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(54) **O-toluene formamide organic intermediates synthesis method**

(57) The present invention discloses drug intermediates o-toluene formamide organic intermediates synthesis method, comprises the following steps: 6-(1-bromide carbonyl)-toluene, cyclooctane solution was added to the reaction vessel, controlled the stirring speed, controlled the temperature of the solution, added the dimethylamine solution with a mass fraction, added 6 mol aluminum isopropoxide, continued to react; then added potassium sulfate solution with a mass fraction, added2-ethyl hexanoate zinc powder, raised the temperature of the solution, controlled the stirring speed, continued to react, adjusted the pH with oxalate solution with a mass fraction, reduced the temperature, standed, washed with sodium bromide solution, washed with propargyl alcohol solutionwith a mass fraction, recrystallized in methyl ether solution with a mass fraction, dehydrated with anhydrous calcium chloride dehydration, got the finished product o-toluene formamide. <Figure 1>

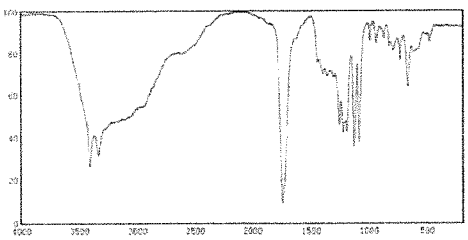


Figure 1

O-toluene formamide organic intermediates synthesis method

FIELD OF THE INVENTION

The present invention relates to a method for preparing an organic synthesis intermediate, relates to o-toluene formamide organic intermediates synthesis method.

GENERAL BACKGROUND

O-toluene formamide is mainly used for organic and pharmaceutical synthesis, the existing methods mostly adopt o-tolunitrile, ethanol, sodium hydroxide, hydrogen peroxide as the reaction raw materials; the raw material o-toluonitrile is toxic, its vapor or smoke can irritate the eyes, mucous membranes and upper respiratory tract; in case of high heat, oxidants can burn, and emit toxic gases, factors above will do harm to the health of the operating personnel. The raw material sodium hydroxide is strongly irritating and corrosive, dust or smoke can irritate the eyes and respiratory tract, corrodes the nasal septum, skin and eye contact with NaOH can cause burns, factors above will have an adverse effect on the health of the production operator; and the strong corrosivity of sodium oxide will lead to the production equipment corrosion requirements increase, equipment manufacturing cost rise, is not conducive to cost control. The raw material hydrogen peroxide has strong corrosion, inhalation of the product vapor or fog has a strong irritation to the respiratory tract, eye contact with liquid can cause irreversible damage or even blindness. In a sealed container with an appropriate ignition source or temperature, a gas phase explosion occurs. Factors above will increase the risk coefficient of the synthesis process, which is not conducive to safe production. Therefore, the above synthesis method has many shortcomings, it is necessary to propose a new synthesis method.

SUMMARY OF THEINVENTION

Based on the technical problems existing in the general background technology, the invention proposed o-toluene formamide organic intermediates synthesis method, including the following steps:

A:6-(1-bromide carbonyl)-toluene, cyclooctane solution was added to the reaction vessel, controlled the stirring speed at 310-330 rpm, controlled the temperature of the solution to 30-36℃, added the dimethylamine solution, added aluminum isopropoxide in batches within 40-60 min, continued to react for 90-120 min;

B:then added potassium sulfate solution, added 2-ethyl hexanoate zinc powder, raised the

temperature of the solution to 40-47℃,controlled the stirring speed at 210-230 rpm, continued to react for 160-190 min, adjusted the pH to 8.5-9 with oxalate solution, reduced the temperature to 5-10℃, standed for 30-50 min, washed with sodium bromide solution for 30-40 min, washed with propargyl alcohol solution for 50-70 min, recrystallized in methyl ether solution, dehydrated with dehydration, got the finished product o-toluene formamide.

Preferably, the cyclooctane solution has a mass fraction of 20-26%.

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

Preferably, the potassium sulfate solution has a mass fraction of 15-22%.

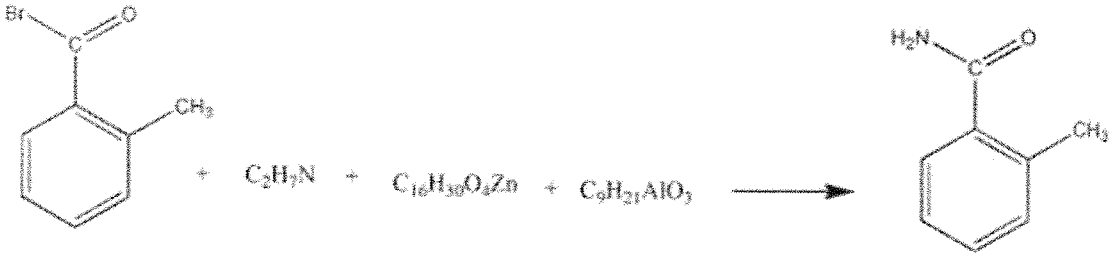
Preferably, the oxalate solution has a mass fraction of 10-16%.

Preferably, the sodium bromide solution has a mass fraction of 5-11%.

Preferably, the propargyl alcohol solution has a mass fraction of 40-46%.

Preferably, the methyl ether solution has a mass fraction of 60-65%.

Throughout the reaction process can be the following reaction formula:



Compared with the synthesis method disclosed in the background art, the invention provides o-toluene formamide organic intermediates synthesis method, it is unnecessary to use o-tolunitrile, sodium hydroxide, hydrogen peroxide as the reaction raw materials, avoiding o-tolunitrile as raw materials harm to the health of the operation personnel; also avoiding sodium hydroxide as raw materials with the strong stimulation and corrosive, increasing the corrosion resistance requirements of the production equipment, resulting in the adverse impact of equipment manufacturing costs rising. Moreover, avoiding hydrogen peroxide with strong corrosive harm to the health of production personnel and the risk of hydrogen peroxide by gas explosion, thereby reducing the risk of the synthesis process coefficient, is conducive to safe production, reducing intermediate links reaction, decreasing the reaction time and improving the reaction yield, while providing a new synthesis method of the invention, laying a good foundation to further improve the reaction yield.

DESCRIPTION OF THE DRAWINGS

Figure 1 is the infrared analysis spectrum of finished product o-toluene formamide.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

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

Embodiment 1:

O-toluene formamide intermediates synthesis method, comprises the following steps:

A: 2 mol 6-(1-bromide carbonyl)-toluene, 900ml cyclooctane solution with a mass fraction of 20% was added to the reaction vessel, controlled the stirring speed at 310 rpm, controlled the temperature of the solution to 30℃, added 4mol the dimethylamine solution with a mass fraction of 10%, added 4 mol aluminum isopropoxide twice within 40 min, continued to react for 90 min;

B: then added 700ml potassium sulfate solution with a mass fraction of 15%, added 2mol 2-ethyl hexanoate zinc powder, raised the temperature of the solution to 40℃, controlled the stirring speed at 210 rpm, continued to react for 160 min, adjusted the pH to 8.5 with oxalate solution with a mass fraction of 10%, reduced the temperature to 5℃, standed for 30 min, washed with sodium bromide solution with a mass fraction of 5% for 30 min, washed with propargyl alcohol solutionwith a mass fraction of 40% for 50 min, recrystallized in methyl ether solution with a mass fraction of 60%, dehydrated with anhydrous calcium chloride dehydration, got the finished product o-toluene formamide 265.41g, yield of 98.3%.

Embodiment 2:

O-toluene formamide intermediates synthesis method, comprises the following steps:

A: 2 mol 6-(1-bromide carbonyl)-toluene, 900ml cyclooctane solution with a mass fraction of 23% was added to the reaction vessel, controlled the stirring speed at 320 rpm, controlled the temperature of the solution to 33℃, added 5mol the dimethylamine solution with a mass fraction of 13%, added 5 mol aluminum isopropoxide 3 times within 50 min, continued to react for 100 min;

B: then added 700ml potassium sulfate solution with a mass fraction of 18%, added 3mol 2-ethyl hexanoate zinc powder, raised the temperature of the solution to 43℃, controlled the stirring speed at 220 rpm, continued to react for 170 min, adjusted the pH to 8.7 with oxalate solution with a mass fraction of 13%, reduced the temperature to 8℃, standed for 40 min, washed with sodium bromide solution with a mass fraction of 8% for 35 min, washed with propargyl alcohol solutionwith a mass fraction of 43% for 60 min, recrystallized in methyl ether solution with a mass fraction of

63%, dehydrated with anhydrous calcium chloride dehydration, got the finished product o-toluene formamide 265.95g, yield of 98.5%.

Embodiment 3:

O-toluene formamide intermediates synthesis method, comprises the following steps:

A: 2 mol 6-(1-bromide carbonyl)-toluene, 900ml cyclooctane solution with a mass fraction of 26% was added to the reaction vessel, controlled the stirring speed at 330 rpm, controlled the temperature of the solution to 36℃, added 6mol the dimethylamine solution with a mass fraction of 15%, added 6 mol aluminum isopropoxide 4 times within 60 min, continued to react for 120 min;

B: then added 700ml potassium sulfate solution with a mass fraction of 22%, added 4mol 2-ethyl hexanoate zinc powder, raised the temperature of the solution to 47℃, controlled the stirring speed at 230 rpm, continued to react for 190 min, adjusted the pH to 9 with oxalate solution with a mass fraction of 16%, reduced the temperature to 10℃, standed for 50 min, washed with sodium bromide solution with a mass fraction of 11% for 40 min, washed with propargyl alcohol solutionwith a mass fraction of 46% for 70 min, recrystallized in methyl ether solution with a mass fraction of 65%, dehydrated with anhydrous calcium chloride dehydration, got the finished product o-toluene formamide 266.76g, yield of 98.8%.

Figure 1 is the infrared analysis spectrum of finished product o-toluene formamide.

Table 1 is the infrared analysis data.

Table 1 infrared analysis data

Serial number	Peak position (cm^{-1})	Transmittance (%)	Width of Half peak (cm^{-1})	Peak difference (%)
1	640	55	9	31
2	681	51	44	34
3	748	49	13	33
4	776	69	27	16
5	1139	58	12	37
6	1395	38	28	45
7	1597	63	15	14
8	1622	29	25	29
9	1658	9	40	42
10	3197	36	66	42
11	3383	17	60	63

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. O-toluene formamide organic intermediates synthesis method, comprises the following steps:

A:6-(1-bromide carbonyl)-toluene, cyclooctane solution was added to the reaction vessel, controlled the stirring speed at 310-330 rpm, controlled the temperature of the solution to 30-36℃, added the dimethylamine solution, added aluminum isopropoxide in batches within 40-60 min, continued to react for 90-120 min;

B:then added potassium sulfate solution, added 2-ethyl hexanoate zinc powder, raised the temperature of the solution to 40-47℃,controlled the stirring speed at 210-230 rpm, continued to react for 160-190 min, adjusted the pH to 8.5-9 with oxalate solution, reduced the temperature to 5-10℃, standed for 30-50 min, washed with sodium bromide solution for 30-40 min, washed with propargyl alcohol solution for 50-70 min, recrystallized in methyl ether solution, dehydrated with dehydration, got the finished product o-toluene formamide.

2. O-toluene formamide organic intermediates synthesis method according to claim 1 wherein the cyclooctane solution has a mass fraction of 20-26%.

3. O-toluene formamide organic intermediates synthesis method according to claim 1 wherein the dimethylamine solution has a mass fraction of 10-15%.

4. O-toluene formamide organic intermediates synthesis method according to claim 1 wherein the potassium sulfate solution has a mass fraction of 15-22%.

5. O-toluene formamide organic intermediates synthesis method according to claim 1 wherein the oxalate solution has a mass fraction of 10-16%.

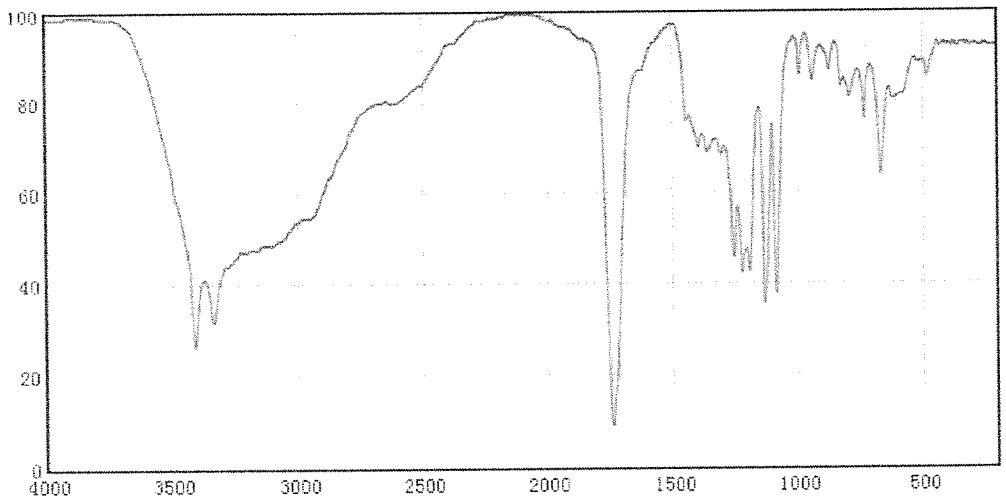


Figure 1