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Improved process for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid

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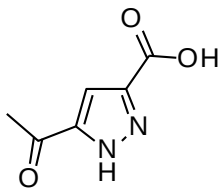
An improved process for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid, which is represented by the following structural formula-1.



Formula-1

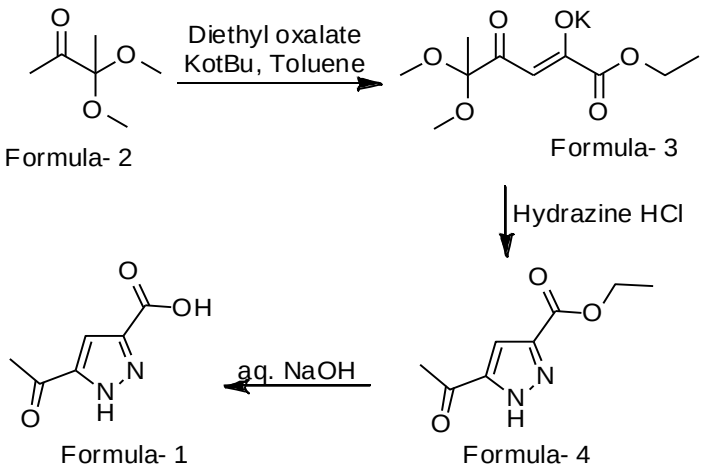
5-Acetyl-1H-pyrazole-3-carboxylic acid is the key starting material for the preparation of Darolutamide, which is chemically known as N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide.

Darolutamide was developed by Orion Corporation and Bayer Health Care. It is an anti-androgen medication which is used for the treatment of prostate cancer in men.

IN 213428 describes the process for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid. The said process uses preparative HPLC to purify the ester of 5-acetyl-1H-pyrazole-3-carboxylic acid. The said process uses high solvent volumes and time consuming processes, suffered with product isolation and produced 5-acetyl-1H-pyrazole-3-carboxylic acid with low yields.

CN111138389 describes the synthesis of 5-acetyl-1H-pyrazole-3-carboxylic acid. Which uses multiple combinations of solvents and reagents for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid.

The present invention provides an improved process for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid with industrially suitable method, which is advantageous over prior described processes. The said improved process is schematically as mentioned below.



The compound of Formula-2 used in the present invention is prepared by any of the processes known in the prior art.

The present inventions process for the preparation of formula-4 from formula-3, does not use any organic solvent to perform the reaction. Uses ecofriendly solvent of water to perform the reaction which reduces the production cost and simplifies the isolation of compound of formula-4.

The following examples specifies the conditions of the process for the preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid.

Examples:

Example-1: Preparation of 5-acetyl-1H-pyrazole-3-carboxylic acid

Potassium tert-butoxide (102 g) was added lot-wise to the pre-cooled mixture of 3,3-dimethoxybutane-2-one (100 g) in toluene (1000 ml) at 5-10°C and stirred for 45 minutes. Diethyl oxalate (132 g) was added to the mixture at 10-15°C and stirred for 4 hours. Filtered the solid. To the filtered solid water (3000 ml) was added and cooled to 5-10°C. Solution of Hydrazine monohydrochloride (51.8 g) was slowly added to the mixture at 5-10°C and stirred for 4 hrs. Dichloromethane (1000 ml) was added to the mixture at 5-10°C and stirred for 15 minutes. Allowed to heat the mixture to 25-30°C and stirred for 15 minutes. Filtered the mixture through hyflow. Organic layer was separated from the filtrate. Distilled-off the organic layer and co-distilled in n-heptane (50 ml). n-heptane (300 ml) was added to the mixture at 25-30°C. Heated the mixture at 45-50°C and stirred for 1 hrs. Allowed to cool the

mixture to 25-30°C and stirred for 3 hours. Filtered the solid. THF (150 ml) was added to the obtained solid. aq. Sodium hydroxide solution was added to the mixture at 10-15°C. Heated the mixture to 55-60°C and stirred for 2 hrs. Allowed to cool the mixture to 25-30°C and stirred for 15 minutes. Separated the aqueous layer from organic layer**.** Water was added to the aqueous layer at 25-30°C. Cooled the mixture to 20-25°C. Treated the mixture with hydrochloric acid at 20-25°C. Allowed to heat the mixture to 25-30°C and stirred for 4 hours. Filtered the solid and dried. Tetrahydrofuran (300 ml) was added to the obtained solid at 25-30°C. Heated the mixture to 50-55°C and stirred for 60 minutes. Allowed to cool the mixture to 25-30°C and stirred for 3 hours. Filtered the solid and dried to get the titled product.

Yield: 63 gm

Purity by HPLC: 99.93%

Example-2: Preparation of potassium (Z)-1-ethoxy-5,5-dimethoxy-1,4-dioxohex-2-en-2-olate

Potassium tert-butoxide (102 g) was added lot-wise to the pre-cooled mixture of 3,3-dimethoxybutane-2-one (100 g) in toluene (1000 ml) at 5-10°C and stirred for 45 minutes. Diethyl oxalate (132 g) was added to the mixture at 10-15°C and stirred for 4 hours. Filtered the solid and dried to get the titled product.

Yield: 180 gm.

Example-3: Preparation of ethyl-5-acetyl-1H-pyrazole-3-carboxylate

Solution of Hydrazine monohydrochloride (51.8 g) was lot-wise added to the pre-cooled mixture of potassium (Z)-1-ethoxy-5,5-dimethoxy-1,4-dioxohex-2-en-2-olate (180 g) in water (3000 ml) at 5-10°C and stirred for 4 hrs. Dichloromethane (1000 ml) was added to the mixture at 5-10°C and stirred for 15 minutes. Allowed to heat the mixture to 25-30°C and stirred for 15 minutes. Filtered the mixture through hyflow. Organic layer was separated from the filtrate. Distilled-off the organic layer. Mixture was co-distilled in n-heptane (50 ml). N-heptane (300 ml) was added to the mixture at 25-30°C. Heated the mixture at 45-50°C and stirred for 1 hrs. Allowed to cool the mixture to 25-30°C and stirred for 3 hours. Filtered the solid and dried to get title product.

Yield: 95 gm.

Example-4: Preparation 5-acetyl-1H-pyrazole-3-carboxylic acid

Aqueous Sodium hydroxide solution was added to the mixture of ethyl-5-acetyl-1H-pyrazole-3-carboxylate (95 g) in tetrahydrofuran (150 ml) at 10-15°C. Heated the mixture to 55-60°C and stirred for 2 hrs. Allowed to cool the mixture to 25-30°C and stirred for 15 minutes. Separated the aqueous layer from organic layer. Water was added to the aqueous layer at 25-30°C. Cooled the mixture to 20-25°C. Treated the mixture with hydrochloric acid at 20-25°C. Allowed to heat the mixture to 25-30°C and stirred for 4 hours. Filtered the solid. Tetrahydrofuran (300 ml) was added to the filtered solid at 25-30°C. Heated the mixture to 50-55°C and stirred for 60 minutes. Allowed to cool the mixture to 25-30°C and stirred for 3 hours. Filtered the solid and dried to get the titled product.

Yield: 63 gm

Purity by HPLC: 99.9%

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