DESCRIPTION

PROCESS FOR PRODUCING OPTICALLY ACTIVE BICYCLIC UREA COMPOUND

TECHNICAL FIELD

[0001]

The present invention relates to a process for producing an optically active bicyclic urea compound useful as an intermediate for medicines, particularly as an intermediate for β-lactamase inhibitor.

BACKGROUND ART

[0002]

As a process for producing an optically active bicyclic urea compound to be used as an intermediate for β-lactamase inhibitor, there has been known a process as shown below (see Patent Document 1, particularly PREPARATIVE EXAMPLE 1, Example 1A).

[0003]

~~[Chemical Formula 1]~~

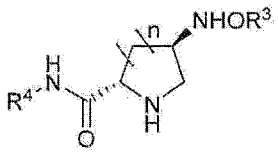
presence of a metal alkoxide and/or an alkaline earth metal salt to produce the corresponding amide compound and further reacting the amide compound with phosgene or a phosgene equivalent, followed by treatment with an acid, thereby completing the present invention.

[0007]

That is, in an aspect, the present ~~invention~~ disclosure relates to a process for producing an amide compound of formula (4):

[0008]

~~[Chemical Formula 3]~~



(4)

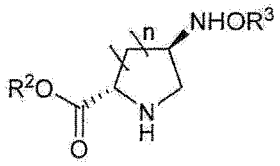
[0009]

wherein R^3, R^4, and n are the same as defined below, comprising:

reacting an ester compound of formula (2):

[0010]

~~[Chemical Formula 2]~~



(2)

[0011]

wherein R^2 and R^3 are each independently C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{3-12} cycloalkyl group, C_{7-12} aralkyl group, or C_{6-12} aryl group; and n is 1 or 2, with an amine of formula (3):

R^4NH_2 (3)

wherein R^4 is hydrogen atom, C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{3-12} cycloalkyl group, C_{7-12} aralkyl group, or C_{6-12} aryl group, in the presence of a metal alkoxide of formula (1):

$M(OR^1)_X$ (1)

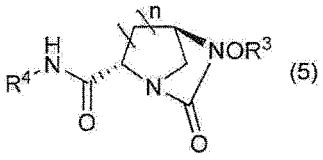
wherein M is magnesium, aluminum, titanium, zirconium, or hafnium; R^1 is C_{1-12} alkyl group; and X is an integer of 1 to 4, and/or an alkaline earth metal salt.

[0012]

The above amide compound can be converted into an optically active bicyclic urea compound of formula (5):

[0013]

~~[Chemical Formula 4]~~



(5)

[0014]

by reacting the compound (4) with phosgene or a phosgene equivalent.

EFFECTS OF THE INVENTION

[0015]

The process of the present invention makes it possible to produce an optically active bicyclic urea compound useful as an intermediate for medicines, particularly

as an intermediate for β-lactamase inhibitor, in a simple and easy manner without using expensive reagents such as catalysts and condensation agents, and without passing through protection and deprotection steps, as well as in high optical purity without causing racemization.

MODE FOR CARRYING OUT THE INVENTION

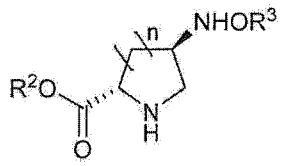
[0016]

First, the following will describe the starting materials to be used in the present invention.

[0017] - [0019]

The ester compound to be used in the present invention is of formula (2):

~~[Chemical Formula 5]~~



(2)

[0020]

wherein R^2 and R^3 are each independently C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{3-12} cycloalkyl group, C_{7-12} aralkyl group, or C_{6-12} aryl group.

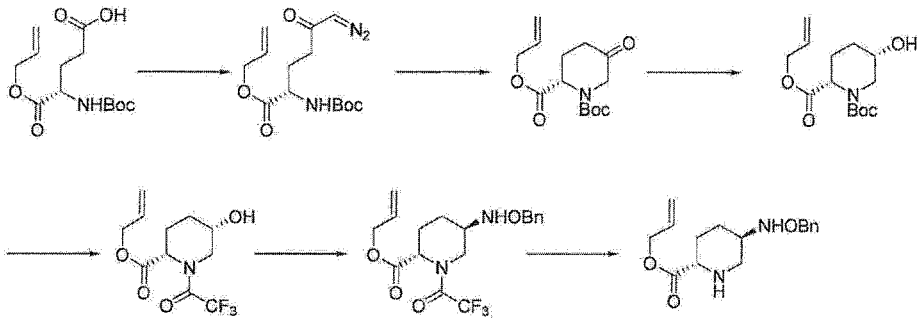
[0021]

These groups may have at least one substituent group. Examples of the substituent group may include halogen atoms such as fluorine atom, chlorine atom, bromine atom, and iodine atom; hydroxy group; alkoxy groups such as methoxy group and ethoxy group; methylthio group; trifluoromethyl group; acetyl group; benzoyl group; cyano group; nitro group; carboxyl group; and alkoxycarboxyl groups such as methoxycarboxyl group and ethoxycarboxyl group.

disclosed in WO2002/010172 or CHEMICAL COMMUNICATIONS, 1996, 349. More specifically, it can be produced by the method described below. Still more specifically, the compound (2) can be produced as follows: a glutamic acid derivative is reacted with diazomethane or the like to give the corresponding diazoketone, which is then subjected to intermolecular cyclization using a rhodium catalyst or the like. The carbonyl group is then reduced with a reducing agent such as sodium borohydride, followed by deprotection of the protecting group on the nitrogen atom, to produce the compound (2). The deprotection can be performed by conversion of, for example, tert-butoxycarbonyl group as a protecting group into trifluoroacetyl group and triflation of the resultant alcohol compound, followed by substitution reaction with benzyloxyamine.

[0033]

~~[Chemical Formula 6]~~



[0034]

The following will describe the amide compound as a product.

[0035]

The amide compound obtained in the present invention is of formula (4):

[0036]

~~[Chemical Formula 7]~~

[0041]

Particularly preferred as the R^4 is hydrogen atom, allyl group, benzyl group, p-methoxyphenyl group, 1-(tert-butoxycarbonyl)piperidin-4-yl group, or 1-(benzyl-oxycarbonyl)piperidin-4-yl group, with more particularly preferred being hydrogen atom or 1-(benzyl-oxycarbonyl)piperidin-4-yl group.

[0042]

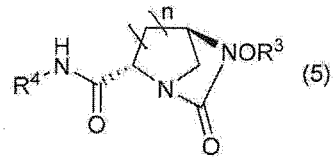
The following will describe an optically active bicyclic urea compound to be obtained by reaction of the amide compound with phosgene or a phosgene equivalent.

[0043]

The optically active bicyclic urea compound to be obtained in the present invention is of formula (5):

[0044]

~~[Chemical Formula 8]~~



(5)

[0045]

wherein R^3, R^4, and n are the same as defined above.

[0046]

The following will describe a process for producing the compound (4).

[0047]

The compound (4) can be produced by reacting the compound (2) with an amine of formula (3):

(3), these reagents may be added after dissolved in an appropriate solvent.

[0061]

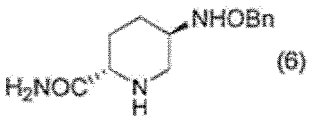
After the reaction in this step, ordinary treatment may be performed as the post-treatment to obtain a product from the reaction solution. More specifically, for example, water is added to the reaction solution, followed by extraction with addition of an organic solvent such as toluene, ethyl acetate, isopropyl acetate, methyl tert-butyl ether, or hexane. The organic solvent is distilled away from the resultant extract by an operation such as heating under reduced pressure, whereby a target product can be isolated. In the case where insoluble matter is precipitated, the insoluble matter may be filtered away, followed by an operation as described above. The target product thus obtained has purity enough to be usable in the subsequent step, but it may further be purified by any of ordinary purification methods such as crystallization, fractional distillation, and column chromatography.

[0062]

The thus obtained compound of formula (6) wherein R^3 is Bn, R^4 is H, and n is 2 is a compound unknown to the public through publication.

[0063]

~~[Chemical Formula 9]~~



(6)

[0064]

The following will describe a process for producing the compound (5).

[0065]

The compound (5) is produced by reacting the compound (4) with phosgene

The reaction temperature in this step is not particularly limited, so long as it is not lower than the freezing point and not higher than the boiling point of the solvent, but it may appropriately be determined, with the preferred lower limit thereof being not lower than -78°C, more preferably not lower than -50°C, and particularly preferably not lower than -30°C, and the preferred upper limit thereof being not higher than 150°C, more preferably not higher than 100°C, still more preferably not higher than 50°C, and particularly preferably not higher than 20°C.

[0070]

The reaction time in this step is preferably not shorter than 0.1 hour, more preferably not shorter than 0.5 hour, and still more preferably not shorter than 0.7 hour, and is preferably not longer than 50 hours, more preferably not longer than 20 hours, still more preferably not longer than 10 hours, and particularly preferably not longer than 5 hours.

[0071]

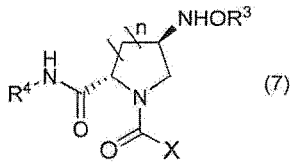
The order of the addition of reagents in this step is, for example, as follows: phosgene or a phosgene equivalent may be added to a solution of the compound (4), or alternatively, the compound (4) may be added to a solution of phosgene or a phosgene equivalent.

[0072]

The reaction of the compound (4) with phosgene or a phosgene equivalent may produce a compound of formula (7):

[0073]

~~[Chemical Formula 10]~~



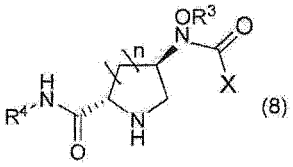
(7)

[0074]

or a compound of formula (8):

[0075]

~~[Chemical Formula 11]~~



(8)

[0076]

wherein X is the residue of phosgene or a phosgene equivalent. In such a case, the compound (5) can be obtained by treating the reaction solution with an acid or a base.

[0077]

Examples of the acid may include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, and citric acid. These may preferably be used as an aqueous solution. Preferred is phosphoric acid.

[0078]

The amount of the acid to be used is not smaller than 0.3 mole, preferably not smaller than 0.5 mole, more preferably not smaller than 0.8 mole, relative to 1 mole of the compound (4), as the lower limit, and is not greater than 10 moles, preferably not greater than 5 moles, and more preferably not greater than 3 moles, relative to 1 mole of the compound (4), as the upper limit.

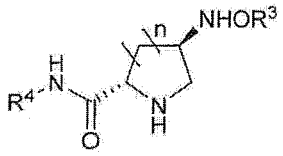
[0079]

CLAIMS

[Claim 1]

A process for producing an amide compound of formula (4):

~~[Chemical Formula 2]~~

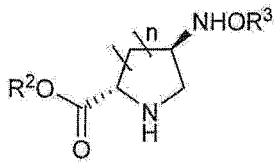


(4)

wherein R^3, R^4, and n are the same as defined below, comprising:

reacting an ester compound of formula (2):

~~[Chemical Formula 1]~~



(2)

wherein R^2 and R^3 are each independently C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{3-12} cycloalkyl group, C_{7-12} aralkyl group, or C_{6-12} aryl group; and n is 1 or 2, with an amine of formula (3):

$$R^4NH_2 \qquad (3)$$

wherein R^4 is hydrogen atom, C_{1-12} alkyl group, C_{2-12} alkenyl group, C_{3-12} cycloalkyl group, C_{7-12} aralkyl group, or C_{6-12} aryl group, in the presence of a metal alkoxide of formula (1):

$$M(OR^1)_X \qquad (1)$$

wherein M is magnesium, aluminum, titanium, zirconium, or hafnium; R^1 is C_{1-12} alkyl group; and X is an integer of 1 to 4, and/or an alkaline earth metal salt.

[Claim 2]

The production process according to claim 1, wherein the metal alkoxide is $Ti(O\text{-}i\text{-}Pr)_4$ or $Al(O\text{-}i\text{-}Pr)_3$.

[Claim 3]

The production process according to claim 1, wherein the alkaline earth metal salt is calcium chloride or magnesium chloride.

[Claim 4]

The production process according to any of claims 1 to 3, wherein the R^2 is methyl group, ethyl group, isopropyl group, allyl group, or benzyl group; R^3 is benzyl group; and n is 2.

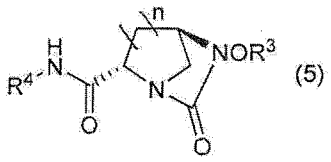
[Claim 5]

The production process according to any of claims 1 to 4, wherein the R^4 is hydrogen atom, allyl group, benzyl group, p-methoxyphenyl group, 1-(tert-butoxy-carbonyl)piperidin-4-yl group, or 1-(benzyloxycarbonyl)piperidin-4-yl group.

[Claim 6]

The production process according to any of claims 1 to 5, further comprising reacting the compound (4) with phosgene or a phosgene equivalent to produce an optically active bicyclic urea compound of formula (5):

~~[Chemical Formula 3]~~



(5)