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## Continuous and green microflow synthesis of azobenzene compounds catalyzed by consecutively prepared tetrahedron CuBr

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#### ABSTRACT

An environmentally friendly and cross-selective process intensification for the continuous synthesis of symmetric aromatic azo compounds by using self-made cuprous bromide as the catalyst under mild conditions in the microreactor was developed. A novel tetrahedron cuprous bromide catalyst which shows outstanding catalytic activity and satisfactory stability has been synthesized in continuous flow microreactor. The online immobilization of self-made cuprous bromide on the catalyst bed achieved oxidative coupling of aromatic amines (oxygen as oxidant) and high-performance gas-liquid-solid three-phase reaction, which strongly limited the possibility of undesired reaction pathways, improving product selectivity and reducing waste generation. Meanwhile, the yield of azo-coupling reaction was up to 98% under optimized condition. As compared with earlier traditional method (diazotization reaction) for synthesizing azobenzene, the designed micro-flow process displays significant advances in terms of selectivity, waste emissions, sustainability and productivity. The combination of online immobilization of self-made cuprous bromide and precise and safe control through the microreactor provides a green solution for the industrial production of valuable aromatic azo compounds.

#### 1. Introduction

Azo dye is a kind of synthetic dye containing azo group (Ar–N—N–Ar). Aromatic azo compounds are important fine chemical raw materials and have countless applications, not merely in the chemical industry, but also in medicinal chemistry (as prodrugs, drug-coating materials and diagnostic probe) [1–4], biotechnology (artificial muscle, molecular machines, bistable memory devices, etc.), and the field of renewable resources. In the dye industry [5], azobenzene dye is one of the major chemical dyes used in textile industries for dying fibre and fabric materials. It accounts for more than 70% of all kinds of dyes. Moreover, there has been a rapid growth in interest in their applications as photoresponsive materials in areas of photochemical molecular switches, liquid crystals, chemosensors and molecular shuttles, owing to their intrinsic ability of photochemical cis/trans-isomerization [6–8].

In terms of the preparation, a myriad of synthetic methods are available nowadays. Prevailing classical routes for the formation of

desired azobenzene involve the oxidation of hydrazine, the coupling of diazonium salts with activated aromatics (azo coupling), the coupling of primary arylamines with nitroso compounds (Mills reaction) and the reductive coupling of aromatic nitro derivatives [9,10]. However, the conventional methods have several drawbacks, such as the use of strong and toxic oxidants or harsh reaction conditions (high pressure, high temperature), which often lead to byproduct formation and low total yields [11,12]. In 2008, Corma and co-workers [13] made a breakthrough when they developed Au/TiO2-mediated synthesis of aromatic azo compounds from the corresponding aniline derivatives. In the following years, many important attempts were made to synthesis azo derivatives in good yields through utilizing precious metals (Au, Pt, or Pd), high pressure, and base additives [14-17]. It is reported that copper-catalyzed homodimerization processes of aromatic amines using air [18-20] as the co-oxidantcan make these conventional processes more facile and avoid the use of heavy-metal salts. However, the incompatibility of functional groups and low yields of desired products are

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still inevitable [21]. Furthermore, the synthesis of azobenzene using copper bromide in traditional batch reactor still brings the reactivity issues and several environmental pollution problems, such as necessitating long reaction times, special reaction conditions, low yield of target product and sedimentation and accumulation of catalyst [22]. With regard to the above-mentioned limits of azobenzene formed, gas-liquid-solid microreactors appear to be a reasonable strategy for the production of valuable aromatic azo compounds.

In recent years, there is a broad range of research for which continuous flow microreactors can be used, including catalysis [23], nanoparticle synthesis [24-26], sensors, electrochemistry [27] and polymerization [28]. Compared with conventional batch reactors, microreactors have helped to minimize reagent consumption and energy waste by increasing the atom efficiency of reaction due to their small dimensions, which in most cases do not exceed 1 mm in at least one dimension. The small volume of microreactors makes it possible to safe handling of even hazardous, unstable intermediates or highly exothermic reactions while facilitating fast and easy parameter screening [29-31]. Because of this, the application of microreactor technology in the synthesis of azo dye is a green chemical process. Moreover, the contained environment and the ease of pressurizing in continuous flow reactors providing novel process windows, an increased parameter space for chemical synthesis and process intensification. Thus, integration of process intensification in flow system and higher synthesis efficiency in microreactor would eliminate the main drawback of traditional way to achieve azobenzene, resulting in an efficient and sustainable production.

In recent years, our research group have made some achievements in the field of microfluidics. In our previous study [32,33], three kinds of co-doped TiO<sub>2</sub>, α-Fe<sub>2</sub>O<sub>3</sub> and CaCO<sub>3</sub> nanoparticles were synthesized by using a continuous precipitation method in a novel micro-flow system and were first employed in a packed bed flow reactor. Motivated by the remarkable progress of heterogeneous catalysis in micro-flow systems, we exploited the benefits of continuous-flow processing for the CuBr-mediated oxidative homocoupling of arylamines to facilitate the time-, cost-, and atom-effective synthesis of valuable symmetric aromatic azo compounds. The use of flow microreactor can realize the application of gas-liquid-solid heterogeneous reaction and give higher yields of aromatic azobenzene. Additionally, increased reaction rate, reduction of side products and improved product purity could be obtained in the compared with conventional method for synthesizing azo compounds. During the research, a new type of tetrahedron cuprous bromide which has not been reported was also conducted, providing a higher yield. Besides, the online prepared cuprous bromide could be automatically filled, washed and applied to the next oxidative coupling reaction without further purification through the control of valves in continuous flow reactor.

#### 2. Experimental section

All the reagents used in this study were commercially available. Standard analytical reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. Cuprous bromide was obtained from Meryer (Shanghai) Chemical Technology Co., Ltd. The quantitative analysis was conducted on a liquid chromatograph system (Agilent 1260). <sup>1</sup>H NMR spectra were recorded on a Bruker-400 (400 MHz). The XRD patterns were obtained on a Bruker D8 ADVANCE X-ray diffractometer with Cu K $\alpha$  radiation at 40 kV and 40 mA. The catalyst was characterized by an S-3400 N scanning electron microscope (SEM).

#### 2.1. General synthesis of cuprous bromide in continuous flow reactor

Cuprous bromide was prepared in a continuous flow reactor by the reduction reaction of soluble divalent copper salt, reducing agent (hydroxylamine hydrochloride, hydroxylamine sulfate or hydroxylamine) and potassium bromide. Two feeds were pumped (LEaD FLUID syringe pump) into a valve assisted micromixer simultaneously. One was the mixed solution of copper sulfate and potassium bromide, the other was the reducing agent. Then the reduction reaction was occurred in a microreactor (PTEF tube). After centrifugation, white precipitates were washed with water and ethanol. Subsequently, the precipitates were dried under vacuum at room temperature for 12 h.

#### 2.2. Typical procedure for synthesis of the azobenzenes in batch mode

The oxidative coupling reaction of aniline was chosen as the model reaction in order to test the catalytic activity of homemade cuprous bromide (Scheme 1). The process was described as follows. In a 25 mL tube, corresponding cuprous bromide (specified amount), toluene (8 mL), aniline (0.1863 g, 2 mmol) and pyridine (0.0142 g, 0.18 mmol) was added under O<sub>2</sub> atmosphere. The tube was sealed and the reaction mixture was heated at a 60 °C in appropriate time. Then samples were analyzed using HPLC after centrifugation.

#### 2.3. General procedure for synthesis of the azobenzenes in a new microflow system

In order to achieve the continuous synthesis of azobenzene derivatives, a simple gas-liquid-solid three-phases flow reactor was assembled (Fig. 1). The online prepared catalyst could be automatically filled and washed in packed column through the control of valves. Initially, when the valve A and D were turned on and the others were turned off, the cuprous bromide was filled in the column. When the column was filled, the valve B and D were turned on and the others were turned off, the column was washed by distilled water in the syringe. Then the valve B was closed and valve C was opened, alternating with ethanol. When the washing was finished, the valve D was turned off and valve E was turned on. Then, the two flows were injected into the tubein-tube flow reactor AF-2400 at set flow rate. One was aniline (1.863 g, 20 mmol) and pyridine (1.582, 20 mmol) solution (40 mL) dissolved with toluene, the other was O2. The flow rate of oxygen was controlled by a mass-flow controller, the liquid was injected by pump (Vapourtec Ltd). Liquid inlet was connected to a standard 1/4-28 UNF, gas inlet was connected to a 10–32 UNF [32]. In the tube-in-tube flow reactor,  $O_2$  and liquid were respectively flowing from the inner tube and the annular channel. O<sub>2</sub> was dispersed into the liquid through the micropores in the membrane [34, 35]. Subsequently, the mixture was injected into the fixed bed flow reactor which was filled with cuprous bromide. The temperature of the flow reactor was adjusted through air heating (R4 reactor heater from Vapourtec Ltd). At set time intervals, the reaction mixture was analyzed using HPLC after centrifugation. The reaction yield was good as the inner diameter of capillary column within 4 mm. The volume of the packed column was calculated by injecting a dye solution through the column at a set flow rate, and the time showed that the column volume was 1.2 mL.

#### 3. Results and discussion

#### 3.1. Synthesis and characterization of cuprous bromide

#### 3.1.1. Optimization of the reaction conditions

The conditions of preparing cuprous bromide were simply optimized in micro-flow system. Initially, the effect of reaction time was investigated. Fig. 2 showed that particle obtained at 3 min had the better



Scheme 1. Model Reaction of research catalytic activity.

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Fig. 1. A continuous flow system for synthesis of the azobenzenes.

dispersion and uniformity compared with at 1min. Meanwhile, cuprous bromide with the yield of 80% was obtained at 3 min, while the reaction time was 1 min, the yield was 60%. It might be attributed to the reason that shorter retention time lead to incomplete reduction reactions. The effect of tube diameter was investigated in Fig. 3. It showed that tetrahedron b (Fig. 3) was slightly broken than a (Fig. 3). The cause of this phenomenon might be that small diameter was not beneficial to crystal formation. The tetrahedron cuprous bromide particles with 5–10  $\mu$ m could be obtained. Thus, the tube diameter (1 mm) and reaction time in 3 min might be the most efficient condition.

#### 3.1.2. Characterization of cuprous bromide

Fig. 4 showed the XRD patterns of the as-prepared CuBr by three different reducing agents in micro-flow system. The results were consistent with the data revealed in the standard card (JCPDS, 06–0292), which demonstrated that cuprous bromide could be obtained by those reducing agents. The morphologies of both homemade CuBr and commercially available CuBr were observed using a SEM. Fig. 5 illustrated that self-made CuBr (a, b) has good particle dispersion compared with commercially available CuBr. Moreover, the shape of CuBr prepared by hydroxylamine hydrochloride or hydroxylamine sulfate reductant was tetrahedron, which was different from the commercially available CuBr. Due to self-made CuBr prepared by hydroxylamine hydrochloride reducing agents has the most excellent particle size uniformity and dispersion than the two other reducing agents, so the hydroxylamine hydrochloride be chosen to apply in next experiment.

#### 3.1.3. Comparison of commercially available cuprous bromide and selfmade cuprous bromide

The catalytic activity of homemade cuprous bromide was compared with commercially available cuprous bromide by varying the reaction time in the range from 1 h to 20 h. As shown in Fig. 6, at the same amounts of catalyst, the final yield of azobenzene catalyzed by self-made cuprous bromide was slightly higher than commercially available cuprous bromide. Obviously, the catalytic rate of self-made cuprous bromide was more significantly increased compared to commercially available cuprous bromide and the yield up to 98% of target product was obtained by using homemade cuprous bromide at 10 h. However, when used commercially available cuprous bromide, a yield of 70% could be obtained. The cause for this phenomenon might be that self-made catalyst had relatively higher specific surface area and better dispersion compared with the commercially available catalyst, just as the morphologies revealed in Fig. 6.

#### 3.2. Synthesis of azobenzene derivatives using self-made CuBr in microflow system

#### 3.2.1. Optimization of the reaction conditions

On the basis of the pioneering study, we investigated the effect of oxygen flow rate, aniline flow rate, temperature and the equivalent of pyridine. As shown in Table 1, when oxygen flow rate varied from 4 mL min<sup>-1</sup> to 10 mL min<sup>-1</sup>, the yield of azobenzene was increased from 40% to 70%. The maximum yield was obtained when oxygen flow rate was 10 mL min<sup>-1</sup>. However, the yield was sharply decreased to 55% when flow rate increasing. This phenomenon might be attributed to two main causes. One was the incomplete reaction resulted by small flow rate, the other was the short residence time in the fixed bed flow reactor under excessive velocity. Next, there had little effect on the vield when changed the flow rate of aniline. The cause might be that gas flow rate was much larger than the liquid flow rate, leading to the residence time in the column could be negligible when slightly changed the flow rate of aniline. Nevertheless, the column pressure increased and column blockage might be occurred when aniline flow rate was too high. The effect of temperature on oxidation coupling reaction was investigated by varying the temperature in the range from 50 °C to 110 °C. Distinctly, when other conditions are the same, the higher the temperature, the



(a)1.5min

(b) 3min

(c) 6min

Fig. 2. The SEM images of CuBr prepared in different reaction time.

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(a) 1mm

(b) 0.5mm

Fig. 3. The SEM images of CuBr prepared in different tube diameter.



#### (a) $NH_2OH$ (b) $NH_2OH.H_2SO_4$ (c) $NH_2OH.HC1$

Fig. 4. The XRD patterns of CuBr prepared by different reducing agents.

higher the yield. While the temperature increased to 110 °C, the yield reached maximum and the conversion rate of aniline achieved nearly 100%. As shown in Table 1, the optimal amount of pyridine was 1 equiv. When the amounts of pyridine raised from 0.4 equiv. to 1 equiv, the yield of azobenzene increased from 47% to 98%. To determine the residence time on the column, a solution of dye and oxygen were pumped through the fixed bed flow reactor at the optimal flow rate, the time that solution of dye through the column was registered. By the

above method, the residence time was obtained with 5 min. Therefore,  $10 \text{ mL} \text{min}^{-1}$  of the oxygen flow rate,  $0.16 \text{ mL} \text{min}^{-1}$  of aniline flow rate, 1 equivalent of pyridine, reaction temperature at 110 °C and reaction time in 5 min were chosen as the optimal reaction condition.

3.2.2. Comparison of batch reactor and microreactor using self-made cuprous bromide

As shown in Fig. 6, the reaction time of typical procedure for synthesis of the azobenzenes in batch mode was nearly 8 h. Compared with conventional batch reactor, microreactor mentioned above have helped



Fig. 6. Investigate the catalytic activity of self-made cuprous bromide. Reaction conditions: aniline (0.1863 g, 2 mmol), pyridine (0.0142 g, 0.18 mmol), CuBr (0.0086 g,0.06 mmol), toluene (8 mL), specified reaction time, stirring speed 500 rpm at 60 °C under  $O_2$ . The yield of azobenzene calculate from HPLC.





Reaction conditions: solution A: 0.1 M of reductant in H<sub>2</sub>O, solution B: 0.2 M of CuSO<sub>4</sub>·5H<sub>2</sub>O and 0.2 M of KBr in H<sub>2</sub>O, tube diameter was 1 mm, reaction time was 3 min at room temperature; (a) NH<sub>2</sub>O·HCl (b) NH<sub>2</sub>OH·H<sub>2</sub>SO<sub>4</sub> (c) NH<sub>2</sub>OH (d) commercially available CuBr.

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#### Table 1

Optimization of aniline and oxygen flow rate for the continuous synthesis of azobenzene derivatives.

Entry	Aniline flow rate (mL/min)	Oxygen flow rate (mL/min)	Temperature ( $^\circ C$ )	Pyridine (equivalent)	residence time (min)	Yield (%,3a)
1	0.16	4	90	1	1.25	55
2	0.16	8	90	1	1.25	68
3	0.16	10	90	1	1.25	61
4	0.16	14	90	1	1.25	68
5	0.12	10	90	1	1.67	40
6	0.2	10	90	1	1	70
7	0.16	10	50	1	1.25	40
8	0.16	10	70	1	1.25	48
9	0.16	10	90	1	1.25	70
10	0.16	10	100	1	1.25	81
11	0.16	10	110	1	1.25	98
12	0.16	10	110	0.4	1.25	47
13	0.16	10	110	0.8	1.25	80

Reaction condition: aniline (1.863 g, 20 mmol) and pyridine were dissolved in toluene (40 mL), specified aniline and oxygen flow rate. The yield of azobenzene calculate from HPLC.

to minify reaction time to minute level due to their small dimensions. Process intensification could be realized in a continuous flow system whose feature size was several micrometers to a few millimeters. The small volume of microreactor makes it possible to safe handling of even hazardous, unstable intermediates or highly exothermic reactions while facilitating fast and easy parameter screening due to real-time online reaction. Moreover, in a limited space, the catalyst was fully utilized, thereby improving the reaction efficiency and productivity. Increased reaction rate, reduction of side products and improved product purity could be obtained in the microreactor compared with conventional batch mode.

# 3.3. Substrate scope for the aromatic amine in gas-liquid-solid three-phase microreactor

Under the above optimized conditions, the substrate scope of the oxidative coupling reaction was studied (Table 2). The reaction showed great tolerance with anilines with electron-donating substituent such as methoxy-, methyl-groups at the para position (Table 2, Entries 1–3). Moreover, the effect of electron-donating groups at the different positions on the phenyl ring could be ignored (Table 2, Entries 3–5). The yields were significantly decreased when anilines have electron-withdrawing substituents (Table 2, Entries 6–8). Multisubstituted anilines can be easily converted into the corresponding azo compound in excellent yield (Table 2, Entry 9) and not be affected by the tremendous steric hindrance. However, anilines with nitro-substituted was failed to give the desired product (Table 2, Entry 10). The result might be attributed to the weak nucleophiles and instability of the amine radical cation resulted in the few conversions.

#### 4. Conclusion

In conclusion, a green and novel continuous-flow methodology was developed for the synthesis of valuable azo compounds. During the research, we were surprised to find a new type of tetrahedron cuprous bromide and we demonstrated the feasibility and superiority of the selfmade cuprous bromide. CuBr microparticles prepared just before use were automatically filled into a fixed bed flow reactor for the oxidative homocoupling of aniline derivatives, which strongly limited the possibility of undesired reaction pathways, improving product selectivity and reducing waste generation. Oxygen as the terminal oxidant, the absence of precious metals, self-made CuBr with better uniformity and continuous flow system make our catalytic protocol greener than other reported systems. The proposed strategy in this study provided a green and effective route for preparation of valuable aromatic azo compounds and reported a new type of cuprous bromide, which may offer new applications in the fields of heterogeneous catalytic reactions. Further investigations to apply this continuous-flow strategy, symmetric

Table	2
Scope	of aniline.



Reaction condition: 1 equiv. of aniline (c = 0.5 M) and 1 equiv. of pyridine in toluene at 110  $^{\circ}$ C, aniline flow rate was 0.16 mL min<sup>-1</sup>, oxygen flow rate was 10 mL min<sup>-1</sup>. The yield of azobenzene calculate from HPLC.

azobenzene compound and new type of cuprous bromide are ongoing in our laboratory.

#### Notes

The authors declare no competing financial interest.

#### Declaration of competing interest

There are no conflicts of interest in this work.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.dyepig.2019.108071.

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