(11) Application No. AU 2005258378 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title

Method for producing 1,2-dihydropyridine-2-one compound

(51)[6] International Patent Classification(s)

C07D 213/64 20060101AFI2006041
(2006.01) 8BHAU
C07D 213/64 PCT/JP2005/012364

(21) Application No: 2005258378 (22) Application Date: 2005.07.05

(87) WIPO No: WO06/004100

(30) Priority Data

(31) Number	(32) Date	(33) Country
2004-198709	2004.07.06	JP

(43) Publication Date : 2006.01.12

(71) Applicant(s)

Eisai R & D Management Co., Ltd.

(72) Inventor(s)

Nishiura, Katutoshi; Kayano, Akio

(74) Agent/Attorney

Davies Collison Cave, 1 Nicholson Street, Melbourne, VIC, 3000

(56) Related Art

MEHUL B. ET AL: 'Copper-Catalyzed Suzuki Cross-Coupling Using Mixed Nanocluster Catalysts.' J. AMER. CHEM. SOC. vol. 124, no. 40, 2002, pages 11858 - 11859

PESSOLANO ET AL: "Novel Nucleophilic Substitution of Alkyl Bromo-2(1H)-pyridones" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 22, 1985, pages 265-272

GISSOT ET AL: "A Functionalized, Deep Cavitand Catalyzes the Aminolysis of a Choline Derivative" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 126, no. 24, 28 May 2004, pages 7424-7425,

WO 2001/096308 A1

WO 2003/047577 A2

DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; 1984, Database accession no. Reaction ID 1794203

(12) 特許協力条約に基づいて公開された国際出願

訂正版

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2006 年1 月12 日 (12.01.2006)

PCT

(10) 国際公開番号
WO 2006/004100 A1

(51) 国際特許分類[7]: C07D 213/64

(21) 国際出願番号: PCT/JP2005/012364

(22) 国際出願日: 2005 年7 月5 日 (05.07.2005)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:
特願2004-198709 2004 年7 月6 日 (06.07.2004) JP

(71) 出願人 (米国を除く全ての指定国について): エーザイ株式会社 (EISAI CO., LTD.) [JP/JP]; 〒1120002 東京都文京区小石川４丁目６番１０号 Tokyo (JP).

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 栢野 明生 (KAYANO, Akio) [JP/JP]; 〒3140255 茨城県鹿島郡波崎町大字砂山２２番地 エーザイ株式会社 鹿島事業所内 Ibaraki (JP). 西浦 克智 (NISHIURA, Katutoshi) [JP/JP]; 〒3140255 茨城県鹿島郡波崎町大字砂山２２番地 エーザイ株式会社 鹿島事業所内 Ibaraki (JP).

(74) 代理人: 浅村 皓, 外(ASAMURA, Kiyoshi et al.): 〒1000004 東京都千代田区大手町２丁目２番１号 新大手町ビル３３１ Tokyo (JP).

(81) 指定国 (表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) 指定国 (表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

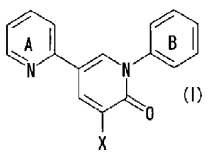
(48) この訂正版の公開日: 2006 年2 月23 日

(15) 訂正情報:
PCTガゼット セクションIIの No.08/2006 (2006 年2 月23 日)を参照

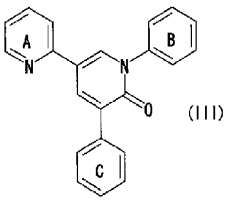
２文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: METHOD FOR PRODUCING 1,2-DIHYDROPYRIDINE-2-ONE COMPOUND

(54) 発明の名称: １，２－ジヒドロピリジン－２－オン化合物の製造方法



(I)



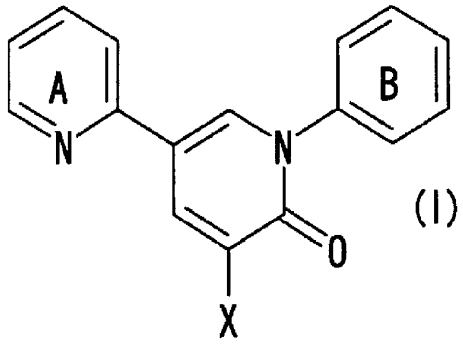
(III)

(57) Abstract: Disclosed is a method for commercially producing a 1,2-dihydropyridine-2-one compound represented by the following formula (III) (wherein the ring A and ring B are as defined below and the ring C represents an optionally substituted phenyl group) with high yield and high purity by reacting a compound represented by the following formula (I) (wherein the ring A represents an optionally substituted 2-pyridyl group, the ring B represents an optionally substituted phenyl group, and X represents a leaving group) with a boronic acid derivative in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

[続葉有]

WO 2006/004100 A1

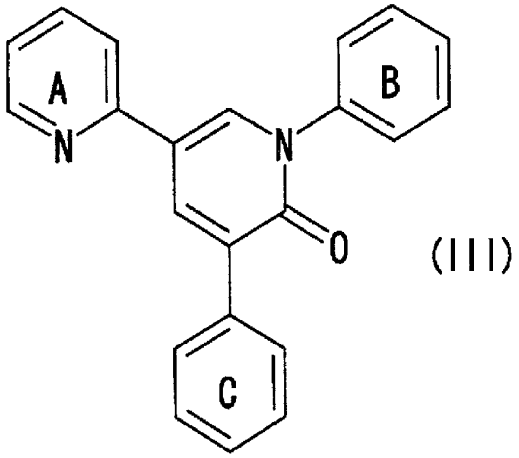
(57) 要約:



(I)

[式中、A環は置換基を有していてもよい2－ピリジル基を、B環は置換基を有してもよいフェニル基を、Xは脱離基を示す]で表される化合物に、パラジウム化合物、銅化合物、リン化合物および塩基の存在下、ボロン酸誘導体を反応させることにより、式(III)

【化2】



(III)

[式中、A環およびB環は前記定義と同意義を示し、C環は置換基を有していてもよいフェニル基を示す]で表される1，2－ジヒドロピリジン－2－オン化合物を、良好な収率で、純度よく工業的に製造することができる。

DESCRIPTION

METHOD FOR PRODUCING 1,2-DIHYDROPYRIDINE-2-ONE COMPOUND

TECHNICAL FIELD

[0001]

The present invention relates to a method for producing a 1,2-dihydropyridine-2-one compound represented by formula (III) which comprises reacting a compound represented by formula (I) with a boronic acid derivative represented by formula (II) in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

The compound of formula (III) represented by 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one is useful as, for example, a therapeutic agent for diseases such as Parkinson's disease, multiple sclerosis, epilepsy, etc.

BACKGROUND ART

[0002]

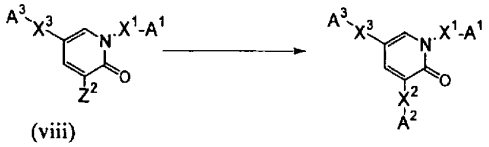
Background art concerning a method for producing the compound of formula (III) is explained below.

In the production method 2 in patent document 1, the coupling reaction of a compound (viii) with an arylboronic acid derivative by the use of a palladium catalyst is described as to a final step for producing

a compound (I-1), but the reaction in the presence of a palladium compound, a copper compound and a phosphorus compound is neither suggested nor described which is characteristic of the present invention.

Production method 2

[Formula 1]

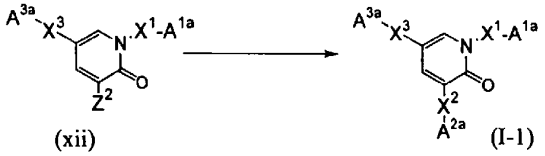


(viii) (I-1)

Also in the production method 3 in patent document 1, the coupling reaction of a compound (xii) with an arylboronic acid derivative by the use of a palladium catalyst is described as to a final step for producing a compound (I-1), but the reaction in the presence of a palladium compound, a copper compound and a phosphorus compound is neither suggested nor described which is characteristic of the present invention.

Production method 3

[Formula 2]

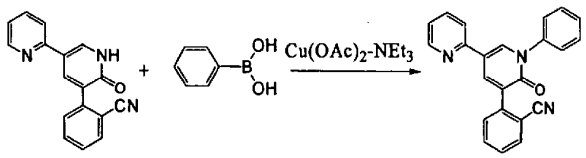


(xii) (I-1)

The compound of formula (III-a) described hereinafter is a well-known compound. In Example 7 in patent document 1, it is known that as shown in the following reaction scheme, this compound may be produced by reacting 3-(2-cyanophenyl)-5-(2-pyridyl)-2(1H)-pyridone with phenylboronic acid in the presence of copper acetate and triethylamine. But, there is neither suggested nor described a method for producing a compound of formula (III) by the reaction of a compound of formula (I) with a compound of formula (II) in the presence of a palladium compound, a copper compound, a phosphorus compound and a base which is characteristic of the present invention.

[0003]

[Formula 3]



[0004]

As to the compound of formula (I) represented by 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (III-a), a method for producing this compound is described in claim 49 and Example 404 in patent document 1.

[0005]

On the other hand, the effect of a copper catalyst in the Suzuki reaction is described in non-patent document 1. Although this reference describes "$Pd(PPh_3)_4$-CuI", copper iodide is used in a large amount of 1.1 equivalents per equivalent of a starting material in the reference. The reference neither suggests nor describes the progress of the reaction in the presence of a palladium compound, a copper compound and a phosphorus compound, in particular, the reaction in the presence of a catalytic amount of the copper compound, which is characteristic of the present invention.

Patent document 1: International Publication No. WO01/96308 pamphlet

Non-patent document 1: G.M. Boland and three others, Synthesis neoflavones by Suzuki arylation of 4-substituted coumarins, J. Chem. Soc., Perkin Trans.1, 2591-2587(1996)

DISCLOSURE OF THE INVENTION

[0006]

When in each of the methods using a palladium catalyst described as the production method 2 and production method 3 in patent document 1, the reaction is carried out in the presence of, for example, "palladium acetate catalyst-cesium carbonate-water", there are various problems such as the following

problems: a considerable amount of compounds are produced as by-products by the cleavage of the carbon-boron bond of a compound (II) (Yoshio Urawa and three others, Pharmacia, 35(7), 706-710(1999)) and the hydrolysis of a substituent such as a nitrile group proceeds. Therefore, an industrial method for producing a compound represented by formula (III) is desired.

[0007]

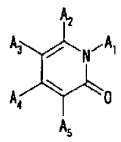
Accordingly, in one or more aspects the present invention may advantageously provide a method for industrially producing a compound of formula (III) having an excellent therapeutic effect on diseases such as Parkinson's disease, multiple sclerosis, epilepsy, etc., in good yield and high purity.

[0008]

The present invention relates to the following production methods 1) to 13).

1) A method for producing a compound represented by formula (III):

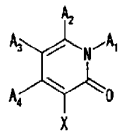
[Formula 6]



(III)

wherein A_1, A_2, A_3, A_4 and A_5 are as defined below, or a salt thereof, which comprises reacting a compound represented by formula (I):

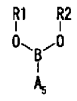
[Formula 4]



(I)

wherein each of A_1, A_2, A_3 and A_4, which may be the same or different, is a hydrogen atom, an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group, and X is a leaving group, or a salt thereof with a compound represented by formula (II):

[Formula 5]



(II)

wherein A_5 is an optionally substituted 6-to 14-membered

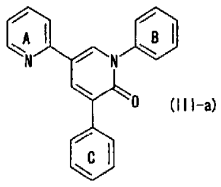
aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group; and R1 and R2 are as follows: 1) each of R1 and R2, which may be the same or different, is a hydrogen atom or a C1-6 alkyl group, and 2) the compound of formula (II) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms, or 3) R1, R2, the oxygen atoms and the boron atom, when taken together, form a 5-or 6-membered ring group optionally substituted by one to four C1-6 alkyl groups, in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

2) A production method according to 1), wherein each of A_2 and A_4 is a hydrogen atom.

3) A production method according to 1) or 2), wherein each of A_1, A_3 and A_5 is a phenyl group, a pyridyl group, a pyrimidyl group, a thienyl group or a furyl group.

4) A production method according to any one of 1) to 3), wherein a compound represented by formula (III-a):

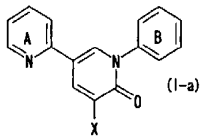
[Formula 9]



(III-a)

wherein the ring A, ring B and ring C are as defined below, or a salt thereof is produced by reacting a compound represented by formula (I-a):

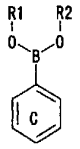
[Formula 7]



(I-a)

wherein the ring A is an optionally substituted 2-pyridyl group, the ring B is an optionally substituted phenyl group, and X is a leaving group, or a salt thereof with a compound represented by formula (II-a):

[Formula 8]



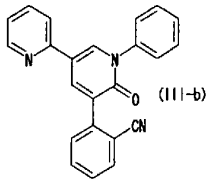
(II-a)

wherein the ring C is an optionally substituted phenyl group; and R1 and R2 are as follows: 1) each of R1 and R2, which may be the same or different, is a hydrogen atom or a C1-6 alkyl group, and 2) the compound of formula (II-a) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms, or 3) R1, R2, the oxygen atoms and the boron atom, when taken together, form a 5-or 6-membered ring group optionally substituted by

one to four C1-6 alkyl groups, in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

5) A production method according to 4), wherein a compound represented by formula (III-b):

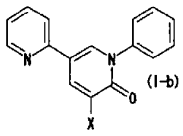
[Formula 12]



(III-b)

or a salt thereof is produced by reacting a compound represented by formula (I-b):

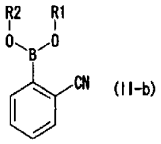
[Formula 10]



(I-b)

wherein X is a leaving group, or a salt thereof with a compound represented by formula (II-b):

[Formula 11]

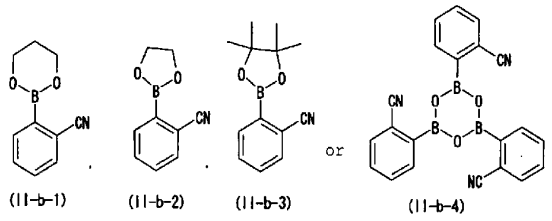


(II-b)

wherein R1 and R2 are as defined above, in a solvent in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

6) A production method according to 5), wherein the compound (II-b) is a compound represented by formula (II-b-1), formula (II-b-2), formula (II-b-3) or formula (II-b-4):

[Formula 13]



(II-b-1) (II-b-2) (II-b-3) (II-b-4)

7) A production method according to any one of 1) to 6), wherein X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group.

8) A production method according to any one of 1) to 7), wherein the palladium compound is palladium acetate, palladium chloride or palladium hydroxide.

9) A production method according to any one of 1) to 8), wherein the phosphorus compound is triphenylphosphine or tri-tert-butylphosphine.

10) A production method according to any one of 1) to 9), wherein the copper compound is cuprous bromide, cuprous iodide, cuprous chloride or cuprous acetate.

11) A production method according to any one of 1) to 10), wherein the base is cesium carbonate, sodium carbonate or potassium carbonate.

12) A production method according to any one of 1) to 11), wherein the copper compound is used in an amount of 0.01 to 0.05 mole per mole of the compound represented by formula (1).

13) A production method according to any one of 1) to 12), wherein the reaction is carried out in a solvent and 1,2-dimethoxyethane or toluene is used as the solvent for reaction.

[0009]

The symbols and terms used in the present specification are explained below.

The term "6-to 14-membered aromatic hydrocarbon ring group" means an aromatic hydrocarbon ring group comprising 6 to 14 carbon atoms and also includes fused-ring groups such as monocyclic groups, bicyclic groups, tricyclic groups, etc. Specific examples of said group are phenyl group, indenyl group, 1-naphthyl group, 2-naphthyl group, azulenyl group, heptalenyl group, biphenyl group, indacenyl group, acenaphthyl group, fluorenyl group, phenalenyl group, phenanthrenyl group, anthracenyl group, etc.

The term "5-to 14-membered heteroaromatic ring group" means a monocyclic, bicyclic or tricyclic 5-to 14-membered heteroaromatic ring group containing one or more heteroatoms selected from the group

consisting of nitrogen atom, sulfur atom and oxygen atom. Specific examples of said group are 1) nitrogen-containing heteroaromatic ring groups such as pyrrolyl group, pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazolyl group, tetrazolyl group, benzotriazolyl group, pyrazolyl group, imidazolyl group, benzimidazolyl group, indolyl group, isoindolyl group, indolizinyl group, purinyl group, indazolyl group, quinolyl group, isoquinolyl group, quinolizinyl group, phthalazyl group, naphthyridinyl group, quinoxalyl group, quinazolinyl group, cinnolinyl group, pteridinyl group, imidazotriazinyl group, pyrazinopyridazinyl group, acridinyl group, phenanthridinyl group, carbazolyl group, carbazolinyl group, perimidinyl group, phenanthrolinyl group, phenazinyl group, imidazopyridinyl group, imidazopyrimidinyl group, pyrazolopyridinyl group, etc., 2) sulfur-containing heteroaromatic ring groups such as thienyl group, benzothienyl group, etc., 3) oxygen-containing heteroaromatic ring groups such as furyl group, pyranyl group, cyclopentapyranyl group, benzofuryl group, isobenzofuryl group, etc., and 4) heteroaromatic ring groups containing two or more heteroatoms of different kinds, such as thiazolyl group, isothiazolyl group, benzothiazolyl group, benzthiadiazolyl group, phenothiazinyl group, isoxazolyl group, furazanyl group, phenoxazinyl group, oxazolyl group, isoxazolyl group, benzoxazolyl group,

oxadiazolyl group, pyrazoloxazolyl group, imidazothiazolyl group, thienofuranyl group, furopyrrolyl group, pyridoxazinyl group, etc.

[0010]

Each of A_1, A_2, A_3 and A_4 is a hydrogen atom, an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group. More preferably, each of A_2 and A_4 is a hydrogen atom and each of A_1 and A_3 is an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group. Most preferably, each of A_1 and A_3 is, for example, an optionally substituted phenyl, pyridyl, pyrimidinyl, thienyl or furyl group.

[0011]

A_5 is an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group. A_5 is more preferably, for example, an optionally substituted phenyl, pyrrolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, thiazolyl, furyl, naphthyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, imidazopyridyl or pyrrolidinyl group. A_5 is most preferably, for example, an optionally substituted phenyl, pyridyl, pyrimidinyl, thienyl or furyl group.

[0012]

When the group represented by any of A_1, A_2, A_3, A_4 and A_5 in the above formula is an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group, it may have one to four substituents which may be the same or different and are selected from the following substituents.

In the above formula, the ring A is an optionally substituted 2-pyridyl group and each of the ring B and the ring C is an optionally substituted phenyl group. The ring A, ring B and ring C may also have one to four substituents which may be the same or different and are selected from the following substituents.

[0013]

The substituents include, for example, hydroxyl group, nitrile groups, halogen atoms, C1-6 alkyl groups, C2-6 alkenyl groups, C2-6 alkynyl groups, C3-8 cycloalkyl groups, C1-6 alkoxy groups, C1-6 alkylthio groups, C1-6 alkoxycarbonyl groups, C1-6 alkanoyl groups (C1-6 alkylcarbonyl groups), C1-6 alkylsulfonyl groups, amino group optionally substituted by a C1-6 alkyl group, amino group optionally substituted by a formyl group, amino group optionally substituted by a C1-6 alkanoyl group, amino group optionally substituted by a C1-6 alkylsulfonyl group, carbamoyl group optionally substituted by one or two C1-6 alkyl groups, and C1-6 alkoxyimino groups. Of

these, the nitrile groups and halogen atoms are preferable.

[0014]

The term "halogen atoms" means a fluorine atom, chlorine atom, bromine atom, iodine atom and the like. The halogen atoms are preferably a chlorine atom and a bromine atom.

[0015]

The term "C1-6 alkyl groups" means alkyl groups of 1 to 6 carbon atoms. Preferable examples of these groups are linear or branched alkyl groups such as methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, i-butyl group, tert-butyl group, n-pentyl group, i-pentyl group, neopentyl group, n-hexyl group, 1-methylpropyl group, 1,2-dimethylpropyl group, 2-ethylpropyl group, 1-methyl-2-ethylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylbutyl group, 2,2-dimethylbutyl group, 2-ethylbutyl group, 1,3-dimethylbutyl group, 2-methylpentyl group, 3-methylpentyl group, etc.

[0016]

The term "C2-6 alkenyl groups" means alkenyl groups of 2 to 6 carbon atoms. Preferable examples of these groups are linear or branched alkenyl groups such as vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-buten-1-yl group, 1-buten-2-yl

group, 1-buten-3-yl group, 2-buten-1-yl group, 2-buten-2-yl group, etc.

[0017]

The term "C2-6 alkynyl groups" means alkynyl groups of 2 to 6 carbon atoms. Preferable examples of these groups are linear or branched alkynyl groups such as ethynyl group, 1-propynyl group, 2-propynyl group, butynyl group, pentynyl group, hexynyl group, etc.

[0018]

The term "C3-8 cycloalkyl groups" means cyclic alkyl groups of 3 to 8 carbon atoms. Preferable examples of these groups are cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, etc.

[0019]

The term "C1-6 alkoxy groups" means groups formed by the replacement of a hydrogen atom of an alkyl group of 1 to 6 carbon atoms by an oxygen atom. Preferable examples of said groups are methoxy group, ethoxy group, n-propoxy group, i-propoxy group, sec-propoxy group, n-butoxy group, i-butoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, i-pentyloxy group, sec-pentyloxy group, tert-pentyloxy group, n-hexyloxy group, i-hexyloxy group, 1,2-dimethylpropoxy group, 2-ethylpropoxy group, 1-methyl-2-ethylpropoxy group, 1-ethyl-2-methylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1-dimethylbutoxy group, 2,2-dimethylbutoxy group, 2-ethylbutoxy group, 1,3-

dimethylbutoxy group, 2-methylpentyloxy group, 3-methylpentyloxy group, hexyloxy group, etc.

[0020]

The term "C1-6 alkylthio groups" means groups formed by the replacement of a hydrogen atom of an alkyl group of 1 to 6 carbon atoms by a sulfur atom. Preferable examples of said groups are methylthio group, ethylthio group, n-propylthio group, i-propylthio group, n-butylthio group, i-butylthio group, tert-butylthio group, n-pentylthio group, i-pentylthio group, neopentylthio group, n-hexylthio group, 1-methylpropylthio group, etc.

[0021]

The term "C1-6 alkoxycarbonyl groups" means groups formed by bonding of a carbonyl group to any of the above-exemplified alkoxy groups. Preferable examples of said groups are methoxycarbonyl group, ethoxycarbonyl group, etc.

[0022]

The term "C1-6 alkanoyl groups (C1-6 alkylcarbonyl groups)" means groups formed by the replacement of a hydrogen atom of an alkyl group of 1 to 6 carbon atoms by a carbonyl group. Preferable examples of said groups are acetyl group, propionyl group, butyryl group, etc.

[0023]

The term "C1-6 alkylsulfonyl groups" means groups formed by the replacement of a hydrogen atom of

an alkyl group of 1 to 6 carbon atoms by a sulfonyl group. Preferable examples of said groups are methanesulfonyl group, ethanesulfonyl group, etc.

[0024]

The term "amino group optionally substituted by a C1-6 alkyl group" means an amino group that may have an alkyl group of 1 to 6 carbon atoms bonded thereto. Preferable examples of such an amino group are amino group, methylamino group, ethylamino group, propylamino group, etc.

[0025]

"Amino group optionally substituted by a formyl group" includes, for example, amino group, formylamino group, etc.

[0026]

The term "amino group optionally substituted by a C1-6 alkanoyl group" means an amino group that may have an alkanoyl group of 1 to 6 carbon atoms bonded thereto. Preferable examples of such an amino group are acetylamino group, propionylamino group, butyrylamino group, etc.

[0027]

The term "amino group optionally substituted by a C1-6 alkylsulfonyl group" means an amino group that may have an alkylsulfonyl group of 1 to 6 carbon atoms bonded thereto. Preferable examples of such an amino group are amino group, methanesulfonylamino group, ethanesulfonylamino group, n-

propanesulfonylamino group, n-butanesulfonylamino group, N-methylmethanesulfonylamino group, etc.

[0028]

The term "carbamoyl group optionally substituted by one or two C1-6 alkyl groups" means a carbamoyl group one or two hydrogen atoms of which may be replaced by one or two, respectively, C1-6 alkyl groups. Preferable examples of said groups are N-methylcarbamoyl group, N,N-dimethylcarbamoyl group, N-ethylcarbamoyl group, N,N-diethylcarbamoyl group, etc.

[0029]

The term "C1-6 alkoxyimino groups" means groups formed by the replacement of a hydrogen atom of an imino group by a C1-6 alkoxy group. Preferable examples of said groups are methoxyimino group, ethoxyimino group, etc.

[0030]

The passage "X is a leaving group" means that X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group.

[0031]

The passage "X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group" means that X is a halogen atom such as fluorine atom, chlorine atom, bromine atom or iodine atom; an alkylsulfonyloxy group such as trifluoromethanesulfonyloxy group; or an arylsulfonyloxy group such as phenylsulfonyloxy group.

X is preferably a halogen atom such as chlorine atom or bromine atom, or an alkylsulfonyloxy group such as trifluoromethanesulfonyloxy group.

[0032]

The sentence "R1 and R2 are as follows: 1) each of R1 and R2, which may be the same or different, is a hydrogen atom or a C1-6 alkyl group, and 2) the compound (II) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms, or 3) R1, R2, the oxygen atoms and the boron atom, when taken together, form a 5-or 6-membered ring group optionally substituted by one to four C1-6 alkyl groups" in the case of the compound (II) means that the compound (II) is, for example, a phenylboronic acid derivative in which the hydrogen atom of the hydroxyl group may be replaced by a C1-6 alkyl group; a 2-phenyl-[1,3,2]-dioxoboronate the ring-forming methylene groups of which may be substituted by one to four C1-6 alkyl groups; or a 2-phenyl-[1,3,2]-dioxoboronate derivative the ring-forming methylene groups of which may be substituted by one to four C1-6 alkyl groups.

In particular, the passage "the compound (II) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms" means that when both R1 and R2 are hydrogen atoms, the compound (II) may be a monomer or may form a cluster such as a dimer or boroxine (a trimer).

[0033]

The term "a palladium compound, a copper compound and a phosphorus compound" means a combination of a palladium compound selected from the palladium compounds described hereinafter, a copper compound selected from the copper compounds described hereinafter, and a phosphorus compound selected from the phosphorus compounds described hereinafter.

[0034]

The compound (I-a) is included in the compound represented by formula (I) and corresponds to a compound of formula (I) in which A_1 is an optionally substituted phenyl group, each of A_2 and A_4 is a hydrogen atom, and A_3 is an optionally substituted 2-pyridyl group.

The compound (I-b) is included in the compound represented by formula (I-a) and corresponds to a compound of formula (I-a) in which A_1 is a phenyl group, each of A_2 and A_4 is a hydrogen atom, and A_3 is a 2-pyridyl group.

The compound (II-a) is included in the compound represented by formula (II) and corresponds to a compound of formula (II) in which A_5 is an optionally substituted phenyl group.

The compound (II-b) is included in the compound represented by formula (II-a) and corresponds to a compound of formula (II-a) in which A_5 is a 2-cyanophenyl group.

The compounds (II-b-1), (II-b-2), (II-b-3)

and (II-b-4) are included in the compound represented by formula (II-b). Each of the compounds (II-b-1), (II-b-2) and (II-b-3) corresponds to a compound of formula (II-b) in which R1, R2, the oxygen atoms and the boron atom are taken together to form a 5-or 6-membered ring group optionally substituted by one to four C1-6 alkyl groups. The compound (II-b-4) corresponds to boroxine (a trimer) formed by a compound of formula (II-b) in which both R1 and R2 are hydrogen atoms.

The compound (III-a) is included in the compound represented by formula (III) and corresponds to a compound of formula (III) in which each of A_1 and A_5 is an optionally substituted phenyl group, each of A_2 and A_4 is a hydrogen atom, and A_3 is an optionally substituted 2-pyridyl group.

The compound (III-b) is included in the compound represented by formula (III-a) and corresponds to a compound of formula (III-a) in which the ring A is a 2-pyridyl group, the ring B is a phenyl group and the ring C is a 2-cyanophenyl group.

[0035]

The production method of the present invention is explained below in detail.

[0036]

A method for producing a compound of formula (III) represented by 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (III-a)

This production method is characterized by converting a compound of formula (I) to the compound of formula (III) by reacting the compound of formula (I) with a compound of formula (II) in a solvent in the presence of a palladium compound, a copper compound and a phosphorus compound.

[0037]

This reaction may be carried out also in a stream or atmosphere of an inert gas such as nitrogen, argon or the like.

[0038]

As the compound (I), there can be used compounds producible by the method described in the production example 2 described hereinafter and "Chemical Society of Japan, Jikken Kagaku Koza (Experimental Chemistry) 19, 4th ed., Organic Synthesis I-Carbon Compounds•Halogen Compounds-", Maruzen Co., Ltd., Jun. 5, 1992, p363-482, well-known compounds, purchasable compounds, and compounds easily producible from a purchasable compound by a method conventionally adopted by those skilled in the art.

As the compound (II), there can be used compounds producible by the method described in F.R. Bean et al., J. Am. Chem. Soc., 54, 4415(1932), J.M. Sugihara et al., J. Am. Chem. Soc., 80, 2443(1958), or the like, well-known compounds, purchasable compounds, and compounds easily producible from a purchasable compound by a method conventionally adopted by those

skilled in the art.

[0039]

The reaction is preferably carried out in a solvent. The solvent for reaction used is not particularly limited so long as it dissolves the starting materials to a certain degree and does not inhibit the reaction. As the solvent, there can be used, for example, organic solvents including ether solvents (e.g. tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether and dioxane), aromatic hydrocarbon solvents (e.g. benzene, toluene and xylene), amide solvents (e.g. N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone), dimethyl sulfoxide, etc.; and mixtures of any of these organic solvents and water. The solvent is suitably, for example, 1,2-dimethoxyethane or toluene.

[0040]

The above term "palladium compound" means, for example, tetrakis(triphenylphosphine)palladium, tris(dibenzylideneacetone)dipalladium, bis(dibenzylideneacetone)palladium, tetrakis(tri-tert-butylphosphine)palladium, palladium acetate, dichlorobis(triphenylphosphine)palladium, dichlorobis(tri-o-tolylphosphine)palladium, dichlorobis(tricyclohexylphosphine)palladium, 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium, palladium chloride, palladium hydroxide, palladium nitrate, di-μ-chlorobis(η-allyl)palladium, bis(acetyl-

acetonato)palladium,
dichlorobis(benzonitrile)palladium,
dichlorobis(acetonitrile)palladium or the like. The palladium compound is suitably palladium acetate, palladium chloride, palladium hydroxide or the like.

[0041]

The above term "copper compound" means cuprous fluoride, cuprous chloride, cuprous bromide, cuprous iodide, cuprous acetate or the like. The copper compound is suitably cuprous bromide, cuprous iodide, cuprous chloride or cuprous acetate.

[0042]

The above term "phosphorus compound" means, for example, triphenylphosphine, tri(2-methylphenyl)phosphine, bis(diphenylphosphino)methane, bis(diphenylphosphino)ethane, bis(diphenylphosphino)propane, bis(diphenylphosphino)butane, bis(diphenylphosphino)pentane, bis(diphenylphosphino)hexane, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, tri-tert-butylphosphine, tri(4-methylphenyl)phosphine, tricyclohexylphosphine, 2-(di-tert-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, 1,1'-bis(diphenylphosphino)ferrocene or the like. The phosphorus compound is suitably, for example, triphenylphosphine, tri-tert-butylphosphine or tri(4-methylphenyl)phosphine, more suitably

triphenylphosphine or tri-tert-butylphosphine.

[0043]

The above term "base" means an inorganic base such as sodium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, potassium phosphate, cesium fluoride, potassium fluoride or the like; an alkali metal alkoxide such as sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide or the like; or an organic amine such as N-methylmorpholine, N,N-dimethylaniline, DBU, triethylamine or the like. The base is suitably, for example, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate or potassium hydrogencarbonate, more suitably sodium carbonate, potassium carbonate or cesium carbonate.

[0044]

The reaction temperature is usually varied depending on the starting materials, the solvent and other reagents used in the reaction and is suitably 100°C to 50°C (the internal temperature of a reactor), more suitably 90°C to 60°C (the internal temperature of the reactor).

[0045]

The reaction time is usually varied depending on the starting materials, the solvent, other reagents used in the reaction and the reaction temperature. It is suitable to conduct stirring for 1 to 10 hours, more

suitably about 4 hours, in the above reaction temperature range after the addition of the reagents.

[0046]

The compound (II) may be used in an amount of 1 to 10 moles, suitably 1 to 3 moles, more suitably 1.5 moles, per mole of the compound (I).

[0047]

The above-mentioned palladium compound may be used in an amount of 0.001 to 0.1 mole, suitably 0.01 to 0.05 mole, more suitably 0.02 mole, per mole of the compound (I).

[0048]

The above-mentioned copper compound may be used in an amount of 0.001 to 0.2 mole, suitably 0.01 to 0.1 mole, more suitably 0.05 mole, per mole of the compound (I).

[0049]

The above-mentioned phosphorus compound may be used in an amount of 0.001 to 0.4 mole, suitably 0.01 to 0.2 mole, more suitably 0.05 to 0.1 mole, per mole of the compound (I).

[0050]

The above-mentioned base may be used in an amount of 1 to 10 moles, suitably 1 to 5 moles, more suitably 1.5 moles, per mole of the compound (I).

[0051]

It is known that in the Suzuki coupling, the addition of water to a reaction system gives a good

result ("Efficient Synthesis of Losartan, A Nonpeptide Angiotensin II Receptor Antagonist", Robert D. Larsen et al., J. Org. Chem., 1994, 59, 6391-6394, "Investigation into the Suzuki-Miyaura coupling aiming at multikirogram synthesis of E2040 using (0-cyanophenyl)boronic esters", Y. Urawa et al., J. Organometallic Chemistry, 653(2002), 269-278). Also in the present invention, the same effect can be obtained by the addition of water. Water may be used in an amount of 1 to 20 moles, suitably 1 to 10 moles, more suitably 3 to 5 moles, per mole of the compound (I).

[0052]

When made into a salt, 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (III) may be stably isolated as substantially colorless crystals.

Preferable examples of the "salt" are hydrohalogenic acid salts such as hydrofluoride, hydrochloride, hydrobromide, hydroiodide, etc.; inorganic acid salts such as sulfate, nitrate, perchlorate, phosphate, etc.; and organic sulfonates such as methanesulfonate, trifluoromethane-sulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, camphorsulfonate, etc. More preferable examples thereof are hydrohalogenic acid salts such as hydrofluoride, hydrochloride, hydrobromide, hydroiodide, etc.; and inorganic acid salts such as sulfate, nitrate, perchlorate, phosphate, etc. The

most preferable examples thereof are hydrochloride, hydrofluoride and carbonate.

Advantages of the Invention

[0053]

According to the present invention, a compound represented by formula (III) may be industrially produced in good yield and high purity by reacting a compound represented by formula (I) with a compound represented by formula (II) in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

BEST MODE FOR CARRYING OUT THE INVENTION

[0054]

The present invention is explained below in further detail with working examples but they are merely for illustration and the production method of the present invention is not limited in any case by the following specific examples. Those skilled in the art may conduct the present invention to maximum by making various modifications to not only the following working examples but also the claims in the present specification, and these modifications are included in the claims in the present specification.

[0055]

Example 1

Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

(1) Synthesis of 5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0056]

[Formula 14]

After the inner atmosphere of a reactor was replaced with nitrogen, a mixture of 5-(2-pyridyl)-1,2-dihydropyridine-2-one (WO2004/009553) (7.33 kg), triphenylboroxine (9.0 kg), copper acetate (anhydrous) (0.80 kg), water (0.50 kg), pyridine (7.1 kg) and N,N-dimethylformamide (66.7 kg) was stirred for 1 hour in the reactor at an internal temperature of 28°C.

While introducing air adjusted to an oxygen concentration of 9% with nitrogen into the reactor at a rate of 30 L/min, the reaction mixture was stirred for 16 hours at 39°C to 40°C (internal temperature) to obtain a reaction mixture 1A.

Water (191 kg) and 25% aqueous ammonia (85.8 kg) were placed in another reactor and cooled to 8.7°C with cold water. Then, the above-mentioned reaction

mixture 1A was added thereto over a period of 3 minutes. The resulting reaction mixture was stirred for 4 hours while being cooled with cold water. The precipitate in the reaction mixture was collected by filtration by the use of a centrifuge and washed with 65 kg of water.

The precipitate, water (97 kg) and 25% aqueous ammonia (43.5 kg) were placed in a reactor and stirred for 1 hour while being kept warm with warm water at 25°C. The precipitate in the reaction mixture was collected by filtration by the use of a centrifuge, washed with 32.6 kg of water and then dried under reduced pressure (60°C, 18 hours) to obtain 9.6 kg of 5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one.

^{1}H NMR (400MHz, DMSO-d_6) δ 8.61-8.50 (m, 1H), 8.36 (d, 1H), 8.29 (dd, 1H,), 7.90 (d, 1H), 7.80 (ddd, 1H), 7.56-7.45 (m, 5H), 7.27 (dd, 1H), 6.62 (d, 1H).

[0057]

(2) Synthesis of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0058]

[Formula 15]

5-(2-Pyridyl)-1-phenyl-1,2-dihydropyridine-2-

one (200 g), N-bromosuccinimide (157.7 g) and ethyl acetate (4 L) were placed in a 10-L reactor, and the reaction mixture was stirred at 30°C (external temperature) in a nitrogen stream for 9 hours and 20 minutes. A 3% aqueous hydrosulfite solution (2 L) and toluene (2 L) were added to the reaction mixture, followed by stirring at 55°C (external temperature) for 30 minutes. After completion of the reaction, the aqueous layer (the lower layer) in the reaction mixture was separated. Then, the organic layer was washed four times with water (2 L), and the organic solvent was removed under reduced pressure with stirring.

Thereafter, 1,2-dimethoxyethane (4 L) was added to the residue and the resulting mixture was concentrated under reduced pressure to obtain crude 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one.

[0059]

(3) Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0060]

[Formula 16]

2-(1,3,2-Dioxaborinan-2-yl)benzonitrile (214.9 g), palladium acetate (3.44 g),

triphenylphosphine (16.07 g), cuprous iodide (7.29 g), 1,2-dimethoxyethane (3.1 L) and potassium carbonate (158.8 g) were placed in a reactor containing the whole of the crude 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one obtained as concentration residue in the above item (2), and the resulting mixture was stirred with heating at 70°C (external temperature) for 30 minutes under a nitrogen atmosphere and then stirred with heating under reflux for 4 hours.

Thereafter, ethyl acetate (2.5 L) was added to the reaction mixture at 70°C (external temperature) and stirred for 10 minutes. The resulting reaction mixture was filtered and the precipitate was washed with ethyl acetate (2.5 L). The whole of the filtrate thus obtained was transferred into a reactor and 12.5% aqueous ammonia (5 L) was added thereto, followed by stirring at 60°C (external temperature) for 53 minutes. The lower layer (the aqueous layer) in the reaction mixture was separated. A 5% aqueous sodium chloride solution (2.5 L) and 25% aqueous ammonia (2.5 L) were added to the remaining organic layer and stirred. Thereafter, the lower layer (the aqueous layer) was separated and a 5% aqueous sodium chloride solution (5 L) was added to the remaining organic layer and stirred, and then the lower layer (the aqueous layer) was separated. The remaining organic layer was concentrated under reduced pressure, followed by adding thereto 4 L of acetone, and the resulting mixture was

concentrated under reduced pressure.

Acetone (7.2 L) and water (0.8 L) were added to the residue and the resulting mixture was stirred at 60°C (external temperature) for 1 hour and 10 minutes to effect dissolution. The resulting solution was cooled with stirring at 38°C (external temperature) for 18 minutes. To the reaction mixture was added 1 g of seed crystals (crystals of hydrate of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one) at an internal temperature of 40°C, and the resulting mixture was stirred at 35°C (external temperature) for 30 minutes. Thereafter, the reaction mixture was stirred while lowering the external temperature by 5°C at intervals of 30 minutes. At an external temperature of 10°C, the reaction mixture was stirred for 17 hours.

Water (2.29 L) was added dropwise to the reaction mixture with stirring over a period of 3 hours and 10 minutes. After completion of the dropwise addition, the resulting mixture was stirred for another 1 hour and 20 minutes. The reaction mixture was filtered and the precipitate was washed with 2 L of 50% acetone-water to obtain 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (526.28 g) as a wet substance (dry weight: 168.3 g).

[0061]

Example 2

Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-

35

1-phenyl-1,2-dihydropyridine-2-one

(1) Synthesis of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0062]

[Formula 17]

5-(2-Pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (300 g), N-bromosuccinimide (236.5 g) and N,N-dimethylformamide (1.8 L) were placed in a 10-L reactor, and the reaction mixture was stirred at 30°C (external temperature) in a nitrogen stream for 3 hours and 15 minutes. 2-Propanol (4.2 L) was added dropwise to the reaction mixture over a period of 9 minutes, followed by adding thereto water (2.1 L) over a period of 7 minutes. The resulting mixture was heated at 85°C (external temperature) with stirring. After confirming the dissolution of the contents, the resulting solution was stirred at an external temperature of 55°C for 1 hour. Thereafter, the solution was stirred at 40°C (external temperature) for another 22 minutes, at 30°C (external temperature) for further another 23 minutes, and then at 10°C (external temperature) for still another 15 hours and 15 minutes. The reaction mixture was filtered and the precipitate was washed with 50% 2-

propanol-water (2.4 L) and then dried under reduced pressure (60°C, 6 hours) to obtain 341.45 g of 3-bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one. Yield: 86.4%.

^{1}H NMR (400MHz, $CDCl_3$)δ 8.59-8.56 (m, 1H), 8.50 (d, 1H), 8.18 (d, 1H), 7.72 (td, 1H), 7.53-7.41 (m, 6H), 7.20 (ddd, 1H).

[0063]

(2) Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0064]

[Formula 18]

3-Bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (100 g), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (85.7 g), palladium acetate (1.37 g), triphenylphosphine (6.4 g), cuprous iodide (2.91 g), 1,2-dimethoxyethane (1.25 L) and potassium carbonate (63.4 g) were placed in a 3-L reactor, and pressure reduction and the replacement of the air in the reaction system with nitrogen by repressurization with nitrogen were carried out 10 times. The reaction mixture was stirred with heating (in an oil bath at

100°C) under a nitrogen atmosphere for 3 hours and 40 minutes.

Thereafter, ethyl acetate (750 mL) was added to the reaction mixture and the resulting mixture was filtered. The precipitate was washed with ethyl acetate (750 mL). To the filtrate thus obtained were added 750 mL of water and 25% aqueous ammonia (250 mL), and the resulting mixture was stirred at 60°C (external temperature) for 30 minutes. The lower layer (the aqueous layer) in the reaction mixture was separated. A 2.5% aqueous sodium chloride solution (370 mL), 25% aqueous ammonia (130 mL) and 1,2-dimethoxyethane (500 mL) were added to the remaining organic layer, followed by stirring at 60°C (external temperature) for 10 minutes. Thereafter, the lower layer (the aqueous layer) was separated and a 2.5% aqueous sodium chloride solution (370 mL), 25% aqueous ammonia (130 mL) and 1,2-dimethoxyethane (200 mL) were added to the remaining organic layer and stirred for 10 minutes, and then the lower layer (the aqueous layer) was separated. A 2.5% aqueous sodium chloride solution (500 mL) and 1,2-dimethoxyethane (200 mL) were added to the remaining organic layer, followed by stirring at 60°C (external temperature) for 10 minutes. Thereafter, the lower layer (the aqueous layer) was separated. The remaining organic layer was concentrated under reduced pressure (external temperature: 65°C), followed by adding thereto 2 L of acetone, and the resulting

mixture was concentrated under reduced pressure (external temperature: 60°C).

Acetone (2.88 L) and water (320 mL) were added to the residue and the resulting mixture was stirred at 55°C (external temperature) for 1 hour and 10 minutes to effect dissolution. The resulting solution was cooled with stirring at 38°C (external temperature) for 38 minutes. To the reaction mixture was added 500 mg of seed crystals (crystals of hydrate of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one) at an internal temperature of 40°C, and the resulting mixture was stirred for 1 hour at an external temperature changed to 30°C. This mixture was stirred for 1 hour at an external temperature changed to 20°C and then stirred for 1 hour and 20 minutes at an external temperature of 8°C.

Water (915 mL) was added dropwise to the reaction mixture with stirring over a period of 2 hours and 50 minutes. After completion of the dropwise addition, the resulting mixture was stirred for another 14 hours. The reaction mixture was filtered and the precipitate was washed with 500 mL of 50% acetone-water and then 500 mL of water to obtain 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (251.5 g) as a wet substance (dry weight: 83.3 g).

^{1}H NMR (400MHz, DMSO-d_6)δ 8.61-8.57 (m, 1H), 8.52 (d, 1H), 8.47 (d, 1H), 8.00 (d, 1H), 7.92 (d, 1H), 7.83 (td, 1H), 7.78(t, 1H), 7.74-7.70(d-like, 1H), 7.61-7.48

(m, 6H), 7.29 (dd, 1H).

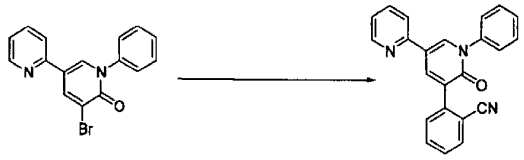
[0065]

Example 3

Synthesis of 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one

[0066]

[Formula 19]



3-Bromo-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (188 g), 2-(1,3,2-dioxaborinan-2-yl)benzonitrile (161.2 g), palladium acetate (2.58 g), triphenylphosphine (12.07 g), 1,2-dimethoxyethane (2.82 L) and ion-exchanged water (41.4 mL) were placed in a 5-L reactor, and pressure reduction and the replacement of the air in the reaction system with nitrogen by repressurization with nitrogen were carried out 5 times with stirring. Potassium carbonate (119.14 g) was added to the reaction mixture and pressure reduction and the replacement of the air in the resulting mixture with nitrogen by repressurization with nitrogen were carried out 5 times. Then, the reaction mixture was stirred with heating (in an oil bath at 95°C) under reflux in a nitrogen atmosphere for 1 hour and 49

minutes.

Thereafter, the oil bath was removed and ethyl acetate (800 mL) was added to the reaction mixture at 65.4°C (internal temperature). The resulting mixture was filtered and the precipitate was washed with ethyl acetate (2.4 L). The filtrate (5.28 kg) thus obtained was divided into halves (2.64 kg x 2) and each half was transferred into a 5-L reactor. Trimercaptotriazine (3.05 g) and ethyl acetate (380 mL) were placed in each of the reactors and the reaction mixture was stirred at 50°C (the external temperature in an oil bath) for 13 hours and 10 minutes. The two solutions thus obtained were filtered in succession by the use of Celite (94 g) previously rinsed with methanol (1 L) and ethyl acetate (1 L) and the precipitate was rinsed with a 4: 3 mixture (1.35 L) of ethyl acetate and 1,2-dimethoxyethane. The filtrate thus obtained was transferred into a 20-L separator and hydrochloric acid prepared from concentrated hydrochloric acid (700 mL) and ion-exchanged water (4.2 L) was added to the filtrate. After stirring at 37.6°C (internal temperature) for 8 minutes, the aqueous layer (the lower layer) was separated. Then, 2N-hydrochloric acid (3.8 L) was added to the organic layer, followed by stirring at 39.3°C (internal temperature) for 8 minutes, and the aqueous layer (the lower layer) was separated. Ethyl acetate (3 L) was added to the combined aqueous layer and stirred for 8 minutes, and

then ethyl acetate (3 L) was added thereto and stirred for 5 minutes. Thereafter, the aqueous layer (the lower layer) was separated. This aqueous layer was cooled to 20°C (internal temperature) with stirring in a cold-water bath, and then 25% aqueous ammonia (2.25 L) was added dropwise thereto over a period of 27 minutes with cooling in an ice-water bath. The resulting mixture was stirred for another 3 hours and 26 minutes. The reaction mixture was filtered under reduced pressure and the precipitate was washed with ion-exchanged water (3 L). The washed precipitate was dried by air blowing (60°C, 16 hours and 6 minutes) to obtain 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one (162.62 g).

^{1}H NMR (400MHz, DMSO-d_6) δ 8.60-8.57 (m, 1H), 8.53 (d, 1H), 8.47 (d, 1H), 8.00 (d, 1H), 7.92 (d, 1H), 7.83 (td, 1H), 7.78(t, 1H), 7.72(d, 1H), 7.61-7.48 (m, 6H), 7.30 (dd, 1H).

INDUSTRIAL APPLICABILITY

[0067]

According to the present invention, a compound of formula (III) represented by 3-(2-cyanophenyl)-5-(2-pyridyl)-1-phenyl-1,2-dihydropyridine-2-one, which is useful as a therapeutic agent for diseases such as Parkinson's disease, multiple sclerosis, epilepsy, etc., may be industrially produced in good yield and high purity by reacting a

compound of formula (I) with a boronic acid derivative of formula (II) in the presence of a palladium compound, a copper compound and a phosphorus compound.

[0068]

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

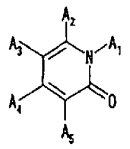
[0069]

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

[1] A method for producing a compound represented by formula (III):

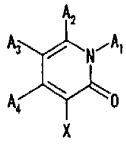
[Formula 3]



(III)

wherein A_1, A_2, A_3, A_4 and A_5 are as defined below, or a salt thereof, which comprises reacting a compound represented by formula (1):

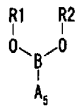
[Formula 1]



(I)

wherein each of A_1, A_2, A_3 and A_4, which may be the same or different, is a hydrogen atom, an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group, and X is a leaving group, or a salt thereof with a compound represented by formula (II):

[Formula 2]



(II)

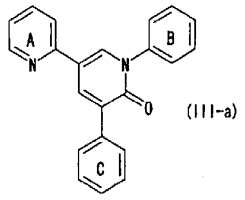
wherein A_5 is an optionally substituted 6-to 14-membered aromatic hydrocarbon ring group or an optionally substituted 5-to 14-membered heteroaromatic ring group; and R1 and R2 are as follows: 1) each of R1 and R2, which may be the same or different, is a hydrogen atom or a C1-6 alkyl group, and 2) the compound of formula (II) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms, or 3) R1, R2, the oxygen atoms and the boron atom, when taken together, form a 5-or 6-membered ring group optionally substituted by one to four C1-6 alkyl groups, in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

[2] A production method according to claim 1, wherein each of A_2 and A_4 is a hydrogen atom.

[3] A production method according to claim 1 or claim 2, wherein each of A_1, A_3 and A_5 is a phenyl group, a pyridyl group, a pyrimidyl group, a thienyl group or a furyl group.

[4] A production method according to any one of claims 1 to 3, wherein a compound represented by formula (III-a):

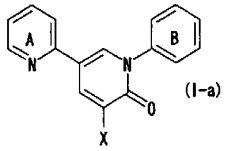
[Formula 6]



(III-a)

wherein the ring A, ring B and ring C are as defined below, or a salt thereof is produced by reacting a compound represented by formula (I-a):

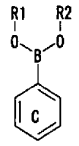
[Formula 4]



(I-a)

wherein the ring A is an optionally substituted 2-pyridyl group, the ring B is an optionally substituted phenyl group, and X is a leaving group, or a salt thereof with a compound represented by formula (II-a):

[Formula 5]

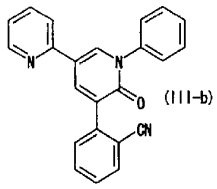


(II-a)

wherein the ring C is an optionally substituted phenyl group; and R1 and R2 are as follows: 1) each of R1 and R2, which may be the same or different, is a hydrogen atom or a C1-6 alkyl group, and 2) the compound of formula (II-a) may form boroxine (a trimer) when both R1 and R2 are hydrogen atoms, or 3) R1, R2, the oxygen atoms and the boron atom, when taken together, form a 5-or 6-membered ring group optionally substituted by one to four C1-6 alkyl groups, in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

[5] A production method according to claim 4, wherein a compound represented by formula (III-b):

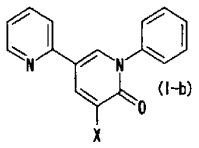
[Formula 9]



(III-b)

or a salt thereof is produced by reacting a compound represented by formula (I-b):

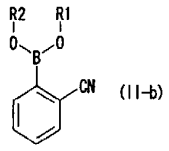
[Formula 7]



(I-b)

wherein X is a leaving group, or a salt thereof with a compound represented by formula (II-b):

[Formula 8]

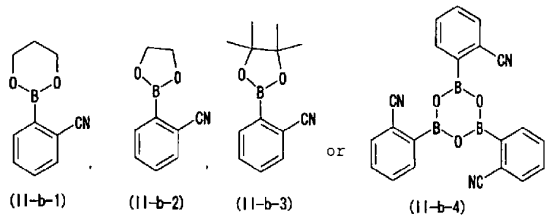


(II-b)

wherein R1 and R2 are as defined above, in a solvent in the presence of a palladium compound, a copper compound, a phosphorus compound and a base.

[6] A production method according to claim 5, wherein the compound (II-b) is a compound represented by formula (II-b-1), formula (II-b-2), formula (II-b-3) or formula (II-b-4):

[Formula 10]



(II-b-1) (II-b-2) (II-b-3) (II-b-4)

[7] A production method according to any one of claims 1 to 6, wherein X is a halogen atom, an alkylsulfonyloxy group or an arylsulfonyloxy group.

[8] A production method according to any one of claims 1 to 7, wherein the palladium compound is

palladium acetate, palladium chloride or palladium hydroxide.

[9] A production method according to any one of claims 1 to 8, wherein the phosphorus compound is triphenylsphosphine or tri-tert-butylphosphine.

[10] A production method according to any one of claims 1 to 9, wherein the copper compound is cuprous bromide, cuprous iodide, cuprous chloride or cuprous acetate.

[11] A production method according to any one of claims 1 to 10, wherein the base is cesium carbonate, sodium carbonate or potassium carbonate.

[12] A production method according to any one of claims 1 to 11, wherein the copper compound is used in an amount of 0.01 to 0.05 mole per mole of the compound represented by formula (I).

[13] A production method according to any one of claims 1 to 12, wherein the reaction is carried out in a solvent and 1,2-dimethoxyethane or toluene is used as the solvent for reaction.

[14] Production method according to claim 1, substantially as hereinbefore described with reference to any one of the examples.

[15] Compound represented by formula (III) as defined in claim 1 produced by the production method defined in any one of claims 1 to 14.