = reaction enthalpy of proton exchange reaction, kJ/mol H_2SO_4
Φ_i = reactant conversion, % (i refers to oleum and AS)
μ = fluid viscosity, mPa s
ρ_i = fluid density, kg/m^3 (i refers to oil, oleum, and nitroso-sulfuric acid solution)
τ = residence time in amidation microreactor, s

Literature Cited

1. Giuffre L, Tempesti E, Fornarol M, Sioli G, Mattone R, Airoldi G. New caprolactam process. *Hydrocarbon Process.* 1973;52:199–204.
2. Sioli G, Giuffre L. Make caprolactam via PMK. *Hydrocarbon Process.* 1974;53:124–126.
3. Dahlhoff G, Niederer JPM, Hoelderich WF. ε-Caprolactam: new byproduct free synthesis routes. *Catal Rev Sci Eng.* 2001;43:381–441.
4. Ikushima Y, Sato O, Sato M, Hatakeda K, Arai M. Innovations in chemical reaction processes using supercritical water: an environmental application to the production of ε-caprolactam. *Chem Eng Sci.* 2003;58:935–941.
5. Yoshida JI, Nagaki A, Yamada T. Flash chemistry: fast chemical synthesis by using microreactors. *Chem Eur J.* 2008;14:7450–7459.
6. Hessel V, Kralisch D, Kockmann N, Noel T, Wang Q. Novel process windows for enabling, accelerating, and uplifting flow chemistry. *ChemSusChem.* 2013;6:746–789.
7. Illg T, Lob P, Hessel V. Flow chemistry using milli- and microstructured reactors–from conventional to novel process windows. *Bioorgan Med Chem.* 2010;18:3707–3719.
8. Yoshida J, Nagaki A, Iwasaki T, Suga S. Enhancement of chemical selectivity by microreactors. *Chem Eng Technol.* 2005;28:259–266.
9. Nagaki A, Togai M, Suga S, Aoki N, Mae K, Yoshida J. Control of extremely fast competitive consecutive reactions using micromixing. Selective Friedel-Crafts aminoalkylation. *J Am Chem Soc.* 2005;127:11666–11675.
10. Chen YZ, Zhao YC, Han M, Ye CB, Dang MH, Chen GW. Safe, efficient and selective synthesis of dinitro herbicides via a multifunctional continuous-flow microreactor: one-step dinitration with nitric acid as agent. *Green Chem.* 2013;15:91–94.
11. Jahnisch K, Baerns M, Hessel V, Ehrfeld W, Haverkamp V, Lowe H, Wille C, Guber A. Direct fluorination of toluene using elemental fluorine in gas/liquid microreactors. *J Fluorine Chem.* 2000;105:117–128.
12. Marre S, Roig Y, Aymonier C. Supercritical microfluidics: opportunities in flow-through chemistry and materials science. *J Supercrit Fluid.* 2012;66:251–264.
13. Leclerc A, Alamé M, Schweich D, Pouteau P, Delattre C, de Bellefon C. Gas-liquid selective oxidations with oxygen under explosive conditions in a micro-structured reactor. *Lab Chip.* 2008;8:814–817.
14. Noël T, Kuhn S, Musacchio AJ, Jensen KF, Buchwald SL. Suzuki-Miyaura cross-coupling reactions in flow: multistep synthesis enabled by a microfluidic extraction. *Angew Chem Int Ed.* 2011;50:5943–5946.
15. Herath A, Dahl R, Cosford NDP. Fully automated continuous flow synthesis of highly functionalized imidazo[1,2-a] heterocycles. *Org Lett.* 2010;12:412–415.
16. Wang K, Lu YC, Shao HW, Luo GS. Improving selectivity of temperature-sensitive exothermal reactions with microreactor. *Ind Eng Chem Res.* 2008;47:4683–4688.
17. Wang K, Lu YC, Xia Y, Shao HW, Luo GS. Kinetics research on fast exothermal reaction between cyclohexanecarboxylic acid and oleum in microreactor. *Chem Eng J.* 2011;169:290–298.
18. Wang K, Lu YC, Xu JH, Gong XC, Luo GS. Reducing side product by enhancing mass-transfer rate. *AIChE J.* 2006;52:4207–4213.
19. Giuffre L, Tempesti E, Sioli G, Fornarol M, Airoldi G. Nitrosation of pentamethylene-ketene with nitrosylsulphuric acid in aqueous sulphuric acid. *Chem Ind.* 1971:1098–1099.
20. Tempesti E, Giuffre L, Sioli G, Fornarol M, Airoldi G. Mixed anhydrides of cyclohexanecarboxylic acid with sulfonic acids. *J Chem Soc Perkin Trans* 1. 1974:771–773.
21. Mattone R, Sioli G, Toderi F, Giuffre L, Tempesti E, Fornarol M. Small-scale pilot-plant development of epsilon-caprolactam synthesis via pentamethylene-ketene nitrosation with nitrosylsulfuric acid. *La Chimica e L'Industria.* 1973;55:258–261.
22. Wang K, Lu YC, Shao HW, Luo GS. Measuring enthalpy of fast exothermal reaction with micro-reactor-based capillary calorimeter. *AIChE J.* 2010;56:1045–1052.
23. Maggiorotti P. The application of the reaction calorimetry to investigate reactions involving unstable compounds. *J Thermal Anal.* 1992;38:2749–2758.
24. Tempesti E, Giuffre L, Buzziferraris G, Sioli G, Serena F, Montoneri E. Investigation into kinetics of reaction between cyclohexanecarboxylic acid and oleum. *La Chimica e L'Industria.* 1976;58:247–251.
25. Wang K, Lu YC, Shao HW, Luo GS. Strategy for scaling-up of a microsieve dispersion reactor. *Chem Eng Technol.* 2014;37:2116–2122.

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