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Medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method

FIELD OF THE INVENTION

The present invention relates to medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method.

GENERAL BACKGROUND

2,6-dicarboxylic acid pyridine is mainly used as a competitive inhibitor of bovine glutamate dehydrogenase, it can also be used for the preparation of lanthanum and transition metal ligand complex, however, most of the existing synthetic methods are using 2,6-dicarboxylic acid pyridine as the reactant, it is complicated and the final yield is not very high. Therefore, it is necessary to propose a new synthetic method for further improving the quality and yield of the product and reducing the byproduct content, it has important economic significance.

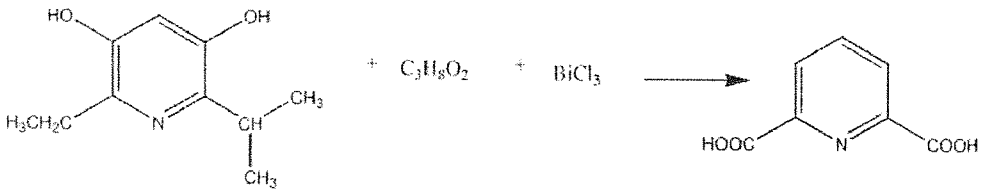
SUMMARY

The purpose of the present invention is to provide medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method, comprises the following steps:

(i) 2 mol 2-isopropyl-3,5-dihydroxy-6-ethylpyridine and 5-7 mol ethylene glycol methyl ether were added to the reaction vessel, controlled the stirring rate at 190-230 rpm, raised the temperature to 60-67 ℃, added 3-4mol bismuth trichloride, kept for 40-60 min, reduced the temperature of the solution to 5-9 ℃, precipitated the solid, filtrated, washed with potassium nitrate solution for 3-7 times, combined the filtrate and washing solution, controlled the stirring speed at 110-130 rpm, adjusted the pH to 2-3 by oxalic acid solution, washed with N-benzylmethylamine solution, washed with benzyl methyl ether solution, recrystallized in propyl phenyl ketone solution, precipitated the crystals, got the finished product 2,6-dicarboxylic acid pyridine; wherein, the ethylene glycol methyl ether solution in step (i) has a mass fraction of 70 to 80%, the mass fraction of the potassium nitrate solution in step (i) is 30 to 40%, the mass fraction of the oxalic acid solution described in step (i) is 20 to 28%, the N-benzyl

methylamine solution mass in step (i) has a fraction of 70-78%, the mass fraction of benzyl methyl ether solution in step (i) is 80-86%, the mass fraction of the propyl phenyl ketone solution described in step (i) is 92-97%.

Throughout the reaction process can be the following reaction formula:



Advantage of the present invention is that: reducing intermediate links reaction, decreasing the reaction time and improving the reaction yield.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

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

medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method.

Embodiment 1

2 mol 2-isopropyl-3,5-dihydroxy-6-ethylpyridine and 5 mol ethylene glycol methyl ether with a mass fraction of 70 %were added to the reaction vessel, controlled the stirring rate at 190 rpm, raised the temperature to 60 ℃, added 3mol bismuth trichloride, kept for 40 min, reduced the temperature of the solution to 5 ℃, precipitated the solid, filtrated, washed with potassium nitrate solution with a mass fraction of 30 % for 3 times, combined the filtrate and washing solution, controlled the stirring speed at 110 rpm, adjusted the pH to 2 by oxalic acid solution with a mass fraction of 20 %, washed with N-benzylmethylamine solution with a mass fraction of 70%, washed with benzyl methyl ether solution with a mass fraction of 80%, recrystallized in propyl phenyl ketone solution with a mass fraction of 92%, precipitated the crystals, got the finished product 2,6-dicarboxylic acid pyridine 303.94g, yield of 91%.

Embodiment 2

2 mol 2-isopropyl-3,5-dihydroxy-6-ethylpyridine and 6 mol ethylene glycol methyl ether with a mass fraction of 75 %were added to the reaction vessel, controlled the stirring rate at 210 rpm, raised the temperature to 63 ℃, added 3.5mol bismuth trichloride, kept for 50 min, reduced the temperature of the solution to 7 ℃, precipitated the solid, filtrated, washed with potassium nitrate solution with a mass fraction of 35 % for 5 times, combined the filtrate and washing solution, controlled the stirring speed at 120 rpm, adjusted the pH to 2.5 by oxalic acid solution with a mass fraction of 25 %, washed with N-benzylmethylamine solution with a mass fraction of 73%, washed with benzyl methyl ether solution with a mass fraction of 83%, recrystallized in propyl phenyl ketone solution with a mass fraction of 94%, precipitated the crystals, got the finished product 2,6-dicarboxylic acid pyridine 310.62g, yield of 93%.

Embodiment 3

2 mol 2-isopropyl-3,5-dihydroxy-6-ethylpyridine and 7 mol ethylene glycol methyl ether with a mass fraction of 80 %were added to the reaction vessel, controlled the stirring rate at 230 rpm, raised the temperature to 67 ℃, added 4mol bismuth trichloride, kept for 60 min, reduced the temperature of the solution to 9 ℃, precipitated the solid, filtrated, washed with potassium nitrate solution with a mass fraction of 40 % for 7 times, combined the filtrate and washing solution, controlled the stirring speed at 130 rpm, adjusted the pH to 3 by oxalic acid solution with a mass fraction of 28%, washed with N-benzylmethylamine solution with a mass fraction of 78%, washed with benzyl methyl ether solution with a mass fraction of 86%, recrystallized in propyl phenyl ketone solution with a mass fraction of 97%, precipitated the crystals, got the finished product 2,6-dicarboxylic acid pyridine 320.64g, yield of 96%.

Claims

1. Medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method, comprises the following steps:

(i) 2 mol 2-isopropyl-3,5-dihydroxy-6-ethylpyridine and 5-7 mol ethylene glycol methyl ether were added to the reaction vessel, controlled the stirring rate at 190-230 rpm, raised the temperature to 60-67 ℃, added 3-4mol bismuth trichloride, kept for 40-60 min, reduced the temperature of the solution to 5-9 ℃, precipitated the solid, filtrated, washed with potassium nitrate solution for 3-7 times, combined the filtrate and washing solution, controlled the stirring speed at 110-130 rpm, adjusted the pH to 2-3 by oxalic acid solution, washed with N-benzylmethylamine solution, washed with benzyl methyl ether solution, recrystallized in propyl phenyl ketone solution, precipitated the crystals, got the finished product 2,6-dicarboxylic acid pyridine; wherein, the ethylene glycol methyl ether solution in step (i) has a mass fraction of 70 to 80%, the mass fraction of the potassium nitrate solution in step (i) is 30 to 40%, the mass fraction of the oxalic acid solution described in step (i) is 20 to 28%, the N-benzyl methylamine solution mass in step (i) has a fraction of 70-78%.

2. Medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method according to claim 1 wherein the mass fraction of benzyl methyl ether solution in step (i) is 80-86%.

3. Medicine intermediates 2,6-dicarboxylic acid pyridine synthesis method according to claim 1 wherein the mass fraction of the propyl phenyl ketone solution described in step (i) is 92-97%.