



(11) **IE 20180242**

(13) **U1**

(19)

Oifig Maoine Intleachtúla na hÉireann
Intellectual Property Office of Ireland

(43) Date of Publication of Application:
19.02.2020 Journal No. 2405

(12)

IRISH SHORT-TERM PATENT APPLICATION

(21) Application Number: **20180242**

(22) Date of Filing: **16.08.2018**

(51) Int. Cl. (2020.01)
C07C 315/00

(71) Applicant(s):
**CHENGDU WEI BO SI TE
TECHNOLOGY CO., LTD.**
Sichuan province
China

(72) Inventor(s):
RUER LIAO

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

(54) **Broad spectrum antimicrobial agents thiamphenicol synthesis method**

(57) The present invention discloses broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps: 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and potassium sulfate solution were added to the reaction vessel, controlled the stirring speed, controlled the temperature of the solution, added n-bromoacetamide, added acetylacetone solution in batches, continued to react; then added cobalt chloride powder, controlled the temperature of the solution, continued to react, added sodium bromide solution, until the solution was stratified, separated the reservoir, washed with cyclopropane solution, recrystallized in diisopropylamine solution, dehydrated with dehydration, got the finished product thiamphenicol.

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Broad spectrum antimicrobial agents thiamphenicol 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 Broad spectrum antimicrobial agents thiamphenicol synthesis method.

GENERAL BACKGROUND

Thiamphenicol belongs to chloramphenicol methyl sulfone derivatives and is a synthetic broad-spectrum antimicrobial. Antibacterial spectrum and antibacterial effect are basically similar to chloramphenicol. It enters into the bacterial cells mainly through the dispersion, reversibly binds to the 50S subunit of the bacterial ribosome, blocks the growth of peptide chain, inhibits the role of transpeptidase, inhibits the formation of peptide chains, and prevents the synthesis of protein, thus makes antibacterial effect. Thiamphenicol still has a strong immunosuppressive effect, 6 times stronger than chloramphenicol, and can inhibit the synthesis of immunoglobulin and production of antibody. Most of the existing synthesis methods using dichloroacetyl chloride, hydrogen peroxide, and acetic anhydride as raw materials for the synthesis of thiamphenicol. The reaction raw material hydrogen peroxide is an explosive strong oxidant. In a sealed container with an appropriate temperature, a gas phase explosion will occur. Hydrogen peroxide has a strong corrosive. These factors show that hydrogen peroxide as a reaction material will greatly increase the risk factor in the synthesis process, it also endangers the health of production staffs. The reaction raw material acetic anhydride is flammable, corrosive and irritating and can cause burns to human body; it is also harmful to the environment, and can pollute water. After inhalation, it can stimulate the respiratory tract, causing cough, chest pain and difficulty breathing; its vapors are irritating to the eye, directly contact to the skin and the eye can cause burns. The analysis of these factors shows that: acetic anhydride as a raw material causes great environmental pollution, the synthesis process is harmful to the health of production operators, which is not conducive to safe production. The above analysis shows that this synthetic method has many

shortcomings, so 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 broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps:

A: 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and potassium sulfate solution were added to the reaction vessel, controlled the stirring speed at 210-230 rpm, controlled the temperature of the solution at 20-26 °C, added n-bromoacetamide, in 20-40 min, added acetylacetone solution in batches, continued to react for 50-80 min;

B: then added cobalt chloride powder, controlled the temperature of the solution at 28-32 °C, continued to react for 2-3 h, added sodium bromide solution, until the solution was stratified, separated the reservoir, washed with cyclopropane solution for 30-50 min, recrystallized in diisopropylamine solution, dehydrated with dehydration, got the finished product thiamphenicol.

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

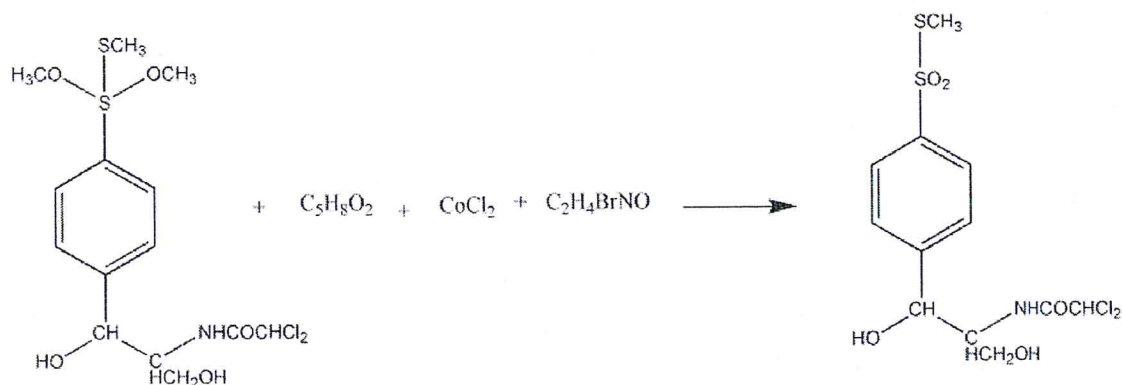
Preferably, acetylacetone solution has mass fraction of 30-36%.

Preferably, sodium bromide solution has mass fraction of 10-16%.

Preferably, cyclopropane solution has mass fraction of 50-55%.

Preferably, diisopropylamine solution has a mass fraction of 60-66%.

Throughout the reaction process can be the following reaction formula:



Compared with the synthesis method disclosed in the background art, the invention provides broad spectrum antimicrobial agents thiamphenicol synthesis

method, it is unnecessary to use hydrogen peroxide and acetic anhydride as reactants, avoids the risk of gas explosion generated by hydrogen peroxide in a sealed container, avoids to cause harm to the health of production operators, and decreases the risk factor of the synthesis process. It also avoids the vulnerability characteristics of flammable, corrosive of acetic anhydride, which have potential risks to damage to the production operators, which is conducive to safety production, reduces the pollution of the environment, reduces pollution control costs to the late response. It also reduces intermediate links reaction, decreases the reaction time and improves 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

Embodiment 1

Broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps:

A: 2mol 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and 800 ml potassium sulfate solution with a mass fraction of 15% were added to the reaction vessel, controlled the stirring speed at 210 rpm, controlled the temperature of the solution at 20 °C, added 4mol n-bromoacetamide, in 20 min, added 4mol acetylacetone solution with a mass fraction of 30% in 2 times, continued to react for 50 min;

B: then added 4mol cobalt chloride powder, controlled the temperature of the solution at 28 °C, continued to react for 2 h, added 1.3 L sodium bromide solution with a mass fraction of 10%, until the solution was stratified, separated the reservoir, washed with cyclopropane solution with a mass fraction of 50% for 30 min, recrystallized in diisopropylamine solution with a mass fraction of 60%, dehydrated with anhydrous calcium sulfate dehydration, got the finished product thiamphenicol 699.184g, yield of 98.2%.

Embodiment 2

Broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps:

A: 2mol 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and 800 ml potassium sulfate solution with a mass fraction of 18% were added to the reaction vessel, controlled the stirring speed at 220 rpm, controlled the temperature of the solution at 23 °C, added 5mol n-bromoacetamide, in 30 min, added 5mol acetylacetone solution with a mass fraction of 33% in 3 times, continued to react for 70 min;

B: then added 5mol cobalt chloride powder, controlled the temperature of the solution at 30 °C, continued to react for 2.5 h, added 1.3 L sodium bromide solution with a mass fraction of 13%, until the solution was stratified, separated the reservoir, washed with cyclopropane solution with a mass fraction of 53% for 40 min, recrystallized in diisopropylamine solution with a mass fraction of 63%, dehydrated with anhydrous calcium sulfate dehydration, got the finished product thiamphenicol 701.32g, yield of 98.5%.

Embodiment 3

Broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps:

A: 2mol 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and 800 ml potassium sulfate solution with a mass fraction of 22% were added to the reaction vessel, controlled the stirring speed at 230 rpm, controlled the temperature of the solution at 26 °C, added 6mol n-bromoacetamide, in 40 min, added 6mol acetylacetone solution with a mass fraction of 36% in 4 times, continued to react for 80 min;

B: then added 6mol cobalt chloride powder, controlled the temperature of the solution at 32 °C, continued to react for 3 h, added 1.3 L sodium bromide solution with a mass fraction of 16%, until the solution was stratified, separated the reservoir, washed with cyclopropane solution with a mass fraction of 55% for 50 min, recrystallized in diisopropylamine solution with a mass fraction of 66%, dehydrated with anhydrous calcium sulfate dehydration, got the finished product thiamphenicol 702.744g, yield of 98.7%.

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. Broad spectrum antimicrobial agents thiamphenicol synthesis method, comprises the following steps:

A: 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and potassium sulfate solution were added to the reaction vessel, controlled the stirring speed at 210-230 rpm, controlled the temperature of the solution at 20-26 °C, added n-bromoacetamide, in 20-40 min, added acetylacetone solution in batches, continued to react for 50-80 min;

B: then added cobalt chloride powder, controlled the temperature of the solution at 28-32 °C, continued to react for 2-3 h, added sodium bromide solution, until the solution was stratified, separated the reservoir, washed with cyclopropane solution for 30-50 min, recrystallized in diisopropylamine solution, dehydrated with dehydration, got the finished product thiamphenicol.

2. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein potassium sulfate solution has a mass fraction of 15-22%.

3. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein acetylacetone solution has mass fraction of 30-36%.

4. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein sodium bromide solution has mass fraction of 10-16%.

5. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein cyclopropane solution has mass fraction of 50-55%.

6. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein diisopropylamine solution has a mass fraction of 60-66%.

7. Drug intermediates 1-methyl-2-quinolinone synthesis method according to claim 1 wherein, comprises the following steps:

A: 2mol 1-p-dimethoxysulfonylphenyl-2-dichloroacetamido-1,3-propanediol and 800 ml potassium sulfate solution with a mass fraction of 22% were added to the

reaction vessel, controlled the stirring speed at 230 rpm, controlled the temperature of the solution at 26 °C, added 6mol n-bromoacetamide, in 40 min, added 6mol acetylacetone solution with a mass fraction of 36% in 4 times, continued to react for 80 min;

B: then added 6mol cobalt chloride powder, controlled the temperature of the solution at 32 °C, continued to react for 3 h, added 1.3 L sodium bromide solution with a mass fraction of 16%, until the solution was stratified, separated the reservoir, washed with cyclopropane solution with a mass fraction of 55% for 50 min, recrystallized in diisopropylamine solution with a mass fraction of 66%, dehydrated with anhydrous calcium sulfate dehydration, got the finished product thiamphenicol.