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Kilogram-Scale Synthesis of 2,4-Dichloro-5-fluorobenzoic Acid by Air Oxidation under the Continuous-Flow Process

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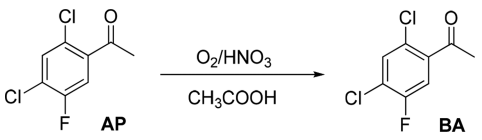
ABSTRACT: A continuous-flow process for the preparation of 2,4-dichloro-5-fluorobenzoic acid (**BA**) has been reported. We chose 2,4-dichloro-5-fluoroacetophenone (**AP**) as starting material and acetic acid as cosolvent to achieve the excellent results in the continuous-flow oxidization system. The nitric acid oxidation of **BA** is a violent exothermic reaction. However, the continuous-flow system includes advantages such as good mass and heat transfer to ensure the safety of the reaction. The influences of different factors, including reactant ratio, temperature, and residence time, were investigated based on single factor tests. The optimal reaction conditions were obtained, in which the yield reached up to 100%. Compared with the traditional tank reactor process, less nitric acid consumption, a higher product yield, less reacting time, being more environmental friendly, and process continuity ensuring higher operation safety are achieved in the continuous-flow system.

INTRODUCTION

During the past decade, heterogeneous gas−liquid oxidation processes played an important role in the fine chemical industry and pharmaceutical industry.[1] In particular, safety advantages were demonstrated for various flow chemistry processes in conducting highly reactive chemical processes, and to date a number of continuous oxidation processes have been reported.[2−6] Oxygen from ambient air is the ultimate "green" oxidant because of its high activity, super abundance, simplicity of operation, and low cost. However, oxidations using molecular oxygen in the presence of organic solvents are associated with safety risks, especially at relatively high temperature and pressure. These hazards can be elegantly avoided by the application of continuous-flow technology. Since the increase of the surface-to-volume ratio is considered to be beneficial for the mass and heat transfer, the possibility of explosion is minimized during the reaction.[7−10]

2,4-Dichloro-5-fluorobenzoic acid is an important pharmaceutical intermediate for drugs, pesticides, and antimicrobial agents.[11,12] Due to its prevalence, numerous procedures for the synthesis of 2,4-dichloro-5-fluorobenzoic acid have been described in literature and patents, such as potassium dichromate oxidation, potassium permanganate oxidation, sodium hypochlorite oxidation, etc. All of these methods could be difficult to industrialize because of serious environmental pollution problems. Furthermore, new reaction routines and techniques are in high demand due to stringent government regulations concerning the emission of chemical wastes and potential safety issues.[13] With the renaissance of flow chemistry, scientists began to focus on applying continuous flow to industrial production. Our research group has been working on continuous-flow synthesis technology and reported a series of practical kilogram-scale continuous-flow processes.[14−16] We would like to apply this technology for the synthesis of 2,4-dichloro-5-fluorobenzoic acid (**BA**) from 2,4-dichloro-5-fluoroacetophenone (**AP**) for industrial production (Scheme 1).

Scheme 1. Oxygen Oxidation of 2,4-Dichloro-5-fluoroacetophenone



Many synthetic methods of **BA** were reported, but these methods required a long reaction time or the use of harsh conditions and toxic reagents, such as heavy metal oxidants,[17−20] which are summarized in Table 1. Without the help of cosolvents, sodium dichromate and potassium permanganate gave a moderate yield, but sodium hypochlorite or nitric acid required the appropriate solvent to achieve better yields. Today, we have developed a continuous-flow process that accomplished nearly full conversion for **BA** within minutes through the oxygen-involved oxidation (Figure 1).

Table 1. Traditional Batch Methodologies for AP Oxidation

entry	oxidants	dosage[a]	T/°C	τ/h	yield/%
1	$KMnO_4$	4:1	50	3	71
2	$Na_2Cr_2O_7$	2:1	50	3	67
3	NaClO	6:1	70	7	17
4	NaClO/PEG	6:1	70	6	78
5	HNO_3/PEG	3:1	55	5	81

[a]Dosage: The molar ratio of oxidant and **AP**.

In the traditional batch reaction to prepare **BA** with nitric acid, nitric acid oxidation is an intense exothermic reaction; therefore, nitric acid was added dropwise into substrate solution of **AP** below 50 °C followed by vigorous stirring at room temperature for several hours. 2,4-Dichloro-5-fluorobenzoic acid was obtained by filtrating the reaction mixture, and large amounts of nitrogen dioxide were released. The heat of reaction had to be removed by a large amount of circulating cooling water. In the design of such a continuous-flow process for **BA**,

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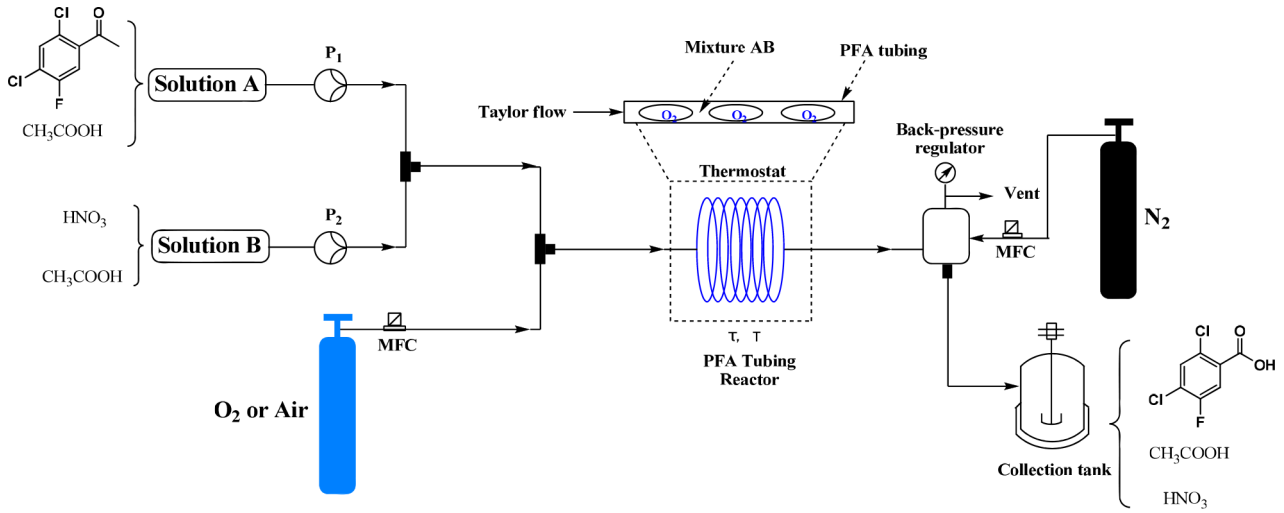

Figure 1. Experimental setup of the continuous-flow oxidation for **AP**. The oxidation reactor is the PFA tube with a 4.35 mm i.d., 6.35 mm o.d., and length 27 m, and P_1 and P_2 at flow rates of 33.3 and 11.1 mL/min, respectively. Liquid and gas flows were adjusted to produce a constant Taylor flow.

our project for the development of a continuous flow synthesis of **BA** is to reduce safety risks and pollutant emissions.

Compared with the **AP** nitric acid oxidation batch processes, continuous-flow gas liquid processes appeared to have more advantages, such as better mass and heat transfer, a larger surface area and volume ratio, and faster mixing.[22−24] These advantages could effectively remove the heat from the vigorous reaction and reduce the risk of flammable organic vapor combustion and even explosion. Among the different flow modes, Taylor flow is a special case of slug flow where the liquid slugs are separated by elongated bubbles. Compared with single-phase laminar flow, Taylor flow has been shown to increase the transfer of heat and mass because of the recirculation within the liquid slugs.[25−28] Therefore, we studied the possibility of oxidation of the **AP** by pure oxygen. In the design of our continuous-flow reactor (Figure 1), we attempt to make it as simple as possible and use cheap PFA tubing with an internal diameter of 4.35 mm to allow simple visual monitoring.

EXPERIMENTAL EQUIPMENT

All reagents, materials, and equipment are purchased from suppliers without further purification.

The experimental setup of the continuous-flow reactor was shown in Figure 1. The equipment consists of two pumps (P_1 and P_2, WOOK WK-100P, China) and oxygen cylinders. Solution A of **AP** in acetic acid and solution **B** of nitric acid were first mixed with a T-mixer (Interchim). A second T-mixer (Interchim) introduced the oxygen. After a residence time, the reaction mixture outflowed the tube and accumulated in the collection tank. The reaction mixture was analyzed by HPLC. The mixture was cooled in the collection tank. The solid was isolated by centrifugation, and the filtrate can be recycled. A nitrogen mass flow meter (Seven-star mass-flow meter) was used, and a micrometering valve controlled the pressure regulator for back pressure. The HPLC analysis was carried out on an Agilent 6890 system equipped with an XDB-C18 250 mm × 4.6 mm column. The conversion of **AP** was determined on the basis of the normalized peak areas for **AP** and **BA**.

RESULTS AND DISCUSSION

The experimental parameters such as reaction temperature, residence time, varying molar ratio of acids, and oxygen pressure or air pressure were systematically optimized under convenient continuous-flow conditions. The effect of varying the residence time and the temperature on conversion of **AP** is shown in Figure 2. Preliminary experiments were started with

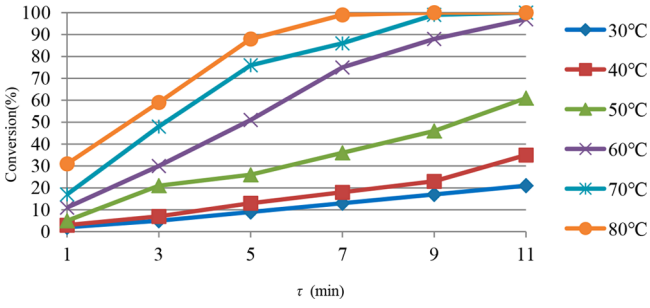

Figure 2. Effect of temperature and residence time on the oxidation with an O_2/AP molar ratio of 2:1 and 0.3 equiv of 50% HNO_3; conversion was determined by HPLC.

PFA tubing (internal diameter of 4.35 mm, length of 27 m), an oxygen pressure of 2 bar, and 1 M **AP** in acetic acid. A constant Taylor flow was generated by adjusting the flow of liquid and gas, and an excess of oxygen compared to the **AP** was used (O_2/**AP** molar ratio of 2:1). After the residence time, the mixture was collected in a 10 L collection vessel with a cooling jacket. The mixture was analyzed by HPLC, and the results were as follows.

Figure 2 shows the influence of temperature and residence time on oxidation. It is known, on the basis of the Arrhenius equation, that the reaction rate increases with temperature. When the reaction temperature was below 50 °C, the reaction rate was slow with a low conversion rate. As the reaction temperature was increased (higher than 70 °C), conversions up to 100% were obtained for **AP** in acetic acid with a residence time of 9 min (Figure 2).

As expected from previous studies, oxidation of **AP** can be performed without metal catalysts.[29] We chose nitric acid as the

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reaction catalyst which is a cheap and easy-to-recover catalyst, using the continuous-flow reactor. The nitric acid catalyst strongly enhanced the rate of oxidation of **AP**, and 60% of conversion could be obtained in less than 10 min, with 10% of nitric acid. Quantitative conversion was obtained with 50% of nitric acid.

Above 2 bar of oxygen and 70 °C, no noticeable improvement in the conversion was observed (Figure 2 and Table 2). While the small online continuous-flow system effectively reduced the risk of combustion and explosion, a reaction temperature higher than 70 °C and system pressure higher than 5 bar were not investigated to reduce the potential for risk.

Table 2. Continuous-Flow Oxidation of AP under Oxygen[a]

sub	HNO_3/%	O_2/bar	T/°C	τ/min	conversion/%
1	0	2	70	9	0
2	10	2	70	9	60
3	30	2	70	9	82
4	50	2	70	9	99
5	50	1	70	9	75
6	50	3	70	9	100
7	50	3	60	9	91
8	50	5	60	9	97

[a]All reagents except oxygen were premixed before use. Conditions: **AP**/acetic acid (1:3 v/v), 2 equiv of O_2, and 0.3 equiv of HNO_3. Reported conversions are HPLC conversions.

By analyzing the experimental data, we could infer that the whole conversion rate was controlled by the mass transfer of oxygen showing the limit of the Taylor flow regime to ensure a high enough mass transfer rate under the chosen experimental conditions (concentration, temperature, channel diameter, and flow velocity).

The use of ambient air to replace oxygen had both economic and safety advantages, so we diverted our attention to the presence of air in a continuous flow reaction. Oxidation of **AP** with air in acetic acid was completed within 10 min. The maximum conversion of **AP** was accomplished as 93% using 5 bar of air and a 9 min residence time by using 50% nitric acid. We also attempted to obtain better conversion rates by increasing the concentration of nitric acid, but no obvious improvement occurred, which showed using air was not as efficient as using oxygen. The extension of residence time and increase in system pressure did not improve the performance of the reaction. These results appeared in Table 3.

Comparison with the reaction performed in a batch manner is shown in Table 4. The continuous-flow progress appears to exhibit many advantages, including giving better reaction yields,

Table 3. Continuous-Flow Oxidation of AP under Air[a]

sub	HNO_3/%	air/bar	T/°C	τ/min	conversion/%
1	50	2	70	9	67
2	50	4	70	9	86
3	50	5	80	9	92
4	68	2	70	9	69
5	68	4	70	9	87
6	68	5	80	9	93

[a]All reagents except air were premixed before use. Conditions: **AP**/acetic acid (1:3 v/v), 2 equiv O_2, and 0.3 equiv HNO_3. Reported conversions are HPLC conversions.

Table 4. Comparison of the Batch Process with Continuous-Flow Process

	Operation manner	
	batch	continuous flow
yield (%)	81.2	99.9
purity (%)	99.8	99.8
reaction time	5 h	9 min
reaction temperature	50 °C	70 °C

raising the reaction temperature to increase the reaction rate, shortening the reaction time, and saving energy consumption. The much higher surface-to-volume ratio under flow conditions renders highly efficient heat transfer. In addition, the smaller online reaction system effectively reduces the safety risk of violent exothermic reactions in the continuous-flow manner. The output of the continuous-flow process was 2.7 kg/h in a 402 mL reactor and can easily be scaled up by prolonging the running time or operating several reactors in parallel.

Recycling of Filtrate. In order to realize clean cycle production, we attempted to recycle the filtrate. We have established the filtrate of the experiment, and we have set up a recycling experiment device (Figure 3). The filtrate consists of 50% nitric acid, acetic acid, **BA**, and a trace of **AP**. Recycling experiments were carried out under the above-mentioned optimal reaction conditions. Below 30 °C, **AP** barely reacted with nitric acid. Therefore, we first premixed the filtrate and **AP** in the reaction kettle and then the mixture was pumped into the tube reactor via the second T-mixer by P_1. Oxygen was introduced to the tube reactor via the Sevenstar mass-flow controller and the second T-mixer. The results after four recycling experiments are shown in Table 5. The quality of the product significantly decreased. The decrease in purity was mainly attributed to the decreasing conversion rate, and the decrease in conversion rate was mainly attributed to the decreasing nitric acid concentration. As the reaction proceeded, the decreasing nitric acid concentration resulted due to the water produced by the reaction and the volatilization of nitric acid in the post-treatment process. It could be solved by adding the proper amount of nitric acid.

CONCLUSION

In conclusion, we have demonstrated that 2,4-dichloro-5-fluoroacetophenone (**AP**) could be safely and readily transformed into 2,4-dichloro-5-fluorobenzoic acid (**BA**) using molecular oxygen in flow. The reaction conditions were optimized, and full conversion toward carboxylic acid was obtained at 70 °C using 2 bar of pressure. Air instead of molecular oxygen gave rise to a similar result. Comparison of the batch process with continuous-flow processes revealed that the continuous flow was safer and easy to operate and gave a high product yield with high purity.

EXPERIMENTAL SECTION

All reagents, materials, and equipment were purchased from suppliers without further purification.

HPLC analysis for **BA** was carried out on an Agilent 6890 system equipped with an XDB-C18 250 mm × 4.6 mm column and detected at 242 nm. Melting points were determined on a BUCHI Melting Point M-560 apparatus and were not corrected.

Batch Experiment. The experiment was conducted in a 1 L thermo-regulated stainless steel autoclave (600 mL useful

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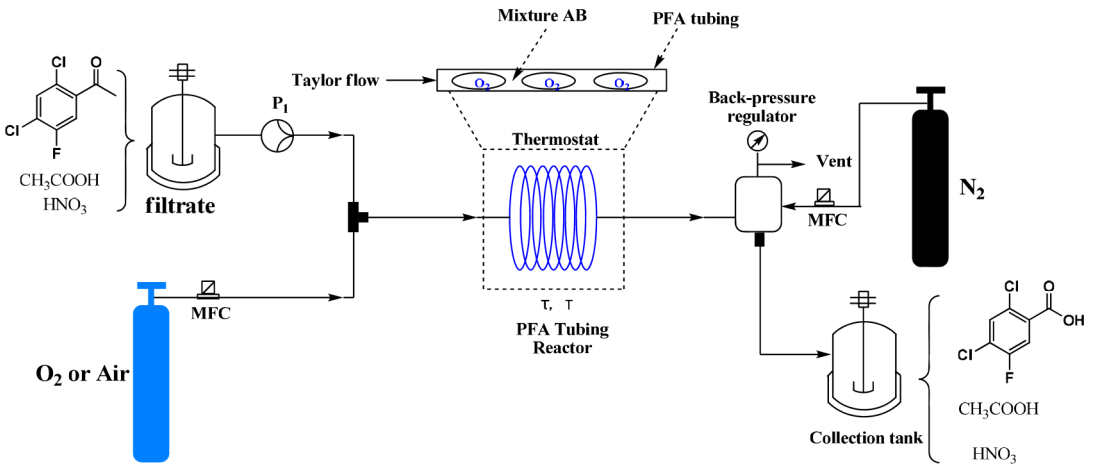

Figure 3. Experimental setup for the recycling of filtrate.

Table 5. Filtrate of Recycling Experiments[a]

recycling times	Conversion of **BA** (%)	purity of **BA** (%)
1	98	99.0
2	97	98.2
3	97	98.0
4	96	98.0

[a]All reagents except oxygen were premixed before use. Conditions: *T* = 70 °C, residence time 9 min, **AP**/filtrate (1:3 v/v), 2 equiv of O_2. Reported conversions are HPLC conversions.

capacity) operating in batch mode. A mixture of 50% aqueous acetic acid (360 g, 4 mol acetic acid), nitric acid (0.5 mol, 64 g, 50%), and **AP** (207 g, 1 mol) was placed in a 1 L agitated stainless steel autoclave and stirred to a homogeneous liquid. The reaction temperature was set to 50 ± 5 °C, and then oxygen was introduced into the reactor continuous with oxygen cylinders. The mixture was stirred powerfully at 400 r/min for 5 h, and a large amount of white solid precipitated. The mixture was filtrated with suction, using Büchner funnels, and the filtrate can be recycled. The white needle crystals were washed with 100 mL of water and dried in vacuum. This resulted in 169.7 g of **BA**, with an isolated yield of 81.2%. The product **BA** was analyzed at the end of each experiment using an Agilent 6890 HPLC, with 99.8% HPLC purity.

Continuous-Flow Experiment. Solution A of **AP** (1035 g, 5 mol) in 900 g acetic acid and solution B of nitric acid (2.5 mol, 320 g, 50%) were pumped into the tube reactor (PFA, 4.35 mm i.d., 6.35 mm o.d., length 27 m) via a T-mixer by P_1 and P_2 at flow rates of 33.3 and 11.1 mL/min, respectively, and the oxygen (Seven-star mass-flow meter) weas fed via two separate lines and brought together using another T-mixer. A back pressure of 2 bar was applied using a back pressure regulator controlled with a nitrogen flow (Sevenstar massflow controller) and micro-metering valve. The outlet port of the tube reactor was connected to a 10 L collection vessel with a cooling jacket. Liquid phase was retrieved from back-pressure regulator and could be further analyzed by an Agilent 6890 HPLC. The general experimental procedure is as follows. **AP** and the mixture (nitric acid and 50% aqueous acetic acid) were loaded in 2 and 4 L glass flasks respectively, and oxygen (Sevenstar mass-flow controller) was pumped into the tube reactor via the second T-mixer. The residence time control was achieved by varying the flow rate of the organic phase and oxygen. The conversion of **AP** was determined on the basis of the normalized peak areas for **AP** and **BA** obtained by HPLC. The suspension was cooled in the collection tank. The solid was isolated by centrifugation, and the filtrate can be recycled. The white needle crystals were washed with 1 L of water and dried in vacuum. This resulted in 972.9 g of **BA**. If we evaporated the acetic acid in the filtrate, we obtain 72 g of white solid **BA** by BUCHI rotary evaporator, with an isolated total yield of up to 99.9%; the product **BA** was analyzed at the end of each experiment using an Agilent 6890 HPLC, with 99.8% HPLC purity: bp 140.8−142.1 °C (lit.[19] bp: 141.3−142.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.61 (d, 1H, J = 7.2 Hz), 8.01 (d, 1H, J = 9.8 Hz).

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Notes

The authors declare no competing financial interest.

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