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(72) Inventor(s):
RUER LIAO

(73) Proprietor(s):
CHENGDU KA DI FU TECHNOLOGY CO., LTD.
No. 68, Yu Lin Nan Road
High-tech Zone, Chengdu city
Sichuan province
China

(74) Agent and/or Address for Service:
Hongzhe Zhu
Via Niccolo da uzzano 95
Firenze Toscana
50126
Italy

S180259

Drug intermediates N-methylpyridin-2-one synthesis method

FIELD OF THE INVENTION

The present invention relates to a method for preparing a pharmaceutical intermediate which belongs to the field of organic synthesis, more particularly, relates to drug intermediates N-methylpyridin-2-one synthesis method.

GENERAL BACKGROUND

N-methylpyridin-2-one is mainly used as a synthesis intermediate for pharmaceuticals. Most of the existing synthesis methods requires the use of dimethyl sulfate, potassium ferricyanide and sodium hydroxide as raw materials. This synthesis method using dimethyl sulfate, potassium ferricyanide as the reaction material, dimethyl sulfate is of high toxicity, the function is similar to mustard gas, acute toxicity is similar to phosgene, 15 times more than chlorine, it has a strong stimulating effect on respiratory tract, it has a strong corrosive effect on skin, it can cause conjunctival hyperemia, edema, corneal epithelial shedding, trachea, bronchial epithelial cell necrosis, perforation leads to mediastinoscopy or subcutaneous emphysema. In addition, it can also damage the liver, kidney and myocardium, skin contact can cause burns, blisters and deep necrosis. Potassium cyanide inhalation, ingestion or absorption through the skin is harmful to the body, which can cause kidney damage, it can produce hydrogen cyanide under heating or acid. Therefore the use of dimethyl sulfate, potassium ferricyanide as synthesis of raw materials will lead to increased risk factor in the synthesis process, the health of synthesis operators get greater impact, it is not conducive to safe production, therefore, it is necessary to propose a new synthesis method.

SUMMARY

Based on the technical problems of the background technology, the purpose of the present invention is to provide drug intermediates N-methylpyridin-2-one synthesis method, comprises the following steps:

A: 6-methoxypyridine, potassium chloride solution, heptane solution are added to

the reaction vessel, controls the temperature of the solution to 10-15 ℃, the aqueous solution and aluminum isopropoxide are added, controls the stirring speed at 350-370 rpm, continues to react for 90-120 min;

B: then osmium chloride powder is added, controls the temperature at 20-26 ℃, continues to react for 2-3 h, and then reduces the temperature to 3-8 ℃, put it aside for 30-50 min, the solution layers, separated from the oil, washed several times with sodium sulfate solution, washed several times with xylene solution, recrystallized in cyclohexene solution, dehydrated with dehydration, gets the finished product N-methyl pyridin-2-one.

Preferably, the potassium chloride solution has a mass fraction of 16-22%.

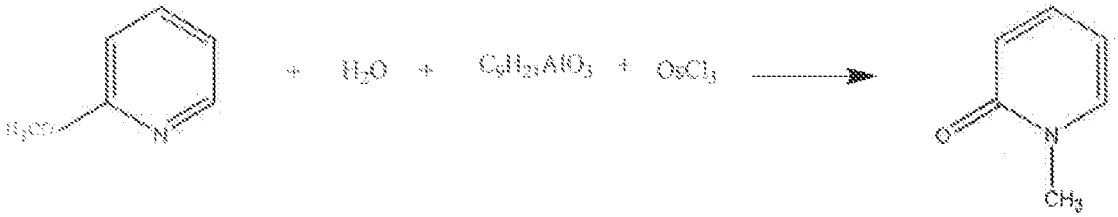
Preferably, the mass fraction of the heptane solution is 20-26%.

Preferably, the sodium sulfate solution has a mass fraction of 10-15%.

Preferably, the xylene solution has a mass fraction of 70-77%.

Preferably, the mass fraction of cyclohexene solution is 80-86%.

Throughout the reaction process can be the following reaction formula:



Compared with the synthesis method disclosed in the background art, the invention provides drug intermediates N-methylpyridin-2-one synthesis method, it is unnecessary to use dimethyl sulfate, potassium ferricyanide as reaction material, avoiding the damage of high toxicity dimethyl sulfate to synthesis operators, as well avoiding the risk of potassium ferricyanide producing hydrogen cyanide when heated or acid, reducing the risk factor of synthesis process, reducing the health hazards on synthesis operators, it is conducive to safe production, reducing intermediate links reaction, decreasing the reaction time and improving the reaction yield, at the same time, the present invention provides a new synthetic route which has laid a good foundation for further enhancing the yield of the reaction.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following examples with reference to specific embodiments of the present invention are further illustrated:

Embodiment 1

Drug intermediates N-methylpyridin-2-one synthesis method, comprises the following steps:

A: 2 mol 6-methoxypyridine, 700ml potassium chloride solution with a mass fraction of 16%, 1.2L heptane solution with a mass fraction of 20% are added to the reaction vessel, controls the temperature of the solution to 10 ℃, the aqueous solution and 4 mol aluminum isopropoxide are added, , controls the stirring speed at 350 rpm, continues to react for 90 min;

B: then 4 mol osmium chloride powder is added, controls the temperature at 20 ℃, continues to react for 2 h, and then reduces the temperature to 3 ℃, put it aside for 30 min, the solution layers, separated from the oil, washed 3 times with sodium sulfate solution with a mass fraction of 10%, washed 6 times with xylene solution with a mass fraction of 70%, recrystallized in cyclohexene solution with a mass fraction of 80%, dehydrated with anhydrous sodium sulfate dehydration, gets the finished product N-methyl pyridin-2-one 214.294g, yield 98.3%.

Embodiment 2

Drug intermediates N-methylpyridin-2-one synthesis method, comprises the following steps:

A: 2 mol 6-methoxypyridine, 700ml potassium chloride solution with a mass fraction of 19%, 1.2L heptane solution with a mass fraction of 23% are added to the reaction vessel, controls the temperature of the solution to 12.5 ℃, the aqueous solution and 5 mol aluminum isopropoxide are added, , controls the stirring speed at 360 rpm, continues to react for 115 min;

B: then 5 mol osmium chloride powder is added, controls the temperature at 23 ℃, continues to react for 2.5 h, and then reduces the temperature to 5.5 ℃, put it aside for 40 min, the solution layers, separated from the oil, washed 4 times with sodium sulfate solution with a mass fraction of 12.5%, washed 7 times with xylene solution with a mass fraction of 73.5%, recrystallized in cyclohexene solution with a mass fraction of

83%, dehydrated with anhydrous sodium sulfate dehydration, gets the finished product N-methyl pyridin-2-one 214.948g, yield 98.6%.

Embodiment 3

Drug intermediates N-methylpyridin-2-one synthesis method, comprises the following steps:

A: 2 mol 6-methoxypyridine, 700ml potassium chloride solution with a mass fraction of 22%, 1.2L heptane solution with a mass fraction of 26% are added to the reaction vessel, controls the temperature of the solution to 15 ℃, the aqueous solution and 6 mol aluminum isopropoxide are added, , controls the stirring speed at 370 rpm, continues to react for 120min;

B: then 6 mol osmium chloride powder is added, controls the temperature at 26 ℃, continues to react for 3 h, and then reduces the temperature to 8 ℃, put it aside for 50 min, the solution layers, separated from the oil, washed 5 times with sodium sulfate solution with a mass fraction of 15%, washed 8 times with xylene solution with a mass fraction of 77%, recrystallized in cyclohexene solution with a mass fraction of 86%, dehydrated with anhydrous sodium sulfate dehydration, gets the finished product N-methyl pyridin-2-one 216.038g, yield 99.1%.

The embodiments of the present invention are merely preferred embodiments of the present invention, but the range of the present invention is not limited this, and any person who is familiar with those skilled in the arts, within the technical range of the present invention. It is intended that the technical solution and its inventive concept be replaced or modified equivalently with reference to the range of the invention.

Claims

1. Drug intermediates N-methylpyridin-2-one synthesis method, comprises the following steps:

A: 6-methoxypyridine, potassium chloride solution, heptane solution are added to the reaction vessel, controls the temperature of the solution to 10-15 ℃, the aqueous solution and aluminum isopropoxide are added, , controls the stirring speed at 350-370 rpm, continues to react for 90-120 min;

B: then osmium chloride powder is added, controls the temperature at 20-26 ℃, continues to react for 2-3 h, and then reduces the temperature to 3-8 ℃, put it aside for 30-50 min, the solution layers, separated from the oil, washed several times with sodium sulfate solution, washed several times with xylene solution, recrystallized in cyclohexene solution, dehydrated with dehydration, gets the finished product N-methyl pyridin-2-one.

2. Drug intermediates N-methylpyridin-2-one synthesis method according to claim 1 wherein the potassium chloride solution has a mass fraction of 16-22%.

3. Drug intermediates N-methylpyridin-2-one synthesis method according to claim 1 wherein the mass fraction of the mass fraction of the heptane solution is 20-26%.

4. Drug intermediates N-methylpyridin-2-one synthesis method according to claim 1 wherein the sodium sulfate solution has a mass fraction of 10-15%.

5. Drug intermediates N-methylpyridin-2-one synthesis method according to claim 1 wherein the xylene solution has a mass fraction of 70-77%.