

# Continuous-Flow Diazotization of Weakly Basic Aromatic Amines in a Microreaction System

Yifeng Zhou, Zong Yao, Xuejing Zhang, Rujing Yang, Yiqiang Jin,\* and Jinpei Huang\*



Cite This: *Ind. Eng. Chem. Res.* 2023, 62, 4995–5001



Read Online

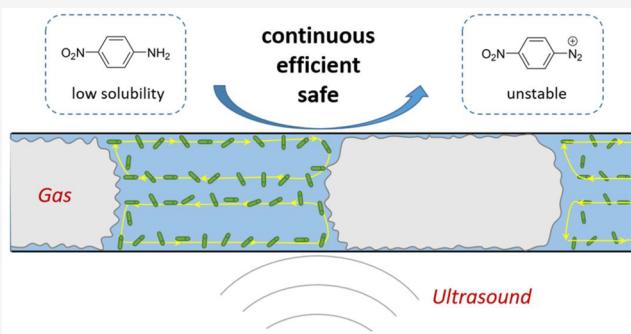
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

**ABSTRACT:** Due to the characteristics of high transfer efficiency, controllable process, and intrinsic safety in microreactors, there have been many studies on the miniaturization of diazotization reactions. However, diazotization of weakly basic aromatic amines is difficult to be reformed by continuous microreaction technology due to its poor solubility. In this paper, first, by improving the crystallization process, the miniaturization of diazotization with low solid content was realized. The effects of various parameters (flow rate, temperature, reagent dosage, and concentration) on the reaction yield were investigated systematically. As for high solid content, by introducing the gas–liquid Taylor flow and ultrasonic assistance, the mass transfer process was strengthened, and the slurry flow pattern was improved. Finally, at 0.40 mol/L, a residence time of 94 s in the delay loop with a 5 °C cold trap was employed to produce a diazonium salt in 96% yield with high stability.



## INTRODUCTION

Diazonium salt intermediates which have many applications in medicine, pesticides, dyes, and other fine chemical industries<sup>1</sup> are usually prepared by diazotization reactions. However, in batch reactors, the diazotization reactions have been plagued by process safety due to the potentially highly explosive diazonium salt intermediates, the large associated heat release, and the evolution of nitrogen gas from side reactions. Continuous microreaction technology has the characteristics of high transfer efficiency, controllable process, intrinsic safety, and easy scale-up,<sup>2–9</sup> which provides a new method to tame hazardous chemistry. In recent years, researchers have already realized the miniaturization of the diazotization reaction on the microreaction systems in many cases.<sup>10–17</sup> Compared with the batch processes, the continuous processes with microreactors can increase reaction efficiency, broaden the operation range of reaction parameters, and improve safety. Through further design and development of the continuous process, side reactions can be controlled, and product quality can be guaranteed.

Although many excellent results in diazotization reactions have been obtained by using microreaction technology, still some problems remain to be resolved especially for weakly basic aromatic amines. The diazo components of most monoazo disperse dyes are weakly basic aromatic amines, which have strongly electron absorbing groups in aromatic rings. The introduction of strongly electron absorbing groups can lower the dye excited state energy level, producing the dark effect. Weakly basic aromatic amines, such as *o*-nitroaniline, *p*-

nitroaniline, nitrotoluidine, and 2,5-dichloroaniline, are less alkaline and have difficulty in forming salts with inorganic acids, resulting in poor solubility in the aqueous phase. Not only that, during the reaction processes, diazonium salts with high coupling activity are easy to couple with the free aromatic amines in the solvent to form azo compound precipitation. The microreaction technology can accurately realize the instantaneous mixing of two streams of materials and effectively reduce the backmixing effect. However, the poor aqueous solubility of weakly alkaline aromatic amine and precipitation of side reactions lead to the problems of solid–liquid transport difficulties and microchannel blockages, bringing great challenges to the miniaturization of this kind of diazotization reactions.

Existing studies have proposed several solutions to the above problems in microreactors. In order to prevent microchannel blockages, water-soluble organic solvents such as acetonitrile, methanol, and acetone are added into the aqueous solution. Wootton et al.<sup>18</sup> first reported the application of the microreactor to the preparation of aryl diazonium salts in 2002. They used H<sub>2</sub>O/DMF mixed solvents to prevent the

Received: February 3, 2023

Revised: February 22, 2023

Accepted: February 26, 2023

Published: March 7, 2023



occurrence of solid precipitation in microchannels. A moderate yield of azo dyes was achieved by a continuous process of diazotization and coupling reactions. The biggest difficulty was in separating the products and recycling the organic solvents, which caused high post-treatment pressure. Similarly, organic acids, such as acetic acid, can be used instead of inorganic acids to achieve an increase in the solubility of arylamines,<sup>19,20</sup> but again the problem of postprocessing cannot be overcome. Another solution is using organic reaction systems including organic solvents and organic nitrification reagents, such as *tert*-butylnitrite, isobutylnitrite, and isoamyl nitrite. To prevent diazonium salt precipitation, organic solvents with higher polarity are generally selected, for instance, methanol, acetonitrile, tetrahydrofuran, and *N,N*-dimethylformamide. Sanz et al.<sup>21</sup> selected *tert*-butyl nitro as a nitrification reagent, benzyl triethylammonium chloride as a chlorine source, and acetonitrile and methylene chloride as mixed solvents in the continuous process of diazotization and chlorosulfonylation, without the use of acid. This organic reaction system avoided the corrosion of microchannels by the high concentration of hydrochloric acid and was easily performed continuously. As a result, the optimized microreaction platform prepared a series of aromatic sulfonyl chloride compounds with yields ranging from 25% to 90%. However, the reagent cost of this reaction system is too high to form market competitiveness.

To sum up, the most effective and economical way is still the aqueous reaction system with sodium nitrite as the nitrification reagent. In this work, we developed a microreaction system for continuous diazotization of weakly basic aromatic amines. The diazotization of *p*-nitroaniline using the aqueous reaction system as the typical object of study was chosen. By optimizing the crystallization process, the slurries with small particle sizes were prepared, and the continuous flow synthesis under the condition of low concentration (low solid content) was realized without any assistant methods. In view of high concentration (high solid content) conditions, gas phase and ultrasonic assistance were introduced to further strengthen the mass transfer process, improve the dispersion of slurries, and avoid channel blockage. Finally, a stable and efficient continuous process of diazotization with high yield (~96%), short reaction time (~94 s), and high concentration (0.40 mol/L) was achieved.

## ■ EXPERIMENTAL SECTION

**Materials.** Hydrochloric acid (36–38%, Greagent), sodium hydroxide ( $\geq 96\%$ , pellet, Greagent), sodium nitrite ( $\geq 99\%$ , Greagent), *p*-nitroaniline (99%, Adamas), 6-hydroxynaphthalene-2-sulfonate ( $\geq 98\%$ , Adamas), and sodium bicarbonate (99%, Adamas) were purchased from *Tansoole*. All reagents were not further purified before use.

**Preparation of Reactant Solution.** *Solution A.* Sodium nitrite (3.80 g, 0.055 mol) was dissolved in deionized water (200 mL) in a 500 mL beaker.

*Solution B.* *p*-Nitroaniline (6.09 g, 0.050 mol) and hydrochloric acid (16.7 mL, 0.200 mol) were added to deionized water (25 mL) in a 100 mL beaker. Then, the temperature was raised to 90 °C to obtain an initial clear *p*-nitroaniline hydrochloride solution. After that, the clear solution was dropwise added into the ice water mixture (200 g + 200 g) with stirring to form a slurry (Figure 1). At last, the slurry was supplemented with deionized water to a volume of 500 mL.

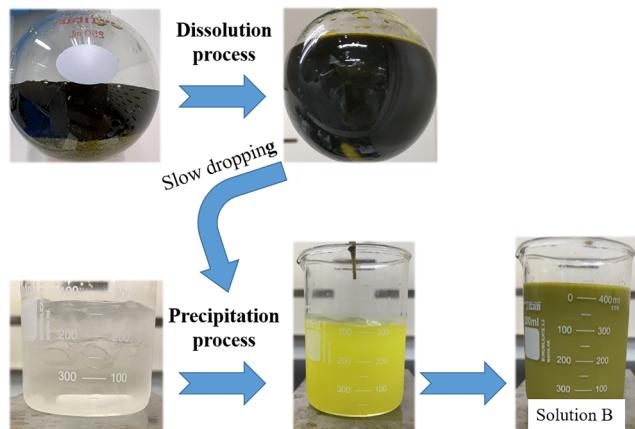


Figure 1. Preparation process of solution B.

*Solution C.* Sodium 6-hydroxynaphthalene-2-sulfonate (10.88 g, 0.0442 mol) and sodium hydroxide (8.68 g, 0.217 mol) were dissolved in deionized water (500 mL) in a 1 L beaker.

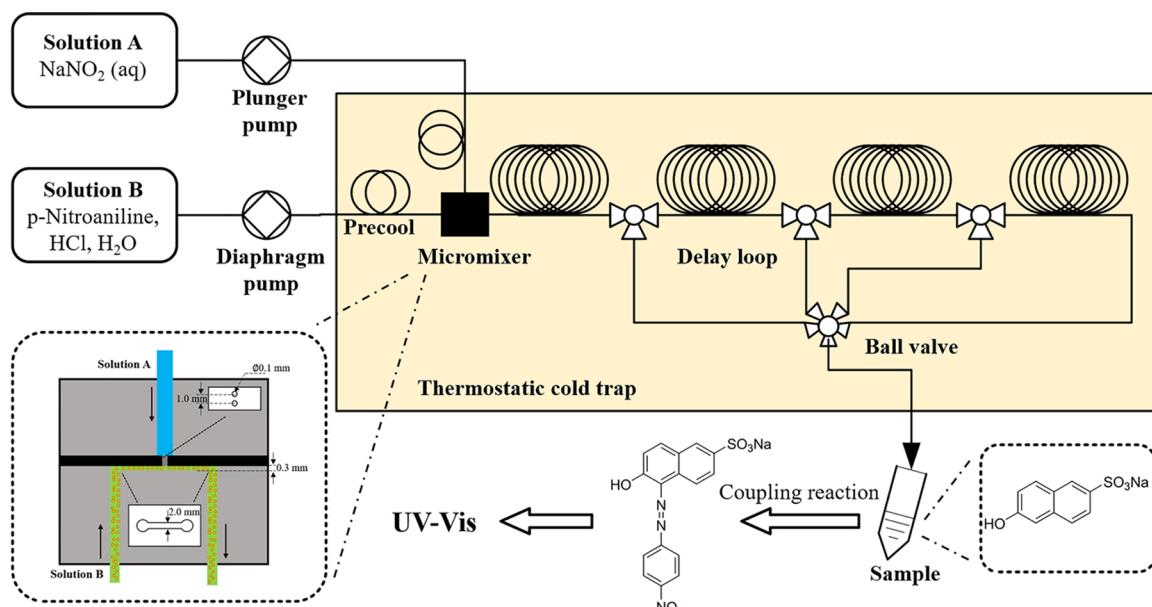
Owing to the changes of the concentration of reactants in different experiments, the above preparation process was a typical case.

## Experimental Procedure of the Continuous Flow Process.

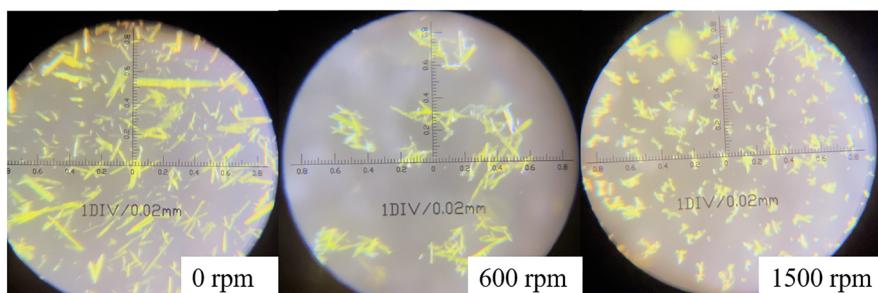
As shown in Figure 2, solution A was carried to the micromixer by a plunger pump (SWEICO, 2PB3020IV). Since solution B was a slurry, it was carried to the micromixer by a diaphragm pump (Prominent, GMXA2504). The micromixer was a micropore dispersion microreactor (homemade<sup>15,22–24</sup>). A delay loop tube (PTFE, 3.0 mm inner diameter, 4.0 mm outer diameter) was connected to the outlet of the micromixer. Both the microreactor and delay loop tube were submerged in the cold trap to control the reaction temperature. To analyze samples, a certain amount of the reaction solution from the outlet was directly added to the excess coupling component (solution C, 10 mL) to capture diazo ions and quench the diazotization reaction. The concentration of the generated azo dye was quantified by UV-vis spectroscopy.<sup>17,25</sup> Based on the quantitative relationship between the concentration of the diazonium salts and the azo dyes, the yield of the diazotization reaction could be obtained (see the Supporting Information for details).

## ■ RESULTS AND DISCUSSION

**Optimization of Slurry Preparation.** The formation process of the *p*-nitroaniline crystal consists of the nucleation and growth stages. Intensifying the burst of nucleation is beneficial to obtain the crystal with a smaller size. Supersaturation is considered to be the driving force for both crystal nucleation and growth. In general, crystal nucleation dominates crystal growth at higher supersaturation, ultimately resulting in smaller size. The slurries with a small particle size are supposed to have a slower sedimentation rate and larger solid–liquid contact area, which are more suitable as starting materials for continuous flow synthesis. Therefore, to keep the supersaturation at a high level during crystallization, the cooling crystallization method of dropping the high-temperature initial clear *p*-nitroaniline solution into the ice water mixture was used. Mixing conditions in a crystallizer can directly impact the kinetics of the crystallization process and the final crystal size. The temperature and concentration



**Figure 2.** Schematic of the microreaction system.



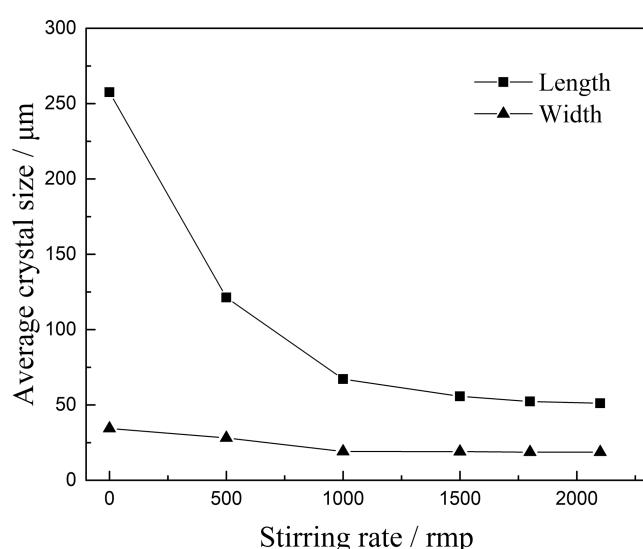
**Figure 3.** Morphology of *p*-nitroaniline crystals at different stirring rates.

gradients in the mixture produce inhomogeneity in the prevailing level of supersaturation. Based on the above understanding, to obtain *p*-nitroaniline slurries with good performance in the continuous flow, the factors affecting crystal formation such as the stirring rate and the concentration of the initial clear *p*-nitroaniline solution were studied.

The physical collision between stirring blade and crystal leads to crystal breakage and secondary nucleation. As shown in Figure 3, the initial morphology of crystal was acicular. Under the high stirring rate, there was an obvious phenomenon of crystal breakage. With the increase in the rotation speed of the agitator, the crystal size changed with a fast reduction and a following plateau phase (Figure 4). The critical stirring rate was about 1500 rpm in our experiments.

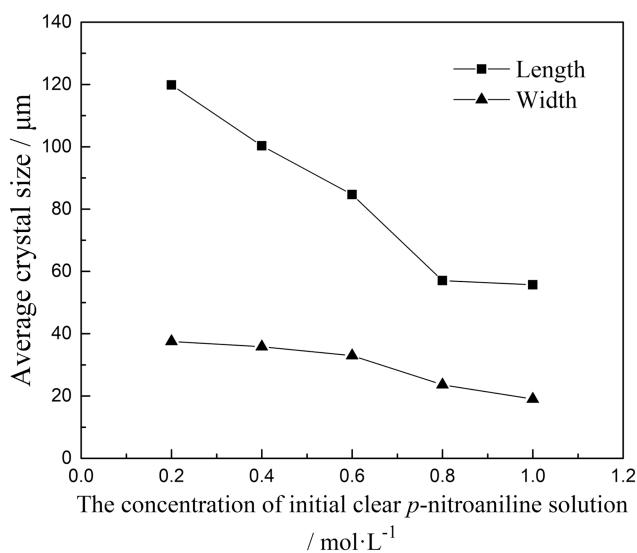
A higher initial concentration implies a higher supersaturation, leading to smaller crystals (Figure 5). However, due to the solubility of *p*-nitroaniline, too high of an initial concentration may have the problem of early precipitation during the feeding process. Thus, we considered 1.0 mol/L to be a preferable choice for the initial concentration of *p*-nitroaniline.

Smaller crystals mean lower sedimentation velocities and are more favorable for flow reactions. As shown in Figure 6, the reaction yield increases rapidly as the apparent sedimentation velocity of the solid particles decreases. The yield of the

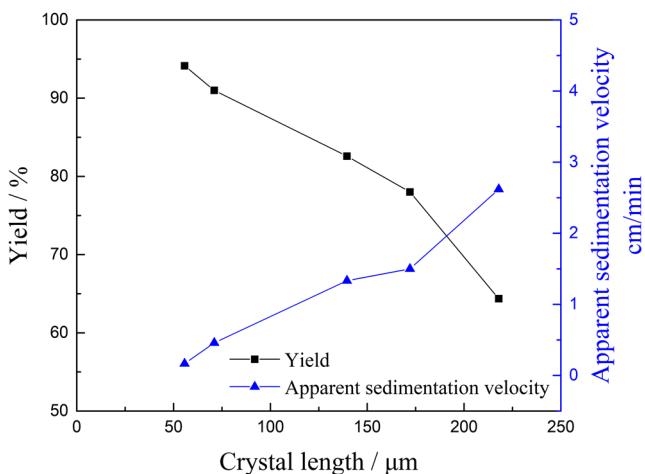


**Figure 4.** Influence of the stirring rate on the size of the crystal. Experimental conditions: the concentration of the initial clear *p*-nitroaniline solution was 1.0 mol/L.

diazonium salt reached 94.1% using the slurries with a crystal of  $\sim 56 \mu\text{m}$  in length and  $\sim 19 \mu\text{m}$  in width, which was



**Figure 5.** Influence of the concentration of the initial clear *p*-nitroaniline solution on the size of the crystal. Experimental conditions: the stirring rate was 1500 rpm.

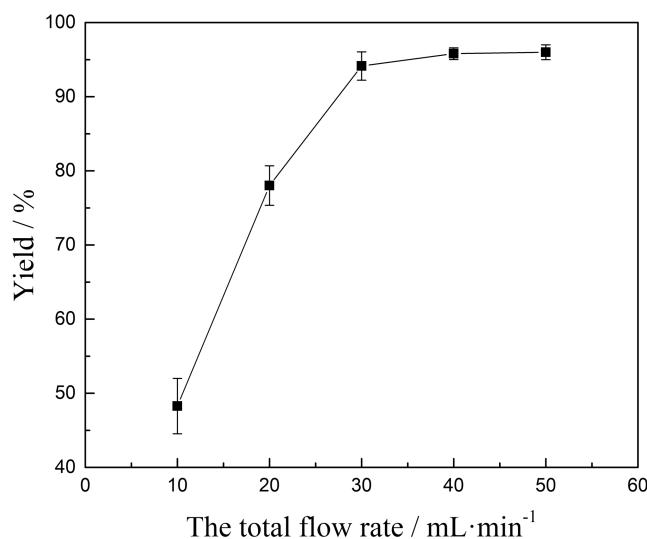


**Figure 6.** Influence of the crystal size on the apparent sedimentation velocity and yield. Reaction conditions: 0 °C, *p*-nitroaniline/NaNO<sub>2</sub>/HCl (mole ratio) = 1:1.2:4.0, *c*(*p*-nitroaniline) in solution B = 0.1 mol/L, total flow rate = 30 mL/min, residence time = 60 s.

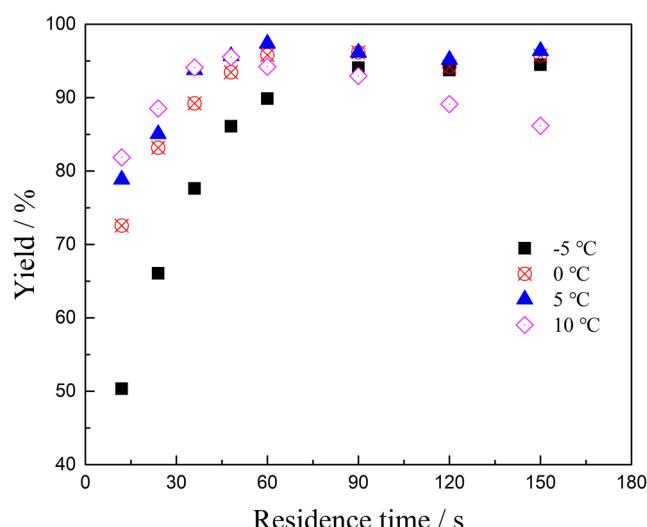
obtained at the stirring rate of 1500 rpm and the concentration of the initial clear *p*-nitroaniline solution of 1.0 mol/L.

**The Influence of Each Parameter on Continuous Synthesis.** *Flow Rate.* The influence of the total flow rate on the yield of the diazotization reaction was studied. As shown in Figure 7, the increase of the total flow rate promoted the yield of the diazotization reaction, and when the total flow rate exceeded 40 mL/min, the yield reached its plateau. On the one hand, the increase of the flow rate was conducive to the rapid mixing of the two streams in the micromixer. On the other hand, a higher flow rate brought a higher *Re* number, which means that the greater the disturbance of the fluid in the delay loop, that can delay the sedimentation of particles and facilitate the flow reaction. On this basis, we carried out all the subsequent experiments at a total flow rate of 40 mL/min.

*Temperature.* Figure 8 showed that the reaction rate of diazotization was significantly affected by the reaction temperature. When the temperature was raised from -5 to 5



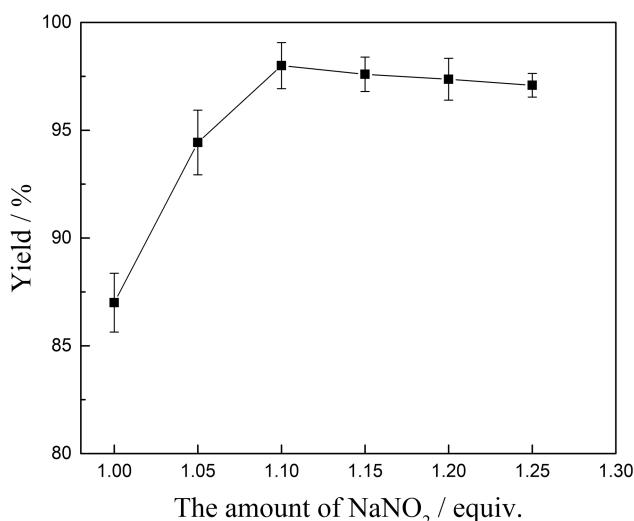
**Figure 7.** Influence of the total flow rate on the yield. Reaction conditions: 0 °C, *p*-nitroaniline/NaNO<sub>2</sub>/HCl (mole ratio) = 1:1.2:4.0, *c*(*p*-nitroaniline) in solution B = 0.1 mol/L, residence time = 60 s.



**Figure 8.** Influence of temperature on the yield. Reaction conditions: *p*-nitroaniline/NaNO<sub>2</sub>/HCl (mole ratio) = 1:1.2:4.0, *c*(*p*-nitroaniline) in solution B = 0.1 mol/L, total flow rate = 40 mL/min.

°C, the reaction rate was greatly increased. At 5 °C and 60 s residence time, the yield reached the peak value. The increase of the reaction temperature was helpful to promote the solubility of *p*-nitroaniline crystals and accelerated the reaction rate. However, when the temperature rose to 10 °C, the diazonium salt became unstable to decompose to impurities, such as *p*-nitrophenol and *p*-nitrochlorobenzene, resulting in obvious bubble formation and a low yield. Therefore, for the continuous flow diazotization process, the optimal reaction temperature was determined to be 5 °C.

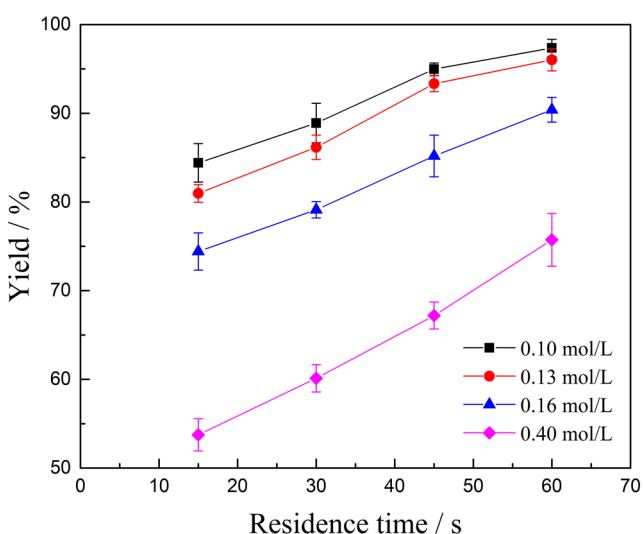
*Amount of Reagents.* The real diazotization reagent in the hydrochloric acid medium was nitrite chloride, which was derived from sodium nitrite. Therefore, the influence of the amount of sodium nitrite on the diazotization process was discussed. The result was shown in Figure 9, and the yield of the diazonium salt increased with the increase in the sodium



**Figure 9.** Influence of sodium nitrite on the yield. Reaction conditions: 5 °C, *p*-nitroaniline/HCl (mole ratio) = 1:4.0, *c*(*p*-nitroaniline) in solution B = 0.1 mol/L, total flow rate = 40 mL/min, residence time = 60 s.

nitrite equivalent. Once sodium nitrite was insufficient, *p*-nitroaniline easily formed insoluble impurities by the coupling reaction with generated diazonium salt intermediates. This kind of insoluble impurities was likely to adhere to the wall surface, causing channel blockage. Thus, the determination of the sodium nitrite equivalent as 1.1 equiv took into account both prevention of impurity generation and atomic economy.

**Concentration.** As shown in Figure 10, the yield of diazotization reaction increased with the increase of the

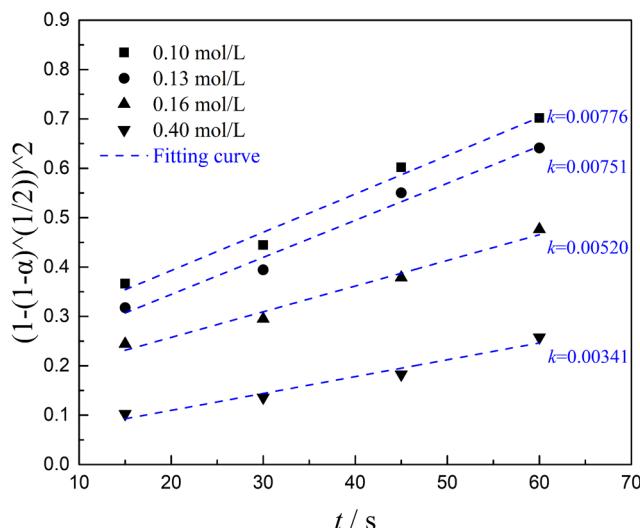


**Figure 10.** Influence of concentration on the yield. Reaction conditions: 5 °C, *p*-nitroaniline/NaNO<sub>2</sub>/HCl (mole ratio) = 1:1:4.0, total flow rate = 40 mL/min, residence time = 60 s.

reaction time under the condition of slurries (solution B) of different concentrations (0.10–0.40 mol/L). The reaction efficiency at high concentrations was much lower than that at low concentration. This means that the solid–liquid mass transfer effect has a significant impact on the reaction process. In addition, it was observed that at the high concentration, there was a pressure surge and blockage phenomenon after a

long time run, which would become the major problem in further experiments.

For simplicity, we assumed the dissolution and diffusion of the crystal of aromatic amines was the rate-limiting step. A solid–liquid reaction model described in the literature was used to simulate this process.<sup>26</sup> The solid–liquid control equation of acicular particles was shown in eq 1, where  $\alpha$  is the fraction of reacted material, and  $k$  is proportional to the diffusion coefficient. As shown in Figure 11, the plot (1-(1-



**Figure 11.** Plot of  $(1 - (1 - \alpha)^{1/2})^2$  versus  $t$  at different concentrations of *p*-nitroaniline and a linear fitting of the experimental data.

$\alpha)^{1/2})^2$  versus  $t$  had good linearity. The result showed that with the increase of concentration, the  $k$  value calculated by linear fitting of experimental data decreases obviously, which means that the solid–liquid diffusion coefficient decreased, thus affecting the normal process of the diazotization reaction. The agglomeration and sedimentation can be inferred from the change of mass transfer resistance.

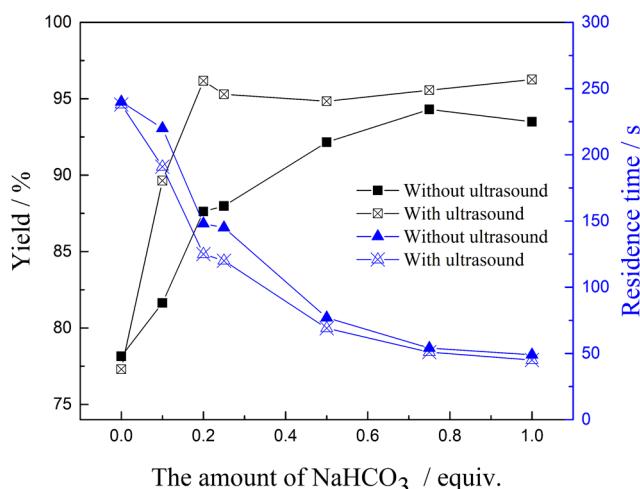
$$(1 - (1 - \alpha)^{1/2})^2 = kt \quad (1)$$

**Introduction of Assistant Techniques.** In order to solve the problems of particle agglomeration and channel blockage, we took two measures in this section: the gas–liquid–solid Taylor flow and ultrasound assistance.

The gas–liquid–solid Taylor flow has been introduced to address the limitations of microreactors that involved solids. The liquid recirculation flow pattern can suspend, transport, and mix solid particles in the liquid slugs, reducing the risk of clogging.<sup>27–29</sup> In our case, as the pressure fluctuation of the solid containing system was relatively large, the introduction of gas through differential pressure by the flow controller was prone to large nonuniformity, which easily leads to instability of the actual gas–liquid reaction process. Considering that the reaction is carried out under strong acidic conditions, a certain amount of NaHCO<sub>3</sub> was added to solution A, and the corresponding amount of HCl was added to solution B, so that carbon dioxide can be released when two streams were mixed. It was observed that the reaction liquid flow was segmented by a gas column (Figure 12), which was helpful to strengthen internal recirculation, reduce pressure drop, and minimize back-mixing. The result in Figure 13 showed that in the case of



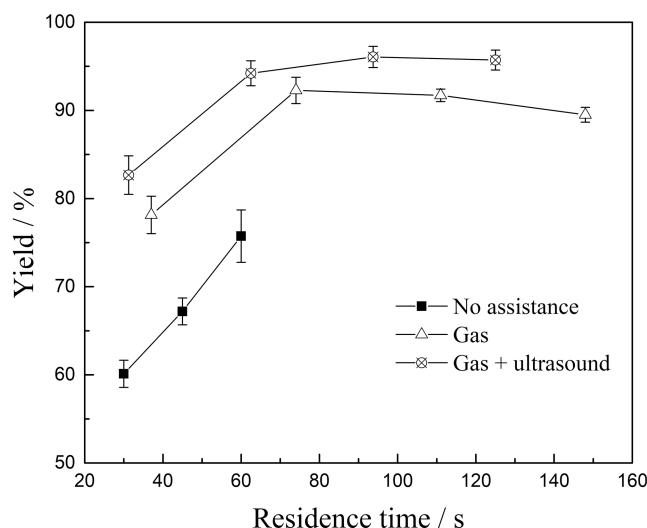
**Figure 12.** Gas–liquid–solid Taylor flow.



**Figure 13.** Influence of the gas–liquid–solid Taylor flow and ultrasound assistance on the yield. Reaction conditions: 5 °C, *p*-nitroaniline/NaNO<sub>2</sub> (mole ratio) = 1:1.1, *c*(*p*-nitroaniline) in solution B = 0.4 mol/L, total flow rate = 40 mL/min.

fixed tube length, with the increase of NaHCO<sub>3</sub>, the amount of gas release became larger, the residence time became shorter, and the yield gradually increased, which indirectly indicated that the mass transfer process was effectively strengthened. After testing, the microreaction system ran for 2 h without clogging and significant yield fluctuation.

For ultrasound assistance, the enhancement effect is mainly caused by acoustic cavitation, which can induce strong local turbulence in the form of cavitation microbeams, liquid jets, and shock waves. It has been shown that cavitation microbeams generated by bubble surface oscillations and periodic bubble length changes can strongly alter and distort the recirculation loop in the liquid plug, thus enhancing mass transfer.<sup>30,31</sup> Here, ultrasound (40 kHz, 360 W) was applied to the reaction in the delay loop (Video S1). The introduction of ultrasound maximized the role of gas in the system. One advantage is that ultrasonic assistance can help reduce the solubility of carbon dioxide and improve reagent utilization, so that more gas can be released, and the residence time becomes shorter (Figure 13). Another advantage is that it can promote gas vibration, so that the gas–liquid two phases collide violently and slow down the agglomeration of particles in high solid content slurries. Benefiting from further enhancement of solid–liquid mass transfer, the reaction efficiency and yield were further improved compared to the single treatment (Figure 14).



**Figure 14.** Comparison of reaction results with or without complementary techniques.

## CONCLUSION

In summary, we have developed an efficient continuous-flow microreaction system to conduct a diazotization reaction of weakly basic aromatic amines. A typical case of diazotization of *p*-nitroaniline was studied systematically. Through the optimization of the crystallization process of *p*-nitroaniline, the slurries with an average crystal size of about 56 μm in length and 19 μm in width were obtained, which has relatively good suspension performance. A continuous diazotization reaction with low solid content can be achieved in a simple continuous-flow microreaction system without using other means. The effects of various parameters (flow rate, temperature, reagent dosage, and concentration) on the reaction yield were investigated. In view of the situation that slurries with high solid content are easily settled and solid–liquid mass transfer is blocked, the gas–liquid Taylor flow and ultrasonic assisted methods are introduced to further strengthen the circulation in the liquid column. Finally, only a residence time of 94 s in the delay loop at 5 °C was employed to produce diazonium salt in 96% yield with high process stability. Compared to the traditional batch production (1–2 h, ~90%), the developed continuous-flow diazotization shows a great prospect in industrial application.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.iecr.3c00337>.

Quantitative analysis method of the diazonium salt; the measurement method of apparent sedimentation velocity (PDF)

Video S1, the ultrasound assistance in the delay loop (AVI)

## AUTHOR INFORMATION

### Corresponding Authors

Jinpei Huang – College of Life Science, China Jiliang University, Hangzhou 310018 Zhejiang, China;  
[orcid.org/0000-0002-8753-1976](http://orcid.org/0000-0002-8753-1976);  
 Email: [huangjinpei1994@cjlu.edu.cn](mailto:huangjinpei1994@cjlu.edu.cn)

Yiqiang Jin – Apeloa Pharmaceutical Co., Ltd., Dongyang 322118 Zhejiang, China; Email: [yiqiang.jin@apeloa.com](mailto:yiqiang.jin@apeloa.com)

## Authors

Yifeng Zhou – College of Life Science, China Jiliang University, Hangzhou 310018 Zhejiang, China

Zong Yao – College of Life Science, China Jiliang University, Hangzhou 310018 Zhejiang, China

Xuejing Zhang – College of Life Science, China Jiliang University, Hangzhou 310018 Zhejiang, China

Rujing Yang – College of Life Science, China Jiliang University, Hangzhou 310018 Zhejiang, China

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.iecr.3c00337>

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge support from the National Natural Science Foundation of China (22108264) for this work.

## REFERENCES

- (1) Mo, F.; Qiu, D.; Zhang, L.; Wang, J. Recent development of aryl diazonium chemistry for the derivatization of aromatic compounds. *Chem. Rev.* **2021**, *121* (10), 5741–5829.
- (2) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The hitchhiker's guide to flow chemistry. *Chem. Rev.* **2017**, *117* (18), 11796–11893.
- (3) Hessel, V.; Cortese, B.; De Croon, M. Novel process windows—Concept, proposition and evaluation methodology, and intensified superheated processing. *Chem. Eng. Sci.* **2011**, *66* (7), 1426–1448.
- (4) Jensen, K. F. Flow chemistry—microreaction technology comes of age. *AICHE J.* **2017**, *63* (3), 858–869.
- (5) Razzaq, T.; Kappe, C. O. Continuous flow organic synthesis under high-temperature/pressure conditions. *Chem.—Asian J.* **2010**, *5* (6), 1274–1289.
- (6) Geng, Y.; Ling, S.; Huang, J.; Xu, J. Multiphase microfluidics: fundamentals, fabrication, and functions. *small* **2020**, *16* (6), 1906357.
- (7) Chen, L.; Yang, C.; Xiao, Y.; Hu, L.; Eggersdorfer, M.; Chen, D.; Weitz, D. A.; Ye, F. Millifluidics, microfluidics, and nanofluidics: manipulating fluids at varying length scales. *Mater. Today Nano* **2021**, *16*, 100136.
- (8) Yan, Z.; Tian, J.; Wang, K.; Nigam, K.; Luo, G. Microreaction processes for synthesis and utilization of epoxides: A review. *Chem. Eng. Sci.* **2021**, *229*, 116071.
- (9) Chen, L.; Chen, J.; Sun, Z.; Wu, B.; Ye, F.; Zhao, C.; Chen, D. Morphology control of trimer particles via one-step co-precipitation and controlled phase separation. *Chem. Eng. Sci.* **2022**, *251*, 117432.
- (10) Chen, J.; Xie, X.; Liu, J.; Yu, Z.; Su, W. Revisiting aromatic diazotization and aryl diazonium salts in continuous flow: highlighted research during 2001–2021. *React. Chem. Eng.* **2022**, *7* (6), 1247–1275.
- (11) Deadman, B. J.; Collins, S. G.; Maguire, A. R. Taming hazardous chemistry in flow: the continuous processing of diazo and diazonium compounds. *Chem.—Eur. J.* **2015**, *21* (6), 2298–2308.
- (12) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-flow technology—a tool for the safe manufacturing of active pharmaceutical ingredients. *Angew. Chem., Int. Ed.* **2015**, *54* (23), 6688–6728.
- (13) Yu, Z.; Dong, H.; Xie, X.; Liu, J.; Su, W. Continuous-flow diazotization for efficient synthesis of methyl 2-(chlorosulfonyl)-benzoate: an example of inhibiting parallel side reactions. *Org. Process Res. Dev.* **2016**, *20* (12), 2116–2123.
- (14) Yu, Z.; Ye, X.; Xu, Q.; Xie, X.; Dong, H.; Su, W. A fully continuous-flow process for the synthesis of *p*-cresol: impurity analysis and process optimization. *Org. Process Res. Dev.* **2017**, *21* (10), 1644–1652.
- (15) Wang, F.; Huang, J.; Xu, J. Continuous-flow synthesis of azo dyes in a microreactor system. *Chem. Eng. Process.* **2018**, *127*, 43–49.
- (16) Wang, F.; Huang, J.; Xu, J. Continuous-flow synthesis of the azo pigment yellow 14 using a three-stream micromixing process. *Org. Process Res. Dev.* **2019**, *23* (12), 2637–2646.
- (17) Wang, F.; Ding, Y.; Xu, J. Continuous-flow synthesis of pigment red 146 in a microreactor system. *Ind. Eng. Chem. Res.* **2019**, *58* (36), 16338–16347.
- (18) Wootton, R. C.; Fortt, R.; de Mello, A. J. On-chip generation and reaction of unstable intermediates—monolithic nanoreactors for diazonium chemistry: azo dyes. *Lab Chip* **2002**, *2* (1), 5–7.
- (19) Lebegue, N.; Gallet, S.; Flouquet, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Leonce, S.; Pierre, A.; Chavatte, P.; Berthelot, P. Novel benzopyridothiadiazepines as potential active antitumor agents. *J. Med. Chem.* **2005**, *48* (23), 7363–7373.
- (20) Hogan, P. J.; Cox, B. G. Aqueous process chemistry: the preparation of aryl sulfonyl chlorides. *Org. Process Res. Dev.* **2009**, *13* (5), 875–879.
- (21) Malet-Sanz, L.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. Preparation of arylsulfonyl chlorides by chlorosulfonylation of in situ generated diazonium salts using a continuous flow reactor. *Org. Biomol. Chem.* **2010**, *8* (23), 5324–5332.
- (22) Huang, J.; Sang, F.; Luo, G.; Xu, J. Continuous synthesis of gabapentin with a microreaction system. *Chem. Eng. Sci.* **2017**, *173*, S07–S13.
- (23) Zhang, J.; Wang, K.; Lu, Y.; Luo, G. Characterization and modeling of micromixing performance in micropore dispersion reactors. *Chem. Eng. Process.* **2010**, *49* (7), 740–747.
- (24) Wang, K.; Lu, Y.; Luo, G. Strategy for scaling-up of a microsieve dispersion reactor. *Chem. Eng. Technol.* **2014**, *37* (12), 2116–2122.
- (25) Wang, F.; Chen, A.; Ling, S.; Xu, J. Continuous-flow diazotization of red base KD hydrochloride suspensions in a microreaction system. *React. Chem. Eng.* **2021**, *6* (8), 1462–1474.
- (26) Dickinson, C. F.; Heal, G. R. Solid-liquid diffusion controlled rate equations. *Thermochim. Acta* **1999**, *341*, 89–103.
- (27) Ge, L.; Peng, Z.; Moreno-Atanasio, R.; Doroodchi, E.; Evans, G. M. Three-dimensional VOF-DEM model for simulating particle dynamics in the liquid slugs of a vertical gas–liquid–solid Taylor flow microreactor. *Ind. Eng. Chem. Res.* **2020**, *59* (16), 7965–7981.
- (28) Peng, Z.; Wang, G.; Moghtaderi, B.; Doroodchi, E. A review of microreactors based on slurry Taylor (segmented) flow. *Chem. Eng. Sci.* **2022**, *247*, 117040.
- (29) Enache, D. I.; Hutchings, G. J.; Taylor, S. H.; Natividad, R.; Raymahasay, S.; Winterbottom, J. M.; Stitt, E. H. Experimental evaluation of a three-phase downflow capillary reactor. *Ind. Eng. Chem. Res.* **2005**, *44* (16), 6295–6303.
- (30) Yang, L.; Xu, F.; Zhang, Q.; Liu, Z.; Chen, G. Gas-liquid hydrodynamics and mass transfer in microreactors under ultrasonic oscillation. *Chem. Eng. J.* **2020**, *397*, 125411.
- (31) Dong, Z.; Yao, C.; Zhang, Y.; Chen, G.; Yuan, Q.; Xu, J. Hydrodynamics and mass transfer of oscillating gas-liquid flow in ultrasonic microreactors. *AICHE J.* **2016**, *62* (4), 1294–1307.