


Cite this: *RSC Adv.*, 2025, 15, 3474

# Development of a scalable and sustainable continuous-flow microreaction process for mononitration of aromatic compounds with high selectivity and yield†

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Nitroaromatic compounds are extensively used in industries such as pharmaceuticals, pesticides, and dyes. However, traditional synthesis methods often face challenges, including high safety risks, significant environmental pollution, and poor selectivity in mononitration reactions. In this study, we developed an efficient and safe continuous-flow microreaction process for mononitration, which achieves high yield and excellent selectivity. This process is applicable for the continuous synthesis of various mononitro compounds, including nitro-*p*-xylene, nitro-*o*-xylene, nitro-chlorobenzene, and nitro-toluene. Furthermore, the process was successfully applied to the synthesis of a key intermediate in the anticancer drug erlotinib, achieving a yield of 99.3%. The process has also been scaled up for the continuous production of nitro-*p*-xylene and nitro-*o*-xylene, with a product output of 800 g h<sup>-1</sup>. Under the same reaction conditions, the yield and selectivity were consistent with, or even improved over, those obtained in small-scale experiments, demonstrating the scalability and industrial potential of the process. Additionally, the process incorporates a waste acid recycling strategy, which has no significant impact on product yield, thus enhancing economic benefits and reducing environmental pollution. This continuous nitration process not only shows broad application potential but also offers a safe and efficient solution for nitration in the pharmaceutical and chemical industries.

Received 31st December 2024

Accepted 21st January 2025

DOI: 10.1039/d4ra09115a

rsc.li/rsc-advances

## Introduction

Nitroaromatic compounds represent a vital class of chemicals that serve as key precursors for aromatic amines, azo compounds, and nitrosoarenes.<sup>1,2</sup> Their derivatives are extensively utilized in industries such as explosives,<sup>3</sup> dyes,<sup>4</sup> pesticides,<sup>5,6</sup> and pharmaceuticals,<sup>7–9</sup> highlighting their significant role in the chemical industry and related sectors. The nitration of aromatic compounds, one of the most fundamental aromatic substitution reactions, has seen notable advancements in synthesis methods in recent years.<sup>10</sup> Common nitrating agents include mixed acid of nitric acid (HNO<sub>3</sub>) and sulfuric acid (H<sub>2</sub>SO<sub>4</sub>),<sup>11</sup> HNO<sub>3</sub>,<sup>12,13</sup> solid acid,<sup>14</sup> nitrogen oxides,<sup>15–17</sup> *N*-nitro reagents,<sup>18,19</sup> and nitrates.<sup>20–23</sup> Although some of these methods

are considered more environmentally sustainable, their adoption in industrial production is often constrained by high costs or difficulties in achieving large-scale implementation.

The nitration process using a mixed acid of HNO<sub>3</sub> and H<sub>2</sub>SO<sub>4</sub> remains the dominant method for synthesizing nitroaromatic compounds, but it is fraught with significant challenges. Among these, safety concerns are particularly critical.<sup>24</sup> Nitro compounds are highly explosive, and their production involves flammable raw materials. Additionally, the highly exothermic nature of the electrophilic nitration reaction exacerbates the difficulty of maintaining stable reaction conditions in traditional batch reactors, thereby heightening safety risks.<sup>25</sup> Furthermore, this process generates substantial amounts of waste acid, which, if not properly treated, can lead to severe environmental contamination, such as acidification of water bodies and soil degradation. Lastly, traditional nitration methods suffer from limitations in reaction selectivity and yield. The inability to precisely control reaction parameters often results in inconsistent selectivity and yield, posing significant challenges for achieving reliable and efficient production.

In recent years, continuous-flow microreaction technology has demonstrated remarkable advantages in nitration

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† Electronic supplementary information (ESI) available: Materials and methods, NMR data and spectrum. See DOI: <https://doi.org/10.1039/d4ra09115a>



processes, such as excellent mixing efficiency, high heat and mass transfer efficiency, minimal reactant volume, short residence times, and rapid responsiveness.<sup>24,26</sup> Building on these benefits, numerous successful applications of microreactor technology in nitration have emerged, offering an efficient, safe, and sustainable direction for the development of industrial nitration processes.<sup>27–34</sup> In 2015, Kulkarni and his team investigated a continuous nitration process for *o*-xylene using a tubular reactor.<sup>35</sup> The process employed fuming HNO<sub>3</sub> (FNA) as the nitrating agent, achieving a 99% conversion rate of *o*-xylene with 7.2% dinitro impurity content. However, the required FNA amount was six times the molar quantity of *o*-xylene, leading to substantial reagent waste, while the maximum yield of nitro-*o*-xylene reached only 91.8%, leaving room for optimization.

In 2023, Shū Kobayashi and colleagues introduced a continuous-flow nitration approach using solid acid catalysts in the presence of HNO<sub>3</sub>.<sup>36</sup> While this method demonstrated effectiveness, its industrial scalability was hindered by the high cost of solid acid catalysts and the use of organic solvents. In 2022, our team developed an efficient continuous-flow nitration process for *o*-xylene and its analogues (Fig. 1). This approach utilized 10 microreaction modules arranged in series, where the double-stage nitration reaction overcame the reaction equilibrium, resulting in a mononitro-*o*-xylene yield of 94.1%. Despite improving substrate selectivity and yield, implementing multiple microreactor modules prolonged reaction times, reduced production efficiency, and increased fixed capital costs. Additionally, the double-stage nitration step introduced procedural complexity and elevated waste acid generation, which together limited its industrial scalability.<sup>37</sup>

In this study, we propose an innovative nitration strategy for aromatic compounds that delivers high yields and enhanced

mononitration selectivity. By optimizing the molar ratio of acid to substrate, the number of microreactor modules was reduced to five, shortening the reaction time from 90 seconds to 29 seconds. This adjustment significantly lowered fixed costs associated with industrial implementation while enhancing process feasibility. Furthermore, integrating a waste acid recycling strategy effectively mitigated the issue of acid disposal. Compared to our previous methodology, this new process achieved notable improvements in product yield and mononitro compound selectivity.

## Results and discussion

### Optimization of nitration in continuous-flow

*p*-Xylene, an important chemical feedstock,<sup>8,38</sup> is widely utilized in the synthesis of dyes, plastics, pharmaceuticals, and pesticides. In this study, *p*-xylene was chosen as a model substrate for optimizing reaction conditions. First, 98% concentrated H<sub>2</sub>SO<sub>4</sub> was diluted with water to the desired concentration and mixed with 97% concentrated HNO<sub>3</sub> at a specific molar ratio to prepare the mixed acid. The mixed acid and *p*-xylene were then fed into a continuous-flow microreactor (Corning AFR Lab reactor equipped with a 2.7 mL microreactor module) through separate inlet streams (Fig. 2). After separating the organic phase from the reaction mixture, the products were analyzed *via* gas chromatography.

The effect of temperature on the reaction was first investigated under initial conditions: *p*-xylene flow rate at 2 g min<sup>−1</sup>, H<sub>2</sub>SO<sub>4</sub> concentration at 70%, H<sub>2</sub>SO<sub>4</sub>/HNO<sub>3</sub> molar ratio at 1.2, and HNO<sub>3</sub>/*p*-xylene molar ratio at 1.1. Within the temperature range of 30 °C to 100 °C, substrate conversion increased with rising temperature, while mononitration selectivity initially increased and then declined. The highest selectivity was

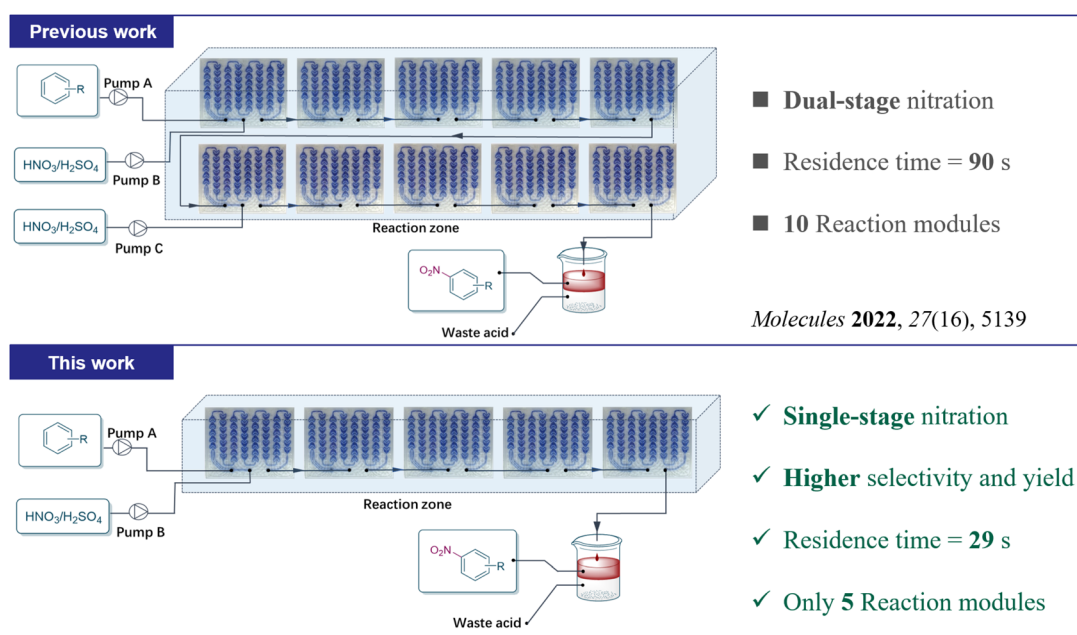


Fig. 1 Our previous work and this work.

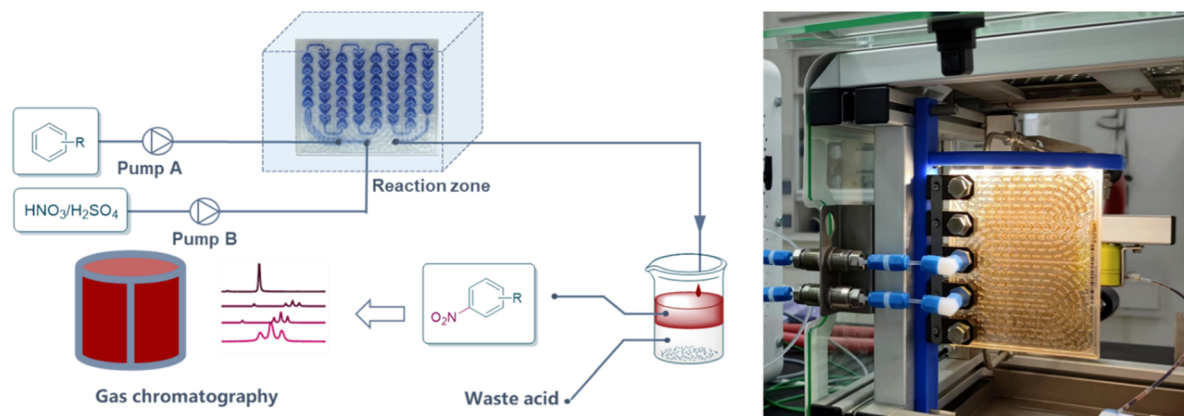


Fig. 2 Continuous-flow reactor setup for condition optimization.

observed at 60 °C (Fig. 3a), with a conversion rate of 46.1% and selectivity of 83.3%. The impact of the  $\text{H}_2\text{SO}_4/\text{HNO}_3$  molar ratio was then examined. Conversion and selectivity improved as the  $\text{H}_2\text{SO}_4/\text{HNO}_3$  ratio increased but declined after exceeding 2.0. While slightly higher ratios offered marginal improvements, 1.6 was chosen as the optimal ratio for its ability to achieve a good balance between high conversion and selectivity, while minimizing the environmental burden associated with excessive acid usage (Fig. 3b).  $\text{H}_2\text{SO}_4$  concentration played a critical role in the nitration reaction, functioning as both a catalyst and a dehydrating agent. Insufficient  $\text{H}_2\text{SO}_4$  concentration hindered the reaction, while excessive concentrations led to an

overabundance of nitronium ions ( $\text{NO}_2^+$ ), promoting the formation of unwanted polynitro by-products. Optimization experiments showed that a  $\text{H}_2\text{SO}_4$  concentration of 70% provided the best selectivity (Fig. 3c).

Despite these optimizations, substrate conversion remained suboptimal, primarily due to the short residence time in the continuous-flow reactor, which limited reaction completion. Increasing the number of microreactor modules to extend the residence time could enhance conversion but would significantly raise the fixed investment costs for industrial-scale equipment. To maintain a short reaction time, the reaction was intensified by increasing the molar ratio of  $\text{HNO}_3$  to

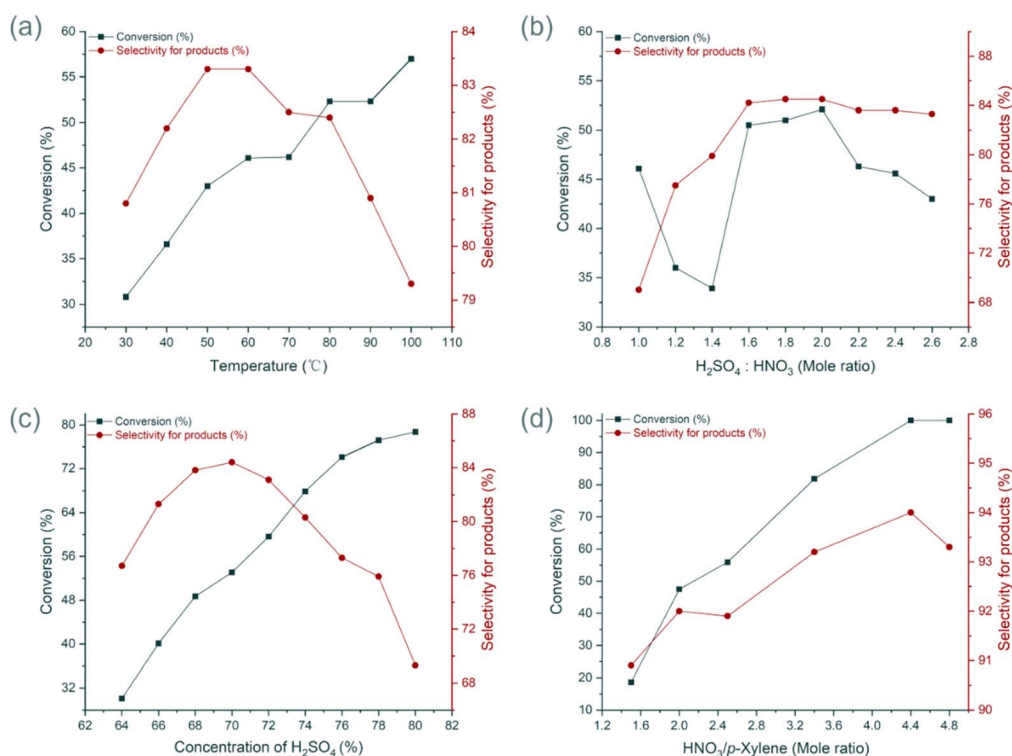
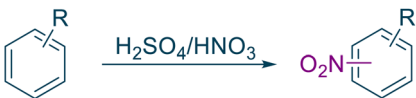
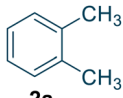
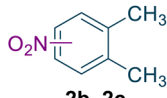
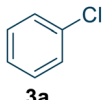
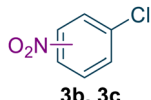
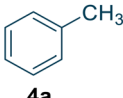
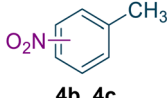


Fig. 3 Optimization of nitration in continuous-flow. (a) The influence of temperature. (b) The influence of mole ratio of  $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$ . (c) The influence of  $\text{H}_2\text{SO}_4$  concentration. (d) The influence of mole ratio of  $\text{HNO}_3$  and  $p$ -xylene.



Table 1 Synthesis of analogues<sup>a</sup>

						
Entry	Substrate	Nitro-product(s)	Selectivity of products <sup>b</sup> (%)	Reaction temperature (°C)	Yield <sup>c</sup> (%)	Residence time (s)
1			96.7	80	96.1 ( <i>o</i> = 54.6) <sup>d</sup> ( <i>p</i> = 45.4) <sup>d</sup>	19
2			99.5	100	99.4 ( <i>o</i> = 65.1) <sup>d</sup> ( <i>p</i> = 34.9) <sup>d</sup>	21
3			98.2	70	98.1 ( <i>o</i> = 61.6) <sup>d</sup> ( <i>p</i> = 39.4) <sup>d</sup>	17

<sup>a</sup> Reaction conditions: H<sub>2</sub>SO<sub>4</sub> concentration = 70%, H<sub>2</sub>SO<sub>4</sub>/HNO<sub>3</sub> mole ratio = 4.4, HNO<sub>3</sub>/substrate mole ratio = 1.6 and flow rate of substrates = 1 g min<sup>-1</sup>. <sup>b</sup> Selectivity of products = (total yield of mononitro-products/conversion of substrates) × 100%. <sup>c</sup> Yields and selectivities were determined by GC. <sup>d</sup> Numbers in parentheses represent regioselectivity.

substrate. Further studies revealed that as the HNO<sub>3</sub>/*p*-xylene ratio increased, both conversion and selectivity improved. Complete substrate conversion was achieved when the molar ratio reached 4.4 (Fig. 3d). Ultimately, under optimized conditions—a substrate flow rate of 1 g min<sup>-1</sup> and a mixed acid flow rate of 12 g min<sup>-1</sup>—the yield of mononitro-*p*-xylene reached 94.0%, with a residence time of only 19 seconds.

### Extension to analogues

To assess the general applicability of this method, we expanded the reaction conditions to include the synthesis of structurally

related compounds (Table 1). Nitro-*o*-xylene serves as a precursor for the synthesis of important compounds, including riboflavin (vitamin B2) and the herbicide dymron, was synthesized using this approach with a yield of 96.1% and a reaction residence time of 19 seconds (Table 1, entry 1). Nitro-chlorobenzene, a key intermediate for azo dyes and herbicides like alachlor, was obtained with a yield of 99.4% within a residence time of 21 seconds (Table 1, entry 2). Similarly, nitro-toluene, a widely used chemical intermediate in the synthesis of dyes and explosives, was produced with a high yield of 98.1% within a residence time of 17 seconds (Table 1, entry 3).

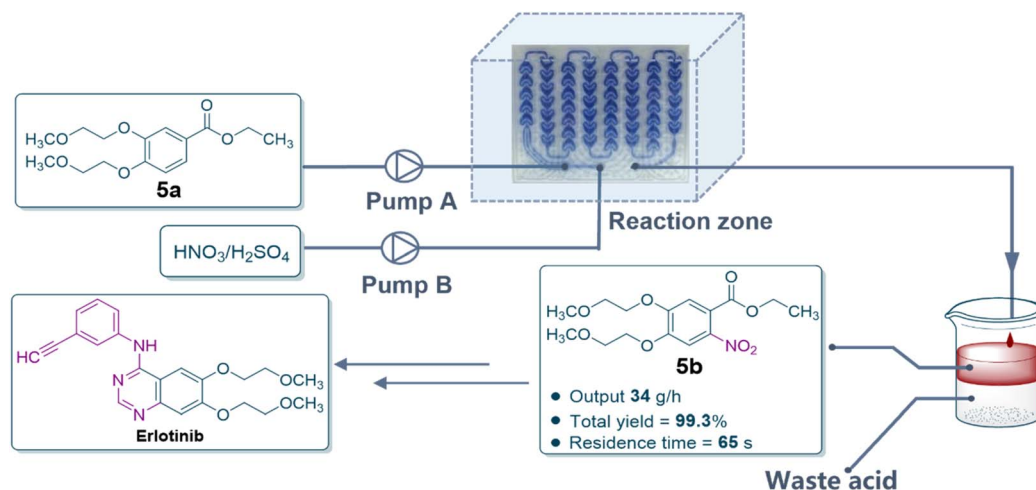


Fig. 4 Continuous-flow synthesis of Erlotinib key intermediate 5b.



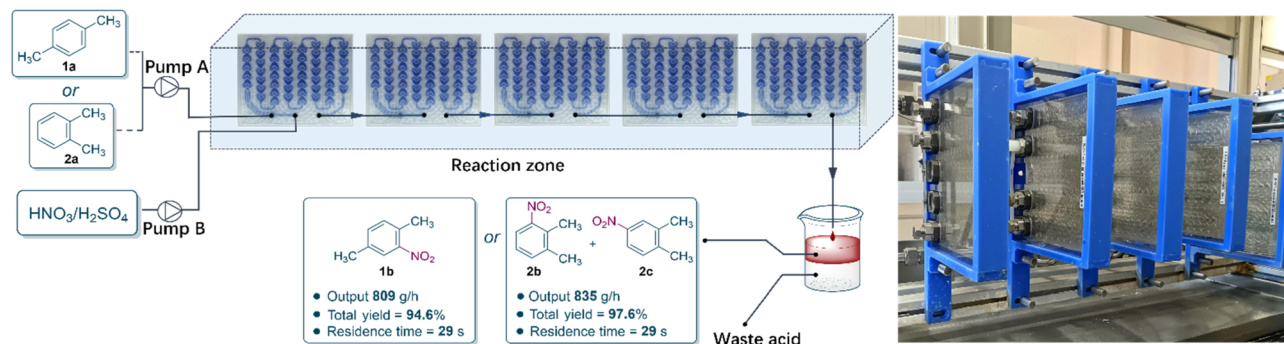


Fig. 5 Continuous-flow scale-up experimental setup.

Table 2 Impact of freshly prepared mixed acid and recycled mixed acid on reaction behavior<sup>a</sup>

Entry	3-Nitro product (%)	4-Nitro product (%)	Conversion (%)	Yield <sup>b</sup> (%)	Impurities <sup>b</sup> (%)	Selectivity of products <sup>c</sup> (%)
1 <sup>d</sup>	53.5	44.1	99.9	97.6	2.4	97.7
2 <sup>e</sup>	52.5	44.8	99.9	97.3	2.6	97.4

<sup>a</sup> Reaction conditions:  $T = 80\text{ }^{\circ}\text{C}$ ,  $\text{H}_2\text{SO}_4$  concentration = 70%,  $\text{H}_2\text{SO}_4/\text{HNO}_3$  mole ratio = 1.6,  $\text{HNO}_3/o\text{-xylene}$  mole ratio = 4.4. <sup>b</sup> yield and impurities were determined by GC. <sup>c</sup> Selectivity of products = (total yield of mononitro-products/conversion)  $\times$  100%. <sup>d</sup> Use freshly prepared mixed acid.

<sup>e</sup> Using recycled mixed acid.

Compound **5b**, a crucial intermediate in the synthesis of Erlotinib, a targeted therapy drug for non-small cell lung cancer (NSCLC) and pancreatic cancer, was also synthesized to further evaluate the versatility of this method (Fig. 4). Under optimized conditions of  $30\text{ }^{\circ}\text{C}$  and using dichloromethane (DCM) as the solvent, the substrate achieved complete conversion, resulting in the successful synthesis of **5b**. The reaction had a residence time of 65 seconds and an impressive yield of 99.3%, with a product output rate of  $34\text{ g h}^{-1}$ .

### Scale-up to pilot plant scale

We then performed scale-up experiments for the continuous nitration of *o*-xylene and *p*-xylene (using the Corning AFR G1 reactor equipped with five standard flow control modules, each with a volume of 8.3 mL) (Fig. 5). In these experiments, the feed rate of the substrates was scaled up to  $600\text{ g h}^{-1}$  and the reaction residence time was 29 seconds. By fine-tuning the reaction temperature, *p*-nitroxylenes were successfully synthesized at  $60\text{ }^{\circ}\text{C}$  with a yield of 94.6% and a product throughput of  $809\text{ g h}^{-1}$ . Similarly, the nitration of *o*-xylene was carried out at  $78\text{ }^{\circ}\text{C}$ , achieving a total yield of 97.6% and a throughput of  $835\text{ g h}^{-1}$ . Compared to the small-scale process, only minor temperature adjustments were required for the scaled-up throughput, while all other parameters remained unchanged. The yields of the final products remained stable and even showed slight improvement, highlighting the excellent scalability of the process and its strong potential for industrial applications.

### Recycling and reuse of waste acid

A major drawback of the mixed acid nitration process is the generation of large quantities of waste acid, which, if not

properly managed, leads to resource loss and significant environmental burdens. Recycling and reusing waste acid, therefore, offer substantial practical and industrial value. Theoretically, nitration of 1 mol of *o*-xylene consumes 1 mol of  $\text{HNO}_3$  and produces an equivalent molar amount of  $\text{H}_2\text{O}$ . Based on the initial composition of the mixed acid, the required amounts of supplemental  $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$  can be calculated. Under optimal reaction conditions, the waste acid is separated and treated, after which the theoretical amount of  $\text{H}_2\text{SO}_4$  is replenished. To account for  $\text{HNO}_3$  decomposition, 1.2 times the theoretical amount of  $\text{HNO}_3$  is added. Experimental results confirm that, compared to the standard conditions (Table 2, entry 1), the use of recycled waste acid (Table 2, entry 2) has a negligible impact on reaction outcomes, demonstrating the feasibility and effectiveness of the waste acid recycling strategy.

## Conclusions

In conclusion, this study developed an efficient and safe continuous-flow microreaction mononitration process, achieving high yields and exceptional mononitration selectivity for a variety of mononitro compounds, including nitro-*p*-xylene, nitro-*o*-xylene, nitro-chlorobenzene, nitro-toluene, and a key intermediate in the synthesis of the anticancer drug erlotinib. The process was successfully scaled up to a production capacity of  $800\text{ g h}^{-1}$  for the continuous synthesis of nitro-*o*-xylene and nitro-*p*-xylene, confirming its scalability and feasibility for industrial implementation. Additionally, the integration of a waste acid recovery and recycling strategy significantly enhanced economic efficiency while mitigating environmental pollution. These advancements highlight the potential of this



process for widespread application in the pharmaceutical and chemical industries.

## Data availability

The data presented in this study are available in the ESI.†

## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (22208268), Sichuan Science and Technology Program (2023NSFSC1977) and Technology Department of Yibin Program (2024GY008 and 2023SF009).

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