



# Process design of two-step mononitration of *m*-xylene in a microreactor

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Received: 21 March 2022 / Accepted: 16 May 2022 / Published online: 8 June 2022  
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## Abstract

In this study, *m*-xylene nitration was scaled up in a microreactor. The effects of temperature, molar ratio, and mass fraction of sulfuric acid on the two synthesis methods were systematically analyzed. The reaction temperature and mass fraction of sulfuric acid are the main factors influencing the generation of poly-nitro impurities when the mixed acid reacts with *m*-xylene. When the mixed acid is used as the nitrating agent, it is difficult to control the product selectivity and the yield of poly-nitro impurities by changing the reaction conditions. A two-step nitration method was designed to solve the problems of product selectivity and yield of poly-nitro impurities. In the first step, nitric acid is used as a nitrating agent to react with *m*-xylene. In the second step, sulfuric acid is added to the second microreactor. It acts as a catalyst to continue activating the nitric acid in the first step to react with the unconverted *m*-xylene. Under the optimal experimental conditions, the yield of mono-nitro products reached 99%, and throughput of 1 kg/h. It has good advantages for industrial production compared with other methods reported in the literature. The way presented in this study can provide a reference for the design of kilogram-scale synthesis with rapid and high exothermic reactions in microreactors.

**Keywords** Microreactor · Two-step · nitration · *m*-xylene · Kilogram-scale

## Introduction

In a conventional batch reactor performing an exothermic reaction, for some reason, thermal runaway can be caused if the heat generated by the reaction process exceeds the heat removed by cooling [1, 2]. The nitration of aromatics compounds is one of the highly exothermic reactions [3]. In traditional industries, the nitration of aromatic compounds was mainly carried out in a batch or semi-batch way [4–6]. Nitration is a hazardous chemical process since reaction rates are susceptible to variations in operating conditions [7–9]. At the same time, the nitration of aromatic compounds is a liquid-liquid heterogeneous reaction and generates a lot of heat in the reaction process. Suppose the heat transfer efficiency is insufficient. In that case, it may

lead to heat accumulation and significant temperature rise, which will lead to side reactions and increase the risk of reaction [10–14]. Thermal runaway frequently occurs during the nitration of aromatic compounds in batch reactors. The nitration reaction often causes explosions, so it is one of the most dangerous chemical reactions in the industries [15–18]. The safety issue of nitration has been a long concern due to frequently occurring accidents.

In this context, using small volume reactors and continuous reaction processes is an attractive and safe way to perform nitration experiments. Compared with the batch reactors, the advantages of the microreactor are the high surface to volume ratio, small online liquid holding capacity, and small dimensions of pathways. The specific surface area in microreactors can achieve  $10^3$  to  $10^4 \text{ m}^2 \cdot \text{m}^{-3}$ , which is one to two orders of magnitude higher than that of the batch reactor [19–24]. Therefore, the microreactor has high heat transfer efficiency and can ensure the temperature stability of the reaction process. The high heat transfer and heat removal efficiency and continuous operation process reduced the risk of thermal runaway and improved the essential safety of the reaction process. On the other hand, due to the tiny microchannel size, the total amount

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of dangerous reactants in the reactor is small [25, 26]. The potential explosion severity in a microreactor is low. In addition, the reaction time can be reduced to a few milliseconds due to the small amount of liquid held. Therefore, the microreactor is suitable for rapid and high exothermic reaction process design. Microreactor technology has developed rapidly in the last two decades. It is widely used in chemical synthesis. Most successfully, using microreactor technology for rapid reactions with mixing or transport limitations can improve reaction performance, such as nitration [27–29]. Russo [30] reported the synthesis of nitrobenzaldehyde by benzyl alcohol with mixed acids in a microreactor. The yields of the ortho- and meta-isomers products can reach 42% and 96%, respectively, which is impossible in a batch reactor. Xie [31] reported a method for synthesizing kilogram-scale piperacillin in a microreactor. The micro-flow system consists of two membrane dispersion microreactors connected in series. By varying the size and cross-sectional area of the membranes, yields of 94.70% and purity exceeding 99.7% were obtained. Yu [32] reported an experimental study of adiabatic reactions in a microreactor. In the microreactor, the yield of 1-methyl-4-(methylsulfonyl)benzene with mixed acids reached 98% within a residence time of 5 s. Sharma et al. [33] studied the reactions of different nitrifiers to *o*-xylene in microreactors and discussed the economic feasibility. The results show that adopting the digital method is the most economical way to increase production capacity. Although the scale-up design and high-throughput capacity of micro-reaction processes are achieved in these studies, thermal management is often neglected, and safety issues are not taken seriously.

The earliest report in the literature was the synthesis of nitro-*m*-xylene by the reaction of *m*-xylene catalyzed by boron trifluoride and silver nitrate proposed by Olah [34]. Dong [35] reported the nitration of *m*-xylene catalyzed by zeolite H $\beta$  with nitric acid and acetic anhydride via acetyl nitrate as nitrating species. Kantam [36] et al. reported the nitration of *m*-xylene catalyzed by b-zeolite with nitric acid and acetic anhydride. Bharadwaj [37] nitrated *m*-xylene catalyzed by Al(H<sub>2</sub>PO<sub>4</sub>)<sub>3</sub> and acid phosphate-impregnated titania. Wang [38] and coworkers reported the regioselective nitration of *m*-xylene under phase-transfer catalysis. An efficient and environmentally friendly catalyst is a sought-after goal. But it is still not available for industrial production. The constraints of applying this method are the lengthy reaction time, complicated operation process, and time-consuming catalyst characterization process, so it is only suitable for laboratory studies. A large amount of literature has reported methods for the nitration of aromatic compounds in microreactors. Sagandira [39] reported a flow procedure for the synthesis of nitration of *m*-xylene in a 2 mL glass chip reactor affording assay yields greater than 90% and

95% selectivity in 6 min residence time with a throughput of 16.6 g/h. The nitration of *m*-xylene in microreactors has been rarely reported, especially synthesis process at the kilogram level. In summary, the development and design of the nitration of *m*-xylene in a microreactor is the most promising potential for industrial production.

Several reviews have demonstrated that microreactor technology can successfully perform nitration reactions [40–42]. However, there are still bad cases of process design and scale-up of highly exothermic reactions in a microreactor. Here we focus on design. Process safety should draw more attention as the enlarged reactor may not be inherently safe anymore. We first used the process parameters for the synthesis of nitro *m*-xylene in a batch reactor as the basis for our study. A two-step nitration process consisting of two microreactors connected in series was designed. Finally, we compare the process with those reported in the literature and provide an outlook.

## Experimental

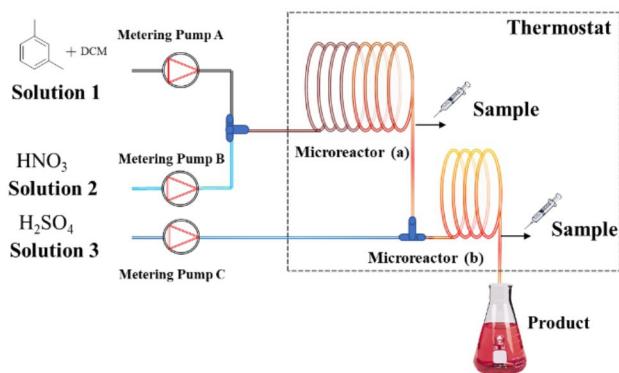
### Materials and devices

*m*-xylene, Na<sub>2</sub>SO<sub>4</sub>, methylene chloride, and NaOH were purchased from Nanjing JuYou Technology Co., Ltd, China, H<sub>2</sub>SO<sub>4</sub> (concentration of > 98%) and HNO<sub>3</sub> (concentration of > 96%) were supplied by NanJing University Science &Technology, China. All chemicals were used without further purification.

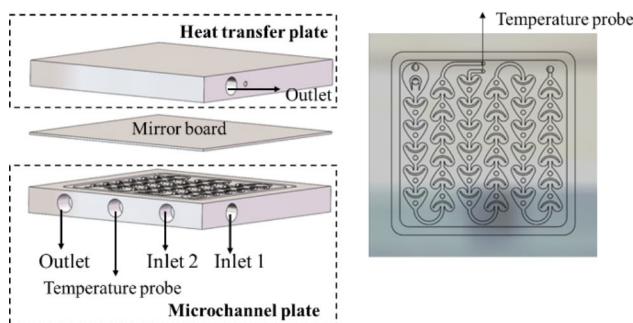
Metering Pump (Sanotac-MPF0502C, China), refrigerated/heated circulator (GDSZ-50 L-30 °C, Zhengzhou Ruihan Instrument Co., Ltd., China), microreactor (VMRHS0030-1903, HC276, China), microreactor (entrance diameter 3 mm, width 1.5 mm, groove depth 1.3 mm, column diameter 2 mm, total liquid volume 60mL, each microchannel plate liquid volume 3mL).

### Procedures

Continuous flow nitration of *m*-xylene is illustrated in Figure 1 and Figure 2. The experimental setup consisted of three metering pumps. Solution 1 contains *m*-xylene and dichloromethane (DCM) (1:1, w/w), solution B (nitric acid, 98 wt%), solution 3 (sulfuric acid, 80 wt%). Solutions 1 and 2 were introduced to the microreactor (a) via metering pumps a and b. Solution 3 and the solution of microreactor (a) entered the microreactor (b). The temperature control system of the two microreactors is controlled by high and low-temperature circulation equipment. Samples were collected in a fixed quantity of ice-cold water at different outlets (corresponding to other residence times). The primary body



**Fig. 1** Scheme of the setup for micro-flow synthesis mono-nitration of *m*-xylene



**Fig. 2** Structure diagram of the microreactor

material of the microreactor was fabricated by Hartz alloy (HC276). It consists of three layers: the heat transfer layers are located on the top and bottom, and the reaction layer is in the middle. The reaction layer comprises many heart-shaped cells (six rows, 36 cells). Each heart-shaped unit has a different cross-section and internal obstacles, a cylindrical column, and a U-shaped structure (see Figure 2), forming a series of convergent-divergent sections to increase the mass transfer rate.

## Analysis

Collected samples were analyzed by Gas chromatography (GC, Bruker 450-GC), equipped with an AESE-54 capillary column ( $30\text{ m} \times 0.32\text{ mm} \times 0.5\text{ }\mu\text{m}$ ) and a flame ionization detector (FID). The column temperature started at  $100\text{ }^\circ\text{C}$  for 3 min, then increased to  $280\text{ }^\circ\text{C}$  at a rate of  $10\text{ }^\circ\text{C}/\text{min}$  and held for 15 min. The temperatures of the gasification chamber and detecting chamber were both  $300\text{ }^\circ\text{C}$ .

The following equations calculate the selectivity:

$$\text{Selectivity} = \frac{C_{MP}}{C_{MP} + C_{SP}} \quad (1)$$

$C_{MP}$  is the concentration of the main product in the collected samples, mol/mL;  $C_{SP}$  is the concentration of side product in the collected samples, mol/mL.

Residence time ( $t$ ) in microreactor is defined as follows Eq. (2):

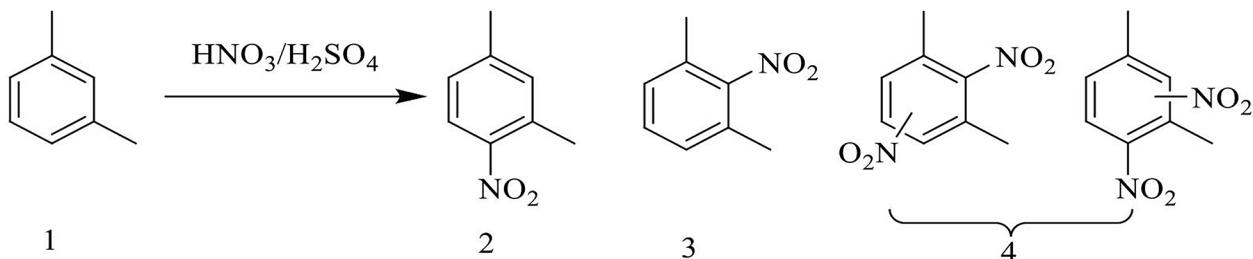
$$t = \frac{V}{Q_{or} + Q_{aq}} \quad (2)$$

Where  $V$ ,  $Q_{aq}$ , and  $Q_{or}$  are the microchannel volume, aqueous volumetric flow rate, and organic volumetric flow rate.

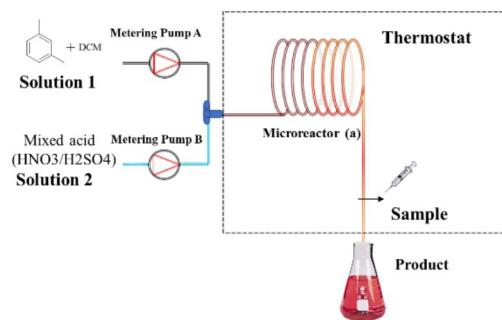
## Results and discussion

### Traditional nitration method: mixed acid reacted with *m*-xylene

The research on traditional nitration of aromatic compounds mainly used mixed acid to react with aromatic compounds to obtain nitro-aromatic compounds. The current industrial production of mixed acid mainly consists of nitric acid and sulfuric acid [43, 44]. The most common nitration method in the micro-flow system is the aromatic compounds and mixed acid introduced into the microreactor by metering pumps. Figure 3 shows the flow chart of the reaction of



**Scheme 1** Nitration of *m*-xylene. (1): *m*-xylene (2) 2,4-Dimethyl-nitrobenzene (2,4-nitro) (3): 2,6-Dimethyl-nitrobenzene (2,6-nitro) (4): poly-nitro impurity



**Fig. 3** Schematic of traditional nitration method

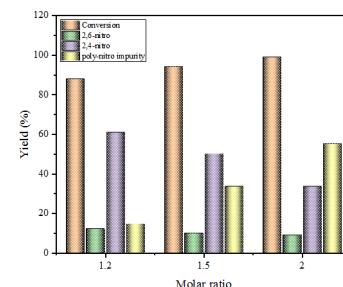
*m*-xylene with mixed acid. Prepared mixed acid solution and *m*-xylene solution introduced into the microreactor by two metering pumps and adjusted the molar ratio of nitric acid to *m*-xylene by changing the volume flow rate and increasing the residence time by increasing the microchannel plate. The synthesis route is shown in scheme 1.

#### Effect of molar ratio of $\text{HNO}_3/\text{m-xylene}$

The molar ratio is one of the most important influencing factors of nitration reaction, which affects the conversion rate of *m*-xylene and directly relates to the generation of poly-nitro products. At the same time, nitric acid is an unstable compound, which is readily decomposed under high-temperature conditions and brings trouble to the reaction process, so it is crucial to choose a suitable molar ratio. Figure 4 shows the effect of the molar ratio of nitric acid to *m*-xylene on the reaction. Experimental data were obtained by adjusting the volume flow rate of mixed acid and *m*-xylene at the same residence time conditions. It is clear from the figure that the molar ratio has a positive relationship with the conversion and poly-nitro impurities yield. The conversion increased from 88% to 99%, and the poly-nitro impurities rose from 14.6% to 55.3%. It is not difficult to understand that the increase in molar ratio leads to the rise in  $\text{NO}_2^+$  in the mixture, which improves the contact chance of  $\text{NO}_2^+$  with *m*-xylene. However, although the molar ratio increases the conversion, the yield of the mono-nitro products gradually decreases because the mono-nitro products continue to be replaced by  $\text{NO}_2^+$  to form the poly-nitro products. It was evident that the molar ratio is an essential factor affecting the reaction. Although a good conversion was obtained, the content of poly-nitro impurities failed to reach the desired target.

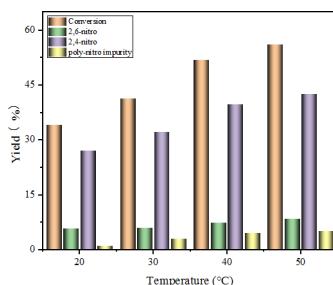
#### Effect of temperature on the reaction

Nitration reaction is a fast exothermic reaction. At the same time, the reaction rate is closely related to the reaction temperature. The side reactions are susceptible to the reaction

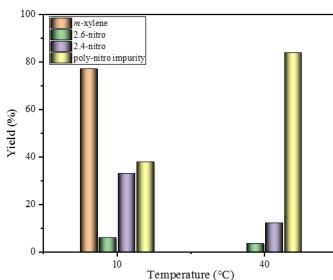


**Fig. 4** Effect of molar ratio of  $\text{HNO}_3/\text{m-xylene}$ .  $\text{H}_2\text{SO}_4 = 90\text{wt}\%$ ,  $\text{HNO}_3 = 98\%$ ,  $\text{S/N} = 1.45$ ,  $T = 20\text{ }^\circ\text{C}$ , total residence time = 1 min,  $Q_{\text{total}} = 30\text{ mL/min}$ ,  $Q_{\text{or}} = 13.2 \sim 16.9\text{ mL/min}$ ,  $Q_{\text{aq}} = 13.1 \sim 16.8\text{ mL/min}$

temperature. High reaction temperature or local hot spots are some conditions leading to side reactions. The strength of sulfuric acid directly affects the rate of  $\text{NO}_2^+$  production. Figure 4 shows that when  $\text{S/N} = 1.45$  and 90% of sulfuric acid, the content of poly-nitro impurities 12%~50% in the molar ratio of nitric acid to *m*-xylene is between 1.2~2. Therefore, we designed to examine the effect of temperature on the reaction results at a lower molar ratio of sulfuric acid to nitric acid. The experimental results are presented in Figure 5. The conversion of *m*-xylene, the yield of mono-nitro products, and poly-nitro impurities are all positively proportional to the reaction temperature at 20–40 °C. The conversion of *m*-xylene has a significant growth rate from 34.1 to 51.8%. However, when the reaction temperature is 40–50 °C, the conversion rate increases slowly. It may be because the nitration capacity of nitration agents is weak, and the growth of reaction temperature accelerates the decomposition rate of nitric acid, so the conversion rate increases slowly. Compared with Figure 3, the conversion rate decreased significantly with decreasing sulfuric acid mass fraction and molar ratio of sulfuric acid to nitric acid under the same conditions. According to the nitration reaction mechanism, the water produced decreases nitration capacity. When sulfuric acid is diluted by water, the catalytic ability decreases, lowering the reaction rate. Therefore, it isn't easy to obtain satisfactory results under low sulfuric acid content conditions, even if the reaction temperature increases. Figure 6 shows the effect of sulfuric acid strength on the reaction at temperatures of 10 and 40 °C, respectively. At the strength of  $\text{HNO}_3$  (70%) and  $\text{H}_2\text{SO}_4$  (98%) and  $\text{HNO}_3/\text{m-xylene}$  ratio (1.5:1) and  $\text{S/N} = 2.33:1$ , the results indicated that poly-nitro impurities are the major products. The yield of poly-nitro impurities reached 37% at 10 °C. When the reaction temperature was 40 °C, the yield of poly-nitro impurities reached 84%. It may be because the generation rate of  $\text{NO}_2^+$  is greater than the nitration reaction of *m*-xylene. It can be concluded from Figure 5 and Figure 6 that the reaction temperature and the strength of sulfuric acid are the main factors affecting the production of poly-nitro impurities.



**Fig. 5** Effect of temperature on the reaction.  $\text{H}_2\text{SO}_4=70\text{wt}\%$ ,  $\text{HNO}_3=98\%$ ,  $\text{S/N}=0.8$ , total residence time = 1 min, molar ratio ( $\text{HNO}_3/m\text{-xylene}$ ) = 2:1,  $Q_{\text{or}}=14.2 \text{ mL/min}$ ,  $Q_{\text{aq}}=15.8 \text{ mL/min}$



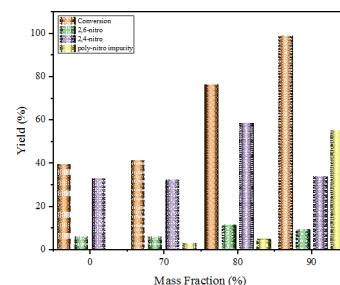
**Fig. 6** Effect of temperature on the reaction.  $\text{H}_2\text{SO}_4=98\text{wt}\%$ ,  $\text{HNO}_3=70\%$ ,  $\text{S/N}=2.33$ , total residence time = 1 min, molar ratio ( $\text{HNO}_3/m\text{-xylene}$ ) = 1.5:1,  $Q_{\text{or}}=10 \text{ mL/min}$ ,  $Q_{\text{aq}}=20 \text{ mL/min}$

### Effect of the sulfuric acid mass fraction on the reaction

In the nitration reaction, the attack of  $\text{NO}_2^+$  on the aromatic compounds determines the reaction rate. The rate of  $\text{NO}_2^+$  production depends on the strength of sulfuric acid, so it is crucial to study the effect of the sulfuric acid mass fraction on the reaction. In the nitration process, sulfuric acid's high viscosity and strength may limit the reaction rate and affect the mass transfer effect [45, 46]. Figure 7 shows the effect of sulfuric acid with mass fractions from 0 to 90% on the reaction, with a significant increase in conversion and impurity yield as the mass fraction of sulfuric acid increases. In particular, the poly-nitro impurity yields increased 11-fold from 4.9 to 55% at 80% and 90% sulfuric acid mass fractions. The nitration capacity and reaction rate of the nitration agent is a function of sulfuric acid. The higher the strength of sulfuric acid, the higher the conversion and the lower the selectivity. At the same time, temperature affects one of the main factors of by-product generation. The experimental results revealed an interesting phenomenon. When only nitric acid was used as a nitrating agent, almost no poly-nitro impurities were formed.

### Two-step nitration process

Figure 5 shows that the higher temperature, the higher the content of poly-nitro products. Nitration is a rapid exothermic



**Fig. 7** Effect of sulfuric acid mass fraction on the reaction.  $\text{H}_2\text{SO}_4=70\sim90\text{wt}\%$ ,  $\text{HNO}_3=98\%$ ,  $\text{S/N}=1$ ,  $T=20^\circ\text{C}$ , total residence time = 1 min, molar ratio ( $\text{HNO}_3/m\text{-xylene}$ ) = 2:1,  $Q_{\text{total}}=30 \text{ mL/min}$ ,  $Q_{\text{or}}=13.2\sim14.2 \text{ mL/min}$ ,  $Q_{\text{aq}}=15.8\sim16.8 \text{ mL/min}$ . (The mass fraction “0” means the reaction is done without  $\text{H}_2\text{SO}_4$ )

reaction. The main ways to avoid thermal runaway include reducing the exothermic reaction rate and increasing the coolant heat removal rate. In general, poly-nitro products require very high temperatures. A high sulfuric acid strength favors conversion rate but degrades selectivity. As shown in Figure 7, at the same temperature, the content of poly-nitro products when the mass fraction of sulfuric acid reaches 90% is 11 times that when the mass fraction comes to 70%. The concentrations of reactants were high at the beginning, leading to a fast reaction rate and high heat generation rate. In the case of speedy and strongly exothermic reactions, even the superior heat transfer characteristics of the micro-reactor may not be sufficient to avoid hot spots in the inlet region of the reactor, and side reactions may still occur.

Temperature ( $T$ ) and concentration of the reactants ( $C$ ) vary with the reaction process or time, and the reaction rate can be expressed as a function of time ( $t$ ), namely  $r=f(t)$ . However, in the microreactor,  $T$  and  $C$  vary along the reactor channel, which means they are dependent on the location, namely  $r=f(z)$  [47]. The batch operation can control the reaction time and reduce the exothermic rate of the reaction by adding the material slowly to the batch reactor. However, the heat release rate of reaction in the microreactor is a function of space, and the heat release of reaction is mainly concentrated in the front of microchannel plates. Therefore, by controlling the heat removal rate of the front reaction module or reducing nitration capacity, the heat release rate of the reaction can be promoted smoothly. For industrial-scale amplification, increasing the heat removal rate of coolant requires high energy consumption, and the heat transfer area can not be infinitely amplified. Based on this, we designed a method to reduce the nitration capacity of the nitration agent and reduce the heat release rate of the reaction.

Inspired by the above experimental results (Figure 7), no poly-nitro products were generated when nitric acid was used as a nitrating agent. However, the *m*-xylene is difficult to achieve complete conversion due to the mild nitration

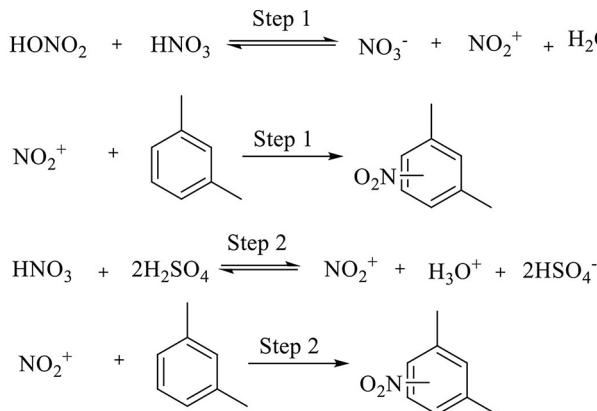
capacity of nitric. When mixed acid was chosen as a nitrating agent, sulfuric acid improved the  $\text{NO}_2^+$  production capacity [48]. It is difficult to find the optimal reaction temperature and composition of the mixed acid to ensure high conversion of *m*-xylene and low yield of poly-nitro impurities. We designed a two-stage nitration method assembled by three metering pumps and two microreactors. In the first step, *m*-xylene reacted with nitric acid in the first microreactor. The water produced by the reaction reduced the nitration capacity of nitric acid, resulting in the incomplete conversion of *m*-xylene. In the second step, sulfuric acid is used to catalyze nitric acid to react with the remaining *m*-xylene.

### Mechanism of two-step nitration process

The reaction mechanism was shown in Scheme 2. The nitration process of *m*-xylene consists of two steps. Fuming nitric acid is used as a nitrating agent in the first step. One molecule of nitric acid acts as a protonic acid to supply  $\text{H}^+$  to another molecule of nitric acid, causing the nitric acid to undergo protonation to form nitronium ions ( $\text{NO}_2^+$ ) [49, 50].  $\text{NO}_2^+$  is a powerful electrophilic reagent and reacts electrophilically with *m*-xylene. The nitration ability of nitric acid was weak. The nitration activity of nitric acid was gradually inhibited by the water produced by the reaction as the reaction proceeded. Therefore, we obtained the idea of the second nitration step method. Nitric acid in the first step has a weak nitration capacity. The solid acid (sulfuric acid) as a strong protonic acid can activate nitric acid well, and it is easier to form  $\text{NO}_2^+$ , which facilitates the nitration reaction.

### Effect of temperature on the reaction

Combining the results of the studies in 3.1.1 and 3.1.3, we first determined the molar ratio of nitric acid to *m*-xylene to be 2:1, the mass fraction of sulfuric acid 80%, and the molar ratio of sulfuric acid to *m*-xylene 1.5:1. The effect of reaction temperature on the reaction was studied, shown in Figure 8.

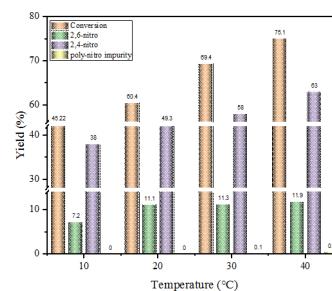


**Scheme 2** Mechanism of two-step nitration of *m*-xylene

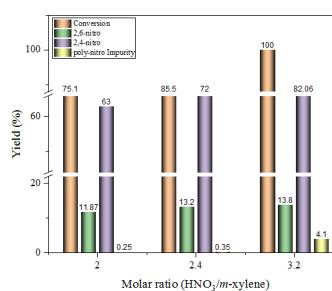
First, it can be seen that there is a significant reduction in the yield of poly-nitro impurities, which indicates that this method is feasible. As with the above analysis, the conversion of *m*-xylene and the yield of the mono-nitro products positively correlate with the reaction temperature. Since the nitration reaction is exothermic, the reaction temperature was not further increased for safety reasons. It is because too high a temperature will vaporize the solvent and cause a change in the flow pattern in the channel. Compared with mixed acids as nitrating agents, poly-nitro impurities were formed when the temperature reached 30 °C. In contrast, when mixed acids were used as a nitrating agent, poly-nitro impurities were always present at 10 ~ 40 °C.

### Effect of molar ratio on the reaction

Figure 9 shows the effect of the molar ratio of nitric acid to *m*-xylene on the reaction. The conversion, mono-nitro products, and poly-nitro impurities yields are proportional to the molar ratio. It can be seen that when the molar ratio reaches 3.2, the conversion of *m*-xylene reaches 100%, the yield of the mono-nitro products reaches 95.9%, and the poly-nitro impurities yield reaches 4.1%. Compared with the mixed acid as a nitrating agent, the poly-nitro impurities yield reduced from 55% (Figure 7) to 4.1%. The higher the



**Fig. 8** Effect of temperature on the reaction.  $\text{H}_2\text{SO}_4=80\text{wt}\%$ ,  $\text{HNO}_3=98\%$ , total residence time = 104 s, molar ratio (*m*-xylene/ $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) = 1:2:1.5,  $Q_{m-\text{xylene}}=21.1$  mL/min,  $Q_{\text{HNO}_3}=8.9$  mL/min,  $Q_{\text{H}_2\text{SO}_4}=11.2$  mL/min



**Fig. 9** Effect of molar ratio of  $\text{HNO}_3$  to *m*-xylene.  $\text{H}_2\text{SO}_4=80\text{wt}\%$ ,  $\text{HNO}_3=98\%$ ,  $T=40$  °C, total residence time = 104 s, molar ratio (*m*-xylene/ $\text{H}_2\text{SO}_4$ ) = 1:1.5,  $Q_{m-\text{xylene}}=18 \sim 21.1$  mL/min,  $Q_{\text{HNO}_3}=8.9 \sim 12$  mL/min,  $Q_{\text{H}_2\text{SO}_4}=9.6 \sim 11.2$  mL/min

mass fraction of sulfuric acid, the faster the reaction rate, the more challenging it is to control the side reactions, and the higher the content of poly-nitro impurities.

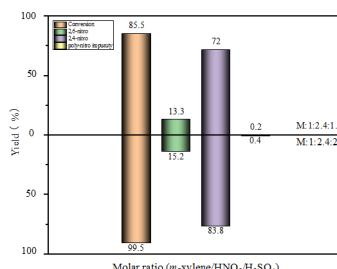
Figure 10 shows the effect of the molar ratio of sulfuric acid to *m*-xylene on the reaction. In agreement with the previous analysis, the conversion of *m*-xylene and the yield of poly-nitro impurities increased significantly with the increase of the molar ratio of sulfuric acid to *m*-xylene. The optimum molar ratio of 1:2.4:2 was obtained from the above analysis.

### Effect of the sulfuric acid mass fraction on the reaction

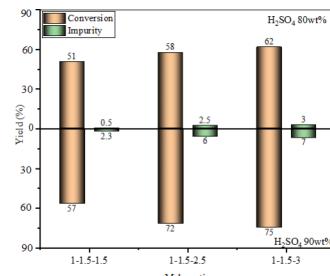
The effect of the mass fraction of sulfuric acid on the reaction has been discussed in Sect. 3.1.3. Increasing the molar ratio and concentration of sulfuric acid increases the conversion of *m*-xylene. Therefore, Figure 11 shows the conversion of *m*-xylene and poly-nitro impurities yield change by increasing the molar ratio and mass fraction of sulfuric acid examined under the same molar ratio of nitric acid to *m*-xylene. The same conclusion was reached as before, the molar ratio and mass fraction of sulfuric acid have a positive relationship with *m*-xylene conversion and poly-nitro impurities yield. Conversions of *m*-xylene reached 62% and 75%, and the poly-nitro impurities yields 3% and 7%, respectively, on the molar ratio of 1:1.5:3 and 25 °C. It shows that the method is not feasible. Because the yield of poly-nitro impurities is challenging to control, as the molar ratio of sulfuric acid increases, the reaction rate increases, and the reaction temperature must be reduced to prevent the generation of side reactions. However, long reaction times must be sacrificed to achieve the desired conversion rate, which is the opposite of what we designed for, so we did not continue our research in this area.

### Effect of residence time on the reaction

The residence time is one of the critical factors affecting the reaction, and an appropriate residence time can effectively reduce the yield of poly-nitro impurities. Meanwhile,



**Fig. 10** Effect of molar ratio of H<sub>2</sub>SO<sub>4</sub> to *m*-xylene. H<sub>2</sub>SO<sub>4</sub>=80wt%, HNO<sub>3</sub>=98%, T=40 °C, total residence time=104 s, molar ratio (*m*-xylene/HNO<sub>3</sub>)=1:2.4, Q<sub>*m*-xylene</sub>=20 mL/min, Q<sub>HNO<sub>3</sub></sub>=10 mL/min, Q<sub>H<sub>2</sub>SO<sub>4</sub></sub>=10 mL/min and 14.1 mL/min

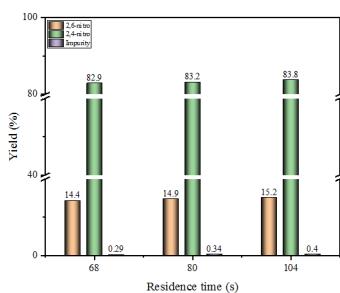


**Fig. 11** Effect of sulfuric acid mass fraction on the reaction. T=25 °C, total residence time=104 s, molar ratio (*m*-xylene/HNO<sub>3</sub>)=1:1.5, Q<sub>*m*-xylene</sub>=22.8 mL/min, Q<sub>HNO<sub>3</sub></sub>=7.2 mL/min, Q<sub>H<sub>2</sub>SO<sub>4</sub></sub>=12.1 mL/min~24.1 mL/min

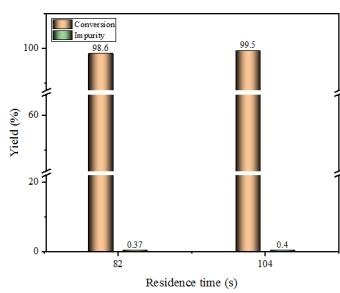
choosing an optimal residence time is also a key parameter for designing the reactor. At the same flow rate, the longer the residence time, the more microreactor plates are required, increasing the manufacturing cost. Figure 12 represents the variation of residence time in the first nitrification reaction by increasing the number of reactor plates. The first microreactor was selected with 4, 6, and 10 plates, and the number of plates in the second microreactor was not changed. There was a slight increase in the mono-nitro products and poly-nitro impurities yields, increasing the residence time. Figure 13 shows the effect of varying the residence time of the second segment on the reaction. Since the second microreactor designed only four plates, we chose to take samples in the second reactor plates for comparison. The experimental results show that there has 1.4% *m*-xylene unconverted. Therefore, the above experimental results show that the optimal total residence time is 104 s. Figure 14 analyzes the relationship between conversion rate and residence time for the two-step nitration method. It can be seen that the conversion rate has a positive proportional relationship with the residence time. As the residence time increases, the conversion rate gradually decreases because the water produced by the reaction reduces the nitration capacity. The conversion rate of 90% HNO<sub>3</sub> is significantly lower than that of 98% HNO<sub>3</sub>, demonstrating the effect of water on the nitration reaction. However, the addition of H<sub>2</sub>SO<sub>4</sub> increased the conversion from 69.2 to 99.5%.

### Comparison with *m*-xylene nitration reaction literature

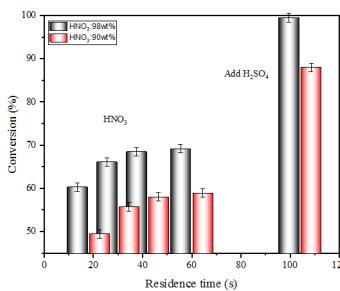
Table 1 shows the experimental data on *m*-xylene nitration that have been reported in the literature so far. Entry 1~5 in Table 1 are batch reactors, and entries 6~7 in Table 1 are microreactors. The *m*-xylene nitration reactions in the literature mainly aim to improve selectivity. High selectivity of entry 1~5 experimental data in Table 1 was achieved under different catalyst conditions with conversions rang 69–100% and reaction times 10 min~12 h. Although the selectivity is



**Fig. 12** Effect of residence time on the reaction.  $\text{H}_2\text{SO}_4 = 80\text{wt}\%$ ,  $\text{HNO}_3 = 98\%$ ,  $T = 40^\circ\text{C}$ , molar ratio (*m*-xylene/ $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) = 1:2.4:2,  $Q_{m\text{-xylene}} = 20 \text{ mL/min}$ ,  $Q_{\text{HNO}_3} = 10 \text{ mL/min}$ ,  $Q_{\text{H}_2\text{SO}_4} = 14.1 \text{ mL/min}$



**Fig. 13** Effect of total residence time on the reaction.  $\text{H}_2\text{SO}_4 = 80\text{wt}\%$ ,  $\text{HNO}_3 = 98\%$ ,  $T = 40^\circ\text{C}$ , molar ratio (*m*-xylene/ $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) = 1:2.4:2,  $Q_{m\text{-xylene}} = 20 \text{ mL/min}$ ,  $Q_{\text{HNO}_3} = 10 \text{ mL/min}$ ,  $Q_{\text{H}_2\text{SO}_4} = 14.1 \text{ mL/min}$



**Fig. 14** Effect of total residence time on the reaction.  $\text{H}_2\text{SO}_4 = 80\text{wt}\%$ ,  $T = 40^\circ\text{C}$ , molar ratio (*m*-xylene/ $\text{HNO}_3/\text{H}_2\text{SO}_4$ ) = 1:2.4:2,  $Q_{m\text{-xylene}} = 20 \text{ mL/min}$ ,  $Q_{\text{HNO}_3} = 10\text{--}10.2 \text{ mL/min}$ ,  $Q_{\text{H}_2\text{SO}_4} = 14.1 \text{ mL/min}$

higher than in this paper, the longer reaction time and the cost of catalyst manufacture are still challenging to achieve

for industrial production. Entry 6 in Table 1 shows the reaction with *m*-xylene in a microreactor using a mixed acid as a nitrating agent. Compared with the entry 6 this work has four advantages. First, the throughput is 1 kg/h, higher than 16.6 g/h. Second, the residence time is 104 s, lower than 6 min. Third, the selectivity is also higher than entry 6. Four, the conversion of this work was 99.5%, and entries 6 was 90%. Unlike the phenomena observed during the entry 6 experimental, this work did not show blockage or other faults. The pressure drop is also lower than the maximum upper limit of the pump (2 mPa). The comparison of the above experimental data is sufficient to prove the applicability of the experimental method designed in this paper. The comparison of reaction time, conversion, and selectivity are the most reported advantages in the literature for industrial production.

### Comparison of batch and continuous flow reaction

Table 2 shows the comparison between batch and continuous flow reactions. Hence, the space-time yield of the microreactor was two orders of magnitude higher than the batch reactor. Reaction temperatures in microreactors are lower than in batch reactors, and the duration in flow systems is much shorter. Moreover, the total inventory of reactants in the microreactor was smaller than that in the batch reactor. It was the crucial point making microreactors inherently safer.

### Conclusions

A continuous flow two-step nitration process was designed and used to synthesize kilograms-scale nitration of *m*-xylene. Several key factors were investigated systematically: temperature, molar ratio, residence time, and sulfuric acid mass fraction. The results show that temperature and mass fraction of sulfuric acid are the most critical factors affecting the reaction. Compared with the batch reactor, the reaction rate is not easy to control when mixed acid is used as a nitration agent in a microreactor. Compared with the traditional one-step nitration method, the two-step nitration

**Table 1** Analysis of literature on *m*-xylene nitration

Entry	Authors	Catalyst	Residence time	Conversion (%)	Isomer selectivity (%)	
					2,6-nitro	2,4-nitro
1	Wang [38]	SDBS	4.5 h	97.8	9.2	90.4
2	Waller [51]	Lanthanide	12 h	95	15	85
3	Kantam [36]	$\beta$ -zeolite	4 h	69	14	86
4	Bharadwaj [37]	$\text{Al}(\text{H}_2\text{PO}_4)_3$	10 min	99	-	90
5	Dong [35]	Zeolite H $\beta$	10 h	100	6.5	93.5
6	Sagandira [39]	NO	6 min	90	20	80
7	In this work	NO	104 s	99.5	15.2	83.8

1~5: Batch reactor; 6~7: Microreactor. 4: The catalyst was prepared at 200–220 °C and heated for 12 h

**Table 2** Comparison between batch and continuous flow reaction

	Batch reaction(a)	Con- tinu- ous flow
Reaction time (s)	16,200	60
Temperature (°C)	50	40
Catalyst	Sodium dodecyl sulfate (1%wt)	No
Space time yield ( $\text{g} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$ )	0.01475	4.093

a Wang [38]: *m*-xylene (0.08 mol), 65%  $\text{HNO}_3$  (0.08 mol), 98%  $\text{H}_2\text{SO}_4$  (0.05 mol), batch reactor (50 mL)

method can effectively reduce the yield of poly-nitro impurities and improve the selectivity of the reaction. Under the optimal experimental parameters, an average content of 99% of mono-nitro products and poly-nitro impurities of 0.45% was obtained.

Compared with the nitration method of *m*-xylene reported in the literature, the conversion rate and mono-nitro products selectivity have good advantages, providing a new pathway for industrial production. A comparison between batch and continuous flow reaction modes was also presented. The results show that the microreactor has apparent advantages in reaction time, temperature, and space-time yield. This also indicates that the tandem nitration process method is applicable and provides an essential strategy for the kilograms-scale synthesis of aromatic nitration reactions in microreactors.

**Acknowledgements** The authors would like to acknowledge the National Natural Science Foundation of China (No. 21875109) to provide funds for conducting experiments.

**Author Contributions** <sup>#</sup>Shuai Guo and Guang-kai Zhu contributed equally.

## Declarations

**Conflict of interest** The authors declared that there is no conflict of interest.

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