

Continuous diazotization of aromatic amines with high acid and sodium nitrite concentrations in microreactors

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Abstract

We design a new continuous diazotization microreaction process in which concentrated acid and sodium nitrite solutions are used. We form oil in water (O/W) microdroplets by mixing amine with sodium nitrite aqueous solution, which react with mineral acid to make the diazotization. In this way, the formed particles are dispersed in the aqueous phase, which can flow with the main stream, and consequently are consumed. Then the fluid can smoothly flow without clogging in the microchannels and we can achieve continuous operation. We use aniline, o-methylaniline, m-methylaniline, and o-ethylaniline as the raw materials, 6 M HCl and 6.5 M H₂SO₄ as the acid as well as sodium nitrite to demonstrate the feasibility. The resulting diazonium salts are converted to iodo-substitute aromatic compounds to measure the yield. The results show that, SIMM-V2 micromixer is efficient to form the emulsion. Mixing the microdroplets with acid in a co-axial flow way can prevent clogging. In hydrochloric acid medium, high reaction yield can be obtained when the reaction temperature is 4 °C and the residence time is 13–15 s. In sulfuric acid medium, high conversion of aromatic amine of up to 99% and yield of approximately 90% can be achieved at the reaction temperature of 9 °C and the residence time of 14–16 s. This process provides efficient continuous diazotization reactions using concentrated acid and sodium nitrite solutions, minimizing the production of waste water.

Keywords Diazotization · O/W microdroplets · Clogging · Microreactor

Introduction

Diazotization reactions are valued building blocks in organic synthesis which are used to prepare many substances [1–4]. Diazotization of aromatic amines is usually performed in batch manner at low temperature with slow addition of sodium nitrite in batch or semi-batch operations. The disadvantages of this reaction include the thermal instability of the

diazonium intermediate, amount of waste, the low efficiency and poor mixing in large vessel that leads to undesired byproducts [5–7].

Over past years, an explosion on continuous flow syntheses has appeared in chemical literatures. Compared to traditional batch vessels, flow reactors have many advantages such as better thermal and mass transfer; more accurate control of reaction parameters and ease to implement continuously. Furthermore, safety hazards in handling exothermic reactions associated with explosive intermediates are minimized because they involve a much smaller volume in the reaction train [8–11]. Commonly, the amine dissolved in diluted acid or sometimes organic solvent as one feed stock and sodium nitrite dissolved in water or/and organic solvent as another feed stock. The obtained conversions of amines and the yields of the products are higher than those of batch reactions with controlling the temperatures at 0–25 °C and the residence time in 10–30 s [12–14].

Like the above practices, amines are dissolved in the acid solutions to form homogeneous solutions to facilitate the feeding of amines to the microreactors by pumps. In the conventional way of performing the reactions, amount of waste

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generated is dealt with at the end of the reaction. What's more, some amines are not completely dissolved in concentrated acids, forming insoluble solid particles [10]. Consequently, more dilute acids and sodium nitrite solutions were used. For example, 3.6 M hydrochloric acid and 2.1 M sodium nitrite solution are used to prepare aromatic fluorides from anisidine, nitroaniline and halogenated aniline [15]. 0.84 M hydrochloric acid and 0.33 M sodium nitrite solution are used to prepare 2-(4-chlorophenyl)acetaldehyde from p-chloroaniline [12, 13]. In addition, mixed water and N,N-dimethylformamide solutions of hydrochloric acid and sodium nitrite, with concentrations of 0.7 M and 0.45 M, respectively, are used to prepare the azo dyes from aniline, o-toluidine and m-toluidine [16]. On the contrary, microreactor technology enables the reduction of waste generated by increasing the atom efficiency of reactions. However, when insoluble solids are formed after mixing the mineral acid with amine, clog the microchannels. Such diazotization has not previously been conducted in micro reactors.

In this paper, we develop a diazotization microreaction process by using concentrated acid and sodium nitrite solutions which can smoothly run without clogging of the microchannels. The process is simply described as first mixing amine with a sodium nitrite aqueous solution to form oil in water (O/W) microdroplets, followed by contacting with mineral acid. Since amine exists in the aqueous phase as very small oil microdroplets, which contact with acid results in the formation of tiny solid particles. These particles are dispersed in the aqueous phase; hence, they can flow with the main stream in microchannels of the microreactor. At the same time, they quickly react with sodium nitrite to generate nitrous acid and consequently diazonium salt. As this reaction step is very fast, the solid particles are quickly consumed. Thus clogging of the microchannel by solids hardly occurs. We demonstrate the feasibility of this process by using aniline, o-methylaniline, m-methylaniline, and o-ethylaniline as the amine, concentrated hydrochloric acid and sulfuric acid as the mineral acid and sodium nitrite solution with concentrations as high as 5.7 M. To examine the efficiency of the reaction, we convert the diazonium salt to iodo-substitute aromatic compounds by dropping the reaction mixture of the diazotization into a sodium iodate solution and reacting at fixed conditions. The conversions of the amines and yields of the iodo-substitute aromatic compounds are obtained and used to determine the efficiency of this micro process.

Results and discussion

Effect of the mixing

As mentioned above, insoluble solids are formed when some aromatic amines and concentrated mineral acids are mixed

when conducting the diazotization reactions. This poses a problem to conduct such reaction in microreactor resulting from the formation of solids after mixing amine with acid. To this end, we propose a process of conducting continuous diazotization reaction which is carried out by mixing liquid amine with a sodium nitrite aqueous solution to form O/W microdroplets, followed by contacting with mineral acid. As such the formed solid particles from amine and acid are to be dispersed in the aqueous phase. Hence they can flow with the main stream in microchannels, avoiding clogging. High concentrations of acid and sodium nitrite solutions can be used. We first examine the mixing of o-ethylaniline with 5.7 M sodium nitrite and consequent mixing with 6 M hydrochloric acid by two $\Phi 1/16''$ T-type connectors at 2 °C. The molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid is 1:1.05:3.2, with the ratio of flow rate of 1:1.44:4.16. Microscopic observation of the flow pattern reveals that amine and sodium nitrite form segmented flow after mixing in the first mixer, and the length of the amine segment decreases with increasing the flow rate at the total flow rate of less than 7.32 mL/min (Fig. 1a-d). After mixing with acid in the second mixer, solids can be observed immediately and clogging occurs in 5 s. We then try to mix amine with sodium nitrite in a co-axle T-type mixer. Segment flow is also formed, resulting in clogging after mixing with acid. Apparently such simple mixing method cannot avoid clogging.

To obtain O/W microdroplets after mixing amine with sodium nitrite, we tested SIMM-V2 that is more suitable to generate such flow pattern because of its more complex mixing principle as well as much smaller channel size than the T-connector [17]. When the total flow rate of o-ethylaniline and sodium nitrite is 1.22 mL/min, microdroplets can be observed, which quickly phase separate to form slug flow (Fig. 1e). Increasing the total flow rate to 1.464 mL/min leads to the formation of much more microdroplets, which can last longer time before they change to slugs (Fig. 1f). We can generate stable O/W flow at the amine and sodium nitrite total flow rate of 2.44 mL/min (Fig. 1g) and the amine droplets get smaller with increasing the flow rate (Fig. 1h). Mixing the O/W mixture with acid in a simple T-type mixer by collision can lead to smooth operation of the reaction for at least 3 min before clogging occurs.

We then examine the way of mixing the O/W mixture with acid on the smooth operation of the diazotization reaction. When the O/W mixture is mixed with acid by shearing, the system can run for 3.5 min, and then clogging occurs. When the O/W mixture and acid are mixed in a co-axial structure, the system can run smoothly for a long time. These results indicate that the co-axial mixing is a suitable way. In the following experiments, we use the designed diazotization setup which is assembled with a SIMM-V2 to mix amine and sodium nitrite, connected with a T-type co-axial mixer to mix with acid to examine the reaction parameters.

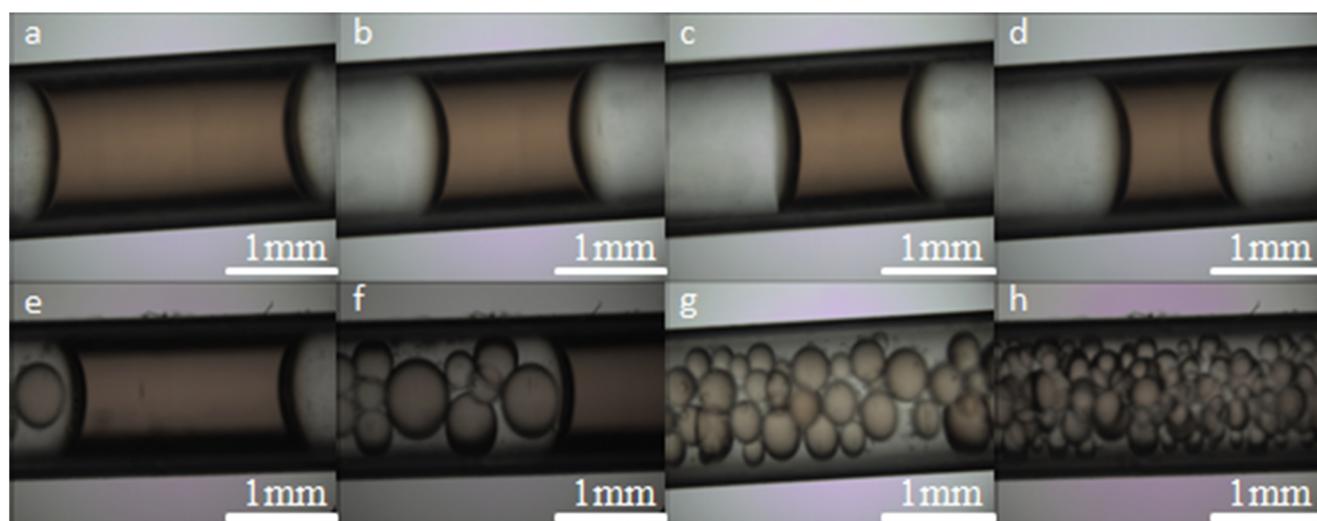


Fig. 1 Flow patterns of the mixture of o-ethylaniline and sodium nitrite at different flow rates by T-type connectors (**a–d**) and SIMM-V2 (**e–h**). The total flow rates of o-ethylaniline and sodium nitrite are (**a, e**) 1.22, (**f**) 1.464, (**b, g**) 2.44, (**c, h**) 4.88, and (**d**) 7.32 mL/min

Effect of reaction parameters

Diazotization reactions were carried out in a microreactor, amine and sodium nitrite aqueous solution were introduced to SIMM-V2 to form O/W microdroplets, which was mixed with hydrochloric acid to prepare the chloride diazonium salt. Finally, the effluent was collected in a flask containing a potassium iodide solution to prepare the iodobenzene and its homologues (Scheme 1). Then we examine the effect of the reaction by using the o-ethylaniline as the raw material. The concentration of the starting o-ethylaniline is 7.8 M.

Effect of the concentration of sodium nitrite The nitroso group of the diazotization reaction is usually supplied by sodium nitrite. In order to make sufficient contact with the raw material amine and enhance the reaction effect by using the organic nitrite instead of sodium nitrite, such as tert-butyl nitrite, etc. [18, 19]. However, It is too expensive to use and the sodium nitrite is widely used. We first examine the effect of the concentration of sodium nitrite to reveal if the diazotization reaction can be operated at high sodium nitrite concentrations to minimize the use of water.

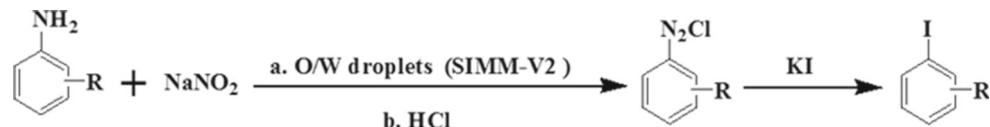
Figure 2 shows the effect of the sodium nitrite concentration on the reaction. With increasing the sodium nitrite concentration from 4.5 to 5.7 M, the conversion of o-ethylaniline changes from 97.7 to 98.9%, and the yield of o-ethyl iodide increases from 73.7 to 78.5%. Further increase in the concentration of

sodium nitrite from 5.7 to 6 M results in the decrease of conversion from 99.4 to 98.7%, the yield of o-ethyl iodide decreases from 78.5 to 73.2%. This may be ascribed to rapid decomposition of nitrous acid formed at high sodium nitrite concentration, as we can observe the formation of gas at these conditions and spray of the liquid at the outlet of the reactor. Therefore, the sodium nitrite concentration is better lower than 5.7 M.

Effect of the concentration of hydrochloric acid The results presented in Fig. 3 indicate that, when the concentration of hydrochloric acid is increased from 4.0 to 6.0 M, the conversion of o-ethylaniline increases from 97.2 to 98.9%, and the yield of o-ethyl iodide increases from 72.9 to 78.5%. Further increasing the concentration 6 to 8 M leads to the decrease in the conversion of o-ethylaniline to 96.5% and the yield to 71.2%. At the same time, we observe the formation of many gases, which result in the spray of effluent with pungent odor. This can be explained by decomposition of some nitrous acid at too high acid concentrations. Therefore, the concentration of hydrochloric acid is set at 6.0 M.

Effect of the molar ratio of acid to amine Figure 4 shows the effect of the molar ratio of hydrochloric acid to o-ethylaniline on the reaction. When the molar ratio of hydrochloric acid to o-ethylaniline increases from 3.0 to 3.2, the conversion of o-ethylaniline increases from 97.8 to 98.9%, and the yield of o-ethyl iodide increases from 76.3 to 78.5%. Further increase in

Scheme 1 Preparation and conversion of chloride diazonium salt



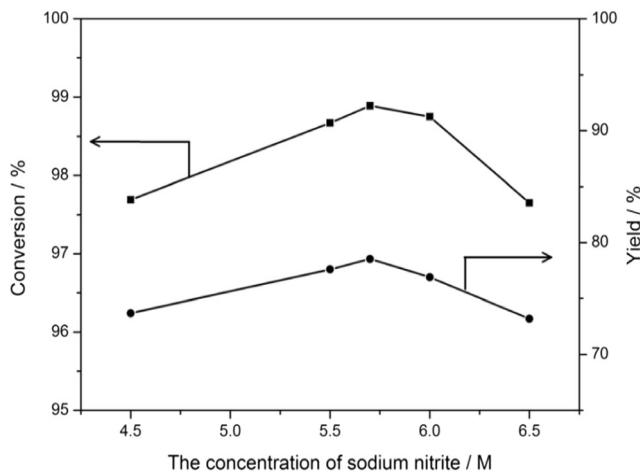


Fig. 2 Effect of the sodium nitrite concentration on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted at 2 °C with a molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid of 1:1.05:3.2, the flow rates of o-ethylaniline and hydrochloric acid of 1.0 and 4.16 mL/min, respectively, the sodium nitrite concentration of 5.7 M, the hydrochloric acid concentration of 6.0 M and the residence time of 13 s

the molar ratio of hydrochloric acid to o-ethylaniline increases to 3.4 results in the decrease in the conversion to 97.6%, the yield of o-ethyl iodide decreases to 77.8%. These results indicate that the molar ratio of hydrochloric acid to o-ethylaniline of 3.2:1 is suitable to create a strong acidic environment to maintain stability of the diazonium salt.

Effect of the residence time Figure 5 shows the effect of residence time on the reaction. From it we can know that, when the residence time is increased from 7 to 13 s, the conversion of o-ethylaniline increases sharply from 93.1 to 98.3%, and

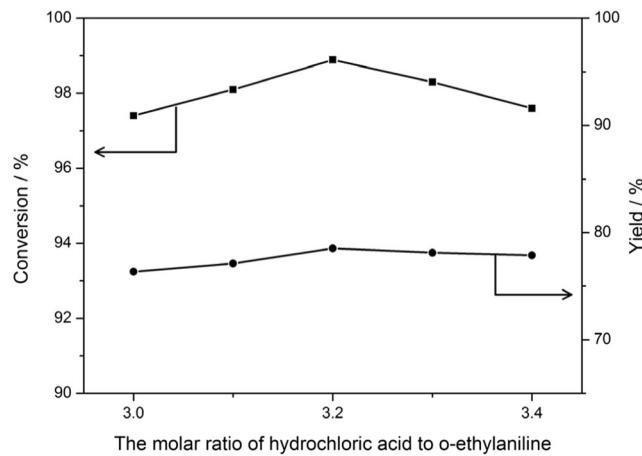


Fig. 4 Effect of the molar ratio of hydrochloric acid to o-ethylaniline on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted at 2 °C with a molar ratio of o-ethylaniline to sodium nitrite of 1:1.05, the flow rates of o-ethylaniline and sodium nitrite of 1.0 and 1.44 mL/min, respectively, the sodium nitrite concentration of 5.7 M, the hydrochloric acid concentration of 6.0 M and the residence time of 13 s

the yield of o-ethyl iodide increases from 78.4 to 82.3%. Further increasing the residence time 26 s leads to the increase in the conversion of o-ethylaniline to 99.7%, however, the yield of o-ethyl iodide decreases to 76.9%. The decrease in yield on increasing the residence time is probably due to some decomposition of the diazonium salt and coupling side reactions. Thus the suitable residence time is considered to be 13 s.

Effect of the total flow rate The total flow rate of o-ethylaniline and sodium nitrite has important influence on the mixing and the productivity.

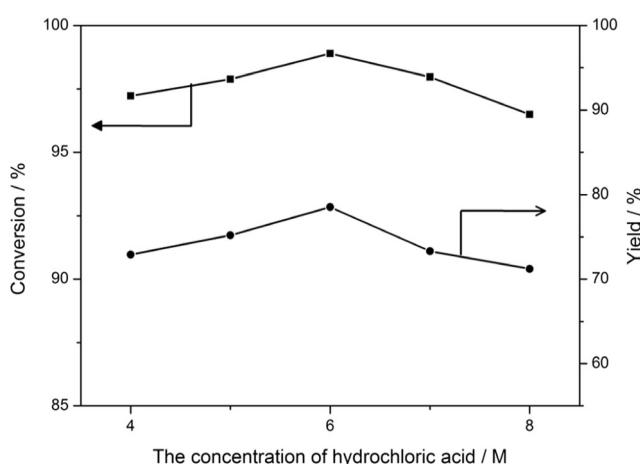


Fig. 3 Effect of the concentration of hydrochloric acid on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted at 2 °C with a molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid of 1:1.05:3.2, the flow rate of o-ethylaniline of 2.0 mL/min, the sodium nitrite molar concentration and flow rate of 5.7 M and 2.88 mL/min, respectively, the sodium nitrite concentration of 5.7 M, and the residence time of 13 s

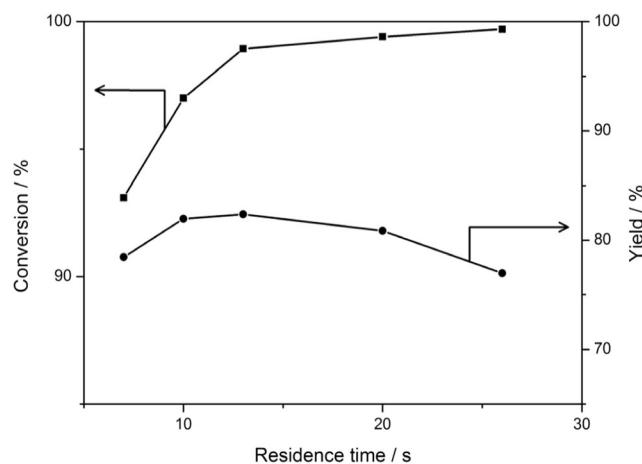


Fig. 5 Effect of residence time on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted at 2 °C with a molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid of 1:1.05:3.2, the flow rate of o-ethylaniline of 2.0 mL/min, the sodium nitrite molar concentration and flow rate of 5.7 M and 2.88 mL/min, respectively, the sodium nitrite concentration of 6.0 M and 8.34 mL/min, respectively

Figure 6 presents the effect of the total flow rate in the range of 2.44 to 14.64 mL/min. Clearly, the conversion of o-ethylaniline is almost unchanged at 99%, while the yield of o-ethyl iodide gradually increases from 78.5 to 83.9%. This may be ascribed to the formation of more uniform-sized microdroplets at higher total flow rate. By considering the length of the delay loop and the pressure drop of the system, we select the total flow rate of o-ethylaniline and sodium nitrite of 9.76 mL/min. From the above results, we can obtain the suitable operation parameters for continuous diazotization reaction with concentrated acid and sodium nitrite solutions as follows: the reaction temperature is 4 °C; the total flow rate of o-ethyl aniline and sodium nitrite is 9.76 mL/min; the flow rate of o-ethylaniline is 4.0 mL/min; the sodium nitrite concentration, the flow rate, and the molar ratio of sodium nitrite to o-ethylaniline, are 5.7 M, 5.76 mL/min, 1.05:1, respectively; the concentration of hydrochloric acid, the flow rate, and the molar ratio of hydrochloric acid to o-ethylaniline are 6.0 M, 16.68 mL/min, and 3.2:1, respectively; the residence time is 13 s. Under such conditions, the conversion of o-ethyl aniline is 100%, and yield of o-ethyl iodobenzene is 86%.

Effect of the temperature Figure 7 illustrates the effect of the temperature on the reaction. When the temperature is increased from 2 to 4 °C, the conversion of o-ethylaniline increases from 99.8 to 100%, and the yield of o-ethyl iodide increases from 83.9 to 86.1%. In addition, the system can run smoothly without gas. When the temperature is increased to 8 °C, gas can be observed to bubble out of the collected liquid, while the system runs smoothly. The conversion of o-ethylaniline decreases to 94.6%, and the yield of o-ethyl iodide decreases to 77.1%. These possibly result from the increased decomposition and cross-

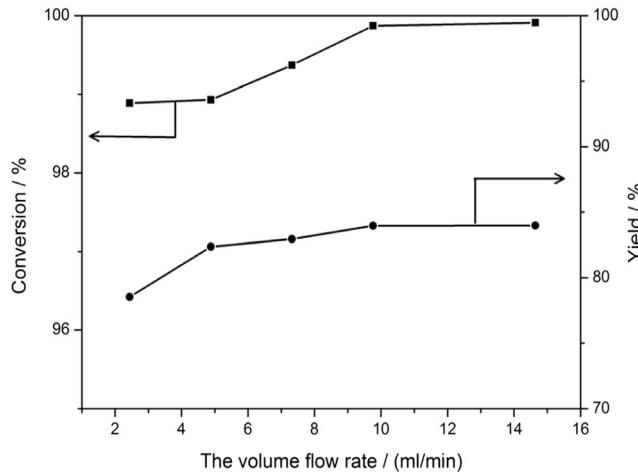


Fig. 6 Effect of the total flow rate of o-ethylaniline and sodium nitrite on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted at 2 °C with a molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid of 1:1.05:3.2, the sodium nitrite concentration of 5.7 M, the hydrochloric acid concentration of 6.0 M, and the residence time of 13 s

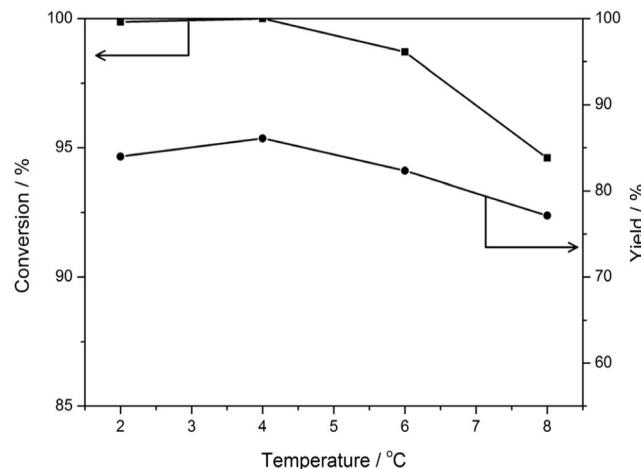


Fig. 7 Effect of temperature on the conversion of o-ethylaniline and the yield of o-ethyl iodide. The reactions were conducted with a molar ratio of o-ethylaniline to sodium nitrite to hydrochloric acid of 1:1.05:3.2, the flow rate of o-ethylaniline of 4.0 mL/min, the sodium nitrite molar concentration and flow rate of 5.7 M and 5.76 mL/min, respectively, the hydrochloric acid concentration and flow rate of 6.0 M and 16.68 mL/min, respectively, and the residence time of 13 s

coupling reactions at high temperatures. Hence, the suitable temperature is 4 °C.

Continuous diazotization using other aromatic amines and acid

To investigate whether the designed microreactor can be used for smooth operation of diazotization reaction using various aromatic amines and concentrated acid and sodium nitrite solutions, we use aniline, o-methylaniline and m-methylaniline as raw materials, hydrochloric acid as an acidic medium to carry out the reaction. These raw materials form insoluble solids when contacting with concentrated acid. Table 1 summarizes the reaction results at optimized conditions. The reactions run very smoothly without the occurrence of clogging. High raw material conversions can be obtained, with the yields of the products over 85%. The optimized conditions

Table 1 Optimized results of diazotization reactions in micro-reactor using several amines and concentrated hydrochloric acid

| Entry | ArNH ₂ | τ (s) | C/% ^a | Y/% ^b |
|-------|-------------------|-------|------------------|------------------|
| 1 | H | 13 | 99.2 | 85.6 |
| 2 | O-Me | 13 | 99.3 | 88.2 |
| 3 | M-Me | 15 | 98.9 | 83.4 |
| 4 | O-Et | 13 | 100 | 86.0 |

In this experiment, the acid to amine molar ratio and the sodium nitrite to amine molar ratio are 3.2:1 and 1.05:1, respectively (for M-Me, the acid to amine molar ratio is 3.1:1); the reaction temperature is 4 °C; V(HCl) = 16.64 mL/min; C(NaNO₂) = 5.7 M; V(NaNO₂) = 5.76 mL/min. (a) Conversion of amine, (b) Yield of iodobenzene

are slightly different for m-methylaniline, requiring a molar ratio of m-methylaniline to hydrochloric acid of 1:3.1 and a residence time of 15 s. This may be ascribed to much lower activity of the formed m-methylaniline diazonium hydrochloride than the other three diazonium hydrochlorides [20]. Hence, a slightly lower acidity is needed to prevent it from decomposing and forming other side reactions. Since the activities of m-methylaniline and m-methylaniline diazonium hydrochlorides are much lower than those of several other amines or diazonium hydrochlorides [21, 22], the conversion of the amine and the yield of the corresponding iodobenzene are lower.

As the rate of diazotization reaction varies in different acidic media [23], it is necessary to verify the feasibility of the designed microreactor in the diazotization reactions of these raw materials in sulfuric acid. In hydrochloric and sulfuric acid medium, nitrosyl chloride and nitrous anhydride are formed as the active component, respectively. Since the activity of nitrosyl chloride is higher than that of nitrous anhydride [24], we then conduct the experiments at temperatures higher than those in hydrochloric acid. When the temperature is set at 5 °C, the reaction can run smoothly for about 30 s, and then the flow becomes unstable, with obvious observation of solids on the wall. Eventually, clogging occurs. When the temperature is raised to 9 °C, the reaction can run smoothly, with stable flow and without the formation of solids. Further increase in the temperature to 12 °C leads to the formation of large amount of gas and tar, indicating decomposition of the diazonium salt. The reactions can all run smoothly at 9 °C when o-methylaniline, m-methylaniline and o-ethylaniline are used as raw materials. After examining the effect of the sodium nitrite concentration, the molar ratio of sodium nitrite to amine, the sulfuric acid concentration, the molar ratio of sulfuric acid to amine, and the residence time, we obtain the optimized reaction results by using aniline, o-methylaniline, m-methylaniline and o-ethylaniline, as raw materials in sulfuric acid, as listed in Table 2. Conversions of amines more than 98% and yields of about 90% can be achieved by using the designed microreactor, higher than the

values obtained from batch reaction of the same raw materials. For the latter, 2.65 M sodium nitrite and 3.75 M sulfuric acid are used, yielding the yields of iodobenzene and methyl iodobenzene of 80–85% [25].

As for limitations of the current methodology, the amines used as raw material must be highly active liquid aromatic amines in the above practices. Liquid aliphatic amines are also suitable for the current methodology. For example, using the tert-butylamine as raw materials, the conversion is 98.9%, the yield of iodo-substitute compound is 84.7% in the hydrochloric acid system. In the sulfuric acid system, the conversion is 99.3%, the yield is 86.8%, respectively. The solid amines, such as 2-amino-4-cyanotoluene, 2,4-dinitro-6-bromanilin and most heteroaromatic amines, are usually dissolved in acid or added to solvents for continuous reaction. However, when a strong electron withdrawing group ($-X, -NO_2, -C \equiv N$, etc.) is attached to an aromatic amine, its activity is greatly reduced, so that the raw material amine cannot be rapidly converted during the reaction, then it may be easy to form ammonium salt with acids, resulting in the blockage of microchannels.

Conclusions

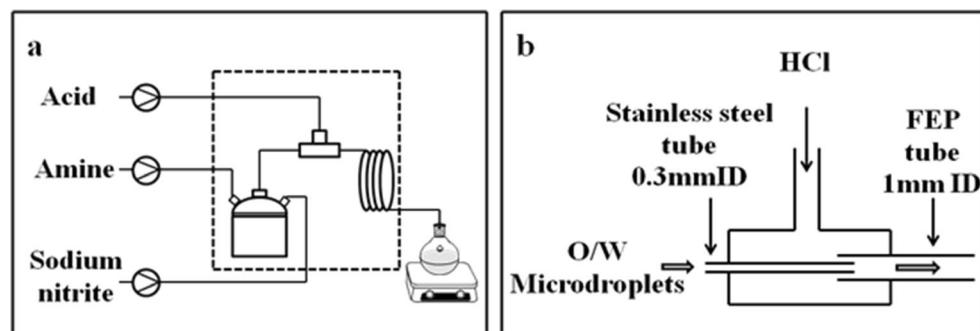
Continuous operation is arguably the most appropriate method to produce large volumes of a product uniformly, consistently, and reliably. A fully continuous flow process has been described to utilize concentrated acid and sodium nitrite solutions in a in-house designed microreactor, which was carried out by first mixing amine with a sodium nitrite aqueous solution in a micromixer to form O/W microdroplets, followed by mixing with mineral acid in a co-axial micromixer. We used aniline, o-methylaniline, m-methylaniline and o-ethylaniline as the raw materials, hydrochloric acid, and sulfuric acid as the acid medium to conduct the reactions for the formation of iodobenzene. These reactions, in which insoluble solids were formed after mixing the mineral acid with amine, could be operated smoothly at suitable temperatures, without the addition of large amounts of water or the extra solvent. In addition, sodium nitrite aqueous solution with concentration of 5.7 M could be used, with a molar ratio of acid to amine of 3.1–3.2. For comparison, 2.1 M of sodium nitrite had to be used in conventional batch reactions. High raw material conversions over 98% and yields of the iodo-substitute aromatic compounds about 90% could be achieved at 2–9 °C and residence times of less than 20 s. Formation of O/W microdroplets by mixing amine with sodium nitrite is crucial, as the formed solids resulting from the contact between amine and acid can be dispersed in the aqueous phase, resulting in their smooth flow with the main stream and consequent, avoiding clogging of the microchannel. Such design of the microreactor and the

Table 2 Optimized results of diazotization reactions in micro-reactor using several amines and concentrated sulfuric acid

| Entry | ArNH ₂ | τ (s) | C/% ^a | Y/% ^b |
|-------|-------------------|-------|------------------|------------------|
| 1 | H | 14 | 99.1 | 90.8 |
| 2 | O-Me | 14 | 99.2 | 91.0 |
| 3 | M-Me | 16 | 98.8 | 89.9 |
| 4 | O-Et | 14 | 99.4 | 91.6 |

In this experiment, the acid to amine molar ratio and the sodium nitrite to amine molar ratio are 3:1 and 1.05:1, respectively; the reaction temperature is 9 °C; C(H₂SO₄) = 6.5 M; V(H₂SO₄) = 14.4 mL/min; C(NaNO₂) = 6.5 M; V(NaNO₂) = 5.04 mL/min. (a) Conversion of amine. (b) Yield of iodobenzene

Fig. 8 **a** Schematic representation of the microreactor setup for the diazotization. The dashed area indicates a cold bath. **b** Detailed illustration of the co-axial dual pipe assembly in a T-connector



operation model provide a simple fast, feasible and controllable process for diazotization reactions.

Experimental

Materials Concentrated hydrochloric acid and concentrated sulfuric acid were purchased from Shanghai Lingfeng Chemical Reagent Co. Ltd. (China); aniline, o-methylaniline, m-methylaniline, anhydrous sodium sulfate and anhydrous sodium sulfite were obtained from Sinopharm Chemical Reagent Co. Ltd. (China); sodium nitrite was purchased from Shanghai Xinbao Fine Chemical Factory; o-ethylaniline was purchased from Aladdin Reagent Co. Ltd. (USA); potassium iodide was purchased from Shanghai Shenbo Chemical Co. Ltd. (China); ethyl acetate was purchased from Wuxi Yasheng Chemical Co. Ltd. (China); sodium hydroxide was purchased from Xilong Chemical Co. Ltd. (China).

Diazotization reactions in micro-reactors Diazotization reactions were carried out in a microreactor shown in Fig. 8a, which was assembled with an interdigital channel configuration micro-mixer (SIMM-V2, IMM, Germany) connected with a $\Phi 1/16''$ T-connector through a stainless steel tube by the way of the co-axial dual pipe, with the T-connector connected with a FEP tube (1.0 mm ID) as residence time delay loop. The microreactor was immersed in a cold bath with the temperature set at 0–10 °C. In a typical operation, o-ethylaniline and 5.7 M sodium nitrite aqueous solution were, respectively, introduced to SIMM-V2 by two syringe pumps to form O/W microdroplets, with the molar ratio of amine to sodium nitrite of 1:0.5–1:1.1. The stream then was mixed with 6 M hydrochloric acid in the T-connector and flowed through in the FEP tube for a time of 5–20 s. The effluent was collected in a flask containing a potassium iodide solution. The mixture was stirred at 60 °C for 5 h. It was then filtered and washed with distilled water and ethyl acetate. The residue was extracted with ethyl acetate. The combined organic layer was washed with 10% aqueous solution of sodium sulfite and then it was dried over anhydrous sodium sulfate. The solvent was evaporated to afford aryl iodides [26]. To obtain the conversion of

the amine and yield of iodo-substitute aromatic compounds, the washed organic phase was weighted and analyzed by Gas Chromatography (GC).

Analysis The flow pattern of the mixed stream was taken as movies by using an inverted microscope (Leica DMI8) equipped with a CCD camera. The GC analysis was carried out on Agilent 7890B equipped with a HP-5 capillary column (30 m \times 0.32 mm \times 0.25 μm) and a flame ionization detector. The column temperature was started at 60 °C for 1 min, then increased to 280 °C at a rate of 10 °C/min. The temperatures of gasification chamber and detecting chamber were 280 and 290 °C, respectively.

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