The continuous flow synthesis of 2,4,5-trifluorobenzoic acid via sequential Grignard exchange and carboxylation reactions using microreactors

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HIGHLIGHTS

- Easily assembled flow microreactor system for liquid/liquid and gas/liquid reactions.
- Efficient synthetic route for 2,4,5-trifluorobenzonic acid.
- Efficient process to produce 2,4,5-trifluorobenzonic acid in high yield and purity.

GRAPHICAL ABSTRACT
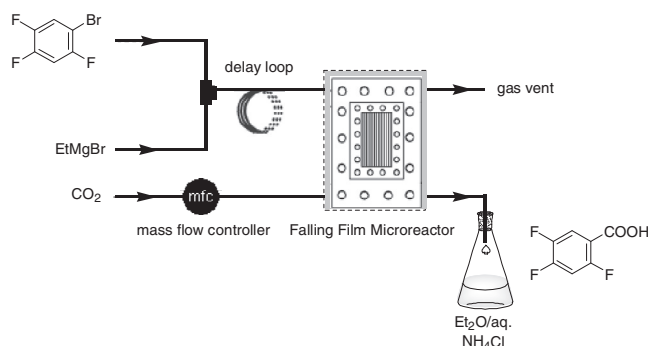
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ABSTRACT

2,4,5-Trifluorobenzoic acid is a valuable synthetic intermediate with important application in pharmaceutical industry and material science. In this paper, we report a facile continuous microflow process for the synthesis of 2,4,5-trifluorobenzoic acid via the generation of an unstable aryl-Grignard reagent followed by its reaction with gaseous CO_2. The microflow system is easily assembled by a simple T-micromixer, a commercial available falling film microreactor, tube microreactor and several pumps. The use of a composed T-micromixer and tube microreactor facilitates the Grignard exchange reaction of 2,4,5-trifluorobromobenzene with ethylmagnesium bromide producing 2,4,5-trifluorophenylmagnesium bromide almost in quantitative yield, and the use of the falling film microreactor enables a highly efficient gas–liquid reaction of the resultant Grignard reagent with CO_2 under an atmosphere pressure, which ultimately gave the product 2,4,5-trifluorobenzoic acid in high yield with high purity after a simple and extractive workup. The influence of reaction parameters on the two steps in microreactors was discussed.

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1. Introduction

Fluorinated arylcarboxylic acid is an important class of compounds that have widespread applications in pharmaceutical industry, agrochemical manufacture and material science [1–3]. In particular, 2,4,5-trifluorobenzoic acid (**1**) is a valuable precursor for the synthesis of a variety of fluoroquinolone antibiotics [4–12]. Ciprofloxacin (Cipro™), norfloxacin (Noroxin™) and pefloxacin (Peflacine™), which are common antibacterial drugs prescribed clinically, are prepared via routes starting from 2,4,5-trifluorobenzoic acid (Fig. 1). Besides, 2,4,5-trifluorobenzoic acid also has applications in material science. For example, it has been employed to

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access new functional molecules with interesting photophysical and electronic properties that can potentially be used as p-type conductivity dopants [13].

Early method to access 2,4,5-trifluorobenzonic acid involved the cyanation of 2,4,5-trifluorobromobenzene with an excess CuCN followed by an acid-promoted hydrolysis reaction [6,14]. Later Chu developed a two-step method via the $AlCl_3$-promoted Friedel–Craft acylation of 1,2,4-trifluorobenzene with acetyl chloride with subsequent oxidation by NaClO/NaOH solution [7]. Although avoiding the use of highly toxic CuCN, the method suffers from the generation of lots of wastes and a tedious workup procedure to remove them. 2,4,5-Trifluorobenzonic acid was also obtained via a multistep procedure involving fluorination and decarboxylation from the relatively cost-effective tetrachlorophthalic anhydride. Apparently, this method is labor-intensive and time-consuming [15,16]. Thus, it appears that the most efficient protocol for its synthesis remains through the metalation of 2,4,5-trifluorobromobenzene followed by the carboxylation reaction [17]. The reactions involved in this protocol are inherently efficient and high-yielding, yet the scaled batch process is costly and inefficient, often requiring low-temperature operation and slow addition of one reagent into the other. In addition, the length of time required to cool and later warm the reactor necessitated for a high yield is also concerned. Thus, improved process for the synthesis of 2,4,5-trifluorobenzonic acid is still highly desirable.

Recently, the flow microreactor technology has gained increasing attention for chemical synthesis in both academia and industry [18–27]. The well-recognized advantages of microreactors over conventional batch reactors such as efficient heat- and mass-transfer and precise control over reaction parameters (stoichiometry, temperature and flow rate) often lead to improved efficiency, high reproducibility and enhanced safety [28–32]. Particularly, fast and highly exothermic reactions can be favorably performed. Another notable feature is the ease of scalability from bench experiment to large-scale production, either by running the flow-reactor for an extended time or by numbering the parallel microreactors, which is quite important from the viewpoint of industry production. In addition, the incorporation of real time monitoring with intelligent feedback loops into a microflow system, also offers considerable possibilities to develop fully automated processes [33–35].

Herein we envisioned a flow protocol by taking advantage of the microreactor technique for the synthesis of 2,4,5-trifluorobenzonic acid. Our approach is based upon an easily assembled microflow system to integrate the Grignard exchange reaction with the subsequent CO_2-involved gas–liquid reaction [36–39]. We used a composed T-micromixer and tube microreactor to realize the generation of high quality of 2,4,5-trifluorophenylmagnesium bromide via Grignard exchange reaction of 2,4,5-trifluorobromobenzene with ethylmagnesium bromide (EtMgBr). Meanwhile, the integration of the falling film microreactor (FFMR) into the flow system facilitated a highly efficient gas–liquid reaction of the resultant Grignard reagent with gaseous CO_2 under an atmosphere pressure. This flow process provides a very simple and fast synthesis of 2,4,5-trifuorobenzoic acid in high yield via tandem liquid/liquid and gas/liquid reactions in microreactors.

2. Experimental

2.1. Materials

Ethyl bromide (EtBr, A.R.), benzaldehyde (PhCHO, A.R.), HBr (aqueous 40%), mesitylene (A.R.) and magnesium turnings were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). 1,2,4-Trifluoroaniline (C.P.) was purchased from Suzhou YACOO Chemical Reagent Co., Ltd. (China). Compressed CO_2 (99.999% purity) was obtained from Nanjing Tianze Gas Co., Ltd. (China). THF was dried and distilled over sodium-benzophenone prior to use. PhCHO was purified by vacuum distillation. Harvard pump (PHD ULTRA, PHD 2000, USA), mass flow controller (CS-200A, SevenStar, China), glass syringe (Hamilton, USA), T-micromixer (i.d. 1.2 mm, 316L, Xiongchuan, China; i.d. 0.33 mm, 316L, Swagelok, USA; i.d. 0.5 mm, CTFE, VICI, USA), falling film microreactor (HT-07030, FFMR, IMM, Germany) were all commercially available. PTFE (i.d. 0.5, 1.0, 2.0 mm), stainless steel tubing (316L, Xiongchuan, China), connectors (316L, Xiongchuan, China; 316L, Swagelok USA; PEEK, VALCO, USA; CTFE, VALCO, USA), nuts (316L, Xiongchuan, China) and fittings (316L, Xiongchuan, China) were also commercially available.

2.1.1. Preparation of 2,4,5-trifluorobromobenzene [40]

A flow microreactor system consisting of T-micromixer (i.d.: 1.2 mm) and tube microreactor (length: 250 cm, i.d.: 1.0 mm) was used. 2,4,5-Trifluoroaniline (18.375 g, 0.125 mol) was dissolved in 40% aqueous HBr (100 mL) and H_2O (75 mL). $NaNO_2$ (8.625 g, 0.125 mol) was dissolved in H_2O (100 mL). The solutions of 2,4,5-trifluoroaniline (2.57 mL/min) and $NaNO_2$ (1.43 mL/min) were introduced to the T-microreactor by syringe pumps, respectively. The solution was passed through tube microreactor at 0 °C for a residence time of 30 s, and then was directly introduced to the flask containing Cu powder (5.0 g) and 40% aqueous HBr (25 mL). The mixture was stirred at 70 °C for 30 min. After the reaction was complete, the crude 2,4,5-trifluorobromobenzene was obtained by steam distillation. 20.3 g (93%, yield) pure product was obtained by further distillation under a reduced pressure.

2.1.2. Preparation and titration of the EtMgBr solution

Several drops of EtBr were added to a mixture of magnesium turnings (5.28 g, 0. 22 mol) and I_2 (a few crystals) in 50 mL of THF under a nitrogen atmosphere. Upon the initiation of the Grignard reaction, the remaining EtBr (14.9 mL, 0.2 mol) in 50 mL of THF was added dropwise. After the addition of EtBr, the reaction mixture was kept stirring at room temperature for another 1 h, and then transferred to a resealable bottle under nitrogen. The concentration of the EtMgBr solution was titrated following a method reported by Knochel [41]. A 10-mL Schlenk tube equipped with a magnetic stirring bar was heated by a heat gun under vacuum and cooled to room temperature under an N_2 atmosphere. The dry Schlenk tube was then charged with anhydrous LiCl (42 mg, 1 mmol), and fitted with a rubber septum. 3 mL of THF was added using a glass syringe and stirring was started. And then, I_2 (254 mg, 1 mmol) was added into the Schlenk tube. After I_2 was completely dissolved, the resulting brown solution was cooled to

ciprofloxacin (R^1 = H, R^2 = C_3H_5)
norfloxacin (R^1 = H, R^2 = Et)
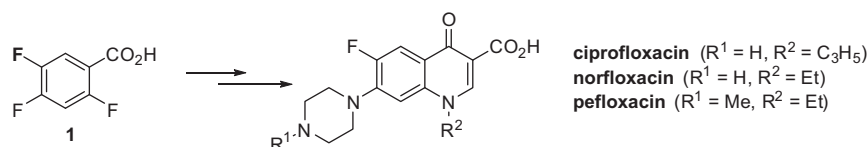pefloxacin (R^1 = Me, R^2 = Et)

Fig. 1. Representative examples of drug molecules prepared from 2,4,5-trifluorobenzoic acid.

0 °C by an ice bath and the EtMgBr solution was added dropwise via a 1.00-mL syringe (0.01-mL graduations) until the brown color disappeared. The concentration of EtMgBr was determined as 1.85 M. The solution was diluted to a specific concentration with dry THF prior to use. *Note: the EtMgBr solution should be carefully kept under a dry N_2 atmosphere, and titrated again after a period of use.*

2.2. Microflow setup and experimental procedure

The Grignard exchange reaction was initially performed with a microflow system consisting of syringe pumps, T-micromixers and delay loop (Fig. 2). 2,4,5-Trifluorobromobenzene (0.5–1.0 M, flow rate: 333–500 μL/min) and EtMgBr (0.5–1.0 M, flow rate: 500–667 μL/min) in THF were introduced to the T-micromixer (i.d.: 1.2 mm) by two syringe pumps, respectively. The reaction mixture was directly introduced into a delay loop (i.d.: 1.0 mm) for a specified residence time (1–40 min). The T-micromixer and delay loop were immersed in a water bath for a specified reaction temperature (T_1, 15–50 °C). Sample was collected in an oven-dried 50 mL round-bottom flask containing H_2O or PhCHO in THF. Et_2O was added to separate products from water solution. The aqueous layer was extracted with Et_2O three times, and the combined organic fractions were dried over Na_2SO_4 and analyzed by GC. The reaction conditions were optimized by varying different parameters such as the reaction temperature, residence time, and mole ratio of EtMgBr to 2,4,5-trifluorobromobenzene and their concentrations, and the inner diameters of microreactors.

The preparation of 2,4,5-trifluorobenzoic acid was carried out using a microflow system consisting of syringe pumps, gas controlled system, micromixers and delay loops (Fig. 3). A solution of EtMgBr (1.0 M, flow rate: 0.4 mL/min) and 2,4,5-trifluorobromobenzene (1.0 M, flow rate: 0.4 mL/min) in THF were introduced into the T-micromixer (i.d.: 1.2 mm) by syringe pumps. The resulting solution was fed into a delay loop (i.d.: 1.0 mm). The T-micromixer and delay loop were dipped into a water bath for maintaining the reaction temperature (T_1). The outlet of the delay loop was connected to one of the inlet of FFMR and CO_2 was introduced to the other inlet of FFMR with the flow rates of 2–50 mL/min adjusted by a mass flow controller with a PC-assisted terminal. The temperature of the FFMR (T_2, 5–35 °C) was controlled by a recycle loop with ethanol. The reaction was quenched by the addition of the reaction mixture to an excess amount of Et_2O and saturated NH_4Cl (V/V = 1:1). The solution was acidified with aqueous HCl (1.0 M), and then extracted with EtOAc (3 × 10 mL). The organic layers were dried over Na_2SO_4 and analyzed by GC. The solvent of organic layers were removed *in vacuo* to give a white solid [7]. ^1H NMR (400 MHz, $CDCl_3$): δ 11.9 (br, 1H), 7.86 (m, 1H), 7.04 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 158.8 (ddd, J = 261.2, 12.0, 1.4 Hz), 154.1 (ddd, J = 259.4, 14.0, 12.0 Hz), 146.5 (ddd, J = 245.6, 12.2, 4.1 Hz), 120.5 (d, J = 20.4 Hz), 113.9 (m), 107.4 (dd, J = 28.0, 20.4 Hz) ppm.
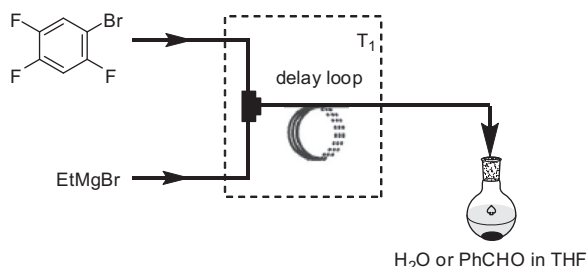

Fig. 2. Schematic diagram of the continuous microflow setup for monitoring the Grignard exchange reaction.

2.3. Analysis

Gas chromatography (GC) analysis was performed on Shimadu GC-2014 equipped with an AOC-20i antoinjector, a HP-5 capillary column (30 m × 0.32 mm × 0.25 μm) and a flame ionization detector (FID). Program: the column temperature was started at 60 °C for 1 min, then increased to 230 °C at a rate of 10 °C/min and held at this temperature for 5 min. The temperatures of gasification chamber and detecting chamber were 280 °C and 290 °C, respectively. The molar mass of the reactants and products were calibrated by comparison with the internal standard mesitylene. For the Grignard exchange reaction, conversion of 2,4,5-trifluorobromobenzene (%) = 1 − (mmol residual 2,4,5-trifluorobromobenzene/mmol initial 2,4,5-trifluorobromobenzene). For the carboxylation reaction, yield of 2,4,5-trifluorobenzoic acid = mmol 2,4,5-trifluorobenzoic acid/mmol initial 2,4,5-trifluorobromobenzene, selectivity = mmol 2,4,5-trifluorobenzoic acid/(mmol 2,4,5-trifluorobenzoic acid + mmol 1,2,4-trifluorobenzene). ^1H and ^{13}C NMR spectra of the product were measured in $CDCl_3$ with TMS as the internal standard on a Bruke Advance 400 MHz NMR spectrometer. Chemical shifts were expressed in ppm and J values are given in Hz.

3. Results and discussion

3.1. Synthetic route

The method used for the preparation of 2,4,5-trifluorobenzoic acid (**1**) involved the metalation of 2,4,5-trifluorobromobenzene (**2**) followed by its reaction with CO_2 (Scheme 1a). The arylmagnesium reagent can be formed by the reaction of magnesium with bromide but sometimes difficult especially for large-scale production [42–44]. The success of the reaction often depends critically on its initiation process and prior activation of magnesium surface is usually required to start the reaction [17]. Alternatively, the metalation process could be achieved via a halogen–metal exchange reaction using an organolithium reagent or a Grignard reagent (Grignard exchange reaction). We used the common EtMgBr as the metalation reagent since this reagent is cheaper and more stable (less reactive) than the common organolithium reagent such as *n*-BuLi. More importantly, the Grignard exchange reaction could be performed at a modest reaction temperature (e.g., room temperature) avoiding low-temperature regulation, while the halogen–Li exchange process, generally conducted at −40–0 °C in microreactors, is still highly energy-consuming from the viewpoint of industrial production [45–50]. In addition, the metalation of bromide **2** with organolithium reagents appears troublesome in some case. For example, Bridges et al. have reported that the lithiation of bromide **2** could occur at different positions of the aryl ring depending on the solvent used [51].

On the other hand, we also recognized that a high conversion of bromide **2** to 2,4,5-trifluorophenylmagnesium bromide (**3**) with a minimal use of EtMgBr was important. It would negatively affect the reaction sequences leading to low yield and poor selectivity of the final product if not under control. As shown in Scheme 1b, major possible byproducts included propionic acid (**4**) from the reaction of the unreacted (or excessive) EtMgBr with CO_2, and 1,2,4-trifluorobenzene (**5**) from protonization of **3**. Particularly, removal of the impurity of acid **4** is often troublesome due to the similar physical and chemical properties [52]. In addition, unreacted bromide **2** could also contaminate the final product if the Br/Mg exchange reaction did not complete. For these reasons, we first optimized reaction conditions of the Grignard exchange reaction of bromide **2** and EtMgBr (Fig. 2), and then studied the gas–liquid reaction of CO_2 with the in situ generated Grignard reagent **3** in FFMR, establishing a reliable synthesis of 2,4,5-trifluorobenzo-
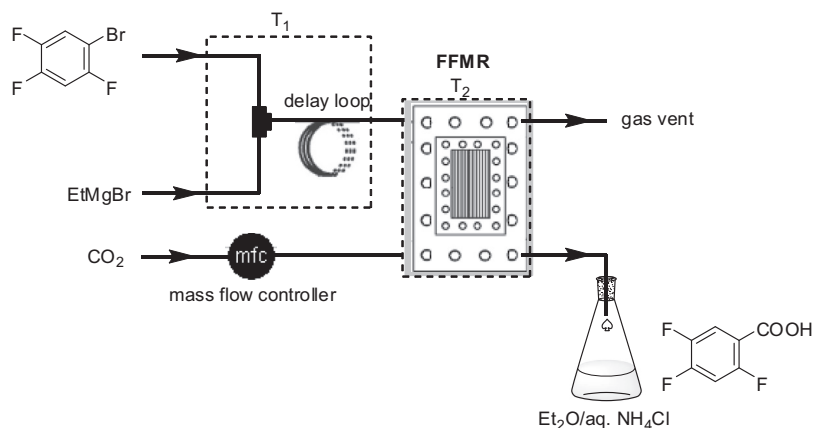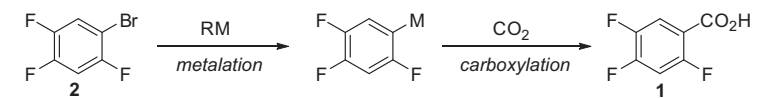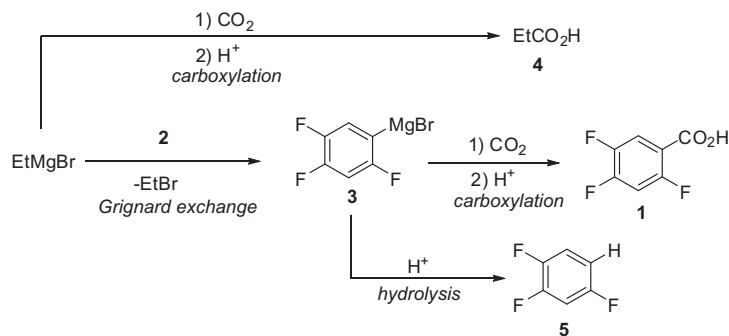
Fig. 3. Schematic diagram of the continuous microflow setup for the synthesis of 2,4,5-trifluorobenzoic acid.

(a) synthetic route for 2,4,5-trifluorobenzoic acid

(b) possible byproducts

Scheme 1. Synthetic route for 2,4,5-trifluorobenzoic acid (a) and possible byproducts (b).

ic acid in flow. It should be noted that the flow carboxylation of Grignard reagents has been studied by the Ley group using a conceptually novel tube-in-tube device [31].

3.2. Grignard exchange reaction

3.2.1. The effect of temperature

Fig. 4 shows the results of the Grignard exchange reaction at different reaction temperatures for a residence time of 2 min. As expected, the reaction of EtMgBr with 2,4,5-trifluorobromobenzene (**2**) indeed could be performed at room temperature (25 °C) under microflow conditions, and a 65% conversion of **2** to **5** was observed after quenching the mixture with H_2O. As can be seen from Fig. 4, the reaction is more efficient at higher temperature. Thus, the conversion dramatically increases from 36% to 93% with the increase of the reaction temperature from 15 °C to 50 °C. Obviously, the temperature effect is much more evident from a range of 15 °C to 30 °C than that of 30 °C to 50 °C. However, it should be noted that the formation of gas burbling in the delay loop was observed when the reaction was performed at 50 °C probably due to the vaporization of the byproduct such as EtBr. The formation of gas burbling in the microreactor should be avoided as this may result in instability of the microflow system and cause incon-
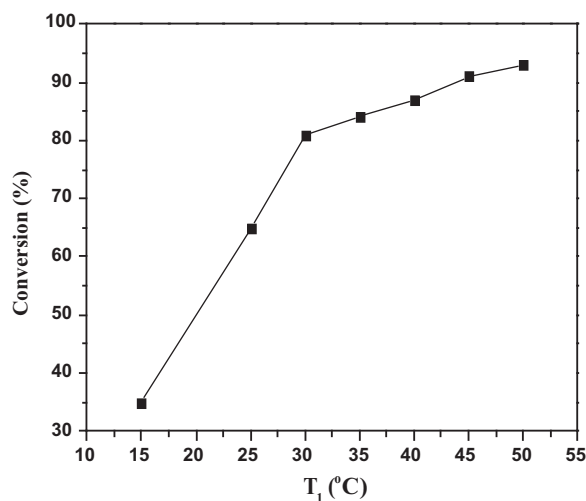

Fig. 4. Temperature effect on the reaction of 2,4,5-trifluorobromobenzene (**2**) and EtMgBr. (Conditions: EtMgBr (0.5 M), 0.5 mL/min; **2** (0.5 M), 0.5 mL/min; residence time: 2 min. The reaction mixture was quenched by water and analyzed by GC analysis.).

venience for downstream reaction in stoichiometry. In addition, it should also be mentioned that, although the reaction was conducted at a relatively high temperature, we did not observe any possible cross- or homo- coupling products from the resultant Grignard reagent **3** and EtBr.

3.2.2. The effect of mole ratio

The mole ratio of EtMgBr to bromide **2** was varied by changing the corresponding flow rates while the total flow rate still maintained to be 1 mL/min. With a residence time of 2 min, the conversion of **2** reached 82% at 30 °C when 1.0 equiv of EtMgBr was used (Table 1, entry 1). The conversion increased with the amount of EtMgBr used (Table 1, entries 1–5). When 2.0 equiv of EtMgBr was used, the conversion could reach to 97% in 2 min. To determine the amounts of unreacted EtMgBr, the reaction mixtures were quenched by a solution of PhCHO in THF. Thus, although the conversion could reach 97% in 2 min in the presence of 2.0 equiv of EtMgBr, the excessive EtMgBr also led to the formation of 1-phenylpropan-1-ol in 22% yield. This may result in the generation of a comparable amount of byproduct such as propionic acid when trapped with CO_2. Thus the use of a minimal amount of EtMgBr for a complete Br/Mg exchange should be achieved. Fortunately, this problem could be solved by extending the residence time. For example, the conversion could reach 98% by prolonging the residence time to 5 min using 1.1 equiv of EtMgBr (Table 1, entry 6), and the reaction using 1.0 equiv of EtMgBr for a residence time of 10 min almost gave the debromination product quantitatively.

3.2.3. The effect of residence time

The effect of residence time on the reaction was examined at 30, 40 and 45 °C. As shown in Fig. 5, the reaction proceeded fast, and generally completed within 10 min at reaction temperatures of 40 and 45 °C, and 15 min at 30 °C. When the residence time was longer than 20 min, the conversions were all up to 99%. In addition, it can also be seen from Fig. 5 that a higher conversion was obtained when the reaction was conducted at a high temperature with a same residence time, which is consisted with the results of temperature effect.

3.2.4. The effect of concentration of EtMgBr

The use of higher concentrations of the reactants is benefit for the improvement of space–time yield and the savings of solvents. However, this may also cause some associated problems, i.e., the

Table 1
Results of different mole ratio of EtMgBr and 2,4,5-trifluorobromobenzene (**2**) on the Grignard exchange reaction.[a]

Entry	Mole ratio (EtMgBr:**2**)	t[b] (min)	Conv.[c] (%)
1	1:1	2	82 (6)
2	1.1:1	2	84 (4)
3	1.2:1	2	84 (8)
4	1.5:1	2	90 (16)
5	2.0:1	2	97 (22)
6	1.1:1	5	98 (6)
7	1:1	10	>99 (0)

[a] Conditions: EtMgBr (0.5 M), **2** (0.5 M), total flow rate: 1 mL/min; reaction temperature: 30 °C; the reaction was quenched by benzaldehyde.
[b] Residence time in delay loop.
[c] GC conversion of bromide **2**. Data in parentheses referring to the GC yields of 1-phenylpropan-1-ol based on EtMgBr.

Table 2
Results with different concentrations of the reagents.[a]

Entry	EtMgBr (mol/L)	**2** (mol/L)	Conv. (%)[b]
1	0.5	0.5	99
2	0.8	0.8	>99
3	1.0	1.0	99

[a] Conditions: EtMgBr, 0.5 mL/min; **2**, 0.5 mL/min; reaction temperature: 30 °C; residence time: 10 min.
[b] Quenched by H_2O.

Table 3
Results with different inner diameters of T-microreactor.[a]

Entry	Micromixer (µm)	Microtube (mm)	t (min)	Conv.[b] (%)
1	T-micromixer 1200	4.0	5	90
2	T-micromixer 1200	2.0	5	93
3	T-micromixer 1200	1.0	5	94
4	T-micromixer 1200	0.5	5	–[c]
5	T-micromixer 500	1.0	5	96
6	T-micromixer 330	1.0	5	–[d]

[a] Conditions: total flow rate: 1 mL/min; reaction temperature: 30 °C; mole ratio: EtMgBr:**2** = 1:1 (1.0 M in THF). The GC data given were based on an average of three runs.
[b] Quenched by benzaldehyde.
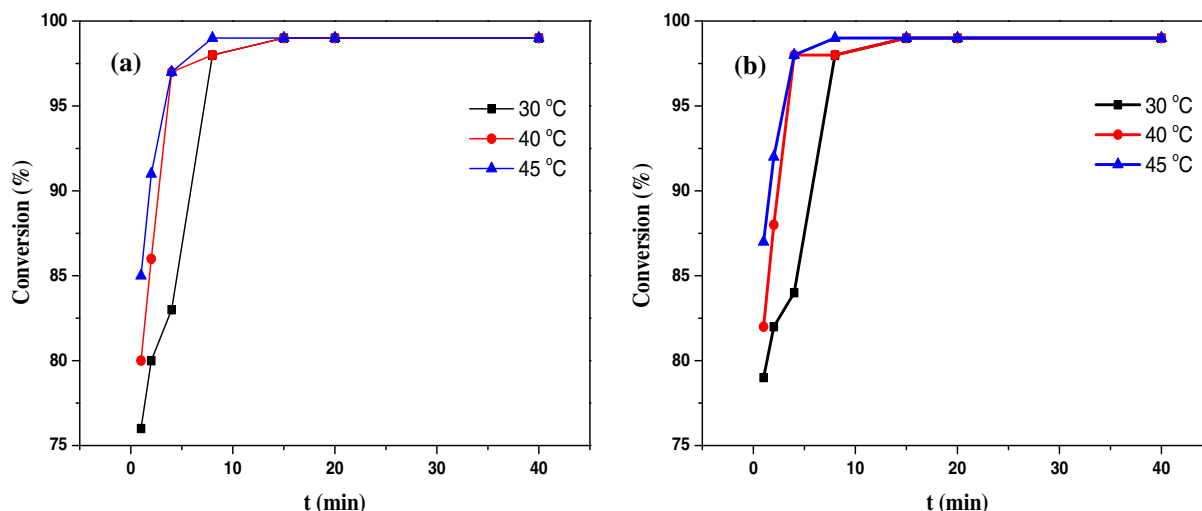[c] Clogging in microtube.
[d] Clogging in micromixer.

Fig. 5. Effect of residence time on the Grignard exchange reaction at different temperatures: (a) quenched by H_2O and (b) quenched by PhCHO: (a) quenched by H_2O and (b) quenched by PhCHO. (Conditions: EtMgBr (0.5 M), 0.5 mL/min; **2** (0.5 M), 0.5 mL/min).
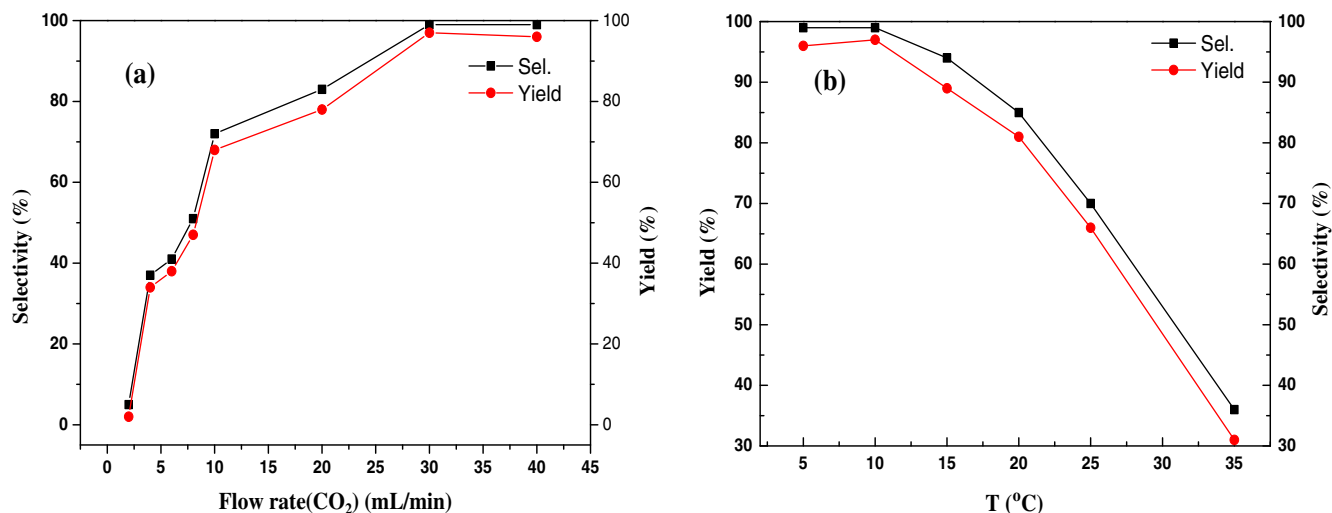
Fig. 6. (a) Flow rate effect of CO_2 and (b) temperature effect on the gas–liquid reaction in FFMR. Conditions: (a) EtMgBr (1.0 M), 0.4 mL/min; **2** (1.0 M), 0.4 mL/min; T_1: 45 °C; residence time: 10 min; T_2: 10 °C; (b) EtMgBr (1.0 M), 0.4 mL/min; **2** (1.0 M), 0.4 mL/min; T_1: 45 °C; residence time: 10 min; CO_2: 30 mL/min.

increased viscosity of the liquid mixture which often needs high pressure to facilitate the flow system work smoothly, and insolubility due to over saturation of the mixture which may result in blockage in microreactors. We thus examined the EtMgBr solutions at concentrations of 0.5, 0.8 and 1.0 M together with same level of the bromide **2** solutions. Fortunately, we found that the reactions all proceeded smoothly under the flow conditions without influence on the conversion of the Grignard exchange reaction (Table 2).

3.2.5. The effect of the inner diameter of microreactor

Table 3 shows the results with different inner diameters of T-micromixers and tube microreactor. The conversion decreases slightly with the increase of the inner diameter of microtube (Table 3, entries 1–4). However, the microtube was clogged at the inner diameter of 0.5 mm probably due to the formation of small precipitation. Additionally, the use of the microtube with the small inner diameter led to a high inner pressure in the system. We also tested several T-micromixers with different diameters. While the use of T-micromixers with diameters of 500 and 1200 μm proved to be successful, a T-micromixer with a diameter of 330 μm unfortunately led to clogging (Table 3, entry 6). These results may indicate that the reaction took place upon mixing and produced some tinny solid to block the micromixer or microtube.

3.3. Carboxylation reaction in FFMR

3.3.1. The effect of flow rate of CO_2

On the basis of the results obtained from the study of the Grignard exchange reaction, a microflow setup to combine the carboxylation reaction with CO_2 was constructed (Fig. 3). The generated (2,4,5-trifluorophenyl)magnesium bromide (**3**) was introduced into one inlet of a research-standard FFMR which composed of a gas chamber, microstructured stainless steel plates (64 straight parallel microchannels, width × thickness: 300 × 100 μm) and microtube heat exchanger. The maximal flow rate of this plate is ca. 0.83 mL/min. Therefore, the flow rates of EtMgBr and 2,4,5-trifluorobromobenzene were both adjusted to be 0.4 mL/min (Total flow rate: 0.8 mL/min). The paper-thin liquid film was formed by gravity in the microchannels of FFMR while CO_2 was full filled in the gas chamber. Fig. 6a shows the effect of the flow rate of CO_2 on the gas–liquid carboxylation reaction in FFMR. The yields of 2,4,5-trifluorobenzoic acid increase dramatically with the increase of flow rate from 5 to 30 mL. Further increase in the flow rate led to a small decrease of the yield. When the flow rate is 30 mL/min, the selectivity and yield reach 99% and 97%, respectively. A rough calculation indicated that ca. 8.96 mL/min of CO_2 under an atmosphere pressure was required for the stoichiometric carboxylation reaction with (2,4,5-trifluorophenyl)magnesium bromide (**3**). Thus, such a high flow rate of CO_2 should be responsible for the effective concentration of CO_2 in the gas–liquid reaction stream.

3.3.2. The effect of temperature

The effect of reaction temperature in FFMR is shown in Fig. 6b. When the reaction was performed at 0 °C, solid content was generated to block the microchannels in FFMR. At 5 and 10 °C, the gas–liquid reactions produced the product in 96% and 97% yields, respectively. However, the yield dropped significantly when the reaction was conducted at elevated temperature. Thus, the reaction performed at 20 °C gave the product in 81% yield, while the reaction at 35 °C gave a yield of 30% only. The decreasing solubility of CO_2 with the increase of temperature may be responsible for the inefficiency of the reaction at high temperature.

4. Conclusion

In summary, we have realized a continuous microflow system for the preparation of an important synthetic intermediate 2,4,5-trifluorobenzoic acid via a two-step reaction involving Grignard exchange and carboxylation reaction. The Grignard exchange reaction was conducted in a simple T-microreactor and generated the 2,4,5-trifluorophenylmagnesium bromide almost quantitatively from 2,4,5-trifluorobromobenzene and EtMgBr, while the use of the commercially available FFMR facilitated the gas–liquid carboxylation reaction. The procedure is simple, convenient and efficient, and the product could be obtained in high yield.

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Appendix A. Supplementary data

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