CHE261 PATENT APPLICATION

APPLICANT	Mollycule
INVENTORS	Somya Yadav , Dhruv Bajaj
CHEMICAL FORMULA	C7H5Cl2FN2O3
CHEMICAL NAME	Fluroxypyr

a) Synthesis of Fluroxpyr

fluroxypyr at lab-scale can be achieved through a simplified phase transfer catalysis method.

Starting material:

4-Amino-3,5-dichloro-2,6-difluoropyridine (CAS 2176-62-7)

Reagents:

- Ethyl glycolate (CAS 623-50-7)
- Potassium carbonate (K_2CO_3)
- Tetrabutylammonium iodide (phase transfer catalyst)
- Toluene (solvent)
- Dilute hydrochloric acid (HCl) or sulfuric acid (H_2SO_4) for acidification
- Deionized water

Utilities required

- Heating and cooling Units
- Vacuum units
- Water supply and treatment
- Air and Gas supply
- Electrical Power
- Analytical Equipment
- Safety Equipment
- Storage Facilities

1. Reaction Setup

Use a round-bottom flask equipped with a reflux condenser and a nitrogen inlet. Add:

- 4-Amino-3,5-dichloro-2,6-difluoropyridine (10 g, 1 eq)
- Toluene (100 mL)
- K_2CO_3 (acid-binding agent, 1.2 eq)
- Tetrabutylammonium iodide (catalyst, 0.05 eq)

Stir the mixture at room temperature until fully dissolved.

2. Esterification

- Add: Ethyl glycolate (1.1 eq) dropwise under nitrogen.
- Heat: Reflux at **80–100°C for 10–12 hours** (monitor via TLC/HPLC).
- **Yield: ~90–95% of fluroxypyr ethyl ester (intermediate).**

3. Workup

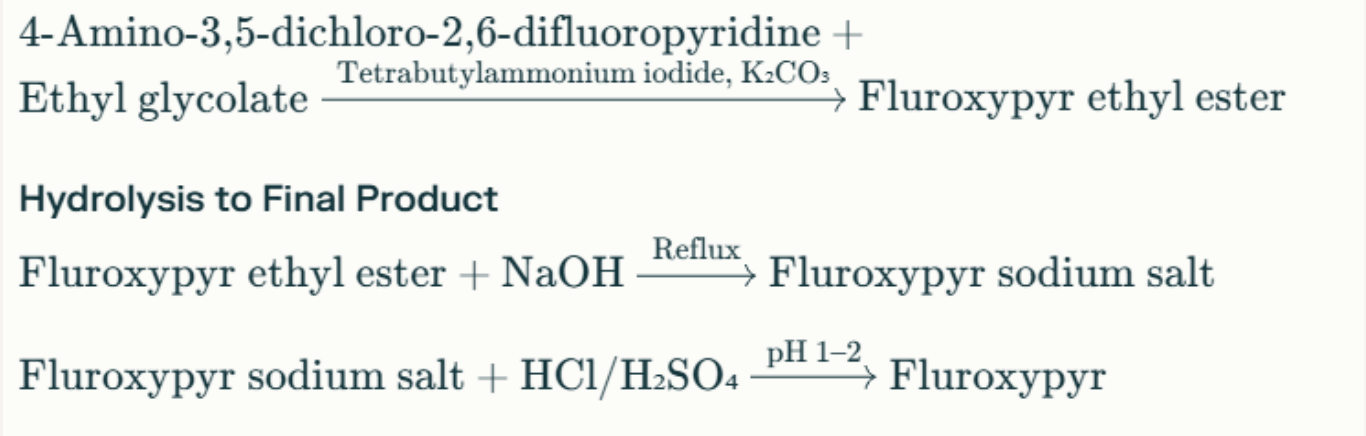
- Cool the reaction mixture to room temperature.
- Add water (50 mL) and stir for **15 minutes.**
- Separate layers: Extract the organic (toluene) layer.
- Dry: Use anhydrous Na_2SO_4, then filter and concentrate under reduced pressure.

4. Hydrolysis to Final Product

- Dissolve the ester intermediate in NaOH solution (1M, 50 mL).
- Heat: **Reflux at 90°C for 2 hours.**
- Acidify: Slowly add dilute HCl/H_2SO_4 to **pH 1–2 to precipitate fluroxypyr.**
- Filter and wash the solid with cold water.
- Dry: Vacuum-dry at **50°C for 6 hours.**

Final product: White crystalline solid, 85%-95% purity (HPLC).

Reaction Equation



Reaction conditions:

Catalyst loading = 0.05–0.1 eq (vs. substrate)
Temperature = 80–100°C (esterification)
Reaction time = 10–12 hours
Acidification pH = 1–2 (critical for purity)

Separation steps for Final Purity

To achieve high purity, the following separation steps are employed:

1. Liquid-Liquid Extraction
   - After hydrolysis, the reaction mixture is cooled and subjected to liquid-liquid extraction to separate the organic layer containing fluroxypyr from the aqueous phase.
   - Water is added to the mixture, and the organic layer is extracted using solvents like toluene or ethyl acetate.
   - This step helps **remove water-soluble impurities** and concentrates the product in the organic phase.
2. Drying and Concentration
   - The organic layer is dried with anhydrous Na_2SO_4 to remove any residual water present.
   - The solution is then concentrated under reduced pressure using a rotary evaporator to remove excess solvent.
   - Drying prevents hydrolysis during storage, and concentration increases the product's concentration for easier crystallization.
3. Crystallization
   - The concentrated solution is cooled slowly to allow crystallization of fluroxypyr.
   - Crystallization is an effective method for purifying the product by removing impurities that do not crystallize under the same conditions.
   - This step **significantly enhances purity by selectively precipitating** the desired compound.
4. Filtration
   - After crystallization with the help of a Büchner funnel the crystallized product are separated.
   - Then Washing the solid with cold water remove the impurities present in it.
   - Filtration process is crucial as it separates the solid product from any remaining impurities or solvents.
5. Vacuum Drying
   - On Drying the filtered solid under vacuum at 50°C for several hours gives us the ***final product that has high purity(>95%)***
   - This step is important during the separation process as it removes any residual moisture present, ensuring the product's stability and high purity.

The final yield in terms of purity is >95%, indicating that the separation process effectively removes impurities. However, the overall yield of the process (amount of product obtained) is typically 85–95%

Reference(s)

- https://pubchem.ncbi.nlm.nih.gov/compound/Fluroxypyr
- https://fzgxjckxxb.com/wp-content/uploads/2022/11/34-JBS1609.pdf
- https://patents.google.com/patent/CN106187872A/en
- https://chemicalengineeringguy.com/the-blog/general/most-common-separation-processes/

b) Another method of Synthesis of Fluroxpyr

This method of synthesis is based on a technical bulletin from Agriguard ltd. for the use on broad-leaf plants and is a **four** step process.

Abstract:

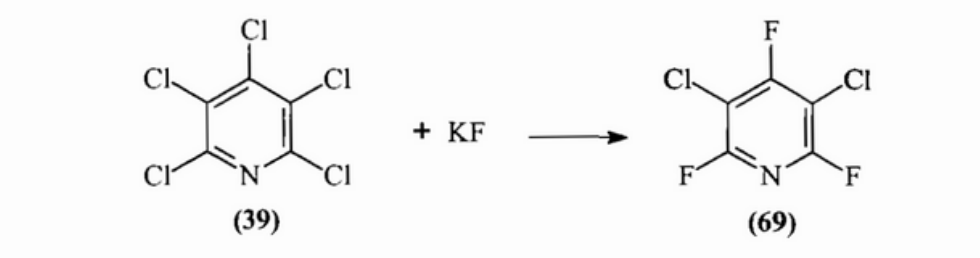
This process starts from **Pentachloropyridine** via **3,5-dichloro-2,4,6-triflouropyridine** which is then converted to **potassium 4-amino-3,5-dichloro-6-fluoro-pyridinate** by treatment with ammonia and then potassium hydroxide. The potassium salt formed without isolation is treated with methyl chloroacetate and subsequently by treatment with 2-octanol its converted to **fluroxypyr**.

Raw Materials & Reagents:

1. Pentachloropyridine
2. Potassium fluoride (KF)
3. Sulfolane (solvent)
4. Ammonium hydroxide (NH_4OH)
5. Potassium hydroxide (KOH)
6. Methyl chloroacetate ($ClCH_2COOCH_3$)
7. N-Methylpyrrolidone (NMP, solvent) (75)
8. 2-Octanol ($CH_3(CH_2)5CH(OH)CH_3$) (74)
9. Tetrabutyl titante (catylyst for the final reaction)

Reactions Steps:

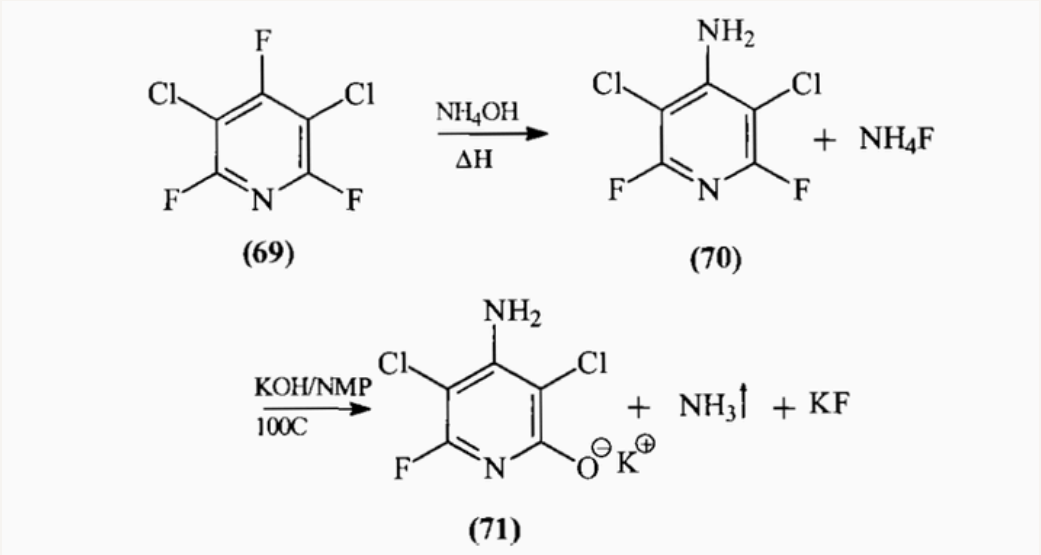
Stage 1 - synthesis of 3,5-dichloro-2,4,6-triflouropyridine(69)



(39) (69)

- The first reaction (using sulpholane as solvent) involving a nucleophilic substitution reaction of pentachloropyridine(39) reacting with **potassium fluoride** to obtain 3,5-dichloro-2,4,6-triflouropyridine(69).
- The molar ratio of pentachloropyridine(39) to potassium fluoride is **1:5**
- The reaction conditions reported were at 192°C and the amount of solvent used is **200g**.
- The maximum yield of **76%** is reached after **30 minutes**.

Stage 2, synthesis of potassium 4-amino-3,5-dichloro-6- fluoro-2-pyridinate (71) from 3,5-dichloro-2,4,6-trifluoropyridine (69).

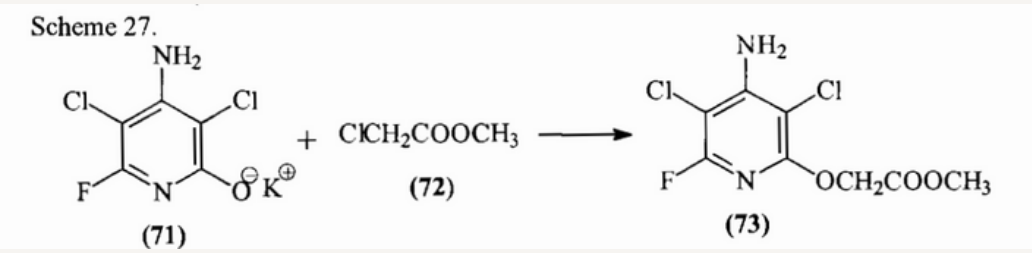


(69) (70) (71)

- The second stage of the process involves ammonation followed by the hydrolysis without the removal of the ammonium fluoride produced in the ammonation of 3,5-dichloro-2,4,6-trifluoropyridine (69) as shown in the reaction above.
- The molar ratio of 3,5-dichloro-2,4,6-trifluoropyridine (69) to ammonia is **1:3**.
- The yield of **97%** was found using 25% ammonia solution and 40% potassium hydroxide solution.
- The excess ammonia was removed as a gas by heating.

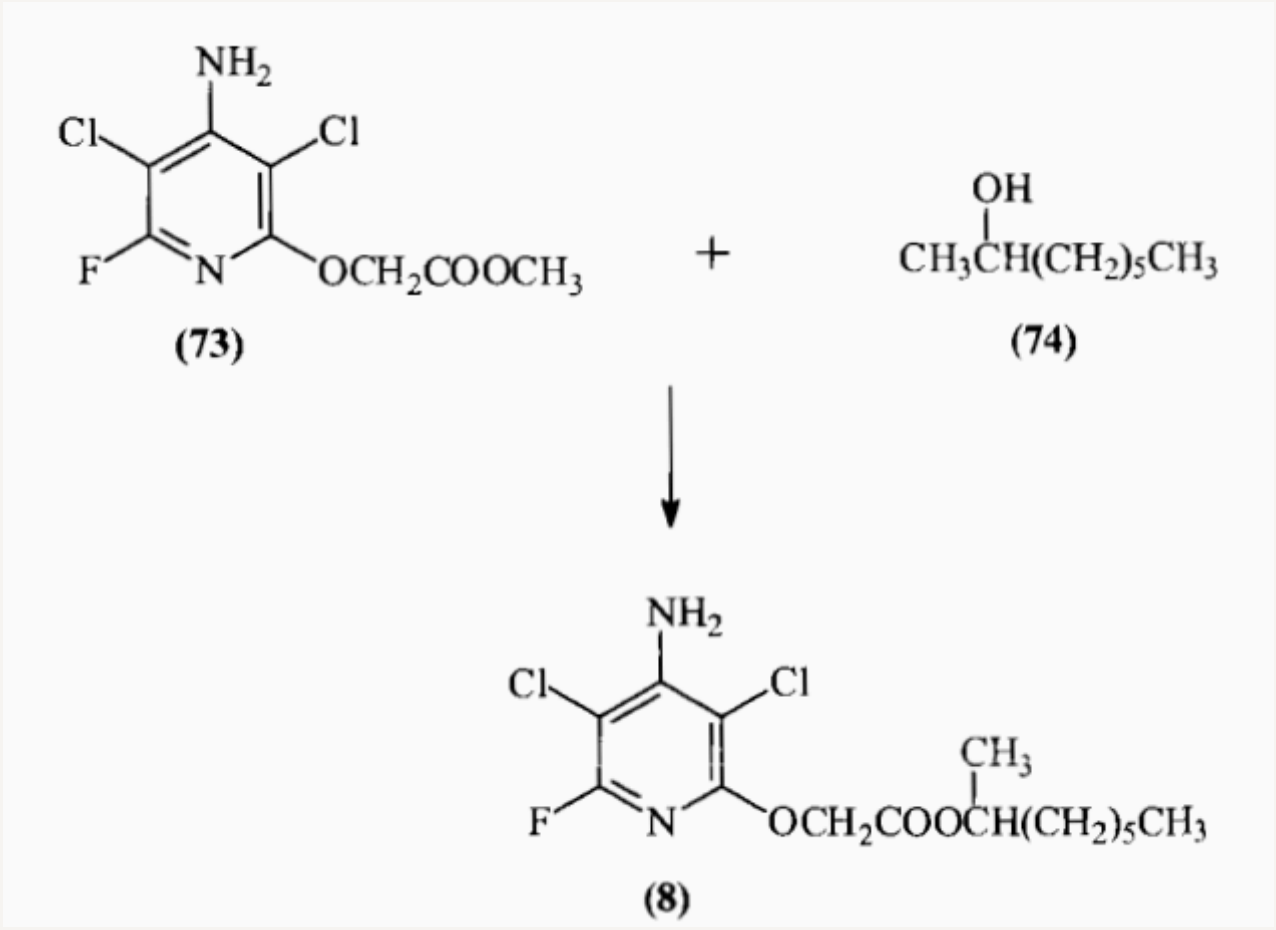
- Potassium fluoride and potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71) were separated by adding **N-methyl-2-pyrrolidone (NMP)** to the aqueous mixture, forming two liquid phases. The bottom aqueous phase contained potassium fluoride, while the upper organic phase held compound (71) in NMP. The layers were separated by decantation, and residual water in the organic phase was removed by distillation.

Stage 3, the synthesis of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) from potassium 4-amnio-3,5-dichloro-6-fluoro-2-pyridinate (71).



- The third stage of the process involved the alkylation of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71) with **methyl chloroacetate (72)**, as shown above.
- The ratio of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71) to methyl chloroacetate (72) is **1:1.1** .
- The reaction gets completed in 2 hours on a **250cm³ scale** involving 0.05 moles of potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71). The yield of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) was **80%** with respect to 3,5-dichloro-2,4,6-trifluoropyridine (69).
- The product has a melting point of 124.5°C -125.5°C.

Stage 4, synthesis of 1-methylheptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (8) [FLUROXYPYR] from methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73).



- The fourth and final stage of the process involved the transesterification of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) to 1-methyl heptyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (8) **[Fluroxypyr]** with 2-octanol (74) as shown above.
- The optimal reaction ratio of methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) to 2-octanol (74) is **1:3** .
- The reaction was conducted in the presence of a catalyst tetrabutyl titanate at **180°C**.
- The reaction time is 1 hour when using a 10gram scale of methyl (4- amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) and yielded **93%** 1-methylheptyl (4-amino-3,5-dichloro-6-luoro-2-pyridinyloxy) acetate (8) as a light brown solid.
- The reaction is carried out in 1-liter reaction vessel fitted with an overhead mechanical stirrer, fractionation column (30cm³) with a distillation head and vacuum source.

Separation and Purification Steps

The separation and purification of Fluroxypyr in this method involved the following key steps:

1. **Phase Separation** (After Ammonation and Hydrolysis – Stage 2)
    - Potassium fluoride and potassium 4-amino-3,5-dichloro-6-fluoro-2-pyridinate (71) were separated by adding **N-methyl-2-pyrrolidone (NMP)** to the aqueous mixture.
    - This created two liquid phases:
        - Bottom phase: Water containing excess potassium fluoride (removed by decantation).
        - Upper phase: Organic NMP layer containing compound (71).
    - Any residual water in the organic phase was removed by distillation under reduced pressure.
2. **Organic Layer Extraction** (After Esterification – Stage 3)
    - The reaction mixture containing methyl (4-amino-3,5-dichloro-6-fluoro-2-pyridinyloxy) acetate (73) was **cooled**.
    - The product was extracted into ethyl acetate or toluene, separating it from unreacted reagents and side products.
3. Drying and Solvent Removal
    - The organic phase was dried using **anhydrous sodium sulfate (Na_2SO_4)** to remove residual moisture.
    - The solvent was evaporated under reduced pressure using a **rotary evaporator**.
4. Transesterification & Post-Reaction Purification (Stage 4)
    - After the transesterification step with 2-octanol, excess alcohol and residual solvent were removed via **vacuum distillation**.
    - The crude **Fluroxypyr** (8) was obtained as a **light brown solid**.

*The final yield in terms of purity is >**94%**,. However, the **overall yield** of the process (amount of product obtained) is typically **47.8%** and by adjusting the mol ratios we could go upto **54.2%**.*

Reference(s)

- https://arrow.tudublin.ie/scienmas/26/
- https://patents.google.com/patent/CN106187872A/en
- https://chemicalengineeringguy.com/the-blog/general/most-common-separation-processes/

List of contributors of each author:

Somya yadav (231023)

- Designed and implemented a chemical synthesis route for the production of fluroxypyr including raw material selection and process design
- contributed to the development and optimization of various stages in the synthesis process, such as esterification and all

- Adjusted the reaction conditions to increase the yield and understand the reaction mechanism more clearly. Also, observed the separation process to better compare and evaluate the yield under different conditions.

Dhruv Bajaj (230365)

- Contributed to the development of an alternative synthesis route for Fluroxypyr by researching and analyzing process efficiency and yield optimization.
- Adjusted reagent molar ratios and solvent selection to streamline the reaction mechanism in various reactions, thereby reducing processing time and energy consumption.
- Introduced modifications in reaction conditions to suppress side reactions and also introducing catalysts in reactions like transesterification, leading to a cleaner synthesis with higher selectivity for the desired product thereby increasing the final purity.

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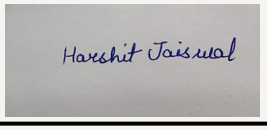
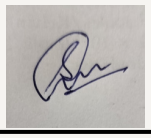
HARSHITJAISWAL	230460	
SOMYA YADAV	231023	
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