# CHE261 PATENT APPLICATION

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| **APPLICANT** | Mollycule |
| **INVENTORS** | Dhruv Bajaj, Somya Yadav |
| **CHEMICAL FORMULA** | $C_{10}H_{11}N_5O$. |
| **CHEMICAL NAME** | Pymetrozine |

## Intoduction

Pymetrozine is a specialty insecticide that uniquely targets insect feeding behavior, making it effective against pests like aphids while being safer for beneficial insects.

## a) Synthesis of Pymetrozine

Pymetrozine can be prepared at lab scale by a simple **3-step** process.

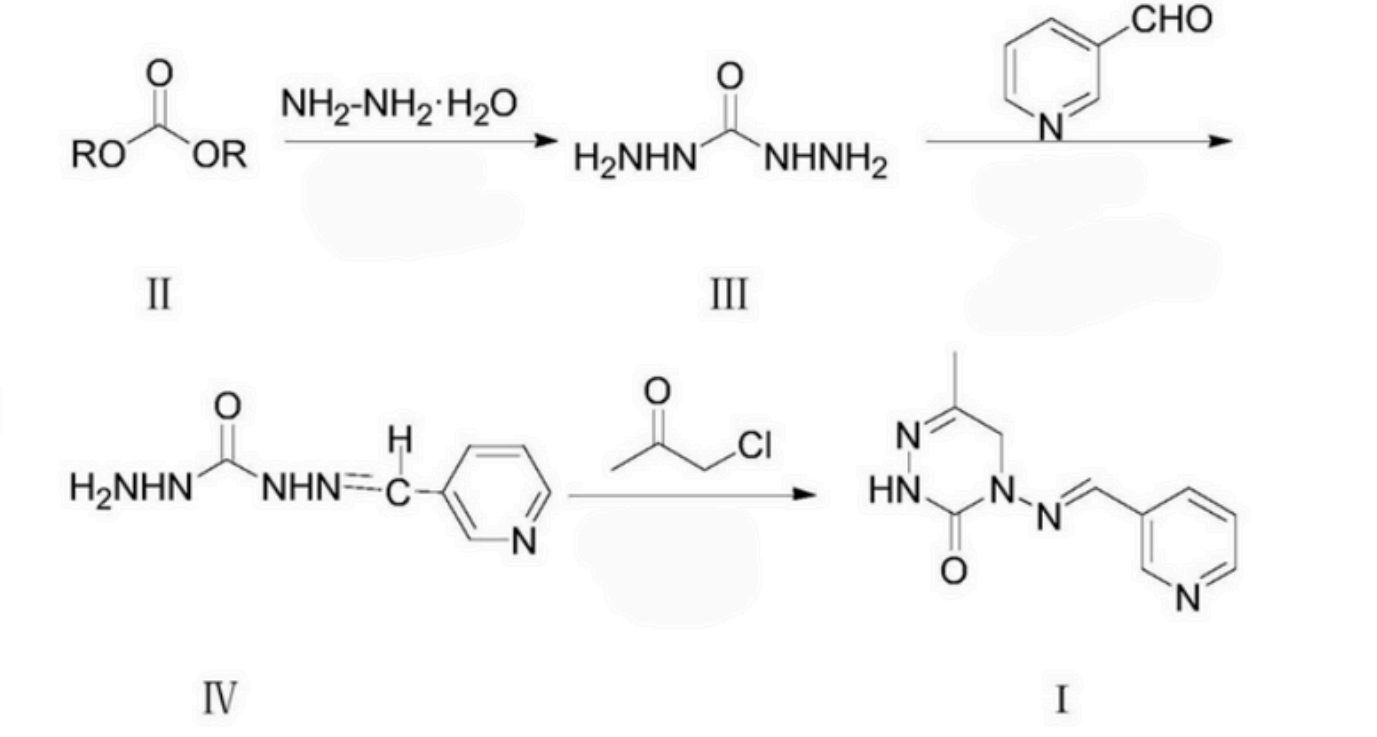

**Abstract:**

This process is a three-step synthesis for pymetrozine. In the first step, a **hydrazidation** reaction converts the **carbonate ester (II)** into **hydrazide (III)** using **hydrazine hydrate** in a suitable solvent. The second step involves a **condensation** reaction between hydrazide (III) and 3-formylpyridine, forming intermediate (IV). Finally, a **cyclization** reaction between intermediate (IV) and monochloroacetone, in the presence of an acid-binding agent, yields **pymetrozine (I).**


**Raw Materials & Reagents:**

1. Carbonate ester (ROCOOR)
2. Hydrazine hydrate
3. methanol,ethanol (solvent)
4. 3-formylpyridine
5. monochloroacetone
6. potassium carbonate/sodium carbonate (acid binding agent)

**Overall Reaction:**




**Stage 1 - preparation of Carbodihydrazide (III)**

- In step (1), the hydrazidation reaction of the **carbonate ester (II)** and **hydrazine hydrate** is carried out in solvent A, preferably, the solvent A is one or a combination of two or more of water, methanol or ethanol; the mass ratio of the solvent A to the compound of formula II is (**3-7**).

- Preferably In step (1), the hydrazidation reaction temperature of the compound of formula II and hydrazine hydrate is **75-80°C.**

- In (1) preferably, the molar ratio of the hydrazine hydrate and the compound of formula II is (**2.2 - 3.0 mol**). Generally reaction takes 2-4 hrs to complete.

- In a 1000 ml four-necked flask equipped with a stirrer, thermometer, and reflux condenser was charged with 200 g of ethanol, 200 g of water, 118.1 g (1.0 mol) of diethyl carbonate (II), and 275.0 g (2.2 mol) of 40% hydrazine hydrate. The mixture was heated and stirred at 75–80°C for 2 hours.

- After completion of the reaction, the mixture was cooled to 20–25°C, filtered, and the filter cake was washed with 20 g of water. The solid product was then dried to yield 88.9 g of carbodihydrazide (III) with a yield of **98.8%** and a liquid-phase purity of **99.9%**..

**Stage 2- The synthesis of pyridin-3-ylmethylenecarbodihydrazide (IV)**

- In step (2), the condensation reaction of 3-formylpyridine and Carbodihydrazide (III) is carried out in solvent B, Preferably, the solvent B is one or a combination of water, methanol, ethanol, isopropanol, tert-butanol, acetonitrile, chloroform, 1,2-dichloroethane, tetrahydrofuran, 2-methyltetrahydrofuran or toluene.

- Preferably, the mass ratio of the solvent B and the compound of formula III is (**5-10**). and the molar ratio of the Carbodihydrazide (III) and 3-formylpyridine is (**0.95-1.1**).

- In step (2), 3-formylpyridine is added to the system in a dropwise manner, the dropping temperature is **45-90°C**, and the dropping time is 2-4 hrs.

- Into a 1000 ml four-necked flask equipped with a stirrer, a thermometer, a constant pressure dropping funnel and a reflux condenser were charged 200 g of ethanol, 100 g of water, 45.0 g (0.5 mol) of carbonyldihydrazide (III) were heated while maintaining the temperature between 65 and 70 ℃.

- The solution of 53.0 g (0.5 mol) of 3-formylpyridine and 100 g of ethanol was added dropwise thereto over 3 hours, followed by stirring at 70 to 75 ℃ for 3 hours, cooling to 20 to 25 ℃, filtration, washing the filter cake with 30 g of water, and drying to obtain 89.0 g of **pyridin-3-ylmethylenecarbonyldihydrazide (IV)**.

*The yield obtained was **99.4%**, and liquid phase purity **99.9%**.*

**Stage 3- Preparation of pymetrozine (I)**

- now, the **cyclization** reaction of the compound of formula IV and **monochloroacetone** is carried out in solvent C under the action of an acid binding agent.

- Preferably, the solvent C is one or a combination of water, methanol, ethanol, isopropanol, tert-butanol, acetonitrile, chloroform, 1,2-dichloroethane, tetrahydrofuran, 2-methyltetrahydrofuran or toluene.

- Preferably, the mass ratio of the solvent C and the compound of formula IV is (**4-9**) and the acid binding agent is potassium carbonate or sodium carbonate.

- The mol ratio of acid binding agent to compound IV is 0.5-1.1 and the mol ratio of monochloroacetone to compound IV is 0.95-1.1 .

- Preferably, the cyclization reaction temperature is 40-70°C and cyclization reaction time is 2-6 hours.

- now In a 1000 ml four-necked flask equipped with a stirrer, a thermometer, a constant pressure dropping funnel and a reflux condenser, 200 g of ethanol, 100 g of water, 34.5 g (0.25 mol) of potassium carbonate, 71.6 g (0.4 mol) of pyridin-3-ylmethylenecarbonyldihydrazide (IV) prepared earlier are heated and maintained at 50 to 55 ℃ and added dropwise with a mixed solution of 40.7 g (0.44 mol) of monochloroacetone and 50 g of ethanol.

- after 3 hours of dropwise addition, stirred at 55 to 60 ℃ for 3 hours of reaction, cooled to 20 to 25 ℃, filtered, and the filter cake was washed with 30 g of water and dried to obtain 83.9 g of pymetrozine (I), the yield was 96.6%, and the liquid phase purity was 99.3%.

**Reaction conditions (Summary)**

1. Hydrazidation
- Materials: Dialkyl carbonate (1 mol) + hydrazine hydrate (2.2–3.0 mol)
- Solvent: Water or methanol
- Temperature: 75–80°C
- Time: 2-4 hours

2. Condensation
- Materials: Carbodihydrazide (1 mol) + 3-formylpyridine (1 mol)
- Solvent: Ethanol or THF
- Temperature: 50–90°C
- Time: 2–4 hours

3. Cyclization
- Materials: Compound IV (1 mol) + monochloroacetone (1.05 mol)
- Solvent: Ethanol or THF
- Temperature: 40–70°C
- Time: 2–6 hours

**Seperation step for final purity**

The separation process involves crystallization, filtration, washing, drying, and optional recrystallization to achieve high purity.

**1. Cooling Crystallization**

- Procedure: After the final cyclization reaction, the reaction mixture is cooled to 30–80 °C to initiate crystallization.
- Purpose: cooling allows pymetrozine to precipitate out of the solution as solid crystals.

Ensuring gradual cooling to avoid impurities being trapped within the crystal lattice.

**2. Suction Filtration**

- Procedure: The crystallized pymetrozine is collected using suction filtration.
- Equipment: Use a Buchner funnel and vacuum pump for efficient filtration.
- Purpose: It's to separate solid pymetrozine from the liquid reaction mixture (mother liquor).

**3. Washing**

- Procedure: Wash the filtered solid twice with distilled water (100 mL per wash) or ethanol (150 mL per batch).
- Purpose: Remove residual solvents, by-products, and impurities adhering to the crystal surface.

Using cold washing solutions to prevent dissolution or degradation of pymetrozine.

**4. Drying**

- Procedure: Dry the washed pymetrozine under warm air at 100–105°C for 2–4 hours.
- Equipment: Use a hot-air oven or vacuum dryer for uniform drying.
- Purpose: To remove moisture and residual solvents completely.

**5. Recrystallization (Optional)**

- Procedure: Dissolving crude pymetrozine in hot ethanol or methanol until fully dissolved and then gradually cooling the solution to room temperature and then further to 0–10°C for recrystallization.
- Purpose: This enhances purity by removing remaining impurities trapped in the initial crystallization process.

This step is usually performed slowly to ensure high-quality crystal formation and with high-purity solvents for optimal results.

***After the synthesis process, the crude pymetrozine typically has a purity of approximately 99.3%. and after the separation process, the purity increases to ≥99.5%. This improvement was achieved by removing residual impurities and byproducts trapped during synthesis.***

## Reference(s)


- https://patents.google.com/patent/CN111943931A/en
- https://www.proquest.com/docview/2103953502
- https://patents.google.com/patent/CN104803936A/en


## b) Another method for the synthesis of Pymetrozine

The alternative synthesis route for the pymetrozine, a selective insecticide is below and mainly a **three** step process.

### Raw Materials and Chemicals Needed

- Kharophen triazone
- Acid (HCl or $H_2SO_4$) – Used for acidolysis reaction.
- Nicotinaldehyde
- Solvents: Ethanol, Methanol, Water
- Alkali (NaOH or KOH)

## Reaction Steps

**Step 1**: **Acidolysis Reaction (Formation of Aminotriazine Acid Salt)**

$$C_5H_5N_3O + HCl \rightarrow C_5H_6N_3O^+Cl^-$$

The first step involves the **acidolysis** of **kharophen triazone** in the presence of a mineral acid (e.g., HCl, $H_2SO_4$, $H_3PO_4$) to form aminotriazine acid salt. This reaction enhances stability and prevents unwanted decomposition. The raw materials for lab scale are kharophen triazone (100.0 g), acid (preferred 31% HCL and pure solvent(31%). The yield is **98%** for this step.

In a 1000 mL four-necked reaction flask equipped with a stirrer, thermometer, condenser, and dropping funnel, add 500 mL of pure water at room temperature, with continuous stirring, slowly add 100.0 g of kharophen triazone to the flask. Now gradually add 99.0 g of 31% hydrochloric acid dropwise while maintaining a reaction temperature of **30–60°C**. Continue stirring and heating for **3.0–10.0** hours until the reaction is complete. Upon completion, cool the reaction mixture to 30–40°C before proceeding to the next step.

### Step 2: Condensation Reaction (Formation of Pymetrozine Hydrochlorate)

- The **aminotriazine acid salt** undergoes a **condensation** reaction with **nicotinaldehyde**, forming **pymetrozine hydrochlorate**, an essential intermediate before final neutralization. The raw materials for this step are Aminotriazine acid salt (formed in Step 1), Nicotinaldehyde solution (20–30% concentration) – 295 g and as a solvent: Methanol or ethanol – 500 mL. The yield is **96-98%.**

In a 1000 mL reaction flask (equipped with a stirrer, thermometer, and dropping funnel), maintain the reaction temperature at **30–90°C**, add 500 mL of methanol and stir while gradually adding 295 g of nicotinaldehyde solution over **1.5–3.0 hours** and after complete addition, continue stirring for another 1.0–2.0 hours at the same temperature. Upon completion, cool the reaction mixture to 30°C before moving to the next step.

$$C_5H_6N_3O^+Cl^- + C_6H_5NO \rightarrow C_{11}H_{11}N_5O^+Cl^-$$

## Step 3: Neutralization Reaction (Formation of Pymetrozine)

**Pymetrozine hydrochlorate** is neutralized using an alkali to yield **pymetrozine** in its final purified form. The pH is carefully controlled to optimize product crystallization. The raw materials required are

- Pymetrozine hydrochlorate (from Step 2)
- Alkali: 17% Ammoniacal liquor – 105.5 g
- Solvent: Water or ethanol – 500 mL

In a 1000 mL reaction flask, add 500 mL of ethanol or water and begin stirring. Slowly add 105.5 g of 17% ammoniacal liquor dropwise over **1.0–3.0 hours**, maintaining a temperature of **30–90°C**. Monitor the pH of the reaction system, ensuring it remains within 6.5–7.5. Continue stirring for 3.0–8.0 hours to ensure complete neutralization. After reaction completion, cool the mixture to 20–30°C, induce crystallization, and filter the solid product and Wash with 100 mL of water, then dry at 100–105°C for 3–4 hours.

The purity generally is **97.2–98.0%** (after crystallization and drying).

$$C_{11}H_{11}N_5O^+Cl^- + NH_3 \rightarrow C_{10}H_{11}N_5O + NH_4Cl$$

## Separation and Purification

**Crystallization**: Cool the reaction mixture from 90°C to room temperature, then further cool to approximately 0–10°C to promote crystallization.

**Filtration**: using suction filtration to separate solid pymetrozine from the mother liquor.

**Washing**: Washing the filtered solid with cold ethanol (approximately 150 mL per batch) to remove impurities.

**Drying**: Drying the product under warm air at approximately 100–105°C for several hours.

**Recrystallization (optional)**: Dissolve crude pymetrozine in hot ethanol and allow slow cooling for recrystallization to enhance purity further.

***After the synthesis process, the yield of pymetrozine is approximately 95% based on optimized reaction conditions. On improving efficiency and reducing waste can give a higher yield increased by 2.0–5.0%. The final purity can go as high as 97%.***

## Reference(s)


- https://patents.google.com/patent/CN104844574A/en
- https://pmc.ncbi.nlm.nih.gov/articles/PMC8588918/
- https://www.mdpi.com/1420-3049/23/1/134


## Contribution of each member

Dhruv Bajaj(230365)

- Identified the main synthesis route for pymetrozine by researching and analyzing process efficiency and yield optimization, selecting appropriate reactant ratios for optimal yield and time efficiency.
- found the necessary separation & purification steps for main synthesis route to achieve a high purity of >99%.

Somya Yadav(231023)

- Contributed towards the development of an alternative synthesis route for Pymetrozine by researching and analyzing process efficiency and yield optimization
- Optimize the reaction conditions to enhance yield and gain a clearer understanding of the reaction mechanism. Additionally, analyzed the separation process to effectively compare and evaluate the yield across different conditions.

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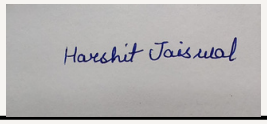
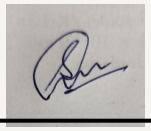
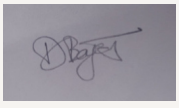
| HARSHITJAISWAL | 230460 |  |
| SOMYA YADAV | 231023 |  |
| DHRUV BAJAJ | 230365 |  |