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The continuous kilogram-scale process for the synthesis of 2,4,5-trifluorobromobenzene *via* Gattermann reaction using microreactors

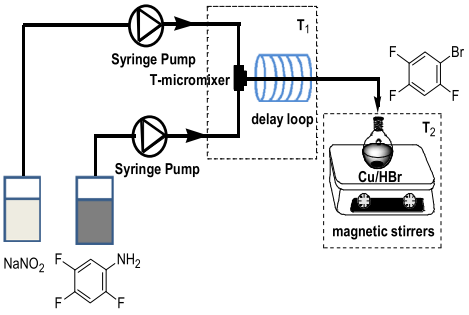
Qiulin Deng [a,b,*], Qin Lei [b], Ruwei Shen [a], Chao Chen [a], Lixiong Zhang [a,*]

[a] State Key Laboratory of Materials-Oriented Chemical Engineering and College of Chemistry and Chemical Engineering, Nanjing Tech University, Nanjing 210009, PR China
[b] School of Materials Science and Engineering, Southwest University of Science and Technology, Mianyang 621010, PR China

HIGHLIGHTS

- Efficient flow process for producing 2,4,5-trifluorobromobenzene in high yield and high selectivity.
- Efficient kilogram-scale synthetic route for 2,4,5-trifluorobromobenzene.
- Provides an easily assembled micro- and batch reactor tandem model for liquid/liquid and liquid/solid reactions.

GRAPHICAL ABSTRACT



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ABSTRACT

2,4,5-Trifluorobromobenzene is a valuable synthetic intermediate with important applications in pharmaceutical industry. We report a continuous microflow process for the synthesis of 2,4,5-trifluorobromobenzene *via* Gattermann reaction in this paper. The microflow system is easily assembled by a simple T-micromixer, microchannel reactors and several pumps. The use of this system facilitated the diazotization reaction of 2,4,5-trifluoroaniline with HBr and $NaNO_2$ to produce the thermally unstable 2,4,5-trifluorophenyl diazonium salts in seconds, which then react with HBr at the catalysis of copper powder to obtain 2,4,5-trifluorobromobenzene. The aqueous HBr containing copper powder was added and stirred for 30 min at 70 °C in the stirred vessel. And then, the CuBr in situ was given and performed a quench-type reaction as catalyst. The influence of the reaction parameters on the diazotization reaction steps was examined and discussed in microreactors. The microflow system had the capacity to promote efficient mass- and heat-transfer and shorten the reaction time. On this basis, the kilogram-scale production of 2,4,5-trifluorobromobenzene was realized in a self-made scale-up microreactor by numbering-up of micromixers and microchannels.

1. Introduction

Aromatic bromides are significant class of compounds that are widely used in the production of dyes, flame retardants, pharmaceuticals, agrochemical products and others important fine chemicals [1–3]. In particular, 2,4,5-trifluorobromobenzene is a valuable intermediate for the synthesis of a variety of antibacterial drugs [4–10] such as ciprofloxacin (Cipro™), moxifloxacin (Avelox™), gatifloxacin (Gatiflo™) and pefloxacin (Peflacine™), which are common medicines prescribed clinically worldwide. Besides, it has also been used as precursor for the synthesis of Sitagliptin [11], an enzyme-inhibiting drug for the treatment of type 2 diabetes mellitus. The Gattermann reaction is a classical method for building C–Br bond from aromatic amines *via* diazotization

* Corresponding authors at: School of Materials Science and Engineering, Southwest University of Science and Technology, Mianyang 621010, PR China (Q. Deng).
E-mail addresses: qiulindeng@swust.edu.cn (Q. Deng), lixiongzhang@yahoo.com (L. Zhang).

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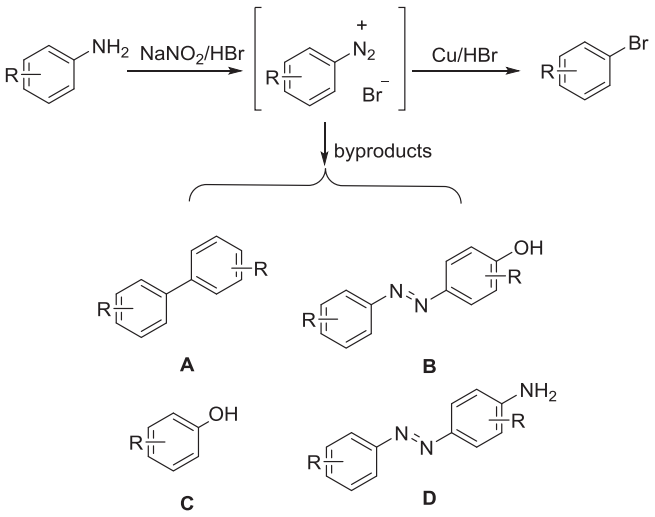
and bromodediazoniation steps (Scheme 1) [12]. A problematic issue lying in this protocol is that the diazotization reaction is strongly exothermal, furthermore the diazonium salts are highly reactive and thermally unstable [13]. Thus, the diazotization reaction is usually performed under vigorous stirring and with special caution to control the reaction temperature in a batch reactor. It will lead to an uncontrollable thermal decomposition of the intermediates and the formation of undesired byproducts if the conditions are not precisely controlled especially for a large-scale synthesis (Scheme 1) [14,15]. Therefore, the development of a controllable process to deliver diazonium salts *via* diazotization reaction is crucial and highly desired for the synthesis of aromatic bromides.

Recently, the continuous-flow microreactors used in chemical synthesis have attracted great interests in both academia and industry [16–23]. The continuous-flow microreactors offer many advantages over the traditional batch reactor such as efficient heat- and mass-transfer, high safety, good reproducibility, and easy scale-up [24–30]. Particularly, highly exothermic reactions and those involved instable intermediates can be smoothly performed. The continuous-flow microreactors are favored to perform the diazotization reaction. For example, the synthesis of aromatic fluorides *via* diazotization reaction has been reported recently using the continuous-flow microreactor [15,31]. To the best of our knowledge, the Gattermann reaction for a microflow synthesis of 2,4,5-trifluorobromobenzene has not been disclosed thus far.

In this paper, we report a continuous microflow protocol for the synthesis of 2,4,5-trifluorobromobenzene *via* Gattermann reaction in microreactors. The microflow system is assembled by a simple T-micromixer, microchannel reactors and several pumps. The use of this system facilitated the diazotization reaction of 2,4,5-trifluoroaniline with HBr and $NaNO_2$ to produce the thermally unstable 2,4,5-trifluorophenyl diazonium salts in seconds, which were reacted with HBr at the catalysis of copper powder to produce 2,4,5-trifluorobromobenzene. We investigated the effects of mole ratio of 2,4,5-trifluoroaniline and HBr, flow rate, residence time, temperature and the amount of copper catalyst on the product yield. Subsequently, a scale-up microreactor containing 40 T-micromixers chips was designed and used to carry out the kilogram-scale manufacture of 2,4,5-trifluorobromobenzene.



Scheme 1. Synthetic route for 2,4,5-trifluorobromobenzene and possible byproducts.

2. Experimental

2.1. Materials and devices

$NaNO_2$ (A.R.), HBr (A.R., 47 wt%), Cu powder, Na_2SO_4 (A.R.) and acetone (A.R.) were purchased from Sinopharm Chemical Reagent Co., Ltd. (China) and Shanghai No. 4 Reagent & H. V. Chemical Co., Ltd. (China). 2,4,5-Trifluoroaniline (C.P.) was supplied by SMK Pharmaceuticals Co., Ltd, China.

Syring Pump (LSP01-1BH, Longer, China), peristaltic pump (BT100-1F, Longer, China), glass syringe (Hamilton, US), T-micromixer (i.d. 1.2 mm, 316L, Xiongchuan, China), PTFE microchannel (i.d. 2.0 mm), connectors (316L, Xiongchuan, China; PEEK, VALCO, USA; CTFE, VALCO, USA), nuts (316L, Xiongchuan, China) and fittings (316L, Xiongchuan, China) were all commercially available. The T-micromixer (i.d. 1.2 mm) for scale up was made by the carving machine (ROLAND, MDX-40A).

2.2. Microflow setup and experimental procedure

2.2.1. The continuous microflow process

The continuous flow microreactor system used for synthesis of 2,4,5-trifluorobromobenzene is shown in Fig. 1. It was assembled with a T-micromixer (i.d. 1.2 mm, 316L, Xiongchuan, China) and microchannel reactor (PTFE tube, i.d. 2.0 mm) as the residence time delay loop. The solutions of 2,4,5-trifluoroaniline (1.0 M in HBr, 6.8 mL/min) and $NaNO_2$ (6.0 M in H_2O, 1.2 mL/min) were loaded using glass syringe, and were injected into the T-micromixer by two syringe pumps, respectively. The mixed solution was passed through the PTFE tube which was immersed in a −10 °C low temperature ethanol bath, and the effluent was directly collected to a flask containing Cu powder (5.0 g) and 47 wt% aqueous HBr (25 mL) at 70 °C. The mixture of Cu powder and aqueous HBr was stirred for 30 min at 70 °C prior to use. After collection of the effluent for about 15 min (ca. 100 mmol in term of product), the mixture was allowed to stir for another 30 min at 70 °C. The crude 2,4,5-trifluorobromobenzene was obtained by steam distillation. The pure product was obtained by further distillation under a reduced pressure.

2.2.2. The scale-up of the continuous microflow process

The kilogram-scale microreactor system was assembled with 40 T-micromixer chips (polymethyl methacrylate, PMMA) and a delay loop (Fig. 2c). The outline size of the T-micromixer was 90.0 × 50.0 × 4.0 mm (length × width × height). And the microchannel size of T-micromixer was 1.2 × 1.0 mm (length × width). The T-micromixer was made by a carving machine (ROLAND, MDX-40A). The inlet and outlet points were

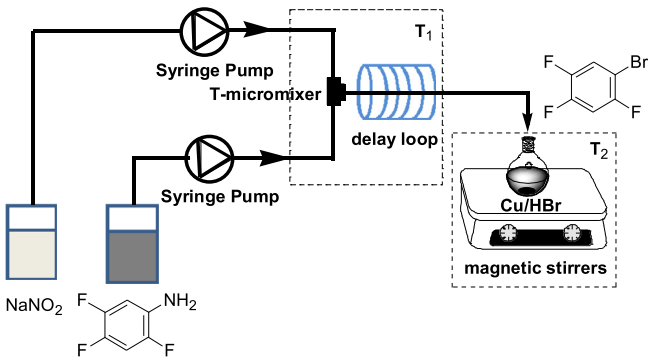


Fig. 1. Schematic of the setup for continuous microflow synthesis of 2,4,5-trifluorobromobenzene.

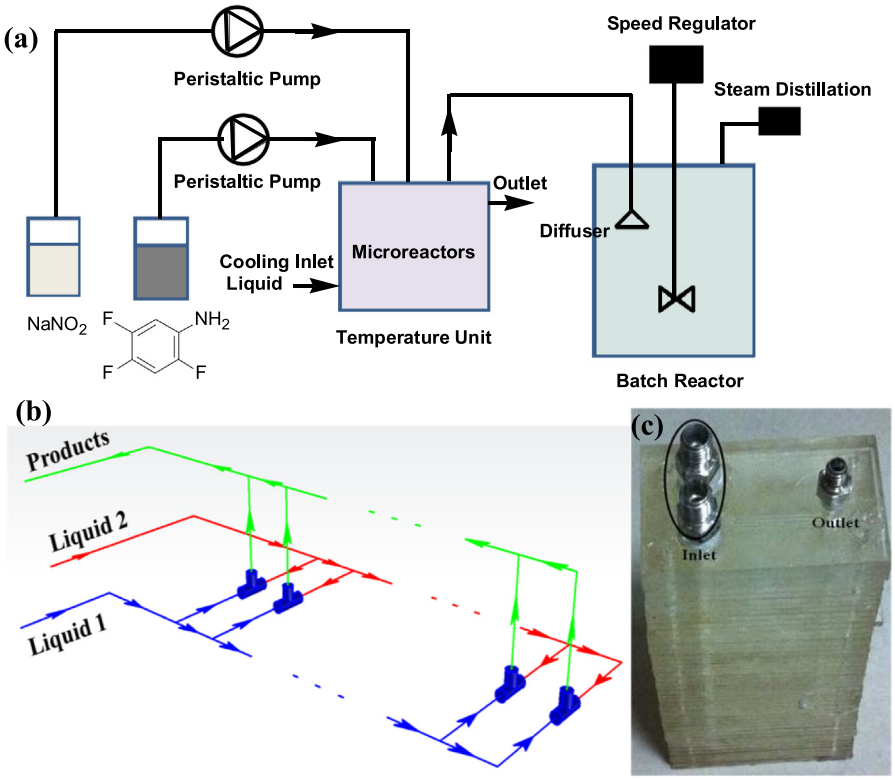


Fig. 2. (a) The microflow scale-up setup for the synthesis of 2,4,5-trifluorobromobenzene *via* Gattermann reaction. (b) The schematic of the scale-up process. (c) The picture of the microreactor of the scale-up setup.

interconnected at corresponding position for passing the raw material and product, respectively. The each T-micromixer chip was pasted to form the scale-up T-micromixer setup as the core reaction components one by one using the agglomerant, which was composed of ethyl alcohol and 1,2-dichloroethane. When the T-micromixer was added a chip, the T-micromixer was compressed at 1.0 MPa and 100 °C for 5–15 min. And finally, the T-micromixer was consisted of 40 T-micromixer as shown in Fig. 2c. Four PTFE tubes (i.d. 2.0 mm, each length: 6.25 m, volume ca. 78.5 mL) and four two-paralled PMMA plate units (the distance of two-paralled plate was 1.2 mm and the size of the each plate was 160 × 100 mm (length × width), volume ca. 76.8 mL) were used as the delay loop, which were connected to the outlet of the T-micromixer. The solutions of 2,4,5-trifluoroaniline (1.0 M in HBr, 254 mL/min) and $NaNO_2$ (6.0 M in H_2O, 46 mL/min) were introduced into the system by peristaltic pumps, respectively. The reaction temperature of the system was kept at −10 °C by a low temperature bath. The residence time was 30 s. The effluent was directly collected in a container filled with Cu powder (0.5 kg) and HBr (3.65 kg, 47 wt%) at 70 °C. The mixture of Cu powder and HBr solution was stirred for 30 min at 70 °C prior to use. The collecting time was 40 min, and the obtained mixture was stirred for another 60 min at 70 °C. The crude 2,4,5-trifluorobromobenzene was obtained by steam distillation. The pure product was obtained by distillation under a reduced pressure.

2.3. Analysis

The crude product was dried over Na_2SO_4 prior to analysis, and EtOAc as solvent. Gas chromatography (GC) analysis was performed on Shimadu GC-2014 equipped with an AOC-20i antoinjector, a HP-5 capillary clolumn (30 m × 0.32 mm × 0.25 μm) and a flame ionization detector (FID). The column temperature was started at 60 °C for 3 min, and then increased to 280 °C at a rate of 10 °C/min and hold for 1 min. The temperatures of gasification chamber and detecting chamber were both 290 °C. The yield of 2,4,5-triflluorobromobenzene was calculated as mmol 2,4,5-tri fluorobromobenzene/mmol initial 2,4,5-trifluoroaniline.

3. Results and discussion

3.1. The effect of mole ratio

The functions of HBr in diazotization include the following: 1) HBr reacts with 2,4,5-trifluoroaniline to generate the ammonium salts which are soluble in water. 2) HBr reacts with $NaNO_2$ to form HNO_2 which participates in the diazotization reaction as the reagent. 3) 2,4,5-trifluorobenzene diazonium generated from 2,4,5-trifluoroaniline by diazotization reaction is more stable in strong acid and low temperature. Theoretically, the mole ratio of HBr and 2,4,5-trifluoroaniline to 2.0 is enough. Otherwise, the diazoamino compound is easily generated from the coupling reaction of 2,4,5-trifluorobenzene diazonium and 2,4,5-trifluoroaniline. It will decompose or generate solid, leading to the blocking of the microchannel. Thus, it is better to use more amount of HBr to suppress this reaction. The effect of the mole ratio of HBr to 2,4,5-trifluoroaniline was shown in Table 1. The yields remained stable and varied from 91.9% to 93.3% along with the decreasing of the mole ratio from 6:1 to 4:1 (Table 1, entries 1–3). Unfortunately, the microchannel was clogged when 3.0 equiv. of HBr was used, because of the formation of a lot of yellow solids (Table 1, entry 4). Due to the decreasing of the acids, it would increase the cross-coupling side reactions and decomposition of the diazonium salts. The yellow solids were generated by cross-coupling side reactions because of the instability of the diazonium intermediate. The reaction process was shown in Scheme 1.

Table 1
Effect of mole ratio of 2,4,5-trifluoroaniline and hydrobromic acid on the yield.[a]

Entry	Mole ratio/HBr: 2,4,5-trifluoroaniline	Yield/%[b]
1	6:1	93.3
2	5:1	91.9
3	4:1	93.1
4	3:1	–[c]

[a] Conditions: residence time: 30 s, flow rate of 2,4,5-trifluoroaniline: 6.8 mL/min, flow rate of $NaNO_2$: 1.2 mL/min, T_1: 0 °C, T_2:70 °C, Cu/HBr: 5.0 g/25 mL, the purity of the crude 2,4,5-trifluorobromobenzene is more than 98%.
[b] Isolate yield, error range ±1%.
[c] Clogging in microchannel.

3.2. The effect of flow rate

As shown in Fig. 3, the yield remained unchanged and even increased along with increasing of the total flow rate. The length of the tubular microreactor assembled after the T-micromixer increases when the total flow rate increases in order to keep the residence time constant. Though, the diffusion coefficient is a material parameter and is not affected by the total flow rate, the Reynolds number will increase with the increasing of the total flow rate. As the Reynolds number increases, the phenomena appeared in the microchannel becomes more and more complex, and the number of the vortex is also increased. It is advantageous to the mixing of 2,4,5-trifluoroaniline with $NaNO_2$. Hence, the yield increases with the increase in the total flow rate. The increase in flow rate and decrease in residence time are beneficial for the improvement of space-time yield and the savings of cost. However, further increase of the total flow rate would lead to an increase of pressure in the microchannel, which may cause the instability of the working flow system and might be potentially risky especially for a scale-up operation.

3.3. The effect of residence time

The reaction time can usually be greatly reduced in microreactors. In fact, the diazotization reaction could be complete in seconds. In microreactors, the residence time could be easily adjusted by the length of the tubular microreactor assembled after the T-micromixer. As shown in Fig. 4, the yields of 2,4,5-trifluorobromobenzene kept at the same levels when the residence time was longer than 10 s. When residence time was less than 10 s, the product yields decreased dramatically. The residence time of 10 s gave the product in 92.2% yield, while the residence time of 8 s and 6 s gave a yield of 81.6% and 37.3%, respectively. At the same time, the formation of some oily and dark byproducts was observed during the bromodediazoniation if the diazotization reaction was performed with a residence time of 6 s. Thus, the optimum residence time of diazotization is 10 s.

3.4. The effect of temperature

Fig. 5 shows the results of the diazotization reaction at the different reaction temperature (T_1). The diazotization reaction could be conducted at room temperature (25 °C) under microflow conditions, and 2,4,5-trifluorobromobenzene was produced in 90.2% yield. As can be seen from Fig. 5, the yield decreased a little along with the increase in reaction temperature of the diazotization step. The yields decreased from 93.3% to 90.2% when the reaction temperature increased from 0 °C to 25 °C. However, it should be noted that the formation of gas bubbles in microchannel was observed when the diazotization reaction was performed at 25 °C, probably due to slight decomposition of the diazonium 2,4,5-trifluorobenzene or HNO_2. The formation of gas bubbles in microreactor should be avoided as it may result in instability of the flow, especially for scale-up. The results indicated that, although the diazotization reaction indeed required to be performed at low temperature (⩽0 °C), the microflow system could be performed at room temperature. Meanwhile, due to efficient heat- and mass-transfer, the black tar is not formed in the flow process. Thus, the micro-flow reaction is better separated from the batch process.

3.5. The effect of the amount of catalyst

CuBr is generated in situ from the reaction of copper powder with HBr. It acts as a catalyst in the bromodediazoniation step. Therefore, the different amounts of Cu will affect formation of the CuBr. Table 2 shows the results of the different amounts of Cu powder effect on the product yields. As can been seen, a decrease in the product yield was observed along with the decrease Cu powder, possibly due to the decrease CuBr formed in the reaction. Although the practically amount of CuBr is less than 24 mol% (Table 2, entry 2), the Cu powder is excessively needed

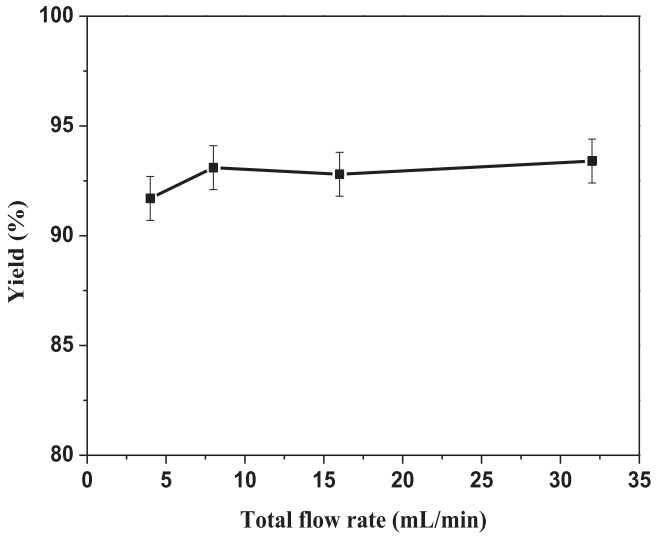


Fig. 3. Results of the different total flow rate on the yield of 2,4,5-trifluorobromobenzene (Conditions: residence time: 30 s, mole ratio$_{HBr:2,4,5\text{-trifluoroaniline}}$: 4:1, T_1: 0 °C, T_2: 70 °C, Cu/HBr: 5.0 g/25 mL. Isolate yield, error range ±1%.)

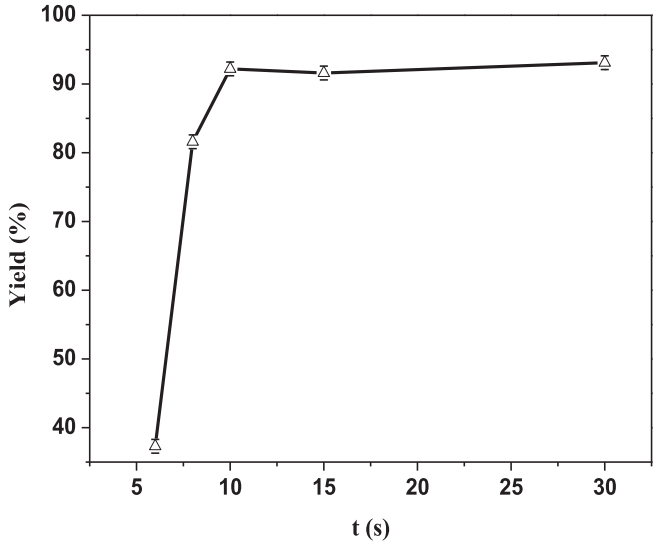


Fig. 4. Effect of residence time on the yield of 2,4,5-trifluorobromobenzene (Conditions: total flow rate: 8.0 mL/min, mole ratio$_{HBr:2,4,5\text{-trifluoroaniline}}$: 4:1, T_1: 0 °C, T_2: 70 °C, Cu/HBr: 5.0 g/25 mL. Isolate yield, error range ±1%.)

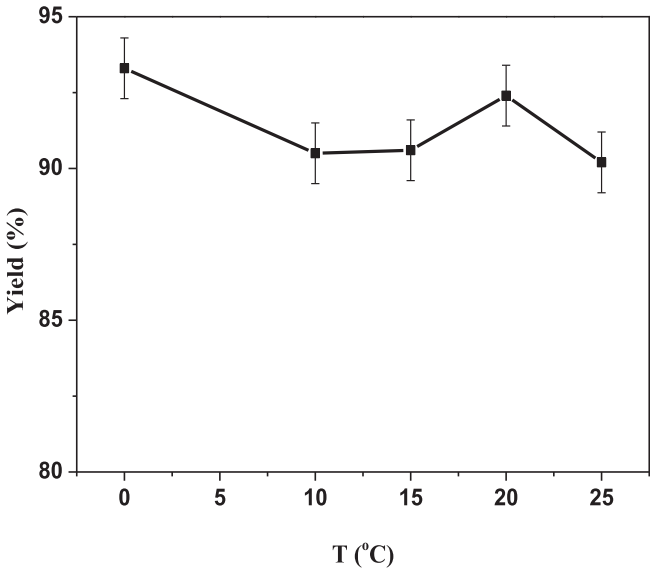


Fig. 5. Effect of temperature of diazotization reaction on the yield of 2,4,5-trifluorobromobenzene (Conditions: total flow rate: 8.0 mL/min, mole ratio$_{HBr:2,4,5\text{-trifluoroaniline}}$: 4:1, residence time: 30 s, T_2: 70 °C, Cu/HBr: 5.0 g/25 mL. Isolate yield, error range ±1%.)

Table 2
Effect of catalyst dosage on the yield of 2,4,5-trifluorobromobenzene.[a]

Entry	Mole ratio/2,4,5-trifluoroaniline: Cu	Unreact Cu/mol% (mol)[b]	Yield/%[c]
1	1:2.14	82.3(0.38)	93.3
2	1:1.34	81.8(0.24)	92.7
3	1:0.67	75.9(0.16)	86.3
4	1:0.27	51.7(0.13)	86.2
5	1:0.22	53.9(0.10)	83.0
6	1:0.11	41.7(0.06)	72.2

[a] Conditions: total flow rate: 8.0 mL/min, mole ratio$_{HBr:2,4,5\text{-trifluoroaniline}}$: 4:1, residence time: 30 s, T_1: 0 °C, T_2: 70 °C.
[b] 1 mol of 2,4,5-trifluoroaniline consumes practically Cu in parentheses.
[c] Isolate yield, error range ±1%.

to form the CuBr. Thus, the key factor of formation CuBr ensures that the Cu powder is enough.

3.6. The scale-up of the continuous microflow process

Based on the optimized conditions, the kilogram per hour scale-up setup was designed for synthesis of 2,4,5-trifluorobromobenzene by the numbering-up (Fig. 2). The schematic of scale-up process was shown in Fig. 2b. The liquids **1** and **2** were pumped into the scale-up T-microreactor by peristaltic pump, respectively. And then, the liquids **1** and **2** were distributed into the single T-micromixer. In order to ensure the same amount of liquid in a single T-micromixer, each of the T-micromixer had the same inside dimension and manufacturing process. The liquids **1** and **2** mixed and reacted in each T-micromixer. The mixture passed into the microchannel reactors and delay loops to extend the residence time for further reaction. Finally, the bromodediazoniation of 2,4,5-trifluorophenyl diazonium was carried out in batch reactor.

The heat-transfer capability of the scale-up setup was tested prior to use. The outlet temperature of the single and scale-up microreactor is measured by on-line temperature sensor, respectively. The temperature of the thermal fluids and cooling liquid is 80 °C and 10 °C, respectively. Under the same other conditions, based on an average of three runs, the outlet temperature of single microreactor is 25.7 °C, and the scale-up setup is only 24.0 °C. The results indicate that the heat- transfer capability of the scale-up setup has achieved the requirements.

The scale-up experiment was performed in the above scale-up system. The yield of crude 2,4,5-trifluorobromobenzene, based on an average of two runs, is 90% (1.93 kg, the purity of crude product is 96%) in 40 min. And further, the yield of 2,4,5-trifluorobromobenzene is 86% (1.84 kg) by distillation *in vacuo*. Thus, the productivity is 2.76 kg/h. The yield of the scale-up setup is (86%) less than the single microractor (93%). Meanwhile, in the scale-up experimental process, the liquid color of diazonium salts is deeper than the single microreactor. The results indicate that the heat- and mass- transfer capability of the single microreactor is superior to the scale-up setup.

4. Conclusion

In summary, a reliable and facile continuous microflow process for the synthesis of 2,4,5-trifluorobromobenzene from 2,4,5-trifluoroaniline *via* Gatternann reaction has been developed. The microflow system is able to promote efficient mass- and heat-transfer and cut greatly down the reaction time. The precise control of the reaction variables using microreactor significantly improves the yield and selectivity over the corresponding batch procedures. Furthermore, the scale-up equipment has also been demonstrated to successfully conduct a kilogram-scale synthesis of 2,4,5-trifluorobromobenzene. This flow process not only offers a simple and fast flow-synthesis of 2,4,5-trifluorobromobenzene for kilogram-scale in high yield and high selectivity, but also provides an important model for kilogram-scale chemical synthesis involving tandem liquid/liquid reaction in microreactors and liquid/solid reaction in batch reactor.

Acknowledgments

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