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A NOVEL AND PRACTICAL SYNTHETIC PROCESS FOR FLUOPYRAM

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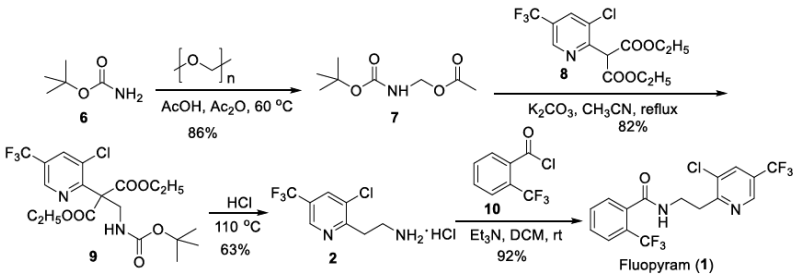
A novel and environment-friendly synthetic process for the nematicidal and fungicidal fluopyram (**1**) has been developed. In the previous methods, the synthesis of the key intermediate 2-(3-chloro-5-(trifluoromethyl) pyridin-2-yl)ethanamine (**2**) is a main challenge due to the long synthesis routes, complicated process, difficulty in purification, and low yield. In this study, a carbamate is used as the starting material to synthesize this intermediate **2**, which innovatively simplify the synthetic route, avoid dangerous hydrogenation processes and expensive catalysts, and thereby reduced the risks and costs in industry. Additionally, the intermediate **2** is obtained in a form of hydrochloride salt, which greatly facilitates the purification and provides a convenient synthesis route for fluopyram (**1**). Furthermore, the reactants in this process can be recycled and reused, to minimize wastes and adhere to the principles of green chemistry.



INTRODUCTION

Fluopyram (**1**) is a novel benzamide fungicide, known as the first nematicide specifically targeting mitochondrial complex II.[1] Its unique mechanism of action, extensive control range, diverse modes of action, high nematicidal activity, and low toxicity endow it with significant advantages in the prevention and control of pests and diseases in the forestry and fruit industry,[2–5] making it highly valuable in the pesticide market. Currently, there are a few reported synthesis routes for fluopyram (**1**). The exploration and research on these routes undoubtedly provide strong technical support for the industrial production of fluopyram (**1**). In these routes with industrial application value, the synthesis of the key intermediate 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (**2**) is particularly important.[6–10]

In 2004, it was reported to utilize 2,3-dichloro-5-(trifluoromethyl)pyridine (**3**) as the starting material for the synthesis of fluopyram (Fig. 1).[6] The compound **3** underwent condensation with ethyl cyanoacetate followed by hydrolysis and decarboxylation, yielding 2-cyanomethyl-3-chloro-5-(trifluoromethyl)pyridine (**4**). Subsequently, a palladium-carbon catalytic hydrogenation process was employed to reduce **4**, during which the amine group was simultaneously protected by acetyl. The protective group was then removed under acidic

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conditions, resulting in the formation of the key intermediate **2**. The intermediate **2** subsequently underwent amidation to yield fluopyram (**1**). However, this synthetic route suffered some disadvantages. Firstly, it comprises several steps, including incomplete condensation, hydrolysis, and hydrogenation, which contribute to a high content of by-products. Secondly, the hydrogenation of cyano requires the use of expensive metal catalysts and high pressure, leading to significant equipment investments and relatively steep costs. Furthermore, the overall yield of this route is rather low. Additionally, the necessity to protect the amine group and subsequent deprotection increases complexity of the process.

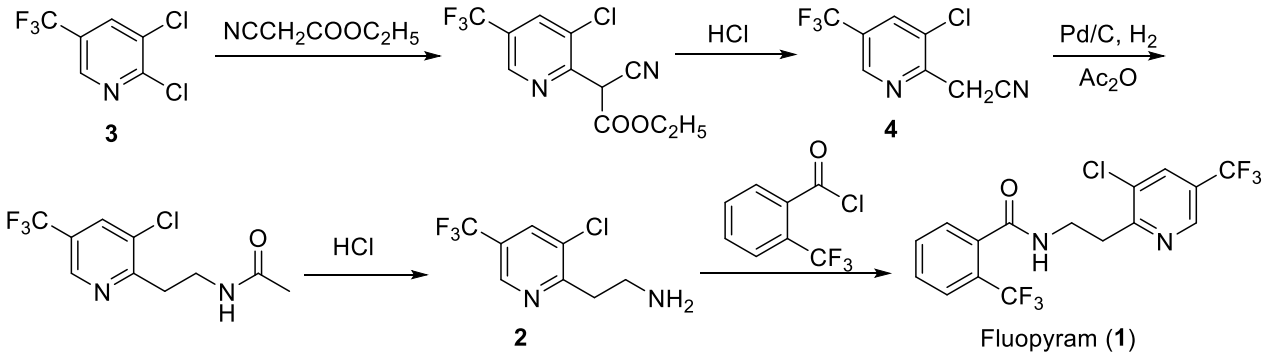

Fig. 1 – Hydrogenation route of fluopyram (**1**).

In 2010, Fodor *et al.* reported a synthetic route for the crucial intermediate 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (**2**) of fluopyram starting from 2,3-dichloro-5-(trifluoromethyl)pyridine (**3**) (Fig. 2),[7] in which **3** initially reacted with diethyl malonate, followed by a condensation reaction with 2-(chloromethyl) phtalimide (**5**), then hydrolysis and hydrazinolysis. These reactions resulted in the formation of the intermediate **2**. However, this synthetic route also has some disadvantages, such as the relatively lengthy reaction steps, the use of expensive compound **5**, and the difficulty of purifying the intermediates.

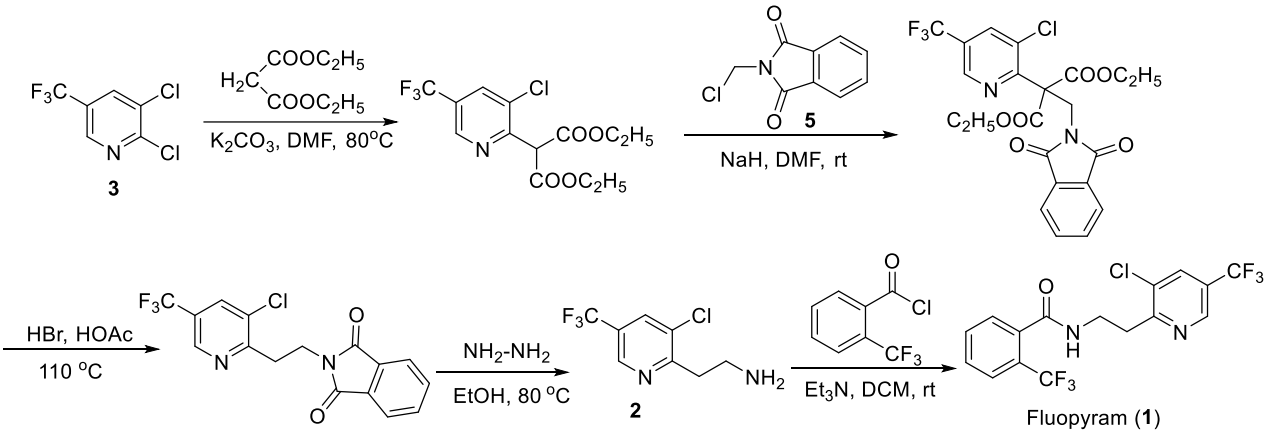

Fig. 2 – Hydrazinolysis route of fluopyram (**1**).

To address the issues of the lengthy synthesis process, high costs, and low yield encountered in the current technological approaches for synthesizing fluopyram (**1**) and its key intermediate **2**, we innovatively designed a new route for preparing them (Fig. 3). This route uses a carbamate as the starting material, mainly involving hydroxymethlylation and condensation reactions, followed by hydrolysis and decarboxylation, to successfully obtain the intermediate **2**. This route not only exhibits high safety and environmental friendliness but also achieves a breakthrough in high yield. Furthermore, we conducted a thorough optimization of each step in the synthesis route, carefully screening critical conditions such as reaction time, temperature, feedstock ratio, and so on, which could effectively reduce industrial production costs and provide a more efficient and economical method for the synthesis of fluopyram (**1**).

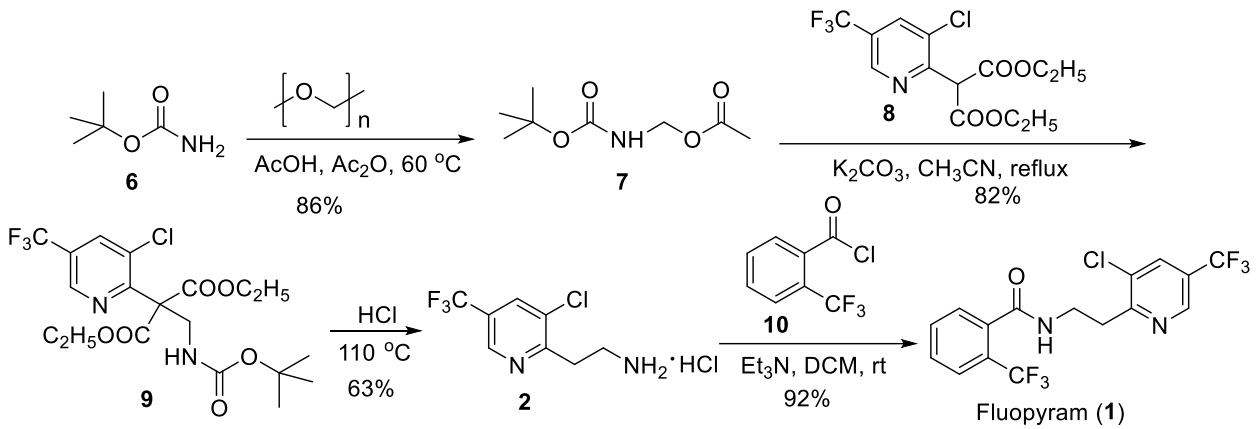

Fig. 3 – The novel synthetic route of fluopyram (**1**).

RESULT AND DISCUSSION

Synthesis of fluopyram (1) using *tert*-butyl carbamate (6) as starting material

We first choose *tert*-butyl carbamate (**6**) as a model starting material for this novel synthesis route, as depicted in Scheme 3. The compound **6** was transformed to ((*tert*-butoxycarbonyl)amino) methyl acetate (**7**) through a one-pot methodology involving hydroxymethylation and subsequent esterification,[11-12] to simplify the process. After that, **7** undergoes a condensation reaction with 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**8**) to generate 2-(((*tert*-butoxycarbonyl) amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**9**). Subsequent hydrolysis of **9** afforded the crucial intermediate **2** in a form of hydrochloride salt. Finally, the amidation of **2** with 2-trifluoromethylbenzoyl chloride (**10**) produced fluopyram (**1**). The reaction conditions in each step were then carefully investigated as follows.

Optimization of synthesis conditions for ((*tert*-butoxycarbonyl)amino)methyl acetate (7)

In an acidic environment, the amino group of *tert*-butyl carbamate (**6**) reacts with formaldehyde (POM) to form hydroxylated intermediates, which then undergo esterification to produce ((*tert*-butoxycarbonyl)amino)methyl acetate (**7**).[13] It was found that the yield of **7** was significantly influenced by the ratio of raw materials and the reaction temperature. To investigate the effect of reactant ratios on the reaction, a series of experiments were conducted, and the results are presented in Table 1. It was observed that the yield gradually increased with the addition of acetic anhydride (Ac_2O) at 60 °C. When the molar ratio of **6**, POM, and Ac_2O reached 1:1.1:28.5, the yield remained almost unchanged. However, as the temperature increased, the yield gradually decreased, accompanied by the formation of more impurities and an increase in pigmentation. Therefore, the optimal ratio of reactants was determined to be n (**6**):n (POM):n (Ac_2O) = 1:1.1:28.5, with a reaction temperature of 60 °C.

Table 1

Effect of material ratio and reaction temperature on the yield of **7** [a]

Entry	n (6):n (POM):n (Ac_2O)	T (°C)	Yield (%)
1	1:1.1:16	60	63
2	1:1.1:20	60	75
3	1:1.1:24	60	83
4	1:1.1:28.5	60	87
5	1:1.1:28.5	70	87
6	1:1.1:28.5	80	85

[a]Reaction conditions: **6** (42.68 mmol), AcOH (38 mL), reaction for 48 h.

Optimization of synthesis conditions for 2-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (9)

The α-hydrogen in the structure of 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**8**) exhibits prominent acidic properties.[14] In an alkaline environment, **8** generates a carbanion, which subsequently launches a nucleophilic attack on ((*tert*-butoxycarbonyl)amino)methyl acetate (**7**), successfully leading to a condensation product 2-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**9**).[15] Initially, we employed molar ratio of 1.3:1 between compound **7** and **8**, and conducted the reaction at reflux. To ensure smooth performance of

the reaction, K_2CO_3 was chosen as the acid-binding agent, and a weakly alkaline solvent was selected to maintain an optimal reaction environment. As shown in Table 2, the results indicated that using acetonitrile (ACN) as the solvent achieved a slightly higher yield and significantly reduced the reaction time. So we selected ACN as the solvent and conducted the reaction under reflux conditions.

Table 2

Effect of solvent on the yield of **9** [a]

Entry	Solvent	Time (h)	Yield (%)
1	Acetone	12	80
2	THF	10	80
3	ACN	5	82

[a]Reaction conditions: **7** (38.27 mmol), **8** (29.44 mmol), K_2CO_3 (88.27 mmol), reacted under reflux conditions.

Optimization of synthesis conditions for 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine hydrochloride (2)

All ester groups of 2-(((*tert*-butoxycarbonyl) amino)methyl)-2-(3-chloro-5-(trifluoromethyl) pyridin-2-yl)diethyl malonate (**9**) are removed to generate the key intermediate 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethanamine (**2**).[16] Due to that the hydrolysis is under acidic conditions, both the basic product and acidic by-products existed in the reaction mixture. To purify the product, the pH of the reaction solution was adjusted to weakly acidic after the reaction was completed, and then extracted with ethyl acetate.[17] Subsequently, the pH of the remaining aqueous phase was adjusted to alkaline and extracted with ethyl acetate again to isolate the desired primary amine product.

The optimization of solvent

Firstly, we conducted a screening of reaction solvents for the acid hydrolysis process. As shown in Table 3, through thin-layer chromatography (TLC) analysis, we found that the reaction was difficult to proceed when dichloromethane (DCM) was used as the solvent and hydrochloric acid (HCl) concentration was 6 mol·L^{-1}. When HCl concentration was increased to 12 mol·L^{-1}, ^{1}H NMR spectrum of the reaction solution indicated a significant increase in the produce of by-products. Similarly, when *N*,*N*-dimethylformamide (DMF), acetic acid (AC), and 1-methyl-2-pyrrolidinone (NMP) were individually employed as solvents, the ^{1}H NMR spectra also showed a higher amount of by-products, making product purification more difficult and ultimately affecting the yield. However, unexpectedly, when water was chosen as the solvent, the analysis using TLC and ^{1}H NMR revealed a significant reduction in the generation of by-products. More importantly, when the reaction solution was adjusted to neutral pH, the product precipitated in a form of hydrochloride salt, which allows effective separation of the product with a final yield of 46%. Based on these findings, water was ultimately selected as the solvent for acid hydrolysis.

Table 3

Effect of solvent on the yield of **2**[a]

Entry	HCl (mol·L^{-1})	Solvent	T (℃)	Yield (%)
1	6	DCM	rt	−
2	12	DCM	rt	−
3	12	DMF	120	−
4	12	AC	80	−
5	12	NMP	150	−
6	12	H_2O	100	46

[a]Reaction conditions: **9** (10.66 mmol), HCl (54 mL), reacted for 2 h.

The optimization of reaction temperature

After determining the reaction solvent, we further screened the reaction temperature. As shown in Table 4, the results indicated that the yield enhanced continuously with the increase of temperature. However, when the temperature was raised to 120 ℃, the reaction induced a high pressure and was not further explored. Therefore, the optimal temperature for this reaction step was initially determined to be 110 ℃.

Table 4

Effect of reaction temperature on the yield of **2**[a]

Entry	T (℃)	Yield (%)
1	90	38
2	100	46
3	110	55
4	120	Violent reaction

[a]Reaction conditions: **9** (10.66 mmol), concentrated HCl (54 mL), reacted for 2 h.

The optimization of HCl concentration

After optimizing the reaction temperature, we further evaluated the impact of HCl concentration on the reaction (Table 5). The results indicated that when HCl concentration was 6 mol·L^{-1}, the hydrolysis could not complete, resulting in a low yield of 26%. A significant increase in yield was

achieved at a concentration of 9 mol·L^{-1}, reaching 50%. When the concentration was further increased to 12 mol·L^{-1}, the yield reached 55%. These results indicated that a higher HCl concentration was beneficial to improve yield. Therefore, the optimal HCl concentration for this reaction step was determined to be 12 mol·L^{-1}.

Table 5

Effect of HCl concentration on the yield of 2[a]

Entry	HCl concentration (mol·L^{-1})	Yield (%)
1	6	26
2	9	50
3	12	55

[a]Reaction conditions: **9** (10.66 mmol), 110 °C, reacted for 2 h.

The optimization of the reaction time

The complete removal of all ester groups from 2-(((tert-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**9**) is a time-consuming process.[18] Even if the starting material was depleted through TLC observation, it did not mean that the reaction had been completed.[19] To ensure complete removal of the ester groups, we optimized the reaction time for hydrolysis process. As shown in Table 6, the yield of primary amine initially increased, but then decreased as the reaction time was extended, reaching the highest value of 63% after 24 h.

Table 6

Effect of the reaction time on the yield of **2**[a]

Entry	Time (h)	Yield (%)
1	2	55
2	24	63
3	48	50

[a]Reaction conditions: **9** (10.66 mmol), 110 °C, concentrated HCl (54 mL).

The optimization of pH value for the formation of hydrochloride salt products

After the reaction was completed, pH value of the reaction solution was measured using a precise pH meter and found to be –1.3. In the subsequent post-treatment phase, fine adjustment of the pH value was carried out to facilitate isolation of the product in a form of hydrochloride salt or free base.[20] As shown in Table 7, when adjusting the pH of the reaction solution with a 5 mol·L^{-1} NaOH solution, we observed that under alkaline conditions with a pH of 11, the alkaline by-products were mixed with the primary amine product, making the purification process extremely challenging. As a result, the yield at this point was only 40% (Entry 8). However, when the pH was adjusted to 6, the product precipitated as a hydrochloride salt, resulting in a significant increase of yield to 55%. Further exploration revealed that when the pH was tuned to 5, 4, 3, 2, 1, and 0, the yield was 54%, 48%, 49%, 58%, 61%, and 58%, respectively, which indicated that in a strong acidic environment, especially at a pH of 1, the yield of hydrochloride salt products reached its maximum.

Table 7

The optimization of pH for producing hydrochloride salt **2**[a]

Entry	pH	Yield (%)
1	0	58
2	1	61
3	2	58
4	3	49
5	4	48
6	5	54
7	6	55
8	11	40

[a]Reaction conditions: **9** (10.66 mmol), 110 °C, HCl (54 mL), reacted for 2 h.

In summary, to achieve the optimal reaction effect, we have determined that the optimal reaction conditions involve using concentrated HCl at 110 °C for 24 h, followed by adjusting the pH of the reaction solution to 1 during the post-treatment stage. These conditions maximize the precipitation of the product (**2**) in a form of hydrochloride salt, thereby significantly enhancing the yield and purity of the product.

Optimization of synthesis conditions for fluopyram (1)

The direct condensation of amine and acid chloride under basic conditions is the most commonly used method for amide synthesis. Consequently, we opted to directly react the intermediate hydrochloride salt (**2**) with 2-trifluoromethylbenzoyl chloride (**10**), employing triethylamine (Et_3N) as the acid binding agent. To investigate the impact of the acid binding agent's quantity on the reaction, a series of screening experiments were conducted (Table 8). These findings revealed that a molar ratio of n (**2**):n (**10**):n (Et_3N) at 1:1.2:3 could achieve the highest yield. An increase in the amount of Et_3N enhanced the alkalinity of the reaction system, favoring the reaction, but excessive addition led to the consumption of some acid chloride (**10**), thereby reducing the yield.

Table 8

Effect of material ratio on the yield of **1**[a]

Entry	n (2):n (10):n (Et_3N)	Time (h)	Yield (%)
1	1:1.2:2	10	85
2	1:1.2:3	6	92
3	1:1.2:4	6	90
4	1:1.2:5	5	87

[a]Reaction conditions: **2** (10.73 mmol), room temperature, CH_2Cl_2 (250 mL)

EXPERIMENTAL

Unless otherwise stated, all solvents and chemicals were used as purchased from commercial sources in their analytically pure form. Tetrahydrofuran (THF) was dried over sodium and freshly distilled under a nitrogen atmosphere before use. NMR spectra were recorded at room temperature on a Bruker AVANCE III 400 MHz or 500 MHz spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) at 0.00 ppm or the residual solvent signals. Mass spectra were recorded using electrospray ionization on an Agilent 1290-6530 UPLC-Q-TOF spectrometer, or using electron impact ionization on a Waters GCT Premier GC-TOF spectrometer.

Synthesis of ((*tert*-butoxycarbonyl)amino)methyl acetate (7)

A mixture of *tert*-butyl carbamate (**6**, 5.0 g, 42.68 mmol) and paraformaldehyde (4.2 g, 46.62 mmol.) was suspended in a mixed solution of acetic acid (38 mL) and acetic anhydride (115 mL, 1.216 mol).[4] The reaction mixture was vigorously stirred at 60 ℃ for 48 h to ensure complete reaction. After completion of the reaction as monitored by thin-layer chromatography (TLC) analysis using a mixture of petroleum ether and ethyl acetate (*v*/*v* = 2:1) as eluent, the solvent was meticulously removed under vacuum at 70 ℃. The obtained crude product was then purified through vacuum distillation, maintaining an oil bath temperature of 150 ℃, resulting in a transparent fraction of pure ((*tert*-butoxycarbonyl)amino) methyl acetate (**7)** (6.9 g, 86% yield) . ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.27 (s, 1H), 5.02 (1.92 s, 1H), 1.92 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 155.4, 81.4, 72.5, 28.4, 20.8.

Synthesis of 2-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (9)

After placing 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**8**, 10.0 g, 29.44 mmol) and K_2CO_3 (12.2 g, 88.27 mmol) into a 250 mL round-bottomed flask, a solution of ((*tert*-butoxycarbonyl)amino)methyl acetate (**7**, 7.2 g, 38.27 mmol) in ACN was introduced. The mixture was gradually heated in an oil bath at 100 ℃ and the reaction was monitored by TLC employing a mixture of petroleum ether and ethyl acetate (*v*/*v* = 5:2) as eluent. After completion of the reaction, the reaction mixture was cooled to room temperature and a suitable amount of water was added. The solution was extracted three times by using DCM as extraction solvent. The extracted organic layers were combined and dried over anhydrous Na_2SO_4. After the solvents were removed under vacuum, the crude product was recrystallized from a mixture of acetone and petroleum ether (*v*/*v* = 1:10) to obtain pure 2-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**9**) as a white solid (11.30 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.92 (dd, J = 2.1, 0.7 Hz, 1H), 5.51 (t, J = 6.6 Hz, 1H), 4.41–4.16 (m, 6H), 1.30–1.19 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 157.4, 155.8, 143.0, 135.6, 133.6, 127.4, 124.0, 121.8, 79.5, 66.9, 62.9, 43.2, 28.5, 14.3. HRMS (ESI/Q-TOF) *m/z*: Calcd. for $C_{19}H_{24}ClF_3N_2O_6$ $[M + Na]^+$: 491.1167, Found: 491.1157.

Synthesis of 2-(3-chlorine-5-(trifluoromethyl) pyridine-2-yl)ethaneamine hydrochloride (2)

After 2-(((*tert*-butoxycarbonyl)amino)methyl)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)diethyl malonate (**9**, 10.0 g, 21.33 mmol) was added to a 250 mL round-bottomed flask, 100 mL of concentrated HCl solution was poured into the flask. The reaction mixture was gradually heated to 110 ℃, initiating a reflux process for 24 h. Upon completion of the reaction, pH of the solution was meticulously adjusted to 1 using a 5 mol·L^{-1} solution of NaOH. The solution was then extracted three times with ethyl acetate. After being dried with anhydrous Na_2SO_4, the solvent was evaporated and the residual solid was further dried under vacuum to afford hydrochloride product **2** as a white solid (3.5 g, 63% yield). ^{1}H NMR (500 MHz, D_2O) δ 8.77 (s, 1H), 8.26 (s, 1H), 3.49 (t, 2H), 3.41 (t, 2H). ^{13}C NMR (101 MHz, D_2O) δ 160.8, 145.5, 136.1, 133.5, 128.2, 123.2, 39.0, 32.6. HRMS (ESI/Q-TOF) *m/z*: Calcd. for $C_8H_9Cl_2F_3N_2$ $[M\text{-}HCl+H]^+$: 225.0401, Found: 222.0400.

Synthesis of fluopyram (1)

The hydrochloride salt of 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethaneamine (**2**, 2.8 g, 10.73 mmol) was added into a round-bottomed flask containing 250 mL of dichloromethane. Subsequently, triethylamine (3.3 g, 32.19 mmol) dissolved in dichloromethane was cautiously added under an ice bath, after which 2-trifluoromethylbenzoyl chloride (2.7 g, 12.95 mmol) dissolved in dichloromethane was added dropwise. After completion of the addition, the reaction mixture was stirred for 10 minutes. The ice bath was then removed, allowing the reaction to proceed at ambient temperature for 10 hours. The reaction was continuously monitored using TLC analysis. Upon completion of the reaction, water was introduced into the mixture and the mixture was extracted with dichloromethane three times. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to procure a crude product of **1**. This crude product was recrystallized from a mixture of ethyl acetate and petroleum ether to furnish **1** as a white solid (3.9 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 7.69–7.62 (m, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.54–7.47 (m, 2H), 6.67 (s, 1H), 4.01 (q, J = 6.1 Hz, 2H), 3.31 (t, J = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 160.9, 143.7, 136.2, 134.0, 132.2, 129.9 128.8, 127.4, 126.5, 124.8, 123.9, 122.6, 121.78, 37.0, 34.2. HRMS (ESI/Q-TOF) *m/z*: Calcd. for $C_{16}H_{11}ClF_6N_2O$ $[M + Na]^+$: 419.0362, Found: 419.0342.

CONCLUSION

This study adopts a carbamate compound as the starting material to synthesize fluopyram (**1**) through several steps including hydroxymethlylation, condensation, hydrolysis, and amidation reaction. Furthermore, the process optimization of each reaction step in the route starting from *tert*-butyl carbamate (**6**) has been conducted. In particular, option of the acid-catalyzed hydrolysis effectively eliminates the secondary amine and other by-products, thereby enhancing the yield. Additionally, choosing to form the hydrochloride salt product facilitates the acquirement of a purer product through direct crystallization, thus greatly simplifying the purification process. Ultimately, fluopyram (**1**) was synthesized in an overall yield exceeding 41% with a purity of more than 98%. This process can be highlighted by its advantages including short synthesis route, high yield, and great practicality for industrial production.

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