

Continuous-Flow Microreactor System for Enhanced Selectivity and Safety in Nitrobenzene Nitration

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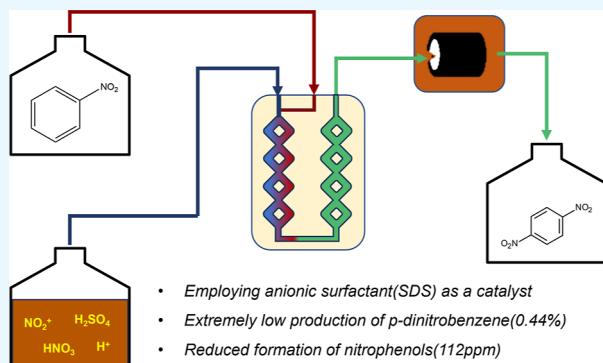
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ABSTRACT: Dinitrobenzene, a crucial intermediate in pesticide and dye production, is typically synthesized through the exothermic nitration of nitrobenzene. This study presents a continuous-flow microreactor system integrated with micromixers to enhance selectivity and safety in the nitration process. An open-source Python program was developed to precisely control the mass flow rate ratio of nitrobenzene to the mixed acid. By optimizing reaction conditions and employing sodium dodecyl sulfate (SDS) as a surfactant, the selectivity of p-dinitrobenzene was minimized to 0.44%, while hazardous nitrophenol byproducts were reduced to 112 ppm—a significant improvement compared to the 509 ppm observed in traditional batch processes. Compared to traditional batch reactors, the microreactor system significantly lowered p-dinitrobenzene selectivity and minimized nitrophenol and trinitrobenzene formation, highlighting its suitability for industrial-scale applications.



INTRODUCTION

m-Dinitrobenzene (*m*-DNB) is a crucial intermediate in the production of pesticides, dyes, and polymerization initiators.¹ It is typically synthesized via the liquid–liquid heterogeneous nitration of nitrobenzene in a batch reactor, yielding approximately 15% byproducts, including *o*-dinitrobenzene (*o*-DNB) and *p*-dinitrobenzene (*p*-DNB), as shown in Scheme 1. These byproducts are usually dissolved in water through a reaction with sodium sulfite and subsequently discarded during the post-treatment process due to their limited market demand and the difficulty of separation, resulting in significant waste.^{2,3} The direct hydrogenation of mixed dinitrobenzenes to obtain mixed diphenylamines, followed by distillation for isomer recovery, is an atom-economical approach. However, due to the close boiling points of *p*- and *m*-diphenylamine, the distillation process is highly energy-intensive and requires a large number of theoretical stages. Therefore, eliminating *p*-DNB can enhance the yield of the desired product, *m*-DNB, and reduce the energy consumption required for distillation, making it a significant research topic in the nitration of nitrobenzene.

However, nitration is a highly exothermic process, releasing approximately -73 to -253 kJ mol^{-1} of energy per nitro group introduced.⁴ The rapid reaction rate often leads to hotspots in conventional batch reactors, causing localized overnitration, reduced selectivity, and the formation of hazardous oxidative byproducts with potentially severe consequences.^{6,7} Microreactors offer significant advantages for handling heterogeneous systems. They enable rapid mixing, efficient heat transfer, precise control of reaction conditions, and enhanced

safety.^{8–11} Since Burns and Ramshaw^{12,13} first applied microreactors to benzene nitration, numerous studies have explored their use in the nitration of aromatic compounds such as cumene,¹⁴ trifluoromethoxybenzene,¹⁵ 1-methyl-4-(methylsulfonyl)benzene,¹⁶ and 3-fluorobenzotrifluoride.¹⁷ Zhao et al.⁵ investigated the nitration of nitrobenzene in microreactors. The maximum flow rate and the yield of *m*-dinitrobenzene were limited to $981.75\text{ }\mu\text{L}/\text{min}$ and 80%, respectively, which are too low for industrial applications.

Selective nitration of aromatic compounds is a promising strategy to enhance the proportion of desired nitration products. A common approach involves modifying reaction conditions¹⁸ or introducing catalysts and mixed acid systems, such as solid acids,¹⁹ ultrasound,²⁰ zeolite molecular sieves,^{6,21} or surfactants.²² For example, Rahaman et al.¹⁸ demonstrated the selective nitration of nitrobenzene at $25\text{ }^\circ\text{C}$ under highly concentrated sulfuric acid conditions, effectively suppressing *p*-dinitrobenzene formation. However, a slight increase in reaction temperature significantly enhances the selectivity for the *p*-dinitrobenzene isomer.

This study focuses on the development of a continuous-flow system combining microreactors to achieve ultralow para-

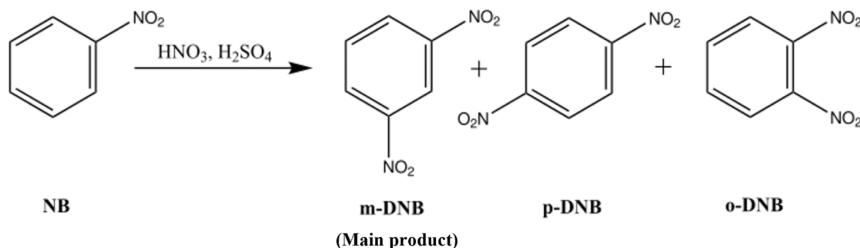
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Scheme 1. Nitration of Nitrobenzene to Prepare Dinitrobenzene


selectivity in nitrobenzene nitration. Precise feeding control of reagents was achieved through a PID-based algorithm, ensuring consistent reaction conditions. By optimizing reaction parameters and employing anionic surfactants as catalysts, the proposed system demonstrates strong potential for industrial-scale implementation. Additionally, the formation pathways of nitrophenols during the nitration process were explored, and enhanced mass transfer significantly reduced the levels of hazardous nitrophenol byproducts in the final products.

RESULTS AND DISCUSSION

Effects of Mass Flow Rate Ratio on *p*-DNB Selectivity. Ensuring a constant mass flow rate ratio of reagents is critical for maintaining the consistency of continuous reactions. To address flow pulsations generated by pumps, back pressure regulators are commonly employed. However, as shown in Figure 2, despite the use of a back pressure valve, pulsations still caused fluctuations in the selectivity of *p*-DNB. Additionally, changing reaction conditions often requires manual readjustment of multiple pump flow rates to achieve proper material matching. Seasonal temperature variations in the laboratory, the presence of high-viscosity reagents, and internal wear of pump components further exacerbate the issue, resulting in discrepancies between the actual and indicated flow rates.

We present an open-source Python program that facilitates precise control of the mass flow rate ratio for two or more reagent streams entering a reactor. The program is highly adaptable and user-friendly. When reaction conditions change, users can simply set the desired feed ratio via the program interface, which then automatically adjusts the flow rates to maintain the specified ratio (Figure S1). The control principle is illustrated in Figure 1.

By applying a PID control algorithm, the mass flow rate ratio between nitrobenzene and mixed acid was dynamically adjusted in real-time, achieving a stable ratio close to the target value of 1.90. Under identical experimental conditions, this precise control resulted in both lower and more stable *p*-DNB selectivity compared to operations with fixed pump flow rates, as demonstrated in Figure 2. This approach significantly enhances the reproducibility and reliability of the flow chemistry process, making it a robust solution for continuous reaction systems.

Effects of Reaction Conditions on *p*-DNB Selectivity. Based on previous work,¹ the optimal conditions for the nitration of nitrobenzene to achieve the highest yield of *m*-dinitrobenzene (*m*-DNB) were determined to be a reaction temperature of 70 °C and a residence time of 4 min, resulting in a dinitrobenzene yield of 99% and an *m*-DNB selectivity of 90.88%. However, the prior study did not investigate how the selectivity of *p*-dinitrobenzene (*p*-DNB) varies with reaction conditions. Maintaining *p*-DNB at a low level may significantly

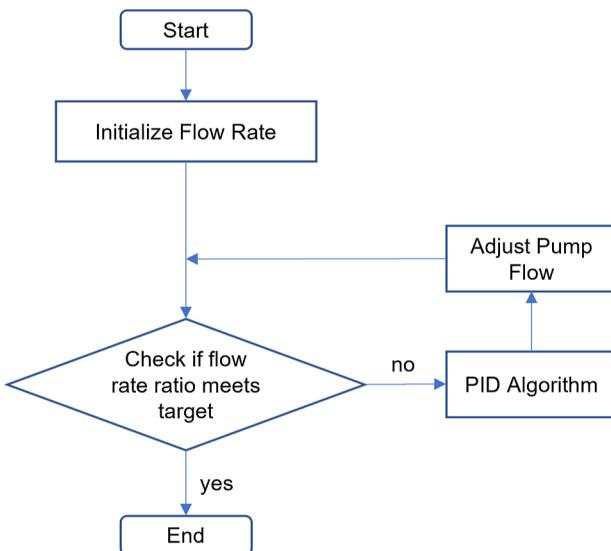


Figure 1. Flowchart of the PID control process developed in this study.

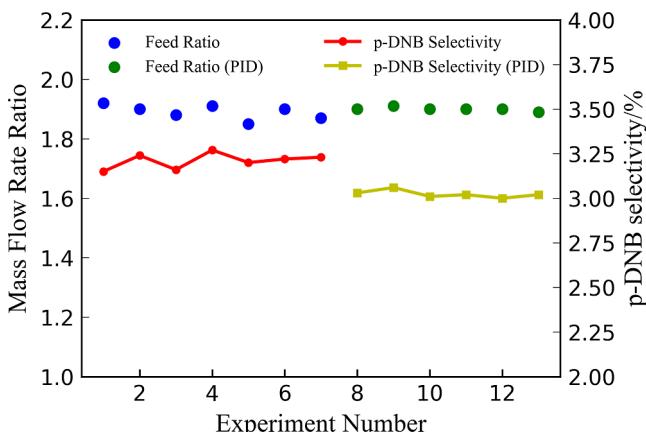


Figure 2. Effect of mass flow rate ratio on *p*-DNB selectivity.

facilitate the separation of phenylenediamines after hydrogenation. Temperature significantly influences both interphase mass transfer and intrinsic reaction kinetics. As reported by Cyrille et al.,²³ the reaction energy barriers for *o*-DNB and *p*-DNB are higher than that of the main product, *m*-DNB. Consequently, lowering the reaction temperature reduces the selectivity of *p*-DNB (Figure 3a).

Given that the nitration reaction primarily occurs at the interface and within the acid phase, higher sulfuric acid concentrations used in preparing the mixed acid enhance the solubility of nitrobenzene in the acid phase. However, this also increases the viscosity of the acid phase, thereby enhancing

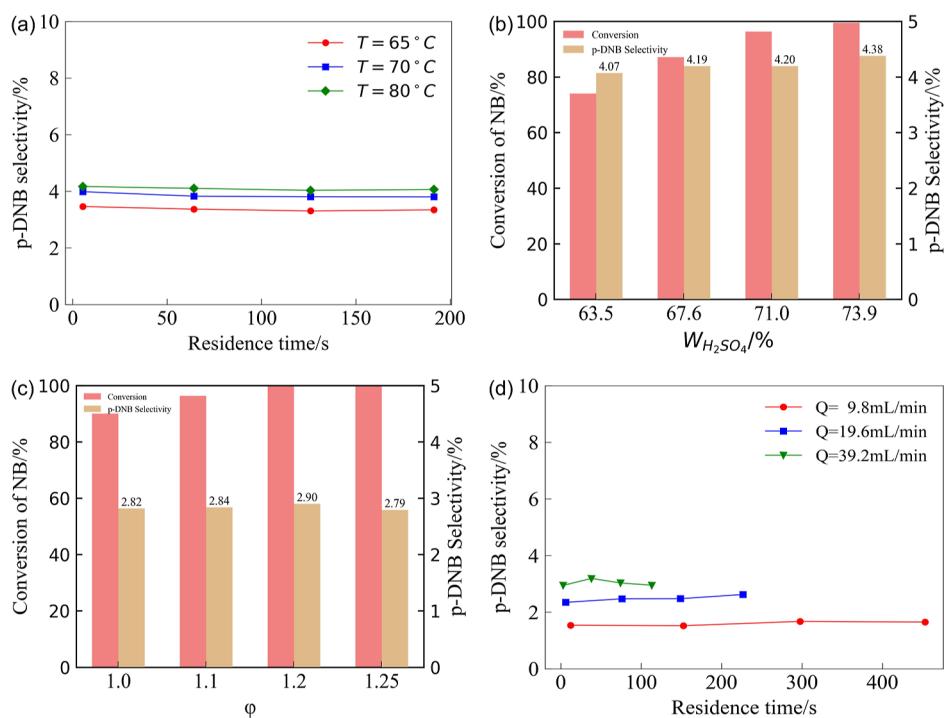


Figure 3. Effect of reaction conditions on *p*-DNB selectivity. (a) Reaction temperature. $W_{H_2SO_4} = 63.5\%$, $Q = 19.6$ mL/min, $\varphi = 1.1$. (b) Sulfuric acid mass fraction. $T = 70$ °C, $\varphi = 1.1$, $Q = 19.6$ mL/min, residence time = 4 min. (c) Molar ratio of HNO_3 to NB. $T = 65$ °C, $W_{H_2SO_4} = 71.0\%$, $Q = 19.6$ mL/min, residence time = 6 min. (d) Total flow rate. $T = 65$ °C, $W_{H_2SO_4} = 71.0\%$, $\varphi = 1.2$.

mass transfer resistance. Consequently, as shown in Figure 3b, the combined effects of these factors result in a slight increase in *p*-DNB selectivity with higher sulfuric acid concentrations. Meanwhile, the stronger water absorption capacity and enhanced nitric acid dissociation promoted by more concentrated sulfuric acid contribute to the increased conversion of NB with rising sulfuric acid mass fraction.

As depicted in Figure 3c, the molar ratio of nitric acid to nitrobenzene (φ) has a relatively minor impact on *p*-DNB selectivity. The selectivity of DNB isomers is primarily influenced by their kinetic parameters and the concentration of NO_2^+ . In this experiment, to control mass transfer effects, the mass flow rates of mixed acid and nitrobenzene were kept constant. Under these conditions, increasing the molar ratio φ leads to a higher proportion of nitric acid in the mixed acid, while the proportion of sulfuric acid correspondingly decreases. Since sulfuric acid facilitates the dissociation of nitric acid into NO_2^+ , a lower sulfuric acid content weakens this effect. Consequently, considering both the increase in nitric acid concentration and the decrease in sulfuric acid proportion, increasing the molar ratio of HNO_3 has no significant impact on the selectivity of *p*-DNB. Nevertheless, at higher φ values, the elevated concentration of undissociated nitric acid or NO_2 in the mixed acid can promote the oxidation of nitrobenzene to nitrophenols. Figure S2 shows that increasing the total flow rate enhances mixing efficiency, with optimal mixing achieved at flow rates exceeding 50 mL/min. Figure 3d demonstrates that higher total flow rates enhance mixing efficiency but also generate significant heat, which may exceed the heat exchange capacity. Therefore, at lower flow rates, the substantial heat generated during the reaction can be more effectively removed, which is associated with higher *p*-DNB selectivity. Considering both *p*-DNB selectivity and NB conversion, the conditions of T

= 65 °C, $W_{H_2SO_4} = 71.0\%$, $Q = 9.8$ mL/min, $\varphi = 1.2$ were identified as the optimal reaction conditions.

Effects of Different Surfactants on *p*-DNB Selectivity.

The addition of small amounts of surfactants during the reaction is known to enhance the interfacial area in heterogeneous reactions, thereby improving mass transfer without significantly affecting the reaction outcome.²² In this study, 0.05 mol % sodium dodecyl sulfate (SDS) and polyethylene glycol (PEG) were introduced into the mixed acid system containing nitrobenzene and tested under the optimal reaction conditions. As shown in Figure 4, under the optimized conditions of the continuous flow system developed in this study, the yield of *m*-dinitrobenzene (*m*-DNB) was higher compared to the batch reactor, while the selectivity for

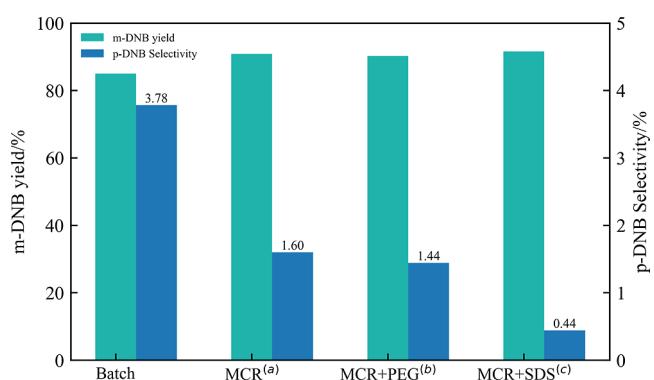


Figure 4. Effects of Different Surfactants on *p*-DNB Selectivity and *m*-DNB Yield. (a) MCR results under the following conditions: $T = 65$ °C, HNO_3/NB molar ratio (φ) = 1.20, $W_{H_2SO_4} = 71.0\%$, and total flow rate (Q) = 9.8 mL/min. (b) Results with the addition of 0.05% PEG. (c) Results with the addition of 0.05% SDS.

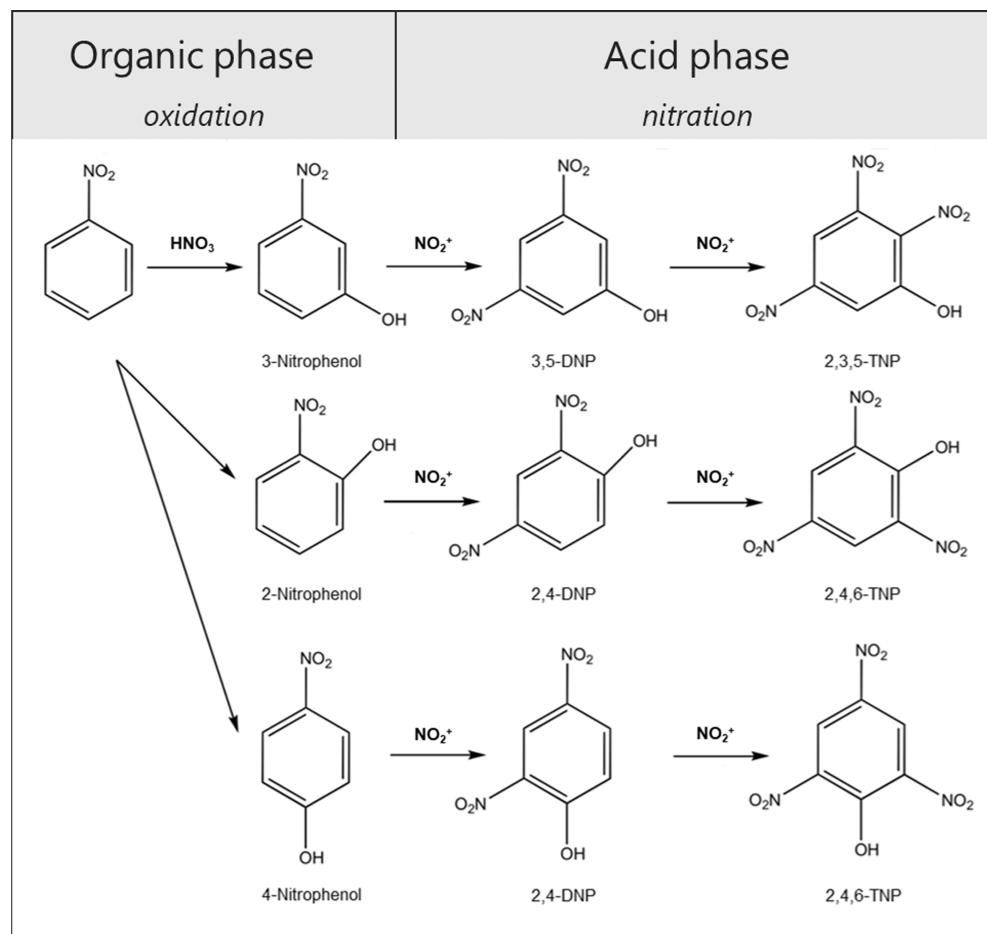


Figure 5. Formation mechanism of nitrophenols in the nitration of nitrobenzene.

Table 1. Results of Batch Reactor and Microreactor

entry	temperature/°C	residence time/min	$W_{\text{H}_2\text{SO}_4}/\%$	TNPs/ppm	TNB
batch ^a	70	180	71.0	509	Detected
MCR-1	70	4	71.0	151	
MCR-2	70	4	73.9	141	
MCR-3	70	4	74.5	103	Detected
MCR-4	65	4	71.0	112	

^aThe HNO_3/NB molar ratio (φ) is 1.20 for both the batch reactor and the microreactor, while the total flow rate (Q) for the microreactor is 9.8 mL/min.

p-DNB was notably lower. This improvement can be attributed to the enhanced mass and heat transfer capabilities of the microreactor system (MCR), particularly when combined with the micromixer.

Compared to the MCR system, the addition of PEG had negligible effects on both the yield of *m*-DNB and the selectivity of *p*-DNB. However, the addition of an equivalent amount of SDS effectively reduced *p*-DNB selectivity. PEG, as a nonionic surfactant, does not dissociate in the acidic phase, resulting in minimal impact on the reaction. In contrast, the anionic surfactant (SDS) interacts with the electrophilic NO_2^+ species through its anionic headgroup, forming a tightly bound electron pair. This interaction facilitates the transfer of NO_2^+ to the organic-acid interface for reaction, acting as a phase-transfer catalyst.²⁴ Additionally, SDS reduces the interfacial tension between the two phases, increasing the interfacial area and thereby suppressing the formation of byproducts,

including not only *p*-DNB but also hazardous compounds such as trinitrobenzene. As a result, the yield of *m*-DNB is enhanced, reaching 91.6% in this study.

Investigation of Nitrophenols Formation During the Nitration of Nitrobenzene. Nitrophenols are hazardous byproducts typically removed during the alkali washing stage. However, their derivatives, such as sodium nitrophenolate or ammonium nitrophenolate, are also unstable and prone to deposition and spontaneous decomposition. Therefore, minimizing the formation of trinitrophenols (TNPs) during the reaction process is critical for ensuring inherent safety.²⁵ This study represents the first attempt to investigate the formation pathways of nitrophenols during the nitration of nitrobenzene (Figure 5), aiming to regulate and reduce their production. The typical chromatograms of TNPs shown in Figure 5 are provided in the Supporting Information (Figure S3).

Nitric acid is a strong oxidizing agent with excellent solubility in nitrobenzene.^{26–28} Afonso et al.²⁹ demonstrated that the formation of nitrophenols originates from the oxidation of benzene or nitrobenzene by undissociated nitric acid in the organic phase. The mechanism involves nitric acid oxidizing benzene or nitrobenzene to form phenols, which subsequently transfer to the acid phase. In the acid phase, the phenols undergo sulfonation with concentrated sulfuric acid to form phenol sulfonic acids. These intermediates are then nitrated by nitronium ions, replacing the sulfonic group to yield nitrophenols.³⁰ This reaction, which occurs at the acid–organic phase interface, proceeds several orders of magnitude faster than the oxidation of benzene or nitrobenzene. The resulting nitrophenols eventually transfer back to the organic phase.

As shown in **Table 1**, a comparison between batch reactors and MCR systems highlights that enhanced mass transfer and the reduced solubility of nitric acid in the organic phase significantly lower nitrophenol production. Increasing the sulfuric acid concentration facilitates the dissociation of nitric acid, thereby reducing the likelihood of oxidation reactions. However, when the sulfuric acid concentration exceeds 74.5%, the formation of trinitrobenzene (TNB) becomes pronounced (**Figure 6**). Furthermore, solid dinitrobenzene produced

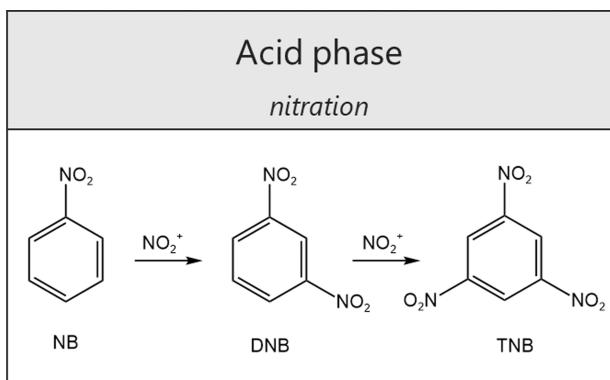


Figure 6. Formation mechanism of TNB in the nitration of nitrobenzene.

during the reaction can dissolve residual nitric acid, making prolonged residence times undesirable as they promote the formation of TNPs. Therefore, optimizing acid concentrations requires balancing the suppression of both TNPs and TNB formation.

CONCLUSION

This study introduces a continuous-flow microreactor system integrated with an open-source Python program designed to optimize nitrobenzene nitration while minimizing *p*-DNB and hazardous byproducts such as TNPs and TNB. Under optimized conditions, the system achieved a 91.6% yield of *m*-dinitrobenzene with a *p*-DNB selectivity of 0.44% using 0.05 mol % sodium dodecyl sulfate (SDS). The formation pathway of nitrophenols during nitration was elucidated, and by maintaining sulfuric acid concentrations below 74.5%, nitrophenol and TNB formation were significantly suppressed. Compared to traditional batch reactors, the microreactor system demonstrated reduced TNP levels (112 ppm) and a shorter residence time (4 min), highlighting its superior safety and efficiency. Under the optimized conditions, *p*-DNB content can be significantly reduced, but the production capacity per unit reactor remains limited to 0.5 kg/h. Enhancing reactor throughput is crucial for future industrial applications.

EXPERIMENTAL SECTION

Materials. The chemicals employed in this study included dichloromethane (>99.9%), fuming nitric acid (>98%), nitrobenzene (NB, >99%), sulfuric acid (>98%), and sodium bicarbonate (>99%). Sodium dodecyl sulfate (SDS, >97%) and polyethylene glycol (PEG, molecular weight 6000) were also used. Deionized water was prepared on-site. All reagents and chemicals were procured from Sinopharm Chemical Reagent Co., Ltd. and used as received without further purification.

Experimental Procedure for Nitration of NB. **Figure 7** shows the schematic diagram of the continuous-flow microreactor system for the nitration of nitrobenzene with the mixed acid. The continuous-flow microreactor system consisted of a coiled tube (316L stainless steel, inner diameter: 1 mm), microreactors (Hartz alloy 276, inner diameter: 1 mm), and a micromixer (tantalum, inner diameter: 1 mm). The mixing and reaction modules were immersed in two thermostatic water baths (Julabo GmnH CORIO CD-200F), maintained at the designated reaction temperature. The detailed designs of the micromixer and microreactor used in this study are shown in **Figure 8a–e**, respectively. In the microreactor, (c) and (e) represent the heat exchange layers, while (d) corresponds to the reaction layer positioned between them.

The mixed acid was prepared by dissolving an appropriate amount of fuming nitric acid in sulfuric acid according to the molar ratio of nitric acid to nitrobenzene. The amount of

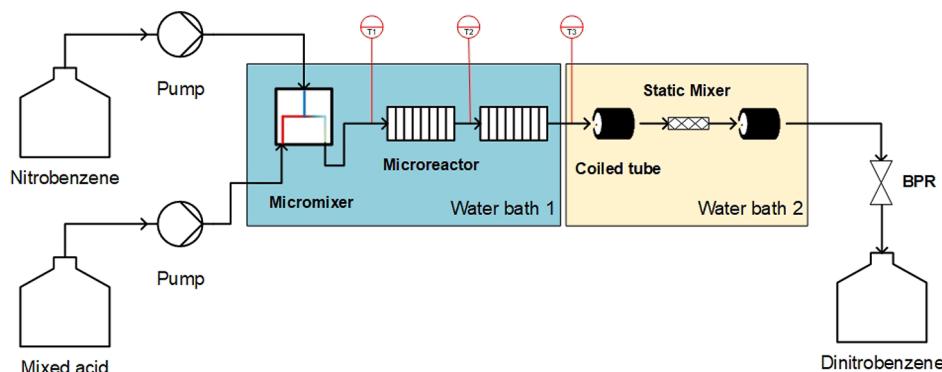


Figure 7. Schematic overview of the experimental equipment.

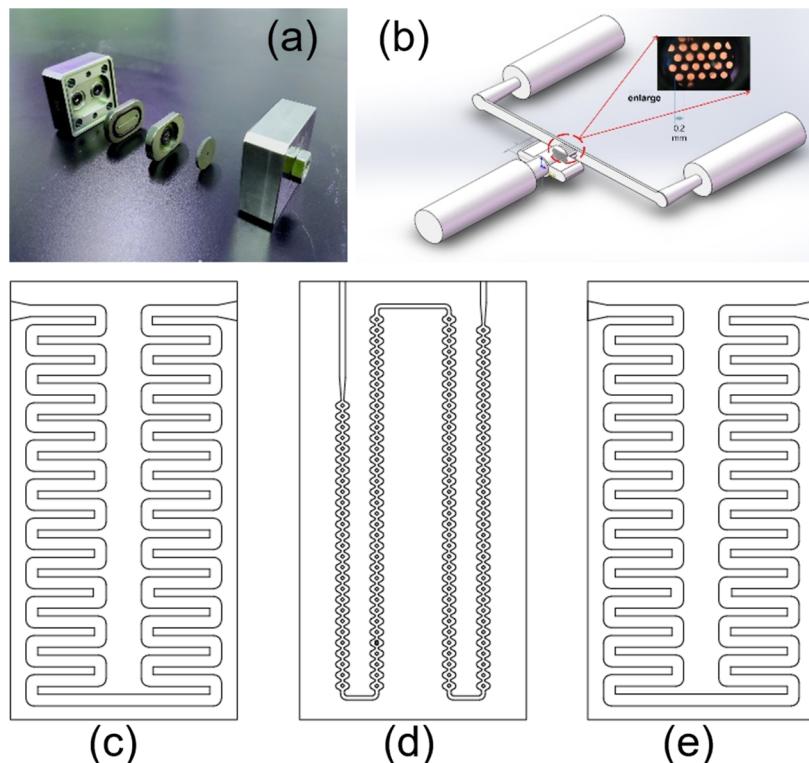


Figure 8. Schematic representation of the micromixer (a,b) and the microreactor (c–e). (b) Shows an enlarged view of the internal structure of the micromixer, (d) illustrates the internal flow channel of the microreactor, and (c,e) depicts the heat exchange layers.

sulfuric acid was determined based on the mass flow rate ratio (f) and mass fraction. When a surfactant was required, 0.05 mol % of it was dissolved in the mixed acid solution in a three-neck flask placed in a cooled water bath. The mixture was stirred for 20 min to ensure complete homogeneity. In this study, the mass flow rate ratio, also referred to as the feed ratio, represents the ratio of the mass flow rates of the two reactants. It was calculated using eq 1.

$$f = \frac{Q_{\text{MA}}}{Q_{\text{NB}}} \quad (1)$$

where Q_{MA} represents the mass flow rate of mixed acid, Q_{NB} is the mass flow rate of nitrobenzene, and f denotes the mass flow rate ratio or the feed ratio.

Nitrobenzene (flow rate: 5–20 mL min⁻¹) and the mixed acid solution (flow rate: 4.8–19.2 mL min⁻¹) were separately delivered by two high-precision piston pumps (Sanotac ISP1020). The fluids were then merged in a micromixer before entering the microreactor, where they remained for several seconds. The residence time was controlled by adjusting either the reaction channel length or the flow rate and was calculated using eq 2.

$$t = \frac{V}{Q} \quad (2)$$

Here, t represents the reaction residence time, V is the volume of the microreactor, and Q denotes the total volumetric flow rates of the nitrobenzene and mixed acid solution.

Upon exiting the microreactor, the reaction mixture was rapidly quenched with cold water within milliseconds. Once steady-state conditions were achieved, samples were collected. Each sample was immediately transferred to a saturated

sodium bicarbonate (NaHCO_3) solution to neutralize any residual acid. The organic phase was separated, washed with deionized water, and extracted with dichloromethane. At the end of each experiment, the microreactor and sampling system were flushed for 15 min. Three samples were collected at each sampling point, and the results were averaged to ensure accuracy.

Additional post-treatment steps were conducted after quenching to analyze nitrophenols. Upon exiting the reactor, 1 g of the sample was rapidly quenched, neutralized, and extracted with 5 mL of dichloromethane. Subsequently, 15 mL of water and an appropriate amount of 1 M NaOH solution were added to the extract to adjust the pH to 12. After phase separation, the aqueous phase was collected and extracted with 20 mL of dichloromethane, and the organic phase was discarded. The remaining aqueous phase was then acidified to pH 12 using 1 M sulfuric acid solution. After dissolving 5 g of NaCl, the aqueous phase was further extracted with 20 mL of dichloromethane. The aqueous phase was discarded, while the organic phase was dried over anhydrous sodium sulfate and concentrated via rotary evaporation for gas chromatography (GC) analysis.

Analytical Methods. Routine sample analysis was conducted using an Agilent 7890A gas chromatograph equipped with a flame ionization detector and a DB-1 column (30 m × 0.25 mm × 0.25 μm). Quantification via GC-FID was performed using the external standard method. Calibration curves were established for quantitative yield calculations of the reactant (NB) and the products (*m*-DNB, *o*-DNB, and *p*-DNB). The respective retention times of the components were as follows: NB (9.8 min), *p*-DNB (14.4 min), *m*-DNB (14.8 min), and *o*-DNB (15.0 min). The carrier gas was nitrogen at a flow rate of 2.5 mL/min. The injection temperature was set to

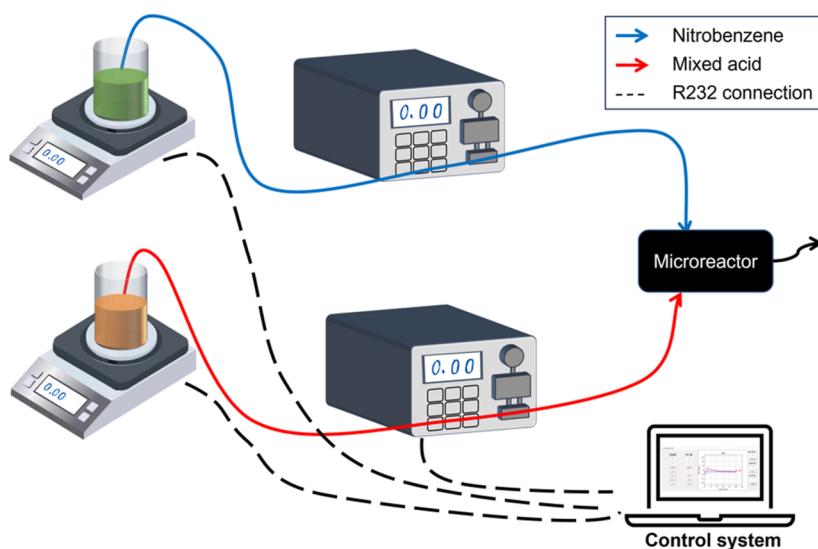


Figure 9. Flow diagram of precise feeding control using PID algorithm in this study.

280 °C, the detector temperature to 300 °C, and the oven program was as follows: 60 °C (held for 3 min) → 200 °C (at 10 °C/min, held for 4 min).

The product composition was quantitatively analyzed using the internal standard method, with toluene dissolved in dichloromethane as the internal standard (eq 3).

$$f_i = \frac{A_S/m_S}{A_i/m_i} \quad (3)$$

Here, i and S represents each component and the internal standard substance, A and m denote the integral area and mass of toluene, respectively, and f_i is the relative correction factor for component i . Prior to analyzing the sample composition, the relative correction factors for nitrobenzene (NB) and various dinitrobenzenes (DNB) were determined. All experiments were conducted in triplicate to ensure reproducibility. The selectivity of *p*-DNB was calculated using eq 4

$$S_{p\text{-DNB}} = \frac{f_{p\text{-DNB}} \times A_{p\text{-DNB}}}{f_{m\text{-DNB}} \times A_{m\text{-DNB}} + f_{p\text{-DNB}} \times A_{p\text{-DNB}} + f_{o\text{-DNB}} \times A_{o\text{-DNB}}} \quad (4)$$

where $S_{p\text{-DNB}}$ represents the selectivity of *p*-DNB. Nitro-phenol samples were analyzed using a DB-5 column with the following oven temperature program: an initial temperature of 50 °C (held for 5 min), ramped to 250 °C at 8 °C/min, and held for 4 min. The retention times for the components were as follows: 2-nitrophenol (13.8 min), 2,5-dinitrophenol (20.5 min), 2,4-dinitrophenol (21.3 min), 2,3,5-trinitrophenol (24.3 min), and 2,4,5-trinitrophenol (25.9 min).

PID Control. As shown in Figure 9, the program developed in this study enables real-time communication between the computer, pumps, and weighing scales via the R232 serial port. Using incremental PID control algorithm, the program automatically adjusts the pump flow rate to maintain the specified mass flow rate ratio. The control principles for proportional, integral, and derivative (PID) actions are described in eq 5³¹

$$u(t) = K_p \left[e(t) + \frac{1}{T_i} \int_0^t e(t) dt + T_d \frac{de(t)}{dt} \right] \quad (5)$$

where $u(t)$ represents the control output from the controller, $e(t)$ is the error signal, defined as the difference between the set point and the output, K_p is the proportional gain, T_i is the integral time constant, and T_d is the derivative time constant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.5c00377>.

The micromixing efficiency of the micromixer, the GC analysis of nitrophenols involved in the reaction, the interface and operation of the program developed in this study ([PDF](#))

Example video demonstrating the program automatically adjusting the mass flow rate ratio are provided. Source code: https://github.com/wzjeh/pump_calibrate ([MP4](#))

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Notes

The authors declare no competing financial interest.

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