## Synthetic Procedure

## Route B – Steps 3-4

**According to the following Chemistry:**



**Amounts of Necessary Raw materials:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **M.W.** | **Weight (g)** | **mmol** | **Stoich. Ex. (eq.)** | **Conc. (%)** |
| **Step3** |  |  |  |  |  |
| Nitropyrazole | 330 | 80.0 | 237.6 |  | 98.0% |
| [Zn](../AppData/Local/Microsoft/Windows/Documents%20and%20Settings/annar/שלב%204%20מסלול%20קרבמט/אולדריץ/,%20Azobisisobutyronitrile,%2078-67-1.htm) | 65 | 47.3 | 712.7 | 3.0 | 98.0% |
| NH4Cl2%- | 53.5 | 80.0 |  | 1.0 | 2.0% |
| acetonitrile |  | 400.0 |  | 5.0 |  |
| **Step4** |  |  |  |  |  |
| HCl2%- | 36.5 | 80.0 |  | 1.0 | 2.0% |
| Methylchloroformate | 94.5 | 25.2 | 261.3 | 1.10 | 98.0% |
| **Product** |  | **Weight (g)** | **mmol** | **Purity (%)** | **Yield (%)** |
| [374] Crude | 374 | 65.0 | 165.1 | 95% | 70% |
| [374] Cryst. | 374 | 58.0 | 153.5 | 99% | 65% |

**1. Operations (base on exp. 457-53):**

1. To a 1 liter reactor, equipped with a condenser, thermometer and stirred mechanically, add:

- 80.0 g (238 mmol) [330] purity- 99%;

- 400.0 g acetonitrile (5:1 W/W).

Begin to stir.

1. Add 80 g of NH4Cl-2% (1:1 W/W). The mixture becomes very thick.
2. Stir and heat to 50oC.
3. At 30oC add 34.7 g. of metal Zn. (3.0 eq.) (Exotherm develop to 50oC). Dividing Zn addition is less favorable.
4. Raise Mixing at maximum (1000 RPM).
5. Stir for 1.5 hour - Stop stirring while monitoring at 90 min. - Zn precipitate at the reactor bottom (In order to reduce extra formation of impurity [300]).
6. Prepare in a 3 necked cooled stirred flask – 160 gram HCl-2% (2:1 W/W to [330]).
7. Siphon 1 - Transfer the solution to a cooled flask by dipipe (Siphon transfer) (In order to prevent extra formation of [610]).
8. Siphon 2 - Add 160 gr. Acetonitrile – 80 gr. Water ((2:1 W/W to [330]). and stir for 10 min. Transfer to the cooled flask (parag. 8) by dipipe (Improve yield from 63% to 70%).
9. Take out the Zn layer and wash the reactor.
10. Cool the flask to 10oC.
11. Add 19.0 g of Methylchloroformate (1.1 eq.). Develops exotherm of 3-4 degrees.
12. Stir for about 0.5 hours.
13. Cool to 5oC. Stir at this temperature for about 0.5 hr.
14. Filter the crude product – Wash with hot Water (3\*80gr.) ((2:1 W/W to [330]) .
15. Dry overnight in the oven at 70oC.
16. Crystallization with EtOH/Water (5:5:1W/W), hot filtration, cooling to 5oC, filtration.

**2. Summery results:**

|  |  |  |
| --- | --- | --- |
| Crude Cake | Assay (%) | Yield |
| 65g | 95% | 70% |
| Cryst. Cake | Assay (%) | Yield |
| 58g | 99% | 65% |
| M.L. Weight | [374] % | M.L. Yield lost |
| 350g. | 1% | 5-10% |
| Conversion | Mass balance |  |
| 100% | **80%** |  |

## Synthetic Procedure

## Route B – Step 5- Catalytic Process

According to the following Chemistry:



Amounts of Necessary Raw materials:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **M.W.** | **Weight (g)** | **mmol** | **Stoich. Ex. (eq.)** | **Conc. (%)** |
| Hydroxy F-Pyrazole | 374 | 100.0 | 264.7 |  | 99.0% |
| NaOH-15% | 40 | 113 | 423.5 | 1.6 | 15.0% |
| Dimethylsulfate (DMS) | 126 | 43.8 | 347 | 1.3 | 98.0% |
| Tetrabutylammonium bromide (TBAB) | 322 | 4.3 | 13.2 | 0.05 | 98.0% |
| Toluene |  | 300.0 |  | 3.0 |  |

**1. Operations:**

1. To a 5-necked 1.0 liter Reactor, equipped with a condenser, thermometer, pH-electrode and stirred mechanically, add while stirring:

- 300.0 g Toluene (3:1 W/W).

- 100.0 g [374] -99% , 0.26 mol.

- 4.2 g TBAB (5 mol%)

1. Stabilize the temp. at 20oC. (below that the reaction is too slow).
2. Add the DMS 43.8g.– (1.3 mol eq.) - (One shot).
3. Drop from dropping funnel **-** NaOH-15%, control the pH during the whole reaction (pH should be between 10.5 – 11.0).
4. Stir for 1.5 hruntil [374] is less than 1 area% (solution become clear at 3% left).
5. Phase Separation at 20oC. (Aqueous phase is lower).
6. 1st. Wash the organic phase at RT (20-30oC) using 100 g. (1:1W/W) NH4OH-24-27% - 30 min. stirring + Phase separation – (Aqueous phase is lower).
7. 2nd. Wash using 100gr. Water at RT – neutralize to PH 7 using HCl – 16%, Phase separation - Aqueous phase is lower.
8. 3rd. Wash using 100gr. Water at RT - Phase separation - Aqueous phase is lower. pH=7.6
9. Solvent Evaporation (temp. max. 70oC/ 20mbar).

Product is obtained as melt.

1. There is an option to crystalize the compound from ethanol/water 3:1 (v/v).