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AN EFFICIENT TON SCALE PROCESS OF CHLORFLUAZURON

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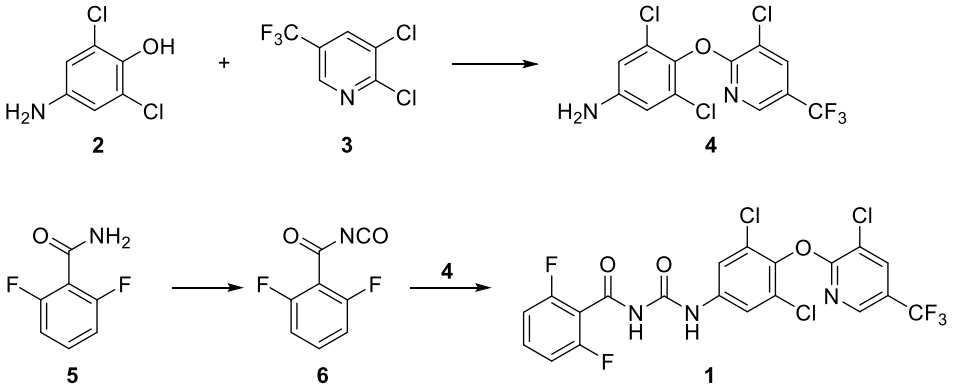
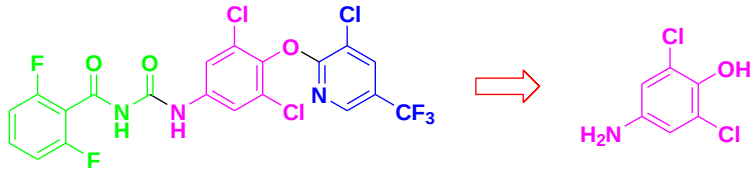
Abstract – An efficient and novel synthetic route of chlorfluazuron (**1**) on a ton scale has been developed, from the commercially available chemicals 3,5-dichloronitrobenzene, 2,3-dichloro-5-(trifluoromethyl)pyridine, and 2,6-difluorobenzamide. The key intermediate, 4-amino-2,6-dichlorophenol (**2**), was synthesized in one step by 3,5-dichloronitrobenzene with 78.1% yield and 99.5% purity. At the same time, 3,5-dichloroaniline (**15**), a co-product with great market demand, was also obtained with 20.9% yield and 99.2% purity. Chlorfluazuron (**1**) was obtained from 4-amino-2,6-dichlorophenol (**2**) in 91.9% yield over two steps and 99.2% purity. Compared with the original process route, the new synthetic route has the advantages of fewer reaction steps, higher overall yield, less process safety hazard and environmental impact.

INTRODUCTION

Chlorfluazuron (**1**, Scheme 1) is a type of benzoylphenylurea insecticide that can inhibit the synthesis of chitin of target pests and cause their death or infertility.[1-3] It is known as a third-generation insecticide and has attracted considerable attention because of its benign friendliness to mammals and broad-spectrum insecticidal activity against lepidopteran, coleopteran, orthopteran and other insect pests.[4-12] Various reports have indicated that the efficient synthesis of 4-amino-2,6-dichlorophenol (**2**) is central for producing chlorfluazuron (Figure 1). In the reported synthesis route, the key intermediate 4-amino-2,6-dichlorophenol (**2**) is used to etherify with 2,3-dichloro-5-trifluoromethylpyridine (**3**) to obtain the etherate 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)aniline (**4**), which then reacts with 2,6-difluorobenzoyl isocyanate (**6**) to obtain chlorfluazuron (**1**, Scheme 1).[13-15]

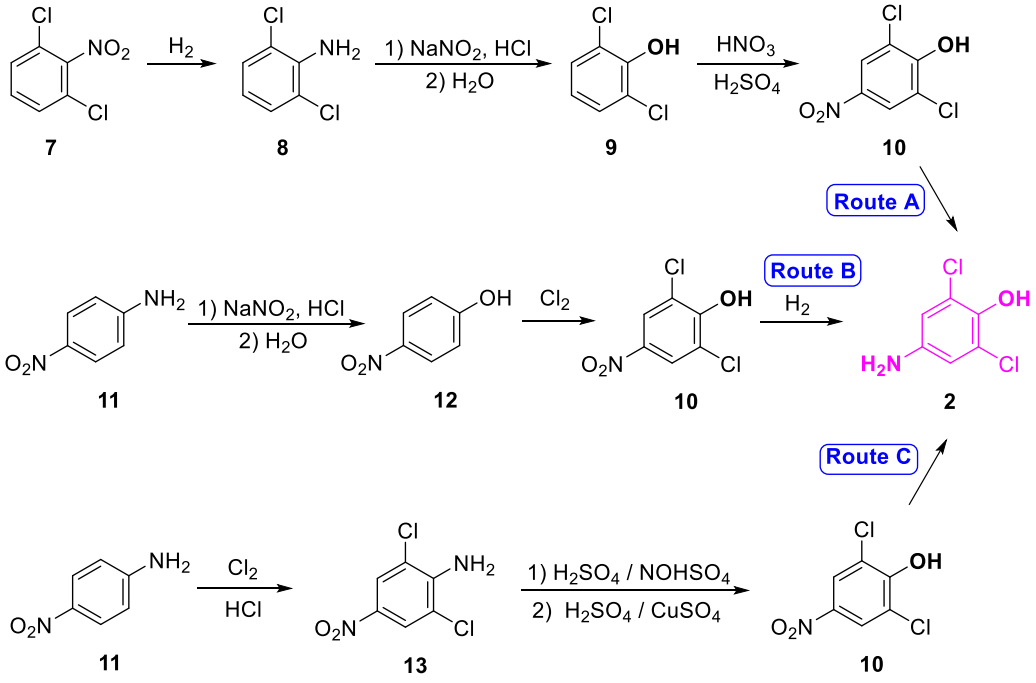


Scheme 1. The reported synthetic routes of chlorfluazuron (**1**)



Chlorfluazuron (**1**)

Figure 1. Structures of chlorfluazuron and its key inetrmediate **2**



Scheme 2. Reported synthetic routes for 4-amino-2,6-dichlorophenol (**2**)

Among several synthetic routes that have been reported, three have shown the potential for the mass production of 4-amino-2,6-dichlorophenol (**2**), a key intermediate of chlorfluazuron (Scheme 2). The first synthetic method (route A) of the key intermediate **2** is completed by 2,6-dichloronitrobenzene (**7**)

through 5 steps in around 72.3% overall yield.[16-18] In this synthtic route, the nitration reaction will produce isomers, and the purification of isomers is difficult. The second synthetic method (route B) of **2** is prepared from *p*-nitroaniline (**11**) through 4 steps in around 74.2% overall yield.[19-21] There are many isomers and the formation of monochlorinated nitrophenol in this route, results in difficult separation, low yield and high energy consumption. Same as the second synthetic route, the third synthetic method (route C) of **2** is also obtained from *p*-nitroaniline (**11**) through 4 steps in 73.5% overall yield.[22-24] Although some improvements have been made, this route still has shortcomings such as the production of monochloronitrophenol, poor selectivity, and difficulty in separation and purification.

In order to solve the problems of the above route, our research team tried a new method and achieved very unexpected results. In the company's conventional production line, 3,5-dichloroaniline (**15**), which had a large production capacity, was obtained using 3,5-dichloronitrobenzene (**14**) as raw material through traditional hydrogenation reduction methods. Recently, we have tried to use the Bamberger rearrangement method to obtain 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichlorobenzene (**15**) in a one-pot process, which not only achieves efficient synthesis of **2** in the ton scale, but also allows us to continue to produce **15** on a large scale. This method realizes the preparation of two products through one raw material and the total yield reaches 99%. It not only greatly improves the production efficiency and reduces the production cost, but also provides a very ideal method for the synthesis of 4-amino-2,6-dichlorophenol (**2**), the intermediate of chlorfluazuron (Figure 2).

Herein, a practical and novel synthetic route for the preparation of chlorfluazuron **(1)** was developed starting with commercially available 3,5-dichloronitrobenzene (**14**). This route generated chlorfluazuron in high purity and 71.8% overall yield on ton scale. This new route is also highly efficient and feasible for scale-up operations (Scheme 3).

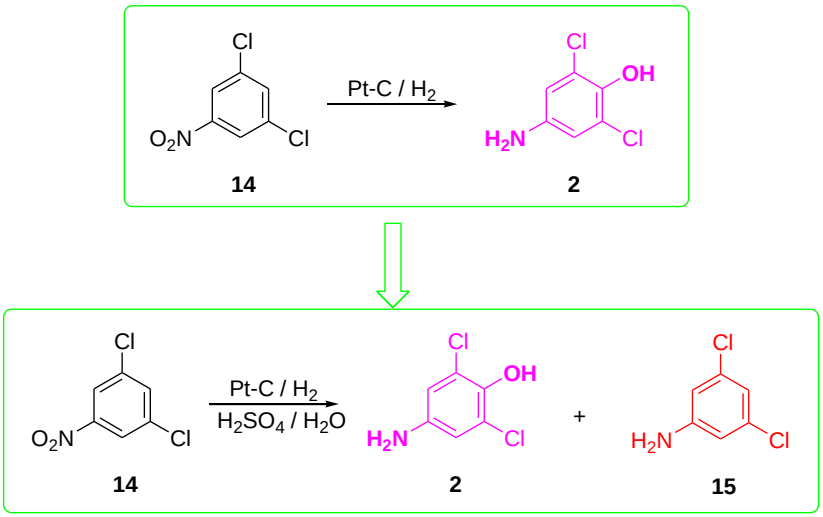
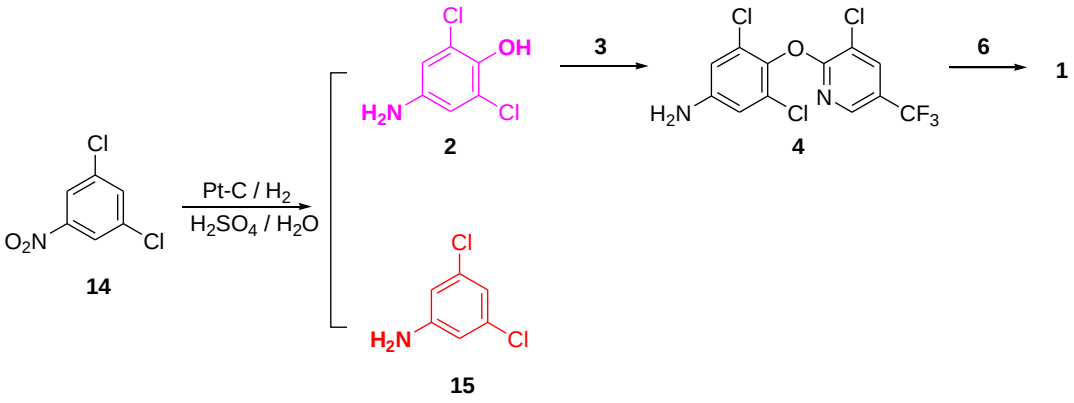


Figure 2. Results of two different hydrogenation conditions of 3,5-dichloronitrobenzene (**14**)



Scheme 3. An efficient and novel synthetic route of chlorfluazuron (**1**)

RESULTS AND DISCUSSION

Schematic mechanism for the hydrogenation of 14 to 2

As shown in Figure 3, the intermediate product 3,5-dichlorophenylhydroxylamine (**16**) can generate both 3,5-dichloroaniline (**15**) and 4-amino-2,6-dichlorophenol (**2**). Therefore, the yield of **2** is determined by the competition between these two parallel reactions. If the activity of the catalyst is high, **16** is easy to continue hydrogenation reduction to generate **15**, resulting in a high yield of **15** and a low yield of **2**. If the catalyst activity is low, it is advantageous for the active intermediate **16** to rearrange into **2** under acidic conditions. Therefore, to obtain a high yield of **2**, it is necessary to have a suitable catalyst activity.

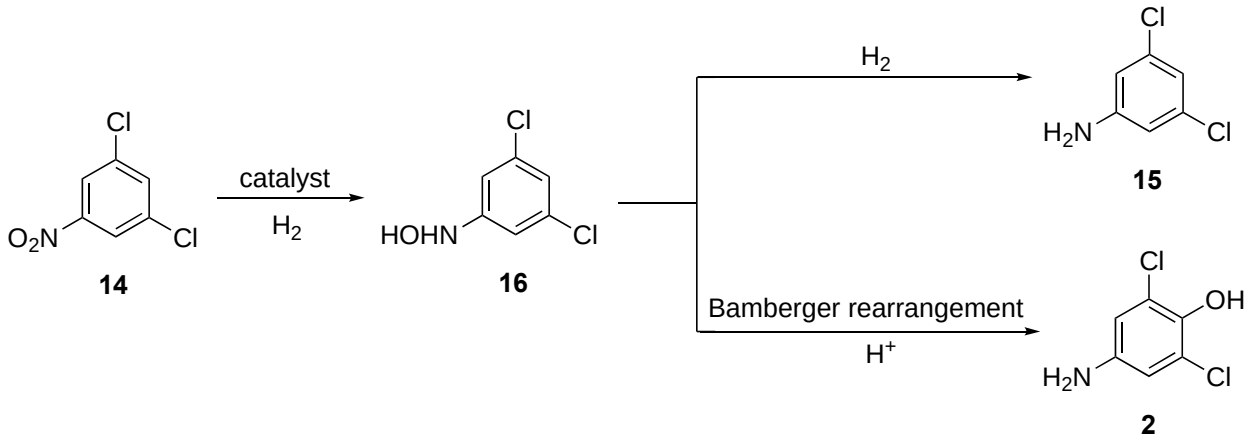


Figure 3. Schematic mechanism for the hydrogenation of **14** to **2**

Effect of catalytic conditions on the reduction reaction

We utilized **14** as the raw material to prepare **2** and performed condition screening. From Table 1, it can be seen that under the conventional reduction system (entry 1 – entry 3), **2** is not obtained and almost all

are **15**. Under the Pt/C catalytic system, adding dilute sulfuric acid (entry 4) results in the formation of **2**, with a ratio of 18.7 : 72.4 for **2** to **15**. After adding an appropriate amount of phase transfer catalyst TBAB (entry 5), the effect is significantly improved, because the reaction system is a "gas-liquid-solid" three-phase heterogeneous reaction. After adding the phase transfer catalyst, it is fully contacted to enhance the reaction effect.

On this basis, we attempted to add pyridine compounds (entry 6 - entry 9), such as 3-aminopyridine (3-AP), 4-aminopyridine (4-AP), 3,5-dimethylpyridine (3,5-DMP), and 2,6-dimethylpyridine (2,6-DMP), which significantly improved the reaction selectivity. With the addition of pyridine compounds, they play a role in passivating and poisoning the catalyst, causing a moderate decrease in catalyst activity, which is conducive to the occurrence of Bamberger rearrangement under acidic conditions, resulting in the main production of **2** in the reaction. Among these pyridine compounds, 4-AP has the relatively best effect (entry 7), with a selectivity of 78.1 : 20.9.

Furthermore, under the optimal conditions mentioned above (entry 7), we compared the selectivity of **2** under different temperatures and pressures (entry 10 - entry 13), and the selectivity did not exceed that of entry 7. Because high temperature and pressure enhance the reaction activity, it is not conducive to the Bamberger rearrangement reaction. However, if the temperature and pressure are too low, some raw materials may not be fully converted, which will also lead to a decrease in selectivity.

Finally, we also compared the differences between the other two commonly used catalysts, Pd/C and Ru/C, and Pt/C (entry14, entry15). The catalytic performance of different catalysts often varies significantly. Pd/C catalysts have strong attraction to oxygen atoms, resulting in a large amount of **15**. Ruthenium has stronger affinity than palladium, and chloronitrobenzene molecules are adsorbed on the surface of ruthenium, covering the active center, causing the catalyst to lose activity. Only platinum has a moderate adsorption capacity, allowing the reduced **16** to smoothly enter the acidic medium and rearrange into **2**, exhibiting high activity and selectivity. Therefore, we finally adopted entry 7 and synthesized **2** by this approach.

Table 1. Effect of catalytic conditions on the reaction of **2**

Entry	Reducing agent	Reaction conditions	Selectivity (**2** : **15**: impurities)
1	Fe + HCl	100 ℃, 0.1 MPa, 4 h	0 : 98.9 : 1.1
2	Raney Ni + H_2	80 ℃, 1.0 MPa, 4 h	0 : 99.2 : 0.8
3	Pt / C + H_2	80 ℃, 1.0 MPa, 4 h	0.2 : 99.1 : 0.7
4	Pt / C + H_2 + H_2SO_4	80 ℃, 1.0 MPa, 10 h	18.7 : 72.4 : 8.9
5	Pt / C + H_2 + H_2SO_4+TBAB	80 ℃, 1.0 MPa, 10 h	46.3 : 49.6 : 4.1
6	Pt / C + H_2 + H_2SO_4+TBAB+ 3-AP	80 ℃, 1.0 MPa, 10 h	76.4 : 22.1 : 1.5
7	Pt / C + H_2 + H_2SO_4+TBAB+ 4-AP	80 ℃, 1.0 MPa, 10 h	78.1 : 20.9 : 1.0
8	Pt / C + H_2 + H_2SO_4+TBAB+ 3,5-DMP	80 ℃, 1.0 MPa, 10 h	74.2 : 24.0 : 1.8
9	Pt / C + H_2 + H_2SO_4+TBAB+ 2,6-DMP	80 ℃, 1.0 MPa, 10 h	72.8 : 25.9 : 1.3
10	Pt / C + H_2 + H_2SO_4+TBAB+ 4-AP	80 ℃, 2.0 MPa, 10 h	62.7 : 34.1 : 3.2
11	Pt / C + H_2 + H_2SO_4+TBAB+ 4-AP	80 ℃, 0.5 MPa, 10 h	70.4 : 27.0 : 2.6
12	Pt / C + H_2 + H_2SO_4+TBAB+ 4-AP	65 ℃, 1.0 MPa, 10 h	72.3 : 23.2 : 4.5
13	Pt / C + H_2 + H_2SO_4+TBAB+ 4-AP	95 ℃, 1.0 MPa, 10 h	61.7 : 35.4 : 2.9
14	Pd / C + H_2 + H_2SO_4+TBAB+ 4-AP	80 ℃, 1.0 MPa, 10 h	27.2 : 70.8 : 2.0
15	Ru / C + H_2 + H_2SO_4+TBAB+ 4-AP	80 ℃, 1.0 MPa, 10 h	0 : 0 : 0

Effect of reaction temperature on etherification reaction

During the etherification reaction, we chose DMF as the solvent, KOH as the binding acid agent, and the molar ratio of **2** and **3** was 1:1 at different temperatures, and the results are shown in Figure 4 below.

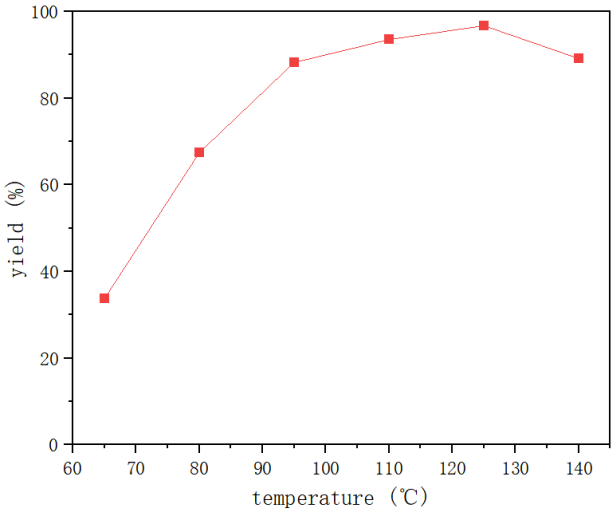


Figure 4. Effect of reaction temperature on etherification reaction

As can be seen from Figure 4, the yield of the etherification product increased and then decreased with the increase of temperature, and was best at 125 ℃. When the reaction temperature was lower than 65 ℃, the induction period of the reaction was long, which made the reaction difficult or insufficient and the yield was not high; with the increasing of the reaction temperature, the yield also showed an increasing trend. However, when the temperature was higher than 125 ℃, the curve showed a decreasing trend, which was because the side reaction caused by high temperature made the isomers more likely to occur and made the product yield decrease accordingly.

CONCLUSIONS

In this highly efficient process, there are mainly four significant process improvements. Firstly, 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichloroaniline (**15**) were efficiently obtained by the one-pot method using 3,5-dichloronitrobenzene (**14**) as the raw material, and the total yield reached 99%, meeting the market demand for both products at one time. Secondly, starting from 4-amino-2,6-dichlorophenol (**2**), each intermediate step in the synthesis process was not dried and purified, and the whole process was simple, which greatly shortened the production cycle, safe and environmental protection, and reduced the production cost. Thirdly, DMF was used as the solvent and potassium hydroxide was used as the acid binding agent in the synthesis of the ethers, and the highest yield of 96.7% was achieved at 125 ℃. After filtering to remove the inorganic salts, DMF was evaporated under reduced pressure, and toluene was added directly to the toluene solution to prepare compound **4**. The whole process is simple, high quality, low cost, less waste, more conducive to environmental protection, and more suitable for industrial production.

EXPERIMENTAL

All solvents and reagents were purchased from commerical suppliers and used without further purification. Melting points were recorded on an RY-1 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian INOVA-400 spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. HPLC area percent was established on an Agilent 1260 liquid chromatography system with a Zorbax Eclipse Plus C18 column, 250 mm × 4.6 mm (5 μm); λ = 254 nm; mobile phase: A (MeOH) and B (H_2O), 80:20 v/v. The HPLC analysis data is reported in area % and is not adjusted to weight %.

4-Amino-2,6-dichlorophenol (2) and 3,5-dichloroaniline (15)

Add 3,5-dichloronitrobenzene (**14**) (500 kg, 2.604 kmol), 30% sulfuric acid (150 kg, 0.459 kmol), deionized water (1500 kg), TBAB (2.5 kg, 7.764 mol), platinum/carbon catalyst with 5% platinum

loading (0.5 kg, 2.564 mol), and 4-aminopyridine (2.5 kg, 26.60 mol) to the 3000 L autoclave. The autoclave was replaced with N_2 and H_2 three times respectively, and then the reaction was carried out at a temperature of 80 ℃ and hydrogen pressure of 0.1 MPa for 10 h. Filtering the reaction solution at 60-80 ℃ to obtain the filtrate and the platinum/carbon catalyst, which is recycled back into the autoclave. The filtrate obtained above was cooled down to 0 ℃ and kept for 4 h, crystals were precipitated and filtered to obtain the crystalline liquor and the product of 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichloroaniline (**15**). The obtained crystalline liquor was returned to the autoclave for recycling. Water and sodium hydroxide solution was added to the filter cake to adjust pH=9 and stir for 30 min, and then filter to obtain 3,5-dichloroaniline (**15**). Finally, add 10% sulfuric acid to the filtrate to adjust pH=4 and filter to obtain 4-amino-2,6-dichlorophenol (**2**). The yields of 4-amino-2,6-dichlorophenol (**2**) and 3,5-dichloroaniline (**15**) were 78.1% and 20.9%, respectively.

4-Amino-2,6-dichlorophenol (**2**): white solid (362.0 kg, 78.1%), HPLC 99.5%, mp 167-170 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.20 (s, 2H, NH_2), 6.58 (s, 2H, C_6H_2), 8.87 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 113.8, 123.5, 139.1, 142.6; LC-MS *m/z*: 177.92.

3,5-Dichloroaniline (**15**): white solid (88.2 kg, 20.9%), HPLC 99.2%, mp 48-49 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (s, 2H, NH_2), 6.52 (s, 2H, C_6H_3), 6.71 (s, 1H, C_6H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.2, 113.3, 118.4, 135.5, 148.3.

3,5-Dichloro-4- (3-chloro-5-trifluoromethyl-2-pyridyloxy)aniline (4)

In a 3000 L glass lined reactor, 4-amino-2,6-dichlorophenol (**2**) (362 kg, 2.034 kmol), potassium hydroxide (120 kg, 1.928 kmol), DMF (600 L) and 2,3-dichloro-5-trifluoromethylpyridine (**3**) (440 kg, 2.037 kmol) were reacted at 125 ℃ for 2 h. Samples were taken and tested, and the residue was qualified when 2,3-dichloro-5-trifluoromethylpyridine (**3**) was ≤0.5%. Remove DMF by evaporation under reduced pressure to 120 ℃, lower the temperature to below 20 ℃, remove inorganic salt by filtration, recover DMF by concentration under reduced pressure, add 1500 L of toluene and 1000 L of tap water to the residue in turn, stir for 30 min, and let stand and stratify. The upper layer of toluene solution was partitioned by reflux to obtain 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridoxyl)aniline (**4**) in toluene solution, which was directly used in the next reaction with a calibrated yield of 96.7%.

2,6-Difluorobenzoyl isocyanate (6)

2,6-Difluorobenzamide (**5**) (318 kg, 2.027 kmol) and toluene (800 L) were put into the 2000 L reaction kettle and stirred, oxalyl chloride (270 kg, 2.126 kmol) was slowly added dropwise at room temperature. After dropping, the temperature was slowly raised to reflux for 4 h, and the tail gas was absorbed by water. After refluxing, the temperature is lowered, the excess oxalyl chloride is recovered by rotary

evaporation, and the distillation product is a toluene solution of 2,6-difluorobenzoyl isocyanate (**6**), which was directly used in the next reaction with a calibrated yield of 97.2%.

Chlorfluazuron (1)

In a 3000 L glass lined reactor, 3,5-dichloro-4-(3-chloro-5-trifluoromethyl-2-pyridoxyl)aniline (**4**) (1.967 kmol) and toluene (1500 L) were put into and stirred, the toluene solution of 2,6-difluorobenzoyl isocyanate (**6**) (1.970 kmol) was slowly added dropwise at room temperature. After dropping, the temperature was slowly raised to reflux for 2 h, then the mixture was cooled, filtered with suction, and dried to afford a white solid.

Chlorfluazuron **(1)**: white solid, 1010 kg, yield 95.0%, HPLC 99.2%, m.p.231-233 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04-7.08 (m, 2H, C_6H_2), 7.47-7.57 (m, 3H, C_6H_3), 8.02-8.03 (m, 1H, C_5NH_2), 8.23-8.24 (m, 1H, C_5NH_2), 9.94 (s, 1H, NH), 10.70 (s, 1H, NH); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.37～-62.10 (m, 3F), -110.62～-110.66 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.2 (t, *J* = 18.3 Hz), 112.9-112.3 (m), 119.0, 120.3, 122.9 (q, *J* = 272.2 Hz), 123.5 (q, *J* = 33.9 Hz), 129.5, 134.2 (t, *J* = 10.4 Hz), 135.7, 136.3 (q, *J* = 3.0 Hz), 142.2, 142.7 (q, *J* = 4.2 Hz), 151.5, 159.5, 160.1 (dd, *J* = 255.6, 5.8 Hz), 162.9; LC-MS *m/z*: 537.91.

ACKNOWLEDGEMENTS

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