

Synthetic route design and development for an anthranilic diamide compound containing 2-methyl-2-amino-propanamide group as a potential insecticide

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Received mm-dd-yyyy

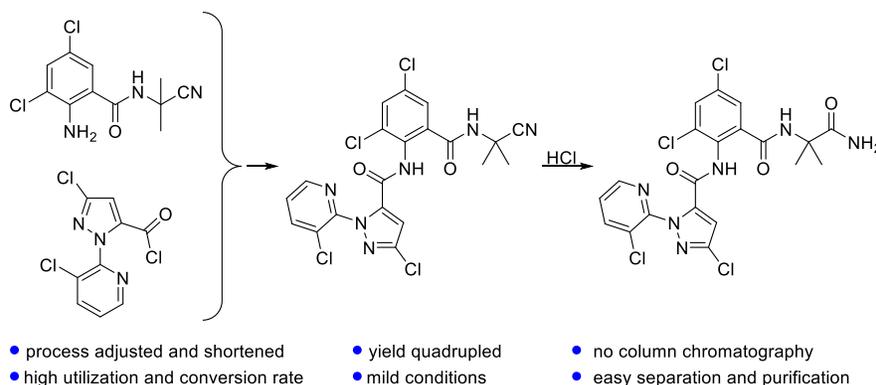
Accepted mm-dd-yyyy

Published on line mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

This article describes exploration of synthetic strategies and determination of the optimal route for a potential insecticide. The target compound was synthesized through a 5-step process in an overall yield of 73%, which was 4 times that of the original route. Based on the optimization for three key steps, the process was adjusted and shortened, and all the chromatographic purification steps were eliminated. All intermediates and the target compound were obtained by convenient processes with high yields. This economic route featured few side products at each step and mild conditions, providing a highly efficient process for large-scale industrial production.



Keywords: Sucking pest, insecticide, anthranilic diamide, route design

Cite as *Arkivoc* 2024 (8) 202412185

DOI: <https://doi.org/10.24820/ark.5550190.p012.185>

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Introduction

It is reported that pests cause about 45% of food production losses per year.¹ Among them, sucking pests cause enormous damage and losses not only via direct feeding on crops, but also by transmitting viruses.²⁻⁴ Nowadays, chemical control is still one of the main means for combatting sucking pests. Based on IRAC (Insecticide Resistance Action Committee), large amounts of synthetic insecticides with different mode of actions have been produced by the agrochemical industry to control sucking pests. Unfortunately, the persistent overuse of synthetic insecticides has led to a continuous evolution of resistance in agricultural pests.^{5,6} For these reasons, the development of new insecticides to suppress resistant sucking pests is of vital importance.⁷

Anthranilic diamide insecticides, a class of highly active insecticides toward sucking pests with novel structure and unique mechanism of action, have become one of the hot areas in new insecticide discovery research. One of the most prominent anthranilic diamide insecticide for sucking pests is cyantraniliprole (Figure 1).⁸⁻¹⁰ In our previous work, we found a series of anthranilic diamide compounds containing 2-methyl-2-amino-propanamide group that have excellent activities not only against chewing pests but also against sucking pests. Among them, compound **1** (Figure 1) showed excellent activities in both greenhouse and field trials, equivalent or superior to cyantraniliprole.¹¹ This compound is a promising insecticide candidate.

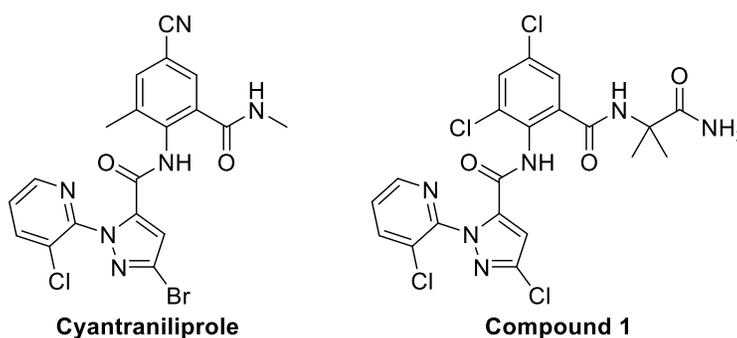


Figure 1. Structure of cyantraniliprole and compound **1**.

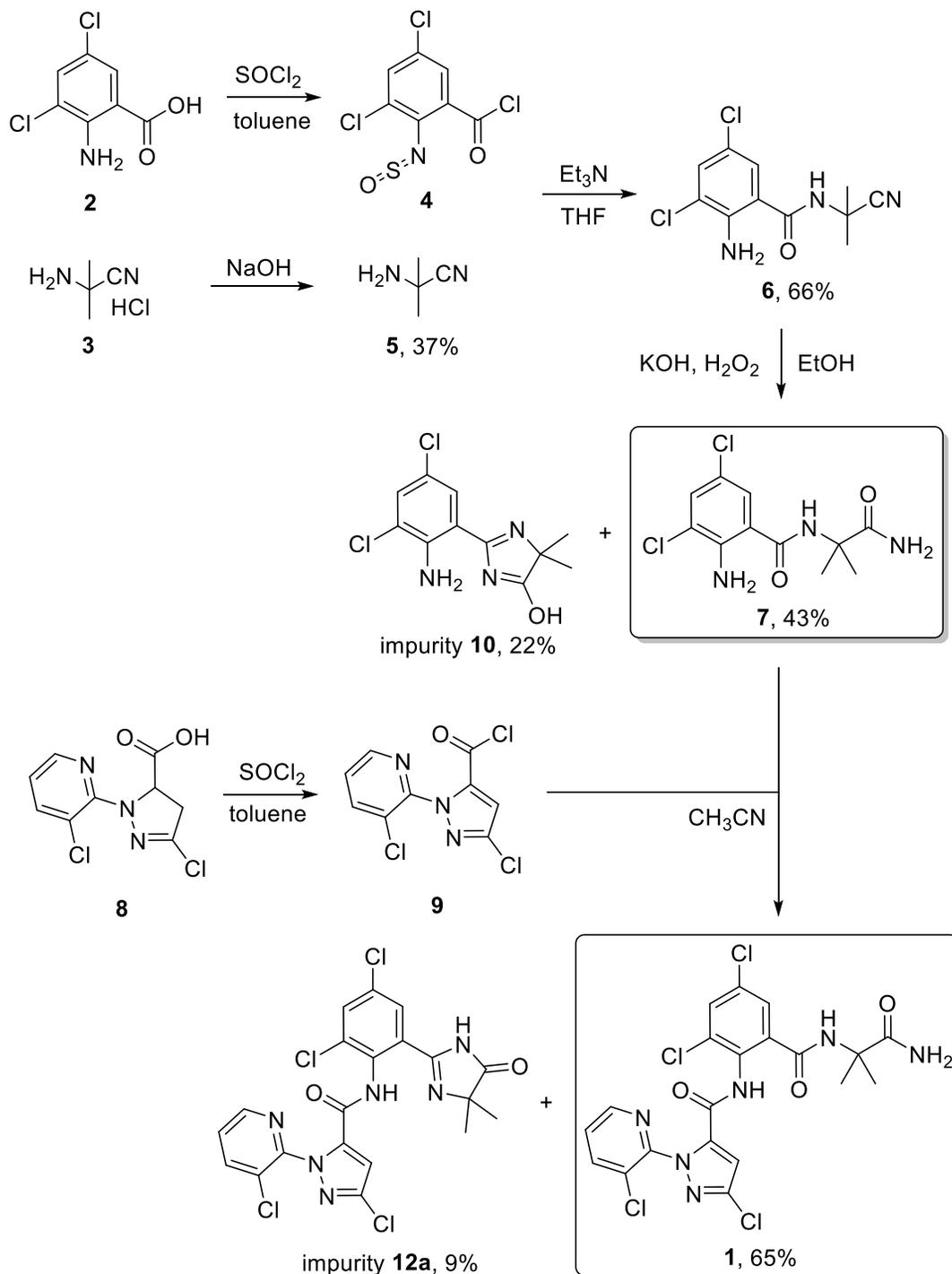
The yield of compound **1** from the original synthesis route was low and impurities produced in some key steps made the process unsuitable for large-scale industrial production.^{11,12} To accelerate the development and application of compound **1**, a series of synthetic routes were designed and explored and the optimal route was determined.

Results and Discussion

The original synthesis route for compound **1** is shown in Scheme 1.

In the original route, commercially available hydrochloride salt **3** was neutralized with a 10% aqueous solution of sodium hydroxide and extracted by dichloromethane to obtain intermediate **5** in a yield of 37%. Intermediate **4** was synthesized from commercially available compound **2** with thionyl chloride in toluene at reflux and condensed with intermediate **5** to obtain compound **6** in a yield of 66% after purification by column chromatography. Intermediate **6** was hydrolyzed through a KOH/hydrogen peroxide system in ethanol, and the mixture was purified by column chromatography to obtain intermediate **7** with a yield of 43%.

Intermediate **9** was obtained from compound **8** through chlorination and oxidation by thionyl chloride in toluene and condensed with intermediate **7** in acetonitrile at room temperature to generate compound **1**. The target compound **1** was purified by column chromatography and obtained in a yield of 65%. The original route provided a 6-step overall yield of 18% (from compound **2**).

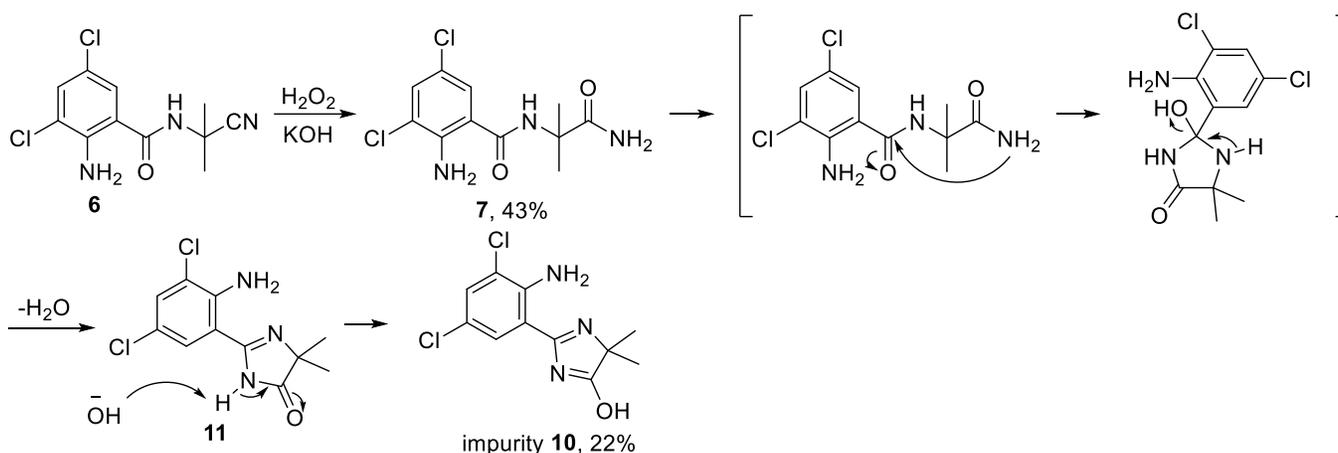


Scheme 1. Original synthesis route for target compound **1**.

This route had three defects and was unsuitable for industrial production.

First, in the preparation of intermediate **6**, we found that the common bases such as triethylamine or pyridine were not strong enough to free the hydrochloride of the compound **3** and the direct condensation with benzoyl chloride **4** produced only a small amount of intermediate **6**, accompanied by a large amount of impurities. To synthesize intermediate **6**, the hydrochloride salt **3** must first be neutralized by a strong base, and then extracted to obtain intermediate **5**. However, because of a low boiling point and water solubility,¹³ the yield of intermediate **5** was low (37%), and the yield of the next step was 66%, resulting in the utilization rate of compound **3** being only 24% in the synthesis of compound **6**.

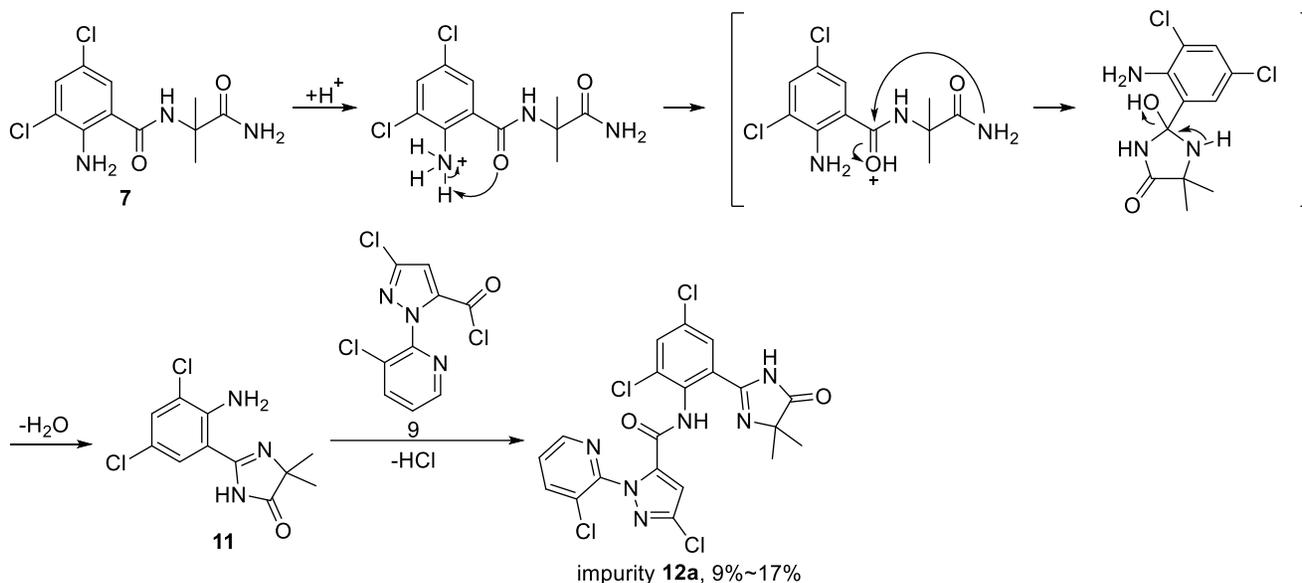
Second, in the preparation of intermediate **7**, the hydrolysis of the cyano-group of intermediate **6** was in an alkaline system. About 20% of the 5-membered imidazolol impurity **10** was unavoidable in this protocol (Scheme 2). The yield was only about 40% and column chromatography purification was required.



Scheme 2. Probable formation mechanism for impurity **10**.

Third, in the synthesis of target compound **1**, the condensation of intermediates **7** and **9** was in an acidic system, and the 5-membered imidazolone cyclization impurity **12a** was unavoidable in this protocol (Scheme 3). The initial reflux method generated 17% of the impurity **12a** and the yield of compound **1** was only about 20%. Considering the high temperature would produce impurities, we lowered the reaction temperature, but the modified method still did not avoid the impurity **12a**. The yield was 65% and column chromatography purification was still required.

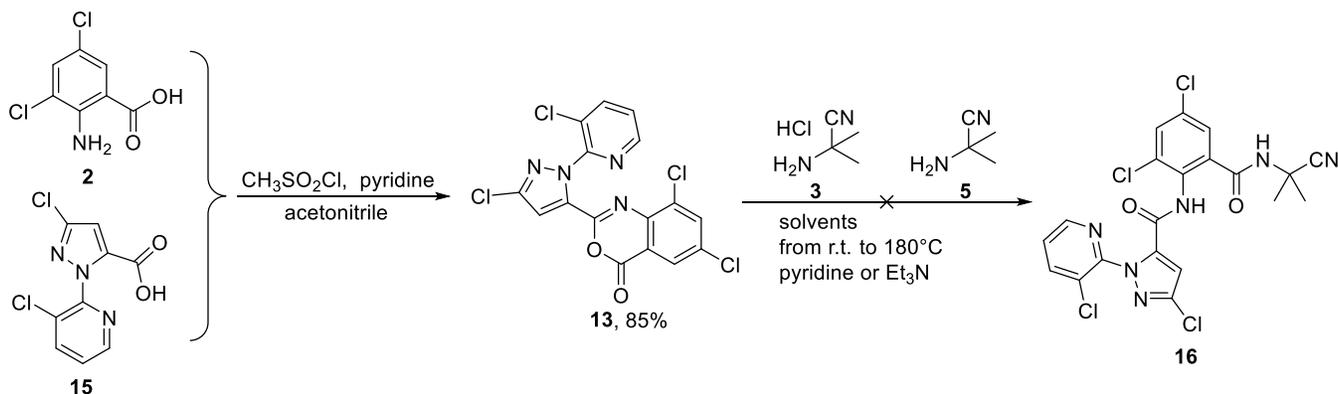
Here, we speculated that the amino group of intermediate **7** activated the benzamide fragment and facilitated cyclization reactions not only under alkaline conditions but also under acidic conditions. According to these mechanistic hypotheses, intermediate **7** was one of the main reasons for the formation of impurities **10** and **12a**. To avoid the defects described above, we designed and explored a new route to bypass the intermediate **7** and skip the condensation of compound **6**.



Scheme 3. Probable formation mechanism for impurity **12a**.

2. Designed route 1 for compound 16

Referring to the reported benzoxazinone synthetic methods, we designed and explored route 1 (Scheme 4).¹⁴⁻²⁰



Scheme 4. Designed synthesis route 1 for intermediate **16**.

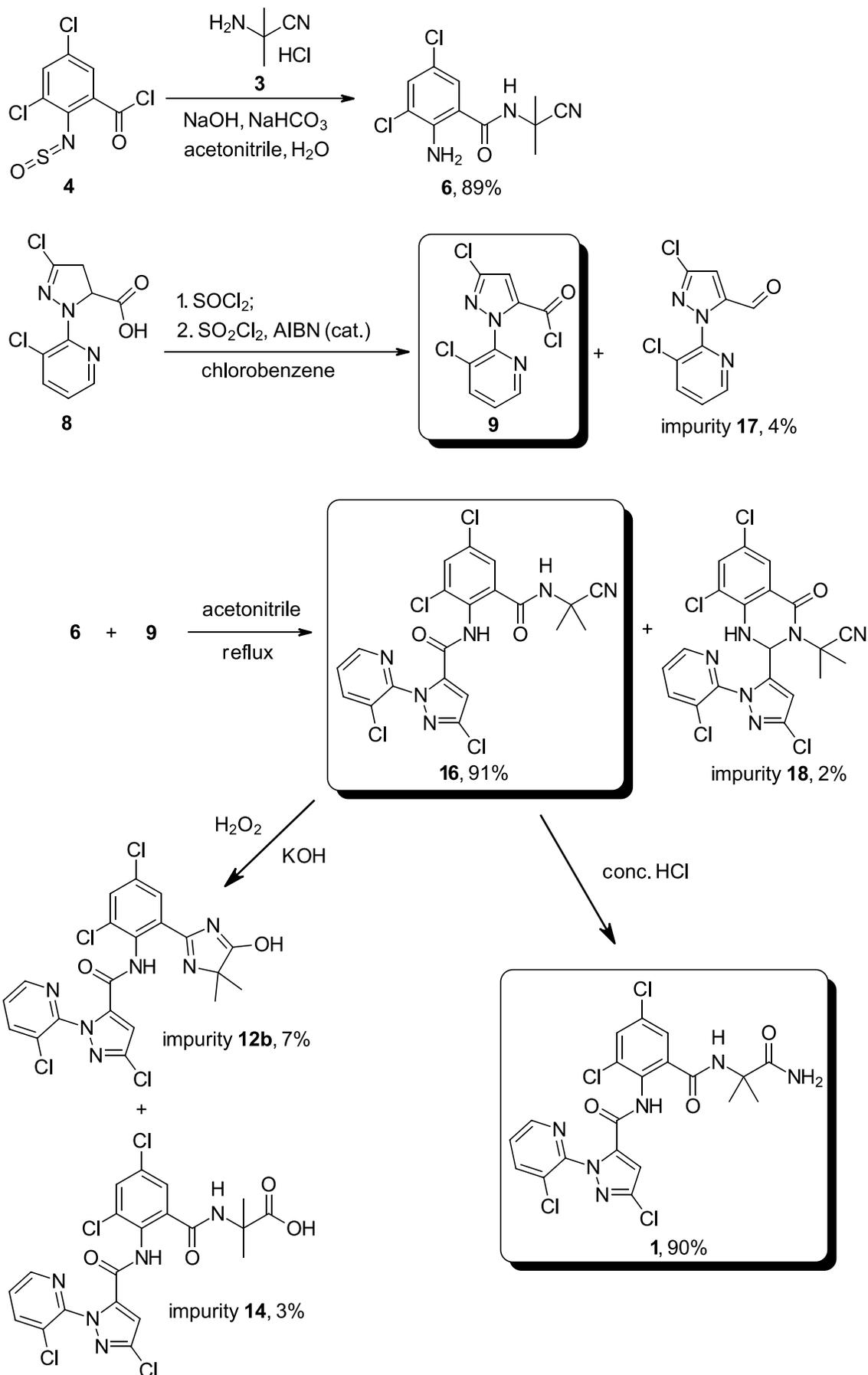
In the designed route 1, the benzoxazinone **13** was obtained by reaction of compound **2** and intermediate **15** using methanesulfonyl chloride and pyridine in acetonitrile at room temperature in an 85% yield.

In the preparation of intermediate **16**, we tried replacing the solvent, changing the temperature from room temperature to 180 °C, adding pyridine or triethylamine as the base and altering the starting materials to hydrochloride **3** or corresponding aminonitrile **5**. All attempts failed to achieve intermediate **16**. Here, we speculated that, compared to the known ring opening reagents, such as methylamine or isopropylamine,¹⁷ due to the electronic effect of cyano-group on isopropylamine, the nucleophilicity of compound **5** was insufficient to realize the ring opening reaction for benzoxazinone **13** to obtain intermediate **16**. Unfortunately, the classic benzoxazinone strategy was not suitable for intermediate **16**.

3. Designed route 2 for compound 1.

According to the above results, we combined the original route and the designed route 1, using compound **6** to synthesize key intermediate **16**, and designed the synthetic route 2 (Scheme 5). In this route, by the study of the condensation conditions, the first defect of the original route was overcome. With the investigation of the chlorination and oxidation for compound **8**, compound **9** was synthesized in high conversion rate and pure intermediate **16** was successfully obtained with high yield. Through the study of the hydrolysis conditions, compound **1** was synthesized under mildly acidic conditions.²¹⁻²³ At this point, all the defects of the above routes were cleared, the process was adjusted and shortened, and the impurities **10**, **12** and **18** were avoided. All the chromatographic purifications were eliminated, and the products of each step could be isolated and purified by simple processes with high yield and purity. This route was determined as the optimal route for compound **1**.

In the designed route 2, intermediate **6** was prepared by direct condensation of intermediate **4** and commercially available hydrochloride **3** in an aqueous solution mixed with acetonitrile, sodium hydroxide and sodium bicarbonate at room temperature with an increased yield of 89%. Compound **8** was reacted with thionyl chloride and subsequently with sulfuryl chloride and AIBN as a catalyst in chlorobenzene to achieve complete conversion to pyrazole carboxylic acid chloride **9**. Intermediate **16** was synthesized by condensation of intermediate **6** and intermediate **9** in acetonitrile at reflux with a yield of 91%. The cyano-group of intermediate **16** was hydrolyzed to the corresponding primary amide by concentrated hydrochloric acid under mild conditions to obtain target product **1** with a yield of 90%. This new route provided a 5-step overall yield of 73% (from compound **2**).



Scheme 5. Designed synthesis route 2 for target compound 1.

3.1. Optimization for intermediate 6.

To optimize the synthesis of compound **6**, we explored the effect of solvents, bases, and temperature on this reaction. The results are shown in Table 1. The condensation reaction was performed in common solvents, the bases included organic and inorganic bases, and the temperature range investigated was from room temperature to the boiling point of the solvent. The results indicated that the solvent and base had a great influence on the reaction. When organic bases were used, about 40% of impurities appeared and the yield was poor (entries 1, 2, 4, 5 and 7). The temperatures had little effect on this reaction (entries 1, 2, 4 and 5). When inorganic bases were used, the impurities were significantly reduced (entries 3, 6, 8, 9, 10, 11 and 12). Inorganic bases suited this reaction better than organic bases. We found that use of dichloromethane and toluene resulted in yields less than 50% (entries 3 and 6). The yields were increased in ethyl acetate, 1,4-dioxane, THF, 2-methoxy-2-methylpropane, and acetonitrile (entries 8, 9, 10, 11 and 12). Specifically, no impurities were detected in acetonitrile and 2-methoxy-2-methylpropane and the yield in acetonitrile was higher (entries 11 and 12). Finally, we determined the preferred conditions of acetonitrile and water as solvent, sodium hydroxide aqueous solution as the base, and sodium bicarbonate as the acid-binding agent. The intermediate **4** was directly added dropwise into the above aqueous mixture containing 1.2 equivalents of compound **3**. The intermediate **6** was obtained in one step with high yield and purity. In addition, compared to the 24% utilization rate of compound **3** in the original route, this new process achieved an almost quantitative yield of intermediate **6**, greatly improving the utilization rate of compound **3** by 3 times.

Table 1. Optimization of the condensation conditions for intermediate **6**.^a

Entry	Solvent	Base	Temp. (°C)	HPLC area (%)		Yield ^b (%)
				Compound 6	Impurity	
1	dichloromethane	Et ₃ N	20	17	37	13
2	dichloromethane	Et ₃ N	40	18	39	12
3	dichloromethane	NaOH/NaHCO ₃	20	73	22	43
4	toluene	pyridine	20	16	36	14
5	toluene	pyridine	110	15	40	12
6	toluene	NaOH/NaHCO ₃	20	79	17.9	49
7	1,4-dioxane	Et ₃ N	20	36	39	24
8	1,4-dioxane	NaOH/NaHCO ₃	20	63.7	9.5	62
9	THF	NaOH/NaHCO ₃	20	85	4.2	63
10	ethyl acetate	NaOH/NaHCO ₃	20	93.8	2.2	66
11	2-methoxy-2-methylpropane	NaOH/NaHCO ₃	20	99	ND	75
12	acetonitrile	NaOH/NaHCO ₃	20	99.4	ND	86

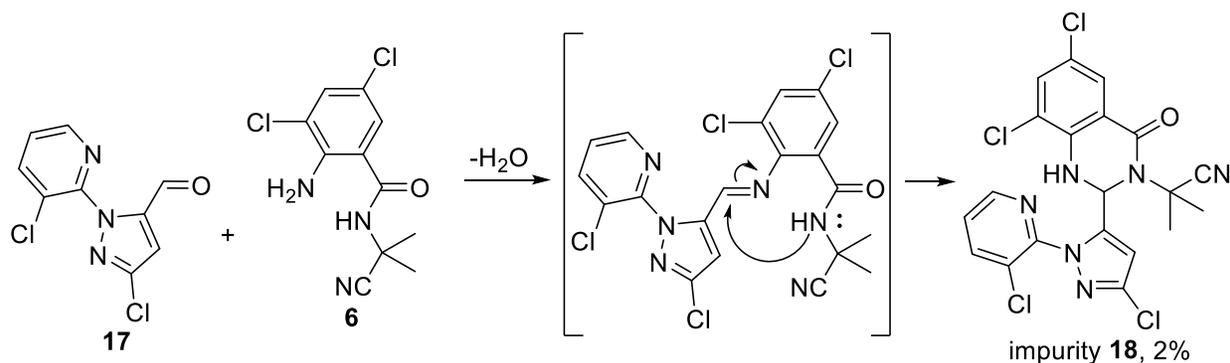
^a Intermediate **4** was prepared from compound **2** through toluene/SOCl₂. All reactions were performed with 5 mmol of intermediate **4** and 6 mmol of compound **3** using 12 mmol organic base in 10 mL of solvent, or 6 mmol NaOH as the base and 6 mmol NaHCO₃ as the acid-binding agent in solvent (10 mL) and water (10 mL) at room temperature overnight. The product was purified by column chromatography.

^b Isolated yield.

3.2. Optimization for intermediate 16.

Efficient production of intermediate **16** was the key for improving the synthetic process. However, in the preparation of intermediate **16**, we found that pyrazole carbaldehyde **17** was formed during the chlorination and oxidation of compound **8**. When pyrazole carboxylic acid chloride **9** containing pyrazole carbaldehyde **17**

was condensed with compound **6**, the formation of dihydroquinazolinone impurity **18** was detected (Scheme 6). In this case, removal of impurity **18** required column chromatography and the yield was unsatisfactory.



Scheme 6. Probable formation mechanism for impurity **18**.

During our previous work on process optimization for synthesis of tetrachlorantraniliprole,¹⁸ a similar dihydroquinazolinone side product was also detected.^{22,23} Based on this previous work, we explored the influence of the chlorinating agents including thionyl chloride and sulfuryl chloride on this reaction to optimize the synthesis of compound **16**. The results are shown in Table 2. Firstly, we used the theoretical amount of 2 equivalents thionyl chloride for chlorination and oxidation (entry 1). We found that about 10% of the impurity **18** was formed, which meant that about 10% of the starting material pyrazoline carboxylic acid **8** was wasted. It did not form pyrazole carboxylic acid chloride **9** but formed pyrazole carbaldehyde **17**. Impurity **17** reacted with intermediate **6** to form impurity **18**, and the yield of the intermediate **16** was only 76%. Secondly, we increased the amount of thionyl chloride by 25% to 2.5 equivalents (entry 2). The impurity was significantly inhibited to 5%, and the yield was also improved, but the conversion rate of the starting material pyrazoline carboxylic acid **8** was still not ideal. Thirdly, we continued to increase the amount of thionyl chloride (entry 3). We found that even when the usage of thionyl chloride was 5 equivalents, there was still 2% impurity **18** present. Based on the above results and our previous work, we concluded that using thionyl chloride for chlorination and oxidation of the pyrazoline carboxylic acid meant that the formation of the pyrazole carbaldehyde was unavoidable. Although the 88% yield was barely acceptable, impurity **18** showed similar properties as intermediate **16** including similar polarity and solubility, which made it difficult to separate by means other than column chromatography. Finally, we adopted the synthetic strategy of the previous research, as shown in entry 4. After the pyrazoline carboxylic acid **8** was completely transformed by adding 2 equivalents thionyl chloride, sulfuryl chloride and AIBN as a catalyst were used to reconvert the generated pyrazole carbaldehyde **17** to pyrazole carboxylic acid chloride **9**. The optimized pure pyrazole carboxylic acid chloride **9** was condensed with intermediate **6**, which avoided the formation of impurity **18** and produced intermediate **16** in high yield. Moreover, the isolation of intermediate **16** could be achieved only by simple filtration, which made it suitable for industrial production.

Table 2. Optimization of the chlorination and oxidation conditions for intermediate **16**.^a

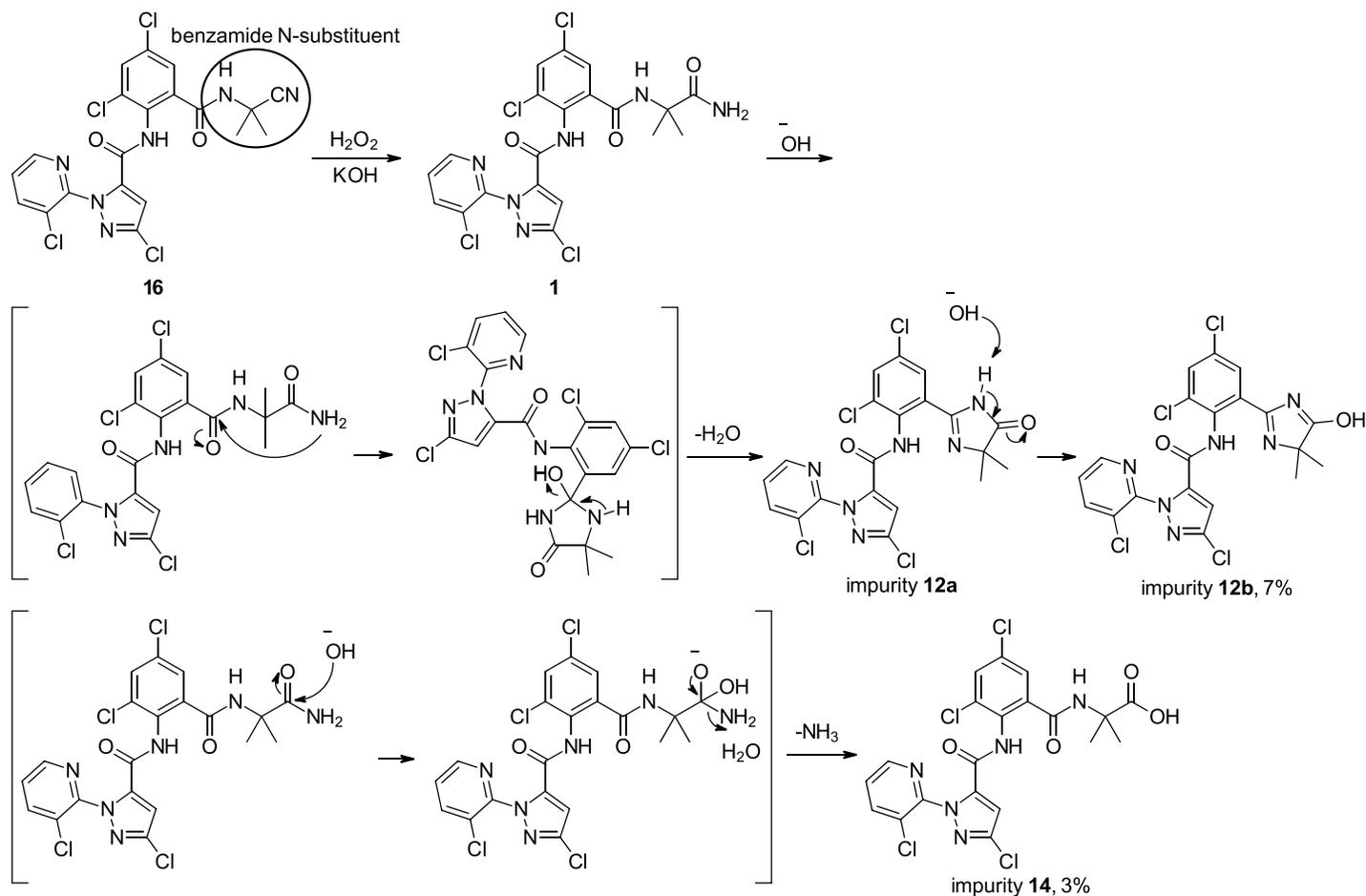
Entry	Equiv. of SOCl ₂	Equiv. of SO ₂ Cl ₂	HPLC area (%)		Yield ^b (%)
			Compound 16	Impurity 18	
1	2	0	83	11	76
2	2.5	0	91	5	82
3	5	0	95	2	88
4	2	0.5	98	ND	92

^a All reactions were carried out with 5 mmol of compound **8** and SOCl₂ at 80 °C in chlorobenzene (20 mL) for 2 hours. Entry 4 was cooled to room temperature and added a catalytic amount of AIBN and 2.5 mmol of SO₂Cl₂, then, heated to 80 °C for another 4 hours. After completing the above operations, all solvents were removed, and the residues were added to compound **6** in acetonitrile (20 mL) and refluxed for 2 hours. The products were purified by column chromatography.

^b Isolated yield.

3.3. Optimization for compound **1**.

In the synthesis of the target product **1**, first, we tried the hydrolytic method for intermediate **6** in the original route. The intermediate **16** was hydrolyzed by KOH and hydrogen peroxide in ethanol. Intermediate **6** and **16** had the same benzamide N-substituent, but the results were different. The hydrolysis of intermediate **16** generated 7% of impurity **12b**, which was much lower than the 22% generation of impurity **10** in the hydrolysis of intermediate **6**. The impurity **14** was also detected (Scheme 7).



Scheme 7. Probable formation mechanism for impurity **12b** and **14**.

This interesting finding led us to the next stage, which was the exploration of the stability of target compound **1**. Through a series of experiments, we found that, in alkaline conditions, such as NaOH or KOH, the amide moiety of compound **1** was hydrolyzed to form carboxylic acid impurity **14** even at room temperature (Scheme 7). In acidic conditions, surprisingly, compound **1** did not undergo cyclization reaction and was stable under relatively mildly acidic conditions. Under strongly acidic conditions, such as 10% *p*-toluenesulfonic acid in toluene at reflux, we detected a small amount of impurity **12a**, but the level was far below the generation of impurity **12a** in the final step of the original route. Under very strongly acidic conditions, such as concentrated hydrochloric acid at reflux, compound **1** converted to carboxylic acid impurity **14**. Here, we speculated that, compared to the activation of the aniline intermediate **7** (Scheme 2 and 3), the pyrazole acyl group of compound **1** stabilized the benzamide fragment, perhaps due to the electron-donating effects of the dimethyl moiety, the amide group of compound **1** was stable only under mildly acidic conditions. Therefore, we concluded that the hydrolysis of intermediate **16** was limited to relatively mildly acidic conditions. Under alkaline or strongly acidic conditions, compound **1** was unstable and side products would be produced.

Finally, we used concentrated hydrochloric acid as the hydrolytic reagent and hydrolyzed the cyano-group below 40 °C, which successfully produced compound **1** with high yield. It is noteworthy that use of the highly dangerous hydrogen peroxide was avoided.

Based on the above conclusions, we determined the optimal route to synthesize target product **1**, employing compound **2** and compound **8** as the starting materials. First, intermediate **4** was prepared from compound **2** by thionyl chloride and condensed directly with commercially available compound **3** in a mixture of acetonitrile and water using inorganic sodium hydroxide as the base and sodium bicarbonate as the acid-binding agent to obtain intermediate **6** in a yield of 89%. Second, the optimized pure pyrazole carboxylic acid chloride **9** was condensed with intermediate **6** in acetonitrile at reflux to afford intermediate **16** in a yield of 91%. Finally, the cyano-group was hydrolyzed to the primary amide by concentrated hydrochloric acid under mild conditions and the target product **1** was obtained with a yield of 90%. In this new route, the formations of impurities **10**, **12** and **18** were avoided, and the 5-step overall yield was 73% which was 4 times bigger than that of the original route. All the chromatographic purifications were eliminated, and the two key intermediates **6**, **16** and the target compound **1** were isolated and purified by simple processes with high yields and purities. All the reaction conditions of this route were mild and convenient, the side products in each step were few, which greatly simplified the purification of the products, thus making the process very suitable for large-scale industrial production.

Conclusions

Synthetic strategies for the anthranilic diamide compound **1**, containing 2-methyl-2-amino-propanamide group, were evaluated and the optimal route was determined. In the new route, compound **1** was synthesized from 2-amino-3,5-dichlorobenzoic acid **2** and pyrazoline carboxylic acid **8** in 5 steps and an overall yield of 73%. This optimized yield was 4 times that of the original route, which represented a great improvement. Intermediate **6** was obtained directly using inorganic bases in water and acetonitrile with high utilization rate of compound **3**. The chlorination and oxidation for compound **8** were investigated and sulfonyl chloride and AIBN as a catalyst were used to reconvert the generated pyrazole carbaldehyde **17** to pyrazole carboxylic acid chloride **9**, achieving a high conversion rate. The hydrolytic method for intermediate **16** was studied and concentrated hydrochloric acid was finally selected as the hydrolytic reagent. Based on the optimization for

the three key steps, the process was adjusted and shortened, and the formation of impurities **10**, **12** and **18** was avoided. All chromatographic purifications were eliminated, and the products from each step were obtained by simple processes and in high yields and purities. This optimal route is suitable for large-scale industrial production.

Experimental Section

General. All solvents and reagents were purchased from commercial providers without further purification. Compound **2** (CAS: 2789-92-6), compound **3** (CAS: 50846-36-1), *p*-toluenesulfonic acid monohydrate (CAS: 6192-52-5) and AIBN (CAS: 78-67-1) were procured from Adamas. Thin-layer chromatography plates (TLC: GF254) were procured from Taizhou Luqiao Sijia biochemical plastic factory and UV light was used to visualize the spots. RY-1 melting-point apparatus was used for measuring melting points (TaiKe Co.) and thermometer uncorrected. Jeol JNM-ECZ600R NMR spectrometer was used for ^1H and ^{13}C NMR spectra. Chemical shift values (δ) were given in ppm and *J* values were given in Hz. UPLC-Q-Exactive Orbitrap spectrometer was used for mass spectra (HRMS). For column chromatography, ethyl acetate and petroleum ether were used as the eluting solvents, and silica gel (300-400 mesh, Qingdao Ocean Chemical Company) was used as the support. Compounds **8** and **15** were prepared according to the patent.¹⁵

Agilent ZORBAX RR StableBond C18 column was used for HPLC separations. HPLC method: The mobile phase consisted of acetonitrile and 0.1% phosphoric acid of water solution (40V : 60V) with a binary isocratic elution by Agilent ZORBAX RR StableBond C18 (150 mm \times 4.6 mm, 3.5 μm). The separation was performed at the flow rate of 1.0 mL/min and the temperature was set at 30 $^\circ\text{C}$. The test compounds were detected at the wavelength of 254 nm.

HPLC retention time of compound **1**: 3.398 min.

HPLC retention time of intermediate **6**: 3.609 min.

HPLC retention time of intermediate **7**: 4.056 min.

HPLC retention time of impurity **10**: 6.814 min.

HPLC retention time of impurity **12a**: 4.950 min.

HPLC retention time of impurity **12b**: 5.371 min.

HPLC retention time of intermediate **13**: 3.864 min.

HPLC retention time of impurity **14**: 4.848 min.

HPLC retention time of intermediate **16**: 3.525 min.

HPLC retention time of impurity **17**: 3.583 min.

HPLC retention time of impurity **18**: 4.043 min.

Synthetic procedures in the original route.

2-Amino-2-methylpropanenitrile (5). To a round-bottom flask was added 2-amino-2-methylpropanenitrile hydrochloride **3** (50 g, 415 mmol) and water (200 mL). Aqueous sodium hydroxide solution (10%, 166 g) was added dropwise and the mixture was stirred at room temperature for 2 hours. The reaction mixture was extracted with dichloromethane (5 \times 100 mL). The organic layer was dried over MgSO_4 , filtered and concentrated in vacuo to give the title compound **5** as a colorless oil (12.9 g; yield: 37%). ^1H NMR (600 MHz, CDCl_3) δ (ppm): 1.81 (br s, 2H, NH_2), 1.41 (s, 6H, 2CH_3). ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ (ppm): 125.14, 45.83, 29.12.

***N*-(1-Cyano-1-methylethyl)-2-amino-3,5-dichlorobenzamide (6).** To a round-bottom flask was added compound **2** (10 g, 48.5 mmol) and toluene (50 mL). Thionyl chloride (23.1 g, 194 mmol) was slowly added. The reaction mixture was heated at reflux for 4 hours. Evaporation under reduced pressure afforded intermediate **4** as a brown oil.

To a round-bottom flask was added compound **5** (4.08 g, 48.5 mmol), THF (200 mL), and triethylamine (7.36 g, 72.7 mmol). After cooling the mixture in an ice bath for 0.5 hours, intermediate **4** in THF (50 mL) was slowly added to the mixture. The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was partitioned between ethyl acetate (500 mL) and water (100 mL). The organic layer was washed with saturated sodium chloride solution (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:3 v/v) afforded the title compound **6** as a yellow solid (8.7 g; yield: 66%; melting point: 214-216 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 8.78 (s, 1H, NH), 7.64 (d, *J* 2.4 Hz, 1H, Ph-H), 7.56 (d, *J* 2.4 Hz, 1H, Ph-H), 6.59 (br s, 2H, NH₂), 1.68 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 167.21, 144.39, 131.54, 127.55, 121.57, 119.71, 117.77, 115.95, 46.30, 26.38. HRMS (ESI) *m/z* calculated for C₁₁H₁₁Cl₂N₃O, [M+H]⁺ 272.0279, found 272.0345.

2-Amino-*N*-(1-amino-2-methyl-1-oxopropan-2-yl)-3,5-dichlorobenzamide (7). To a three-neck round-bottom flask was added compound **6** (69 g, 254 mmol), potassium hydroxide (15.7 g, 279 mmol) and ethanol (200 mL). The mixture was stirred and cooled in an ice bath for 1 hour. Aqueous hydrogen peroxide (30%, 144 g, 1.27 mol) was slowly added to the mixture. The reaction mixture was stirred at room temperature for 24 hours. Ethyl acetate (1 L) and water (500 mL) were added and the organic layer was washed with saturated sodium chloride solution (200 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:1 v/v) afforded the title compound **7** as a white solid (32.2 g; yield: 43%; melting point: 166-168 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 8.34 (br s, 1H, NH), 7.72 (d, *J* 2.4 Hz, 1H, Ph-H), 7.49 (d, *J* 2.4 Hz, 1H, Ph-H), 7.21 (br s, 1H, NH₂-H), 6.79 (br s, 1H, NH₂-H), 6.45 (br s, 2H, NH₂), 1.40 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 175.98, 166.58, 143.92, 130.60, 127.71, 119.23, 118.20, 117.76, 56.39, 25.12. HRMS (ESI) *m/z* calculated for C₁₁H₁₃Cl₂N₃O₂, [M-H]⁻ 288.0385, found 288.0310.

2-(2-Amino-3,5-dichlorophenyl)-4,4-dimethyl-4*H*-imidazol-5-ol (10). The side product impurity **10** was eluted before the compound **7**, with ethyl acetate/petroleum ether (1:3 v/v) as the mobile phase. The title compound **10** was obtained as a yellow solid (15.5 g; yield: 22%; melting point: 170-173 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 11.41 (s, 1H, OH), 7.73 (d, *J* 2.4 Hz, 1H, Ph-H), 7.61 (br s, 2H, NH₂), 7.54 (d, *J* 2.4 Hz, 1H, Ph-H), 1.29 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 186.24, 158.17, 144.38, 130.89, 127.22, 119.35, 117.64, 109.98, 67.54, 24.17. HRMS (ESI) *m/z* calculated for C₁₁H₁₁Cl₂N₃O, [M+H]⁺ 272.0279, found 272.0345.

Caution. Hydrogen peroxide may have a risk of explosion. It is necessary to reduce the addition rate as much as possible and control the reaction temperature below 10 °C. In order to minimize the risk, the crude product can be directly extracted by ethyl acetate without removing the solvent.

***N*-(2-((1-Amino-2-methyl-1-oxopropan-2-yl)carbamoyl)-4,6-dichlorophenyl)-3-chloro-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxamide (1).** To a round-bottom flask was added compound **8** (43 g, 165.6 mmol) and toluene (200 mL). To this solution was slowly added thionyl chloride (98.5 g, 828 mmol) and the resulting mixture was heated to 80 °C for 4 hours. Evaporation under reduced pressure afforded intermediate **9** as a brown oil. To a round-bottom flask was added intermediate **7** (40 g, 138 mmol) and acetonitrile (500 mL). Intermediate **9** in acetonitrile (100 mL) was slowly added to the mixture and stirred at room temperature for 12 hours. After the solvent was removed, the residue was partitioned between ethyl acetate (1 L) and saturated sodium bicarbonate aqueous solution (500 mL). The organic phase was washed with saturated

sodium chloride solution (2 x 100 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (2:1 v/v) afforded the title compound as a white solid (49 g; yield: 65%; melting point: 158-162 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 10.48 (s, 1H, NH), 8.47-8.48 (dd, *J* 4.8, 1.8 Hz, 1H, pyridine-H), 8.35 (s, 1H, NH), 8.15-8.17 (dd, *J* 7.8, 1.8 Hz, 1H, pyridine-H), 7.83 (d, *J* 2.4 Hz, 1H, Ph-H), 7.80 (d, *J* 2.4 Hz, 1H, Ph-H), 7.59-7.62 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.37 (s, 1H, pyrazol-H), 7.15 (br s, 1H, NH₂-H), 6.82 (br s, 1H, NH₂-H), 1.27 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 175.78, 163.76, 155.66, 148.43, 147.10, 139.58, 139.22, 138.53, 138.22, 133.17, 132.05, 130.17, 130.09, 128.05, 127.68, 126.69, 107.55, 56.30, 24.71. HRMS (ESI) *m/z* calculated for C₂₀H₁₆Cl₄N₆O₃, [M+H]⁺ 531.0008, found 531.0073.

3-Bromo-1-(3-chloropyridin-2-yl)-N-(2,4-dichloro-6-(4,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)phenyl)-1H-pyrazole-5-carboxamide (12a). The side product impurity **12a** was eluted before the compound **1**, with ethyl acetate/petroleum ether (1:2 v/v). The title compound **12a** was obtained as a white solid (6.3 g; yield: 9%; melting point: 152-157 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 10.54 (s, 1H, NH), 8.94 (s, 1H, NH), 8.47-8.48 (dd, *J* 4.8, 1.2 Hz, 1H, pyridine-H), 8.15-8.17 (dd, *J* 7.8, 1.2 Hz, 1H, pyridine-H), 7.89 (d, *J* 2.4 Hz, 1H, Ph-H), 7.59-7.62 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.55 (d, *J* 2.4 Hz, 1H, Ph-H), 7.46 (s, 1H, pyrazol-H), 1.52 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 164.35, 155.58, 148.40, 147.10, 139.22, 138.59, 137.10, 133.50, 132.12, 130.63, 130.47, 128.02, 127.21, 126.76, 126.66, 121.23, 111.04, 45.97, 26.18. HRMS (ESI) *m/z* calculated for C₂₀H₁₄Cl₄N₆O₂, [M+H]⁺ 512.9903, found 512.9968.

Synthetic procedure in the designed route 1

6,8-Dichloro-2-(3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4H-benzo[*d*][1,3]oxazin-4-one (13). To a round-bottom flask was added compound **15** (1.3 g, 5 mmol) and acetonitrile (15 mL). The mixture was stirred and cooled in an ice bath for 1 hour. Methanesulfonyl chloride (0.9 g, 7.9 mmol) was added dropwise and the mixture was stirred for 10 mins. Pyridine (1.3 g, 16.4 mmol) was added and the mixture was stirred for 10 mins. Compound **2** (1.55 g, 7.5 mmol) was added and the mixture was stirred for 10 mins. Another portion of pyridine (1.3 g, 16.4 mmol) was added and the mixture was stirred for 15 mins. Another portion of methanesulfonyl chloride (0.9 g, 7.9 mmol) was added and the mixture was stirred for 15 mins. After removing the ice bath, the solution was stirred at room temperature overnight. Water (9 mL) was added and the solution was stirred for 2 hours. The resulting solid was collected by filtration, and dried to give the title compound **13** as a yellow solid (1.82 g; yield: 85%; melting point: 220-222 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 8.58-8.60 (dd, *J* 4.8, 1.8 Hz, 1H, pyridine-H), 8.31-8.33 (dd, *J* 7.8, 1.8 Hz, 1H, pyridine-H), 8.11 (d, *J* 2.4 Hz, 1H, Ph-H), 8.03 (d, *J* 2.4 Hz, 1H, Ph-H), 7.72-7.74 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.53 (s, 1H, pyrazol-H). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 156.19, 148.28, 147.96, 147.64, 140.82, 140.65, 139.88, 135.92, 135.53, 133.20, 131.31, 128.59, 127.32, 126.28, 120.59, 109.94. HRMS (ESI) *m/z* calculated for C₁₆H₆Cl₄N₄O₂, [M+H]⁺ 429.0500, found 428.9285.

Synthetic procedures in the designed route 2

Compound 6. To a round-bottom flask was added compound **2** (30 g, 145 mmol) and toluene (200 mL). Thionyl chloride (86.3 g, 725 mmol) was slowly added and the mixture was heated at reflux for 4 hours. Evaporation under reduced pressure afforded intermediate **4** as a brown oil.

To a round-bottom flask was added compound **3** (21 g, 174 mmol), acetonitrile (100 mL), sodium hydroxide (7 g, 174 mmol), sodium bicarbonate (14.6 g, 174 mmol) and water (100 mL). The mixture was stirred until well blended at room temperature. After cooling the mixture in an ice bath for 1 hour, intermediate **4** in acetonitrile (100 mL) was slowly added to the mixture. After stirring for 2 hours at room temperature, water

(100 mL) was added and the mixture was stirred overnight. The resulting solid was collected by filtration, and dried to give the title compound **6** as a yellow solid (35.5 g; purity: 99%; yield: 89%).

3-Chloro-1-(3-chloropyridin-2-yl)-N-(2,4-dichloro-6-((2-cyanopropan-2-yl)carbamoyl)phenyl)-1H-pyrazole-5-carboxamide (16). To a round-bottom flask was added compound **8** (35 g, 125 mmol) and chlorobenzene (200 mL). Thionyl chloride (30 g, 250 mmol) was slowly added and the mixture heated to 80 °C for 2 hours. After cooling the solution to room temperature, sulfonyl chloride (8.4 g, 62.5 mmol) and AIBN (20.5 mg, 0.13 mmol) were added and the mixture was heated to 80 °C for another 4 hours. Intermediate **9** was obtained as a brown oil by evaporation under reduced pressure.

To a round-bottom flask was added intermediate **6** (34 g, 125 mmol) and acetonitrile (200 mL). The solution was heated to reflux and intermediate **9** in acetonitrile (100 mL) was added slowly. The mixture was heated at reflux for a further 2 hours. After cooling the solution to room temperature, water (200 mL) was added and the mixture was stirred at room temperature overnight. The resulting solid was collected by filtration, and dried to give the title compound **16** as a yellow solid (58.5 g; yield: 91%; melting point: 249-251 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 10.56 (s, 1H, NH), 8.93 (s, 1H, NH), 8.48 (d, *J* 4.8 Hz, 1H, pyridine-H), 8.16 (d, *J* 8.1 Hz, 1H, pyridine-H), 7.88 (d, *J* 2.4 Hz, 1H, Ph-H), 7.59-7.62 (dd, *J* 8.1, 4.8 Hz, 1H, pyridine-H), 7.56 (d, *J* 2.4 Hz, 1H, Ph-H), 7.41 (s, 1H, pyrazol-H), 1.52 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 164.35, 155.69, 148.41, 147.10, 139.59, 139.23, 138.46, 137.12, 133.51, 132.14, 130.63, 130.44, 128.05, 127.20, 126.69, 121.22, 107.67, 45.97, 26.18. HRMS (ESI) *m/z* calculated for C₂₀H₁₄Cl₄N₆O₂, [M+H]⁺ 512.9903, found 512.9968.

Compound 1. To a three-neck round-bottom flask was added concentrated hydrochloric acid (100 mL) and heated to 36-38 °C. The solution was stirred intensely and intermediate **16** (53 g, 104.5 mmol) was added slowly while keeping the temperature approximately below 40 °C. The mixture was stirred for 30 minutes at 36-38 °C, then poured into ice water and stirred for half an hour while keeping the temperature below 10 °C. The resulting solid was collected by filtration, and dried to give the title compound **1** as a white solid (53.6 g; purity: 93%; yield: 90%).

3-Chloro-1-(3-chloropyridin-2-yl)-N-(2,4-dichloro-6-(5-hydroxy-4,4-dimethyl-4H-imidazol-2-yl)phenyl)-1H-pyrazole-5-carboxamide (12b). In the hydrolysis experiments for preparation of intermediate **16**, we found an impurity **12b** and the preparation procedure was as follows. To a three-neck round-bottom flask was added compound **16** (2 g, 3.9 mmol), potassium hydroxide (2.4 g, 4.3 mmol) and ethanol (20 mL). The mixture was stirred and cooled in an ice bath for 1 hour. Aqueous hydrogen peroxide (30%, 2.2 g, 20 mmol) was slowly added to the mixture. The reaction mixture was stirred at room temperature for 24 hours. Ethyl acetate (100 mL) and water (50 mL) were added for extraction. The organic layer was washed with saturated sodium chloride solution (20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified using silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:2 v/v) afforded the title compound **12b** as a white solid (140 mg; yield: 7%; melting point: 192-194 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 11.18 (br s, 1H, OH), 10.67 (br s, 1H, NH), 8.46-8.48 (dd, *J* 4.8, 1.8 Hz, 1H, pyridine-H), 8.15-8.17 (dd, *J* 8.4, 1.8 Hz, 1H, pyridine-H), 7.96 (br s, 1H, Ph-H), 7.71 (d, *J* 2.4 Hz, 1H, Ph-H), 7.59-7.62 (dd, *J* 8.4, 4.8 Hz, 1H, pyridine-H), 7.36 (s, 1H, pyrazol-H), 1.12 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 187.02, 155.81, 155.58, 148.36, 147.17, 139.66, 139.33, 138.75, 133.64, 132.10, 131.38, 131.30, 130.03, 128.00, 127.93, 126.75, 107.74, 68.38, 23.48. HRMS (ESI) *m/z* calculated for C₂₀H₁₄Cl₄N₆O₂, [M+H]⁺ 512.9903, found 512.9967.

2-(3,5-Dichloro-2-(3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamido)benzamido)-2-methylpropanoic acid (14). In the stability studies of compound **1**, we found an impurity **14** and the preparation procedure was as follows. To a stirred solution of sodium hydroxide (1.5 g, 38 mmol) in water (20

mL), compound **1** (2 g, 3.8 mmol) was added at room temperature. After 2 hours, ethyl acetate (20 mL) was added for extraction. The aqueous layer was acidified with a 6M HCl solution to pH value below 2 and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with saturated sodium chloride solution (10 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified using silica gel column chromatography. Elution with ethyl acetate afforded the title compound **14** as a white solid (57 mg; yield: 3%; melting point. 208-210 °C). ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm): 12.28 (br s, 1H, OH), 10.55 (br s, 1H, NH), 8.58 (br s, 1H, NH), 8.47-8.49 (dd, *J* 4.8, 1.8 Hz, 1H, pyridine-H), 8.15-8.17 (dd, *J* 7.8, 1.8 Hz, 1H, pyridine-H), 7.86 (d, *J* 2.4 Hz, 1H, Ph-H), 7.59-7.62 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.43 (d, *J* 2.4 Hz, 1H, Ph-H), 7.42 (s, 1H, pyrazol-H), 1.30 (s, 6H, 2CH₃). ¹³C NMR (150 MHz, DMSO-*d*₆) δ (ppm): 175.18, 163.80, 155.64, 148.51, 147.13, 139.60, 139.24, 138.59, 138.03, 133.68, 132.06, 130.43, 130.30, 128.13, 127.12, 126.73, 107.67, 55.50, 24.63. HRMS (ESI) *m/z* calculated for C₂₀H₁₅Cl₄N₅O₄, [M+H]⁺ 531.9849, found 531.9915.

3-Chloro-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carbaldehyde (17). During the optimization of chlorination and oxidation, we found an impurity **17** and the preparation procedure was as follows. To a round-bottom flask was added compound **8** (1.3 g, 5 mmol) and toluene (20 mL). Thionyl chloride (1.2 g, 10 mmol) was slowly added and the mixture was heated at 80 °C for 2 hours. The solvent was evaporated under reduced pressure to give a mixture of compound **9** and compound **17** as a brown oil. The brown oil in dichloromethane (20 mL) was slowly added to a round-bottom flask containing methanol (20 mL) and the resulting solution was stirred and heated at reflux for 1 hour. The solvent was removed, and the residue was purified by silica gel column chromatography. Elution with ethyl acetate/petroleum ether (1:5 v/v) afforded the title compound **17** as a white solid (48 mg; yield: 4%; melting point. 85-87 °C). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 9.78 (s, 1H, CHO-H), 8.49-8.51 (dd, *J* 4.8, 1.2 Hz, 1H, pyridine-H), 7.95 (d, *J* 1.2 Hz, 1H, pyridine-H), 7.45-7.47 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.01 (s, 1H, pyrazol-H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 178.55, 147.75, 147.22, 142.39, 142.10, 139.96, 128.70, 126.16, 111.77. HRMS (ESI) *m/z* calculated for C₉H₅Cl₂N₃O, [M+H]⁺ 241.9810, found 241.9877.

2-(6,8-Dichloro-2-(3-chloro-1-(3-chloropyridin-2-yl)-1H-pyrazol-5-yl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-2-methylpropanenitrile (18). During the optimization for preparation of intermediate **16**, we found an impurity **18** and the preparation procedure was as follows. To a round-bottom flask was added compound **8** (2.6 g, 10 mmol) and toluene (50 mL). Thionyl chloride (2.4 g, 20 mmol) was slowly added and the mixture was heated at 80 °C for 2 hours. The solvent was evaporated under reduced pressure to give a mixture of compound **9** and compound **17** as a brown oil. To a round-bottom flask was added compound **6** (2.7 g, 10 mmol) and the above brown oil in acetonitrile (20 mL) was slowly added. The solution was heated at reflux for 2 hours. The solvent was removed, and the residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was washed with saturated sodium chloride solution (50 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified using silica gel column chromatography, eluting with ethyl acetate/petroleum ether (1:3 v/v) to afford the title compound **18** as a yellow solid (87 mg; yield: 2%; melting point: 143-145 °C). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.53-8.55 (dd, *J* 4.8, 1.8 Hz, 1H, pyridine-H), 8.05-8.07 (dd, *J* 7.8, 1.8 Hz, 1H, pyridine-H), 7.91 (d, *J* 2.4, 1H, Ph-H), 7.47-7.50 (dd, *J* 7.8, 4.8 Hz, 1H, pyridine-H), 7.39 (d, *J* 2.4, 1H, Ph-H), 6.45 (d, *J* 3 Hz, 1H, NH), 6.16 (d, *J* 3 Hz, 1H, pyrazol-H), 1.86 (s, 3H, CH₃), 1.78 (s, 3H, CH₃). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 161.06, 147.50, 146.33, 144.07, 142.09, 141.92, 139.61, 133.74, 128.12, 127.29, 125.51, 125.20, 120.52, 120.01, 117.86, 107.80, 62.04, 52.90, 27.18, 26.19. HRMS (ESI) *m/z* calculated for C₂₀H₁₄Cl₄N₆O, [M+H]⁺ 496.9954, found 497.0036.

DSC data indicated that the key intermediates **6** and **16** and the target compound **1** were stable up to 200 °C and could be treated with conventional procedures. The decomposition temperature of compound **8** was

166.1 °C. Therefore, the treatment temperature for compound **8** including separation, drying or reaction, etc., should be controlled within 80 °C.

Supplementary Material

The supplementary material includes the following information: general procedures for compound **1**, **6** and **16**, DSC for compound **1**, **6**, **8** and **16**, NMR spectra and HPLC chromatograms for compound **1**, **5**, **6**, **7**, **10**, **12a**, **12b**, **13**, **14**, **16**, **17** and **18**.

References

1. Barathi, S.; Sabapathi, N.; Kandasamy, S.; Lee, J. *Environmental Research* **2024**, *240* (Part 1), 117432. <https://doi.org/10.1016/j.envres.2023.117432>
2. Buchholz, A.; O'Sullivan, A. C.; Trapp, S. *Discovery and Synthesis of Crop Protection Products*. **2015**, Chapter 8, pp 93-109. <https://doi.org/10.1021/bk-2015-1204.ch008>
3. Zogli, P.; Pingault, L.; Grover, S.; Louis, J. *Curr. Opin. Plant. Biol.* **2020**, *56*, 153-161. <https://doi.org/10.1016/j.pbi.2020.06.002>
4. Kosar, V.; Križanac, A.; Zelić, I. E.; Kurajica, S.; Tomašić, V. *Processes* **2023**, *11*, 2588. <https://doi.org/10.3390/pr11092588>
5. Bass, C.; Nauen, R. *Insect Biochem. Mol. Biol.* **2023**, *156*, 103937. <https://doi.org/10.1016/j.ibmb.2023.103937>
6. Hu, J.; Chen, F.; Wang, J.; Rao, W.; Lin, L.; Fan, G. *Agronomy* **2023**, *13*, 2276. <https://doi.org/10.3390/agronomy13092276>
7. Sparks, T. C.; Hunter, J. E.; Lorschbach, B. A.; Hanger, G.; Gast, R. E.; Kemmitt, G.; Bryant, R. J. *J. Agric. Food Chem.* **2018**, *66*, 10337–10346. <https://doi.org/10.1021/acs.jafc.8b03484>
8. Chen, J.; Bai, Y. *World Pesticide* **2021**, *43*, 22-34. <https://doi.org/10.16201/j.cnki.cn10-1660/tq.2021.03.04>
9. Pang, X.; Han, L.; Zhou, C.; Xu, X.; Li, Z. *Advanced Agrochem* **2022**, *1* (2), 157-161. <https://doi.org/10.1016/j.aac.2022.11.005>
10. Selby, T. P.; Lahm, G. P.; Stevenson, T. M.; Hughes, K. A.; Cordova, D.; Annan, I. B.; Barry, J. D.; Benner, E. A.; Currie, M. J.; Pahutski, T. F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6341-6345. <http://dx.doi.org/10.1016/j.bmcl.2013.09.076>
11. Yang, H.; Ying, J.; Song, Y.; Chen, L.; Li, K.; Shi, X.; Feng, C.; Huang, Q.; Fan, X.; Li, B. US Pat. 9,723,838, **2017**. <https://www.freepatentsonline.com/9723838.pdf>
12. Feng, M.; Li, H.; Shi, X. US Pat. 2020/0329707, **2020**. <https://www.freepatentsonline.com/20200329707.pdf>
13. Popov, Y. V.; Mokhov, V. M.; Tankabekyan, N. A. *Russ. J. Org. Chem.* **2014**, *50*, 21-24. <https://doi.org/10.1134/S1070428014010047>
14. Lahm, G. P.; Cordova, D.; Barry, J. D. *Bioorg. Med. Chem.* **2009**, *17*, 4127–4133. <https://doi.org/10.1016/j.bmc.2009.01.018>
15. Li, B.; Wu, H.; Yu, H.; Yang, H. US Pat. 8,217,179, **2012**. <https://www.freepatentsonline.com/8217179.pdf>

16. Yu, H.; Yang, H.; Chen, L.; Wang, G.; Zhao, G.; Wang, X.; Wu, H.; Shi, X.; Dong, Y.; Li, B. *Org. Process Res. Dev.* **2022**, *26*, 3216–3225.
<https://doi.org/10.1021/acs.oprd.2c00141>
17. Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; Freudenberger, J. H.; Cordova, D.; Flexner, L.; Bellin, C. A.; Duba, C. M.; Smith, B. K.; Hughes, K. A.; Hollingshaus, J. G.; Clark, C. E.; Benner, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6274–6279.
<https://doi.org/10.1016/j.bmcl.2007.09.012>
18. Yang, H.; Yu, H.; Cong, Y.; Shi, X.; Hu, Z.; Wang, J.; Song, Y.; Li, B. *Advanced Agrochem* **2023**, *2*, 371–375.
<https://doi.org/10.1016/j.aac.2023.10.001>
19. Yu, H.; Sun, K.; Zhang, M. *Agrochemicals* **2012** (12), 929–932.
<https://doi.org/10.16820/j.cnki.1006-0413.2012.12.026>
20. Wu, J.; Song, B.; Hu, D.; Yue, M.; Yang, S. *Pest Manag. Sci.* **2012**, *68*, 801–810.
<https://doi.org/10.1002/ps.2329>
21. Yu, H.; Zhao, G.; Ying, J.; Wang, F.; Ren, Z.; Yang, H. CN Pat. 110845472, **2022**.
https://worldwide.espacenet.com/publicationDetails/originalDocument?FT=D&date=20220826&DB=&locale=en_EP&CC=CN&NR=110845472B&KC=B&ND=4
22. Ying, J.; Yang, H.; Wang, G.; Yu, H.; Li, B. CN Pat. 116768853, **2023**.
https://worldwide.espacenet.com/publicationDetails/originalDocument?CC=CN&NR=116768853A&KC=A&FT=D&ND=3&date=20230919&DB=&locale=en_EP
23. Ying, J.; Yang, H.; Wang, G.; Yu, H.; Li, B. CN Pat. 116675671, **2023**.
https://worldwide.espacenet.com/publicationDetails/originalDocument?CC=CN&NR=116675671A&KC=A&FT=D&ND=3&date=20230901&DB=&locale=en_EP

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