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# Continuous-Flow Processes for the Production of Floxacin Intermediates: Efficient C–C Bond Formation through a Rapid and Strong Activation of Carboxylic Acids

Shao-Zheng Guo[1] Zhi-Qun Yu[2] Wei-Ke Su[2]*

[1] College of Chemistry and Chemical Engineering, Shaoxing University, Shaoxing 312000, People's Republic of China
[2] Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China

**Address for correspondence** Wei-Ke Su, PhD, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China (e-mail: pharmlab@zjut.edu.cn).

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## Abstract

The development of highly efficient C–C bond formation methods for the synthesis of ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-(dimethylamino)acrylate **1** in continuous flow processes has been described, which is based on the concept of rapid and efficient activation of carboxylic acid. 2,4-Dichloro-5-fluorobenzoic acid is rapidly converted into highly reactive 2,4-dichloro-5-fluorobenzoyl chloride by treating with inexpensive and less-toxic solid bis (trichloromethyl)carbonate. And then it rapidly reacts with ethyl 3-(dimethylamino)acrylate to afford the desired **1**. This process can be performed under mild conditions. Compared with the traditional tank reactor process, less raw material consumption, higher product yield, less reaction time, higher operation safety ensured by more the environmentally friendly procedure, and process continuity are achieved in the continuous-flow system.

**Keywords**
- continuous flow
- acylation
- C–C coupling
- floxacin
- BTC

## Introduction

The third-generation quinolone drugs have been widely used for their wider antibacterial spectrum and stronger antimicrobial effect. Ethyl 3-(2,4-dichloro-5-fluorophenyl)-2-((dimethyl- amino)methyl)-3-oxopropanoate (**1**) is a key and common intermediate for the synthesis of the third-generation quinolone drugs Norfloxacin, Ciprofloxacin, Pefloxacin, and Fleroxacin (►**Fig. 1**).[1–4] There have been many reports about the synthesis of **1**. In traditional synthetic methods, 2,4-dichloro-5-fluorobenzoic acid is converted into highly active 2,4-dichloro-5-fluorobenzoyl chloride with large amounts of thionyl chloride or phosphorous pentachloride. These methods generate a large amount of acid waste and require cumbersome postprocessing to treat the waste. In addition, stricter regulations on chemical waste emissions and potential safety issues have necessitated high standard new reaction routes and technologies to be installed in commercial settings.[5–9]

Phosgene has been used extensively as a gaseous dehydrating agent. However, the use of phosgene has always been challenging in both academia and industry due to its high toxicity.[10] During the last decade of the 20th century, bis (trichloromethyl)carbonate (BTC) has become a more commonly used phosgene substitute.[11] It is widely used in the production of active pharmaceutical ingredients, agricultural chemicals, polymers, and fine chemicals.[12–14] Herein, we report an efficient C–C bond formation based on the concept of rapid activation of carboxylic acids with BTC to produce floxacin intermediates **1**. This activation strategy only generates $CO_2$ and HCl as byproducts, making its utilization as a C–C coupling agent very interesting.

With the development of flow chemistry, scientists have begun to focus on applying continuous flow to the industrial production of chemicals. Continuous flow with a small online volume has garnered much attention as a way to minimize the risks associated with hazardous compounds. In particular, continuous-flow synthesis that enables continuous in situ

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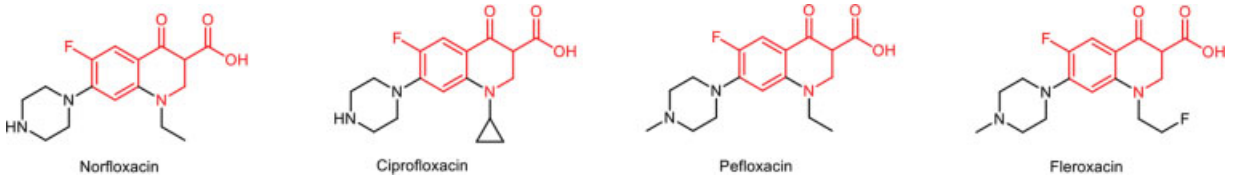



**Fig. 1** Norfloxacin, Ciprofloxacin, Pefloxacin, and Fleroxacin.

generation and consumption of hazardous gas within a closed system is extremely valuable.[15–17] It would be highly desirable to construct a continuous-flow system consisting of simple, inexpensive parts. This system can generate a near-equimolar amount of phosgene relative to a substrate and then consumes it completely in the subsequent reaction. Our group has been committed to developing continuous-flow synthesis technology and has reported several practical kilogram-scale continuous-flow processes.[18–21] We herein describe a practical process which is based on the concept of rapid activation of carboxylic acid. 2,4-Dichloro-5-fluorobenzoic acid is rapidly converted into highly reactive 2,4-dichloro-5-fluorobenzoyl chloride by treating with inexpensive and less-toxic BTC, and it then rapidly reacts with ethyl 3-(dimethylamino)acrylate to afford the desired compound **1**.

## Materials and Methods

### Material

2,4-Dichloro-5-fluorobenzoic acid (**2**) (99.5%, high-performance liquid chromatography, HPLC) and other reagents were purchased from commercial sources and were used without further purification. Pumps and perfluoroalkoxy (PFA) tubing were obtained from the supplier. The continuous-flow reactor that was used to test our concept is shown in ►**Fig. 2**. The equipment consists of four pumps ($P_1$, $P_2$, $P_3$, and $P_4$; WOOK WK-100P, China), two thermostats, and a gas recovery unit. The HPLC analysis was performed on an Agilent 6890 system equipped with a XDB-C18 250 mm $\times$ 4.6 mm column. The conversion of **1** was determined on the basis of the normalized peak areas for **3**, **2**, and **1**.

Two T-shape mixers were connected with PFA tubing and then immersed in an oil bath (100°C). Solution A of carboxylic acid was introduced into the first mixer with a pump. Solution B of BTC was also introduced into the first mixer with a pump. It was speculated that the phosgene, generated in situ by the reaction of BTC with the base, converted 2,4-dichloro-5-fluorobenzoic acid into 2,4-dichloro-5-fluorobenzoyl chloride.[12,15,17] To accomplish C–C coupling, solution C of ethyl 3-(dimethylamino)acrylate was then introduced into the second mixer with a pump. The reaction was quenched by pouring the mixture into a saturated aqueous solution of NaCl. In principle, this method only emits $CO_2$ and HCl salts of a base as waste.

### Experimental Section

All chemicals were purchased from commercial sources and were used without further purification. HPLC analysis for **1** was performed on an Agilent 6890 system equipped with a XDB-C18 250 mm $\times$ 4.6 mm column. Melting points were determined on a BUCHI Melting Point M-560 apparatus and were not corrected.

### Batch Experiment

A mixture of 2,4-dichloro-5-fluorobenzoic acid (209 g, 1.0 mol), DMF (5 mL), and chlorobenzene (300 mL) was stirred at 80°C in a 2 L glass flask and a solution of BTC (0.34 mol, 101 g) and chlorobenzene (200 mL) was added dropwise via an addition funnel over 30 minutes. Then the mixture was placed in an oil bath at 105 to 110°C, off-gas was absorbed by sodium hydroxide solution. After 3 hours, the mixture was cooled to room temperature.

A mixture of ethyl 3,3-dimethylaminoacrylate (143 g, 1 mol) and triethylamine (212.1 g, 2.1 mol) was stirred at room temperature and a mixture of the first step was added dropwise via an addition funnel over 20 minutes. The orange–yellow solution that formed was placed in an oil bath at 85 to 90°C. After

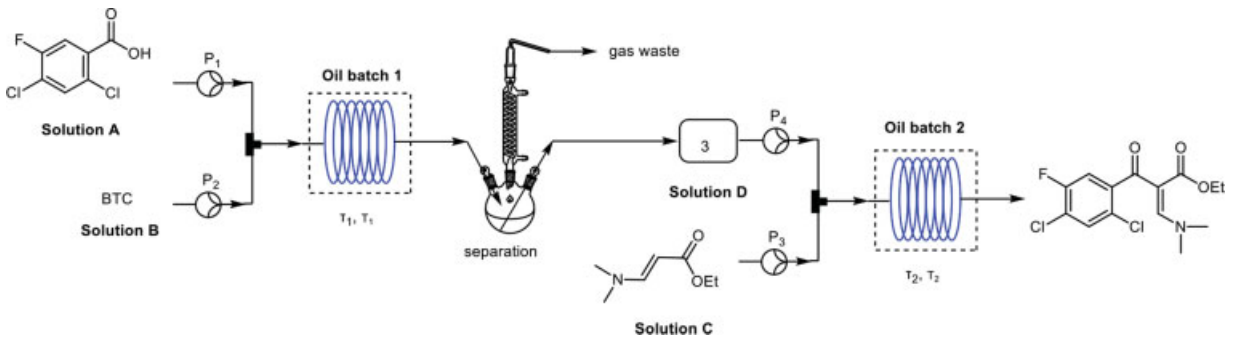



**Fig. 2** Continuous-flow synthesis of **1** from carboxylic acid **2** via in situ formation of acyl chloride by using BTC. BTC, bis(trichloromethyl) carbonate.

3 hours, the saffron mixture was concentrated and filtered, then washed with water (3 × 100 mL), and obtained the tan solid product in 67.8% yield (226.5 g). Recrystallization from 4:1 hexanes/EtOAc gave the product as an off-white solid, Mp: 93.8 to 94.6°C (lit27 mp: 94–95°C).

### Continuous-Flow Experiment

As shown in ►**Fig. 2**, solution A of **2** (1,045 g, 5 mol) in 2 L chlorobenzene and solution B of BTC (1.7 mol, 504.9 g) and 10 mL DMF in 1 L chlorobenzene were pumped into the tube reactor (PFA, 4.35 mm i.d., 6.35 mm o.d., Q4length 12 m) via a T-mixer by $P_1$ and $P_2$ at flow rates of 29.4 and 15.0 mL/min, respectively, after a residence time of approximately 3 minutes at 110°C, in residence thermostat I; the reaction mixture outflowed the tube, separation of gas phase and liquid phase was performed, off-gas was absorbed by sodium hydroxide solution, liquid phase (solution D) and solution C of ethyl 3,3-dimethylaminoacrylate (715 g, 5 mol) and triethylamine (525.2 g, 5.2 mol) in 1 L chlorobenzene were pumped into the tube reactor (PFA, 4.35 mm i.d., 6.35 mm o.d., length 20 m) via another T-mixer by $P_4$ and $P_3$ at flow rates of 17.8 and 11.8 mL/min, respectively; after a residence time of 10 minutes at 100°C, the reaction mixture outflowed the tube and accumulated in the collection tank, separation of water phase and organic phase was performed, the organic phase was washed with water (3 × 500 mL), the light yellow organic-phase decompression and steam out most solvents and was filtered, and dried under vacuum to give the tan solid product in 82.7% yield (1,381.1 g) with 99% HPLC purity: mp 93.8–94.6°C (lit2 mp: 94–95°C). $^1$H NMR (400 MHz, $CDCl_3$) δ/ppm: 1.03 (t, 3H, $J$ = 7.1 Hz), 2.98 (s, 3H), 3.39 (s, 3H), 3.98 (q, 2H, $J$ = 7.1 Hz), 7.19 (d, 1H, $J$ = 8.7 Hz), 7.37 (d, 1H, $J$ = 6.4 Hz), 7.86 (s, 1H).

## Results and Discussions

### Adapting the Batch Chemistry to Continuous Flow

For preparation of intermediate **1** in the traditional batch reactor, acylation with thionyl chloride or phosphorus pentachloride was generally performed by refluxing at 80°C for more than 3 hours, which was followed by coupling at a mild temperature (**Scheme 1**). The amount of thionyl chloride used for acylation was 4 equivalents or more. The large excess of thionyl chloride was quenched at the end of the reaction and the production of phosphorous and sulfur-containing waste is troublesome. Nowadays, BTC is used to replace thionyl chloride for acylation in the traditional batch reactions, generating carbon dioxide, hydrogen chloride, and a trace amount of unreactive phosgene as byproducts. Considering the toxicity of phosgene, a continuous-flow reaction which is easy to control by a distributed control system (DCS) was adapted. Experimental details are presented in the Experimental Section.

**Table 1** Continuous-flow acylation with various solvents and catalysts

| Entry | Solvent | Catalyst | Conversion/% |
|---|---|---|---|
| 1 | Chlorobenzene | Pyridine | 73 |
| 2 | Toluene | Pyridine | 69 |
| 3 | 1,4-Dioxane | Pyridine | 48 |
| 4 | MeCN | Pyridine | 39 |
| 5 | Chlorobenzene | DMF | 82 |
| 6 | Toluene | DMF | 80 |
| 7 | 1,4-Dioxane | DMF | 52 |
| 8 | MeCN | DMF | 47 |

Note: Conditions: flow rate A: 29.4 mL/min, flow rate B: 15.0 mL/min, BTC 0.35 equivalent, 70°C. All reagents were premixed before use. Reported conversions are HPLC conversions.

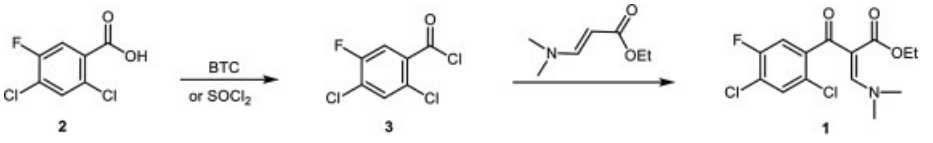
### Optimization of Continuous-Flow Acylation

We first studied the first step of the acylation reaction. The effects of solvents and catalysts were examined, and the results are shown in ►**Table 1**. All experiments were performed at $T_1$ = 70°C for 1.62 minutes. The reaction mixture outflowed the tube and off-gas was absorbed by sodium hydroxide solution; the organic phase was analyzed by HPLC as shown in ►**Fig. 2**. As expected, acylation of **2** can be performed with BTC. Cheap and readily available DMF or pyridine was chosen as the reaction catalyst, making industrialization easy. When the solvent was chlorobenzene, better yields were obtained (►**Table 1**, entries 1 and 5). And DMF turned out to be a better catalyst (►**Table 1**, entry 5).

Continuous-flow synthesis of **3** was examined using a combination of BTC and DMF in chlorobenzene as shown in ►**Table 2**. Elevated reaction temperature or extended residence time gave better yield of **3**. Maximum conversion of **2** was obtained at 110°C with 1.62 minutes of residence time. There was no obvious improvement with further extended residence time.

### Optimization of Continuous-Flow Coupling Reaction

The effect of different bases on coupling reactions was examined, and the results are shown in ►**Table 3**. All experiments were performed at $T_2$ = 80°C for 10 minutes, the




**Scheme 1** Synthetic routes of **1** from carboxylic acid **2** via in situ formation of acyl chloride by using BTC. BTC, bis(trichloromethyl)carbonate.

**Table 2** Optimization of residence time and temperature in continuous-flow acylation

| Entry | *T*/°C | *t*/min | Conversion/% |
|---|---|---|---|
| 1 | 50 | 0.81 | 41.4 |
| 2 | 50 | 1.62 | 67.3 |
| 3 | 70 | 2 | 63.6 |
| 4 | 70 | 1.62 | 82.6 |
| 5 | 90 | 0.81 | 68.1 |
| 6 | 90 | 1.62 | 91.1 |
| 7 | 110 | 0.81 | 75.6 |
| 8 | 110 | 1.62 | 98.9 |
| 9 | 110 | 2.43 | 98.9 |

Note: Conditions: flow rate A: 29.4 mL/min, flow rate B: 15.0 mL/min, BTC 0.35 equivalent. All reagents were premixed before use. Reported conversions are HPLC conversions.

**Table 3** Continuous-flow C–C bond formation with various bases

| Entry | Base | *t*/min | Conversion/% |
|---|---|---|---|
| 1 | DMF | 10 | 32.5 |
| 2 | Pyridine | 10 | 28.2 |
| 3 | *N*-Methylpiperidine | 10 | 52.4 |
| 4 | *N*-Methylpyrrolidine | 10 | 46.6 |
| 5 | DABCO | 10 | 0 |
| 6 | $Et_3N$ | 10 | 71.9 |
| 7 | DIEA | 10 | 69.3 |
| 8 | LiOH | 10 | 0 |

Abbreviations: DABCO, 1,4-diazabicyclo-[2,2,2]octane, DIEA, *N*,*N*-diisopropylethylamine, DMF, *N*,*N*-dimethylformamide.
Note: Conditions: flow rate A: 29.4 mL/min, flow rate B: 15.0 mL/min, ethyl 3-(dimethylamino)acrylate 1 equivalent. All reagents were premixed before use. Reported conversions are HPLC conversions.

reaction mixture outflowed the tubing, and the organic phase was analyzed by HPLC as shown in ►**Fig. 2**. When $Et_3N$ and DIEA (*N*,*N*-diisopropylethylamine) were used as a base, the coupling reaction gave better results (►**Table 3**, entries 6 and **7**). Therefore, $Et_3N$ was chosen as the acid-binding agent and catalyst for the coupling reaction.

The residence time and temperature were also examined as shown in ►**Table 4**. Higher reaction temperature and extended residence time were beneficial to the generation of target products **1**. When the reaction temperature was raised to 100°C and the residence time was set at 4 minutes, the conversion of **2** could reach 84.8%.

The results of comparison between batch and continuous processes are summarized in ►**Table 5**. Obviously, better results were obtained when using the continuous process. Due to BTC, the concentration of a saturated atmosphere is 4.2 g/m$^3$ at room temperature, approximately 100 times higher than the $LC_{50}$ value for rats.[22] Although it is solid, it has a low but significant vapor pressure and sublimes. The continuous-flow process involves a much smaller volume and online reaction volume and can be easily controlled by DCS control.

**Table 4** Optimization of residence time and temperature in continuous-flow C–C bond formation

| Entry | *T*/°C | *t*/min | Conversion/% |
|---|---|---|---|
| 1 | 60 | 5 | 55.2 |
| 2 | 60 | 10 | 61.1 |
| 3 | 60 | 15 | 67.3 |
| 4 | 80 | 5 | 57.2 |
| 5 | 80 | 10 | 71.9 |
| 6 | 80 | 15 | 73.4 |
| 7 | 100 | 5 | 62.4 |
| 8 | 100 | 10 | 84.8 |
| 9 | 100 | 15 | 84.8 |

Note: Conditions: flow rate A: 29.4 mL/min, flow rate B: 15.0 mL/min, ethyl 3-(dimethylamino)acrylate 1 equivalent. All reagents were premixed before use. Reported conversions are HPLC conversions.

**Table 5** Comparison between batch process and continuous process

| Operation | Acylation | Coupling | |
|---|---|---|---|
| | HPLC yield (%) | HPLC yield (%) | Isolated yield (%)[a] |
| Batch process | 92.1 | 71.2 | 67.8 |
| Continuous process | 98.9 | 84.6 | 82.7 |

[a]Yield was calculated from **2**.

## Conclusion

In conclusion, we have demonstrated that 2,4-dichloro-5-fluorobenzoic acid **2** was rapidly converted into highly reactive 2,4-dichloro-5-fluorobenzoyl chloride by treating with inexpensive and less-toxic solid BTC. And then it rapidly reacted with ethyl 3-(dimethylamino)acrylate to afford the desired ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-(dimethylamino)acrylate **1** in continuous-flow processes. The reaction conditions were optimized and a high conversion of 82.7% was obtained under 100°C. This process can easily be scaled up by increasing the reactor size or operating several reactors with high throughput in parallel. The larger scale experiment is still in progress.

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Conflict of Interest
The authors declare no competing financial interest.

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