METHODS FOR SYNTHESIZING 1H-FURO[3,2-B]IMIDAZO[4,5-D]PYRIDINE COMPOUNDS

TECHNICAL FIELD

The present invention relates to the field of pharmaceutical synthesis, in particular to methods for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds.

BACKGROUND

1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds are highly selective JAK1 and TYK2 inhibitors that selectively inhibit the activity of one or more protein kinases relative to other related kinases. Therefore, they are expected to be used in the treatment of diseases mediated by the selectively inhibited kinase or kinases while avoiding the adverse side effects associated with the inhibitions of other kinases, e.g., for the treatment of disorders associated with the activity of JAK1/TYK2, such as autoimmune diseases or disorders, or inflammatory diseases or disorders, as well as cancers or tumor or disorders.

Methods for synthesizing such compounds in the prior art have the problems of high cost and complex operation, so the methods are not suitable for industrial scale (WO 2018/067422 A1, WO 2020/244348 A1 and WO 2020/244349 A1). In light of this, there is a need to develop a method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds, which has the advantages of high yield, fewer impurities, easy control, cost saving, and simple operation, and is thus suitable for industrial scale.

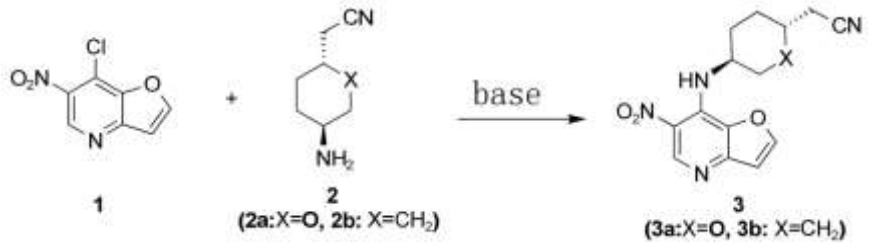
SUMMARY

In view of the above problems existing in the prior art, the purpose of the present disclosure is to provide methods for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds, which save the cost, and are simple and convenient to operate, thus are suitable for industrial scale.

In order to achieve the above purpose, the technical solutions adopted by the present disclosure are as follows.

A method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds (hereinafter referred to as "synthesis route 1", comprises the following steps of:

step 1:



1

2
(2a:X=O, 2b: X=CH2)

3
(3a:X=O, 3b: X=CH2)

ratio of compound 1 to the compound 2 is from 1:0.8 to 1:1.2, for example, 1:0.8, 1:0.9, 1:1, 1:1.01, 1:1.05, 1:1.1, and 1:1.2;

when the compound 2 is in the form of hydrochloride, the molar ratio of compound 1 to the base is from 1:2 to 1:2.5, preferably from 1:2.1 to 1:2.3, more preferably from 1:2.2 to 1:2.25, and most preferably from 1:2.2 to 1:2.23;

when the compound 2 is in a salt-free form, the molar ratio of compound 1 to the base is from 1:1 to 1:1.5, and preferably from 1:1.1 to 1:1.3;

the mass-to-volume ratio (g/mL) of compound 1 to the solvent is from 1:9 to 1:10;

the reaction of the step 1 is optionally carried out under the protection of an inert gas (such as nitrogen);

the reaction is carried out at the temperature of 50-80°C, and lasts for 16-22 hours; and

after the reaction is completed, the reaction solution is cooled, stirred and filtered, and the filter cake is washed and dried to obtain the compound 3 (for example, after the reaction is completed, the reaction solution is cooled to 20-30°C, water is added to the solution and the solution is stirred at 20-30°C for 0.5-2 hours, then cooled to 0-15°C and stirred at 0-15°C for 2-4 hours, then filtered, and the filter cake is washed and dried to obtain the compound 3).

According to the examples of the present disclosure, in the step 2,

the reducing agent used in the reduction reaction is a nitro-reducing agent other than H_2/Pd;

the reducing agent used in the reduction reaction is Fe/acetic acid, or $B_2(OH)_4$, or $SnCl_2$;

when the reducing agent is Fe/acetic acid, the solvent used in the reduction reaction is acetonitrile; the molar ratio of compound 3 to Fe is from 1:6 to 1:9, and the molar ratio of compound 3 to the acetic acid is from 1:12 to 1:14; and a mass-to-volume ratio (g/mL) of the compound 3 to the solvent is from 1:4 to 1:10, and preferably from 1:5 to 1:9; and

when the reducing agent is $B_2(OH)_4$, the solvent used in the reduction reaction is a mixed solvent of water and methanol, wherein a volume ratio (mL/mL, or L/L) of water to methanol is from 1:1 to 9:1, preferably from 3:1 to 5:1, more preferably 4:1; the molar ratio of compound 3 to $B_2(OH)_4$ is from 1:3 to 1:5, and preferably 1:3.5; a mass-to-volume ratio (g/mL) of the compound 3 to the solvent is from 1:4 to 1:10, and preferably from 1:5 to 1:9; and $B_2(OH)_4$ is added portionwise;

when the reducing agent is $SnCl_2$, the solvent used in the reduction reaction is ethyl acetate, wherein the molar ratio of compound 3 to $SnCl_2$ is from 1:2 to 1:9, and preferably from 1:3 to 1:6; and a mass-to-volume ratio (g/mL) of the compound 3 to the solvent is from 1:4 to 1:20, and preferably from 1:5 to 1:15; and

when the reducing agent is $B_2(OH)_4$, 4,4'-bipyridine is optionally added;

the reaction of the step 2 is optionally carried out under the protection of inert gas (such as nitrogen);

the reaction is carried out at a temperature of 15-90°C, and lasts for 1-18 hours;

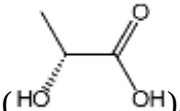
when the reducing agent is Fe/acetic acid, after the reaction is completed, the reaction solution is filtered before cooling down, and rinsed with hot acetonitrile. The pH is adjusted to about 6 (for example, the pH is adjusted to 6) with sodium citrate solution, and then the pH is adjusted to 8-9 with K_3PO_4 solution (for example, 30% K_3PO_4 solution). After concentration, celite, water and ethyl acetate are added to the reaction solution, and the solution is filtered and layered. The obtained aqueous phase is extracted with ethyl acetate and the obtained organic phases are

combined and washed with sodium citrate aqueous solution and brine respectively. Silica gel and anhydrous sodium sulfate are added, and the solution is filtered, washed with ethyl acetate, concentrated. Methyl tert-butyl ether is added, and the precipitate is filtered and dried to obtain the compound 4;

when the reducing agent is $B_2(OH)_4$, after the reaction is completed, the temperature is reduced to 35-45°C. Part of the solvent is concentrated under reduced pressure, then the temperature is reduced to 0-10°C and the reaction solution is stirred and filtered. The filter cake is rinsed with dichloromethane and the filtrate is collected. Sodium bicarbonate is added portionwise and stirred at 20-30°C. The system is allowed to settle, then the organic phase is separated and the aqueous phase is extracted with dichloromethane. The obtained organic phases are combined, dried with anhydrous sodium sulfate. Hydrogen chloride in ethanol solution is dropwise added at 15-25°C and stirred with the temperature kept at 15-25°C. Ethyl acetate is dropwise added at 15-25°C and stirred with the temperature kept at 15-25°C. The mixture is filtered, then the filter cake is rinsed with ethyl acetate, and dried to obtain compound 4 hydrochloride; and

when the reducing agent is $SnCl_2$, after the reaction is completed, the temperature is reduced to room temperature. Sodium bicarbonate is added with an ice bath, then the reaction solution is stirred and filtered. The filter cake is rinsed with ethyl acetate, and the filtrate is collected and washed for three times with aqueous solution of saturated sodium bicarbonate. The obtained organic phases are combined and washed for three times with brine, then the organic phases are combined, dried with anhydrous sodium sulfate, filtered, and the filtrate is concentrated under reduced pressure to obtain the compound 4.

According to the examples of the present disclosure, in the step 3,

the compound 5 is R-lactic acid (), and the compound 5' is acetic acid or acetic anhydride;

the ring-closing reaction is carried out in a solvent, wherein the solvent is toluene, dioxane, acetic acid, methylcyclohexane or acetic anhydride;

when the compound 4 is subjected to the ring-closing reaction with R-lactic acid, the molar ratio of compound 4 to the R-lactic acid is from 1:4 to 1:30, preferably from 1:4 to 1:20, and more preferably from 1:4 to 1:10; and a mass-to-volume ratio (g/mL) of the compound 4 to the solvent is from 1:1.5 to 1:40, preferably from 1:1.5 to 1:30, and more preferably from 1:1.5 to 1:15;

when the compound 4 is subjected to the ring-closing reaction with acetic anhydride or acetic acid, the acetic anhydride or the acetic acid act as a reaction reagent and a solvent simultaneously, and the mass-to-volume ratio (g/mL) of the compound 4 to the acetic anhydride or the acetic acid is from 1:1 to 1:10, and preferably from 1:2 to 1:5;

an acid catalyst is optionally added in the ring-closing reaction of the compound 4 with the compound 5 or the compound 5', wherein the acid catalyst is preferably methanesulfonic acid;

in the ring-closing reaction between the compound 4 and the compound 5', when the reacting reagent/solvent is acetic anhydride, acetic acid (AcOH) or sodium acetate (NaOAc) is optionally added;

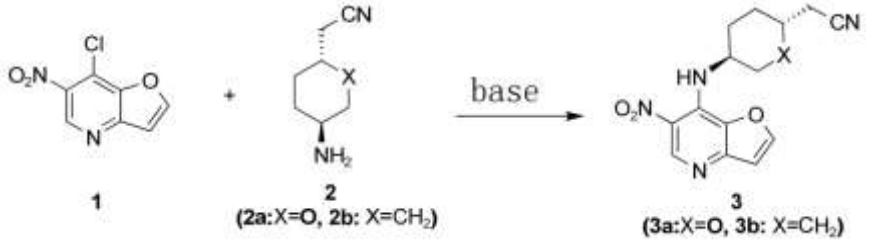
in the ring-closing reaction between the compound 4 and the compound 5', when the reacting reagent/solvent is acetic acid, sodium acetate (NaOAc) is optionally added;

the reaction is carried out at a temperature of 80-120°C, and lasts for 5-24 hours, and preferably 16-18 hours; and

after the reaction is completed, the reaction solution is cooled and extracted, the pH is adjusted to 7-10, and the obtained solid is dried to obtain the compound 6 or the hydrate of the compound 6.

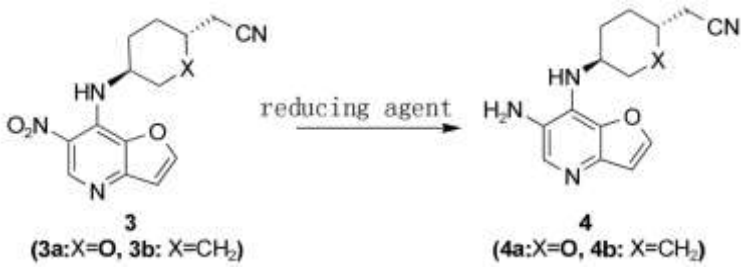
In one aspect, the present disclosure provides a method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds, comprising the following steps of:

step 1:



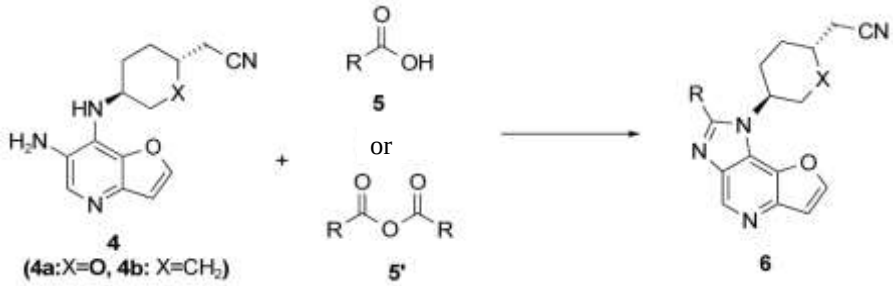
reacting compound 1 with compound 2 or compound 2 hydrochloride in a solvent in the presence of a base to obtain compound 3;

step 2:



subjecting the compound 3 to a reduction reaction to obtain compound 4 or compound 4 hydrochloride; and

step 3:

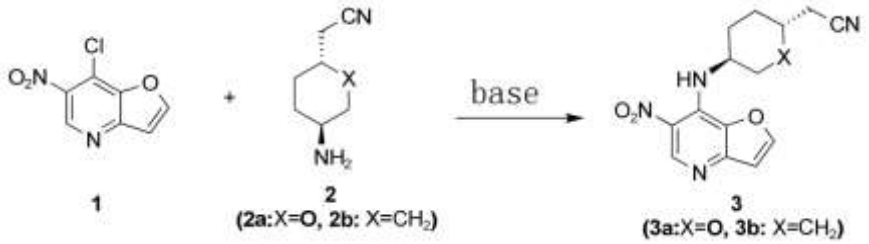


subjecting the compound 4 or compound 4 hydrochloride to a ring-closing reaction with compound 5 or compound 5' to obtain compound 6 or a hydrate of the compound 6, wherein R is methyl or ethyl, the methyl or ethyl is optionally substituted by hydroxyl, and preferably, R is methyl or 1-hydroxyethyl; and

X=CH_2, or O.

According to the examples of the present disclosure, the present disclosure provides a method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compound (using "synthesis route 1", used for synthesizing compound 6A, 6C or a hydrate thereof, preferably a monohydrate), comprising the following steps of:

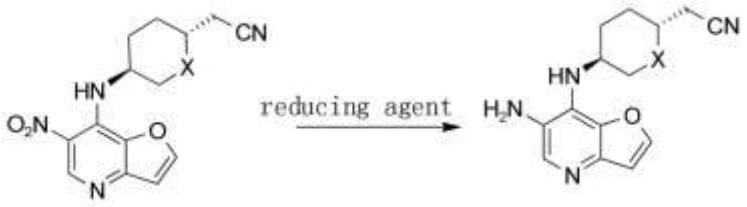
step 1:



1 2 (2a:X=O, 2b: X=CH_2) 3 (3a:X=O, 3b: X=CH_2)

reacting compound 1 with compound 2 or compound 2 hydrochloride in a solvent in the presence of a base to obtain compound 3;

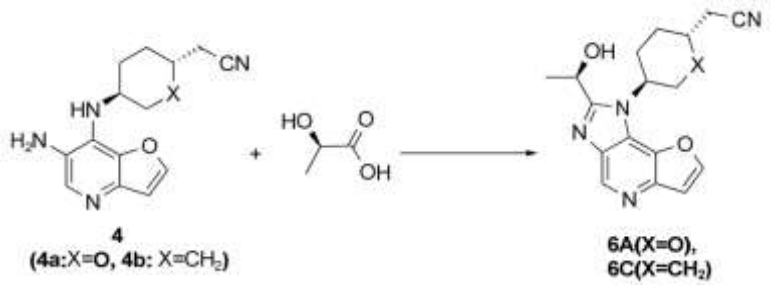
step 2:



3 (3a:X=O, 3b: X=CH_2) 4 (4a:X=O, 4b: X=CH_2)

subjecting the compound 3 to a reduction reaction to obtain compound 4 or compound 4 hydrochloride; and

step 3:



4 (4a:X=O, 4b: X=CH_2) 6A(X=O), 6C(X=CH_2)

subjecting the compound 4 or compound 4 hydrochloride to a ring-closing reaction with the R-lactic acid to obtain the compounds 6A and 6C, or the hydrates thereof.

According to the examples of the present disclosure, in the method for synthesizing compounds 6A and 6C or the hydrates thereof, the step 1 and the step 2 are as described above, and in the step 3,

the ring-closing reaction is carried out in a solvent, wherein the solvent is toluene, dioxane, or methylcyclohexane, preferably toluene or methylcyclohexane, and more preferably methylcyclohexane;

the molar ratio of compound 4 to R-lactic acid is from 1:4 to 1:30, preferably from 1:4 to 1:20, more preferably from 1:4 to 1:10, and most preferably from 1:5 to 1:7;

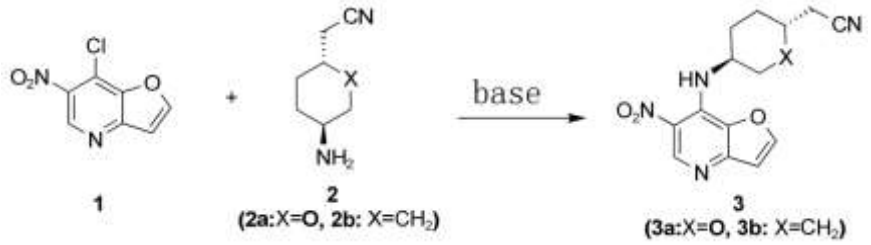
a mass-to-volume ratio (g/mL) of the compound 4 to the solvent is from 1:1.5 to 1:40, preferably from 1:1.5 to 1:30, more preferably from 1:1.5 to 1:15, and most preferably from 1:1.5 to 1:5;

the reaction is refluxed with a Dean–Stark apparatus at 87-110°C for 5-24 hours; and

after the reaction is completed, methanol is added and the methanol layer is separated. Sodium hydroxide solution is added with stirring. Hydrochloric acid is dropwise added to adjust the pH to about 7. The solvent is removed under reduced pressure, and water is added with stirring. The solid is filtered, washed with water, and dried to obtain the compound 6A or 6C (for example, in the process of synthesizing the compound 6A, after the reaction is completed, methanol is added, the reaction solution is cooled to 20-30°C, methanol is added (for example, 3 times the volume), and the resulting mixture is stirred and layered to obtain a methanol layer. The methanol layer is cooled to -10 - 0°C, added sodium hydroxide solution, stirred, and dropwise added hydrochloric acid to adjust pH to 7, then the solvent is removed under reduced pressure, water is added and the obtained system is stirred, filtered, washed with water, and dried to obtain the compound 6A).

According to the examples of the present disclosure, the present disclosure provides a method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compound (using "synthesis route 1") for synthesizing compound 6B or 6D, comprising the following steps of:

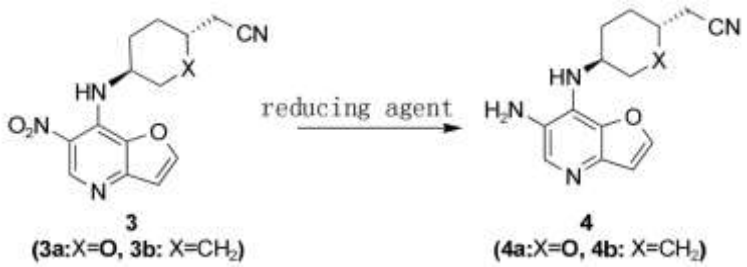
step 1:



1 2 (2a:X=O, 2b: X=CH_2) 3 (3a:X=O, 3b: X=CH_2)

reacting compound 1 with compound 2 or compound 2 hydrochloride in a solvent in the presence of a base to obtain compound 3;

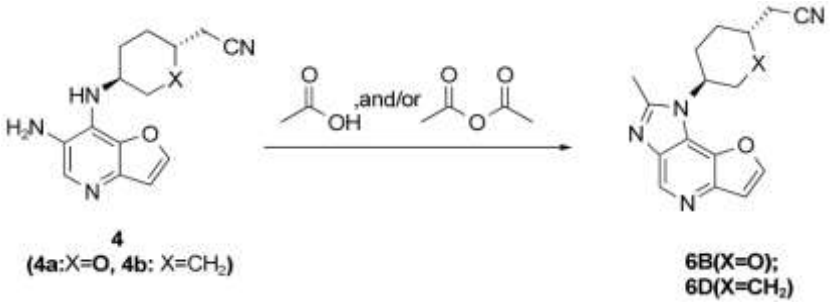
step 2:



3 (3a:X=O, 3b: X=CH_2) 4 (4a:X=O, 4b: X=CH_2)

subjecting the compound 3 to a reduction reaction to obtain compound 4 or compound 4 hydrochloride; and

step 3:



4
(4a:X=O, 4b: X=CH_2)

6B(X=O);
6D(X=CH_2)

subjecting the compound 4 or compound 4 hydrochloride to a ring-closing reaction with the acetic anhydride and/or acetic acid to obtain the compound 6B or the compound 6D.

According to the examples of the present disclosure, in the method for synthesizing compound 6B or 6D, the step 1 and the step 2 are as described above, and in the step 3,

when the compound 4 is subjected to the ring-closing reaction with acetic anhydride, acetic acid or sodium acetate is optionally added, wherein the molar ratio of compound 4 to acetic acid is from 1:0.1 to 1:0.5, and preferably from 1:0.2 to 1:0.3, for example, 1:0.2; and the molar ratio of compound 4 to sodium acetate is from 1:0.2 to 1:1, and preferably from 1:0.4 to 1:0.8, for example, 1:0.5;

when the compound 4 is subjected to the ring-closing reaction with acetic acid, sodium acetate is optionally added, wherein the molar ratio of compound 4 to sodium acetate is from 1:1 to 1:3, and preferably from 1:1.5 to 1:2.5, for example, 1:2;

when the compound 4 is subjected to the ring-closing reaction with acetic anhydride, the mass-to-volume ratio of compound 4 to acetic anhydride is from 1:2 to 1:5, and preferably 1:3;

when the compound 4 is subjected to the ring-closing reaction with acetic acid, the mass-to-volume ratio of compound 4 to acetic acid is from 1:3 to 1:8, and preferably 1:5;

the reaction is carried out at a temperature of 80-120°C, and preferably 90-110°C, and lasts for 12-24 hours, and preferably 12-18 hours; and

after the reaction is completed, methyl tert-butyl ether is added to the reaction solution, and the obtained system is stirred evenly, and filtered. The filter cake is dissolved in a mixed solvent of water and dichloromethane, and NaOH aqueous solution is dropwise added to adjust pH to 7-10. The resulting solution is layered and separated. Then the obtained aqueous layer is extracted with dichloromethane, and the obtained organic phases are combined, dried with anhydrous Na_2SO_4, filtered, and concentrated. To the system was added ethanol, and water with stirring. The obtained system is filtered, then the filter cake is dried to obtain the compound 6B or 6D (for example, in the reaction of synthesizing the compound 6B, after the reaction is completed, the reaction solution is added with methyl tert-butyl ether, stirred evenly at 0-10°C, and filtered, the filter cake is dissolved in the mixed solvent of water and dichloromethane, 10% NaOH aqueous solution is dropwise added to adjust the pH to 7-10. The resulting solution is layered and separated. Then the obtained aqueous layer is extracted with dichloromethane, and the obtained organic phases are combined, dried with anhydrous Na_2SO_4, filtered, concentrated. Ethanol is added and the obtained system becomes clear at 45-55°C. The solution is cooled to 0-10°C for precipitation, then water is added with stirring. The mixture is filtered, and the filter cake is dried to obtain the compound 6B).

According to the examples of the present disclosure, the present disclosure further provides a method for synthesizing compound 1, comprising the following steps of:

step 1-1:

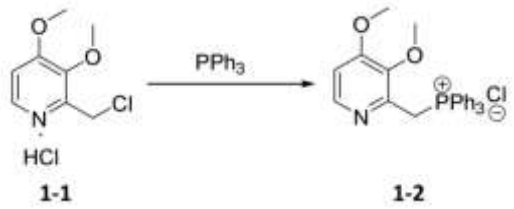


1-6 1

subjecting the compound 1-6 to a chloro-substitution reaction to obtain the compound 1.

According to the examples of the present disclosure, in the method for synthesizing the compound 1, preferably,

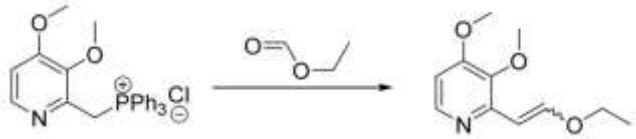
in the step 1-1:



1-1 1-2

sodium carbonate is added to a mixture of compound 1-1, toluene and water in batches. The resulting mixture is stirred under room temperature, and layered. The obtained aqueous phase is extracted with toluene, and the obtained organic phases are combined, washed with brine, dried with anhydrous sodium sulfate, and filtered. Triphenylphosphine is added to the filtrate, and the obtained system is heated to 110-120°C (preferably 108-115°C) with a Dean–Stark apparatus for 14-20 hours (preferably 16-18 hours). The reaction is cooled to 20-30°C, filtered and rinsed with toluene, and then the wet product is dried under reduced pressure to obtain the compound 1-2;

in the step 1-2:



1-2 1-3

the mixture of compound 1-2 and dimethyl sulphoxide is cooled to 18-25°C, an alkali metal tert-butoxide is added in batches and the temperature is controlled at 20-35°C, then the reaction solution is stirred at room temperature for 1-2 hours after the addition. Ethyl formate is dropwise added, and the obtained system is stirred at 40-50°C for 8-12h before cooling to room temperature. Organic solvent and water are added, and the obtained system is extracted and layered. The obtained organic phase is washed with water, adjusted pH to 5-6 with hydrochloric acid, and layered. The obtained aqueous phase is extracted with an organic solvent, adjusted pH is to be greater than or equal to 8 with a base, and layered. The obtained aqueous phase is extracted with organic solvent, and the obtained organic phases are combined, washed with water, dried with anhydrous sodium sulfate, filtered, and concentrated to obtain the compound 1-3;

in the step 1-3:

in the step 1-6:



1-6 1

phosphorus oxychloride is dropwise added to a mixture of the compound 1-6, N,N-dimethylformamide and toluene, and the resulting mixture is stirred at 35-75°C for 1-2 hours. Then the reaction solution is cooled to room temperature and toluene is removed. Dichloromethane and 10% potassium carbonate aqueous solution or 5% sodium bicarbonate aqueous solution are added, and the obtained system is allowed to be layered. The obtained organic phases are washed with brine, dried with anhydrous sodium sulfate, filtered, and the solvent is removed to obtain the compound 1.

According to the examples of the present disclosure, further, in the step 1-1,

in a mixture of the compound 1-1, toluene and water, a mass-to-volume ratio (g/mL) of the compound 1-1 to toluene and water is from 1:5 to 1:6, and a volume ratio of toluene to water is from 8:1 to 9:1;

the molar ratio of compound 1-1 to the sodium carbonate is from 1:1.1 to 1:1.2;

the molar ratio of compound 1-1 to the triphenylphosphine is from 1:1.1 to 1:1.2; and

the reaction of the step 1-1 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, further, in the step 1-2,

the alkali metal tert-butoxide is potassium tert-butoxide or sodium tert-butoxide;

the base used for adjusting the pH is aqueous ammonia or sodium carbonate;

the organic solvent used for the extraction is methyl tert-butyl ether or ethyl acetate;

the mass-to-volume ratio of compound 1-2 to dimethyl sulphoxide is from 1:3 to 1:5;

the molar ratio of compound 1-2 to the alkali metal tert-butoxide is from 1:1.05 to 1:1.15, and preferably 1:1.1;

the molar ratio of compound 1-2 to ethyl formate is from 1:4 to 1:5; and

the reaction of the step 1-2 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, further, in the step 1-3,

A mass-to-volume ratio (g/mL) of the compound 1-3 to the dichloromethane is from 1:6 to 1:10;

the molar ratio of compound 1-3 to the boron tribromide is from 1:2.0 to 1:3.5, and preferably from 1:2.5 to 1:3.2; and

the reaction of the step 1-3 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, further, in the step 1-4,

a mass-to-volume ratio (g/mL) of the compound 1-4 to the concentrated sulfuric acid is from 1:2 to 1:5;

a mass-to-volume ratio (g/mL) of the compound 1-4 to dichloromethane is from 1:25 to 1:26; and

the molar ratio of compound 1-4 to the benzoyl chloride is from 1:1.5 to 1:2.5, and preferably 1:2.

According to the examples of the present disclosure, further, in the step 1-5,

in the acetic acid solution of the compound 1-5, the mass ratio of compound 1-5 to the acetic acid is from 1:9 to 1:11, and preferably 1:10;

the mass ratio of compound 1-5 to the acetic acid in the mixed solution of acetic acid, acetic anhydride and nitric acid is from 1:3 to 1:5;

the molar ratio of compound 1-5 to the acetic anhydride is from 1:2 to 1:5, and preferably from 1:2.6 to 1:4.2;

the molar ratio of compound 1-5 to the nitric acid is from 1:2 to 1:5, and preferably from 1:2.5 to 1:4.0; and

the reaction of the step 1-5 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, further, in the step 1-6,

the molar ratio of compound 1-6 to N,N-dimethylformamide is from 1:1 to 1:1.2;

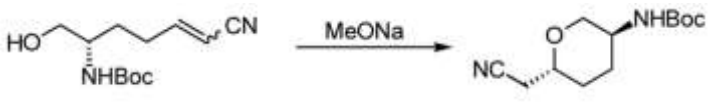
the mass-to-volume ratio of compound 1-6 to toluene is from 1:9 to 1:11, and preferably 1:10;

the molar ratio of compound 1-6 to phosphorus oxychloride is from 1:1.8 to 1:2.2, and preferably 1:2; and

the reaction of the step 1-6 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, when the compound 2 is compound 2a, the present disclosure further provides a method for synthesizing compound 2a hydrochloride, comprising the following steps of:

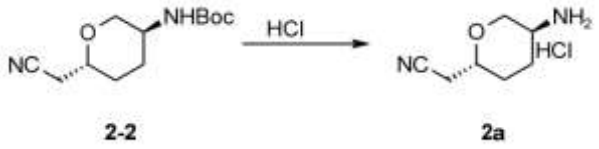
step 2-1:



2-1 2-2

subjecting compound 2-1 to a ring-closing reaction under the catalysis of sodium methoxide to obtain compound 2-2; and

step 2-2:

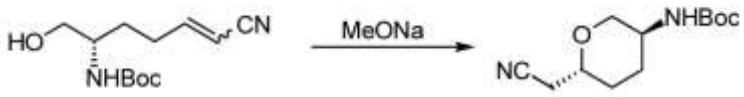


2-2 2a

reacting the compound 2-2 with hydrochloric acid to obtain the compound 2a hydrochloride.

According to the examples of the present disclosure, in the method for synthesizing the N, N compound 2a hydrochloride, preferably,

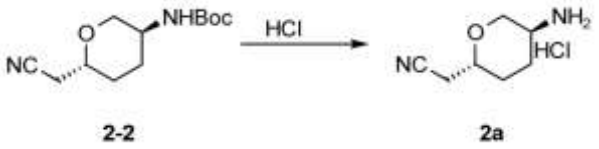
in the step 2-1:



2-1 2-2

a methanol solution of sodium methoxide is dropwise added to a mixture of compound 2-1 and tetrahydrofuran, and the temperature of the system is controlled at 0-10°C during the dropwise addition. The system is stirred at 20-30°C for 3-8 hours. After the reaction is completed, an ammonium chloride solution is dropwise added into the reaction solution at 15-25°C to adjust the pH to 7-8. The resulting mixture is extracted with methyl tert-butyl ether, washed with sodium chloride solution, dried with anhydrous sodium sulfate, cooled to 0-10°C, and filtered, and then the filter cake is dried to obtain the compound 2-2; and

in the step 2-2:



2-2 2a

an ethanol solution of hydrogen chloride is dropwise added to a mixture of the compound 2-2 and dichloromethane. The reaction is stirred at 20-25°C for 4-8 hours. The reaction mixture is cooled to 0-5°C, and filtered, and then the filter cake is rinsed with dichloromethane, and dried to obtain the compound 2a hydrochloride.

According to the examples of the present disclosure, further, in the step 2-1,

the mass-to-volume ratio (g/mL) of compound 2-1 to tetrahydrofuran is from 1:10 to 1:12, and preferably from 1:10 to 1:11;

the molar ratio of compound 2-1 to sodium methoxide in methanol solution is from 1:0.2 to 1:0.3, and preferably 1:0.25; and

the reaction of the step 2-1 is optionally carried out under the protection of an inert gas (such as nitrogen).

According to the examples of the present disclosure, further, in the step 2-2,

the mass-to-volume ratio of compound 2-2 to dichloromethane is from 1:5 to 1:7, and preferably

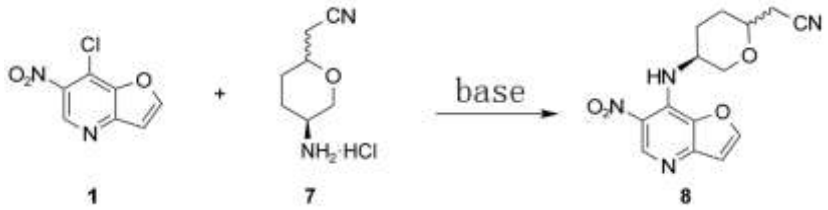
1:6;

the molar ratio of compound 2-2 to hydrogen chloride in ethanol solution is from 1:2 to 1:5, and preferably 1:3; and

the reaction of the step 2-2 is optionally carried out under the protection of an inert gas (such as nitrogen).

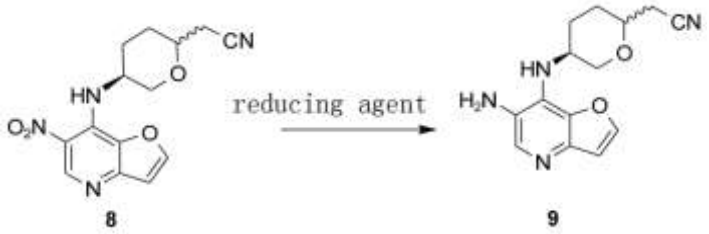
The present disclosure provides another method for synthesizing a 1H-furo[3,2-b]imidazo[4,5-d]pyridine compound (hereinafter referred to as "synthesis route 2" for synthesizing compounds 6A and 6B), comprising the following steps of:

step 1A:



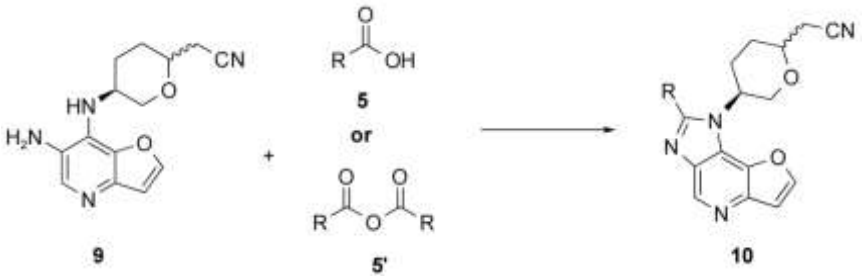
reacting compound 1 with cis-trans isomer mixture 7 in a solvent in the presence of a base to obtain cis-trans isomer mixture 8;

step 2A:



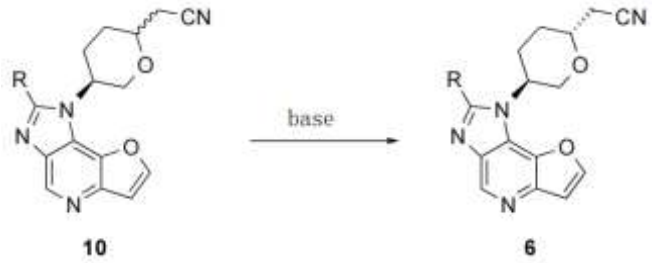
subjecting the cis-trans isomer mixture 8 to a reduction reaction to obtain cis-trans isomer mixture 9 or the mixture 9 hydrochlorides;

step 3A:



subjecting the cis-trans isomer mixture 9 or the mixture 9 hydrochlorides to a ring-closing reaction with compound 5 or compound 5' to obtain a mixture 10 or hydrates of the mixture 10, wherein R is methyl or ethyl, the methyl or ethyl is optionally substituted by hydroxyl, and preferably, R is methyl or 1-hydroxyethyl, and the hydrates of the mixture 10 is preferably monohydrates of the mixture 10; and

step 4A:

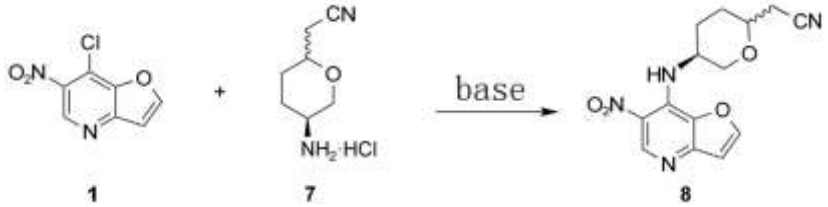


10 6

subjecting the mixture 10 or the hydrates of the mixture 10 to an isomer transformation reaction under basic condition to obtain compound 6 or a hydrate of the compound 6, wherein the hydrate of compound 6 is preferably a monohydrate of compound 6.

In another aspect, the present disclosure provides a method for synthesizing 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds, comprising the following steps of:

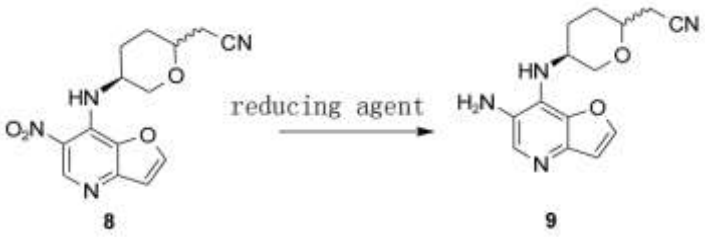
step 1A:



1 7 8

reacting compound 1 with cis-trans isomer mixture 7 in a solvent in the presence of a base to obtain cis-trans isomer mixture 8;

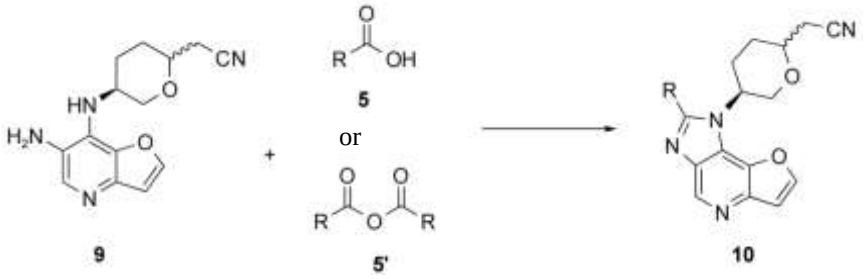
step 2A:



8 9

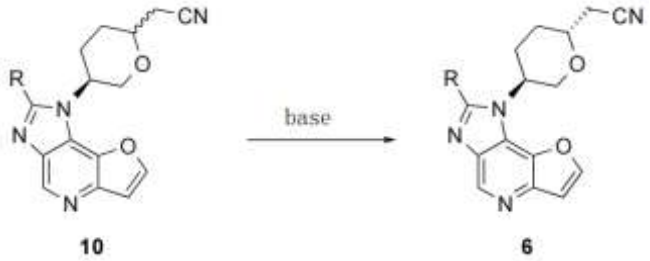
subjecting the cis-trans isomer mixture 8 to a reduction reaction to obtain cis-trans isomer mixture 9 or the cis-trans isomer mixture 9 hydrochlorides;

step 3A:



subjecting the cis-trans isomer mixture 9 or the cis-trans isomer mixture 9 hydrochlorides to a ring-closing reaction with compound 5 or compound 5' to obtain mixture 10 or hydrates of the mixture 10, wherein R is methyl or ethyl, the methyl or ethyl is optionally substituted by hydroxyl, and preferably, R is methyl or 1-hydroxyethyl; and

step 4A:

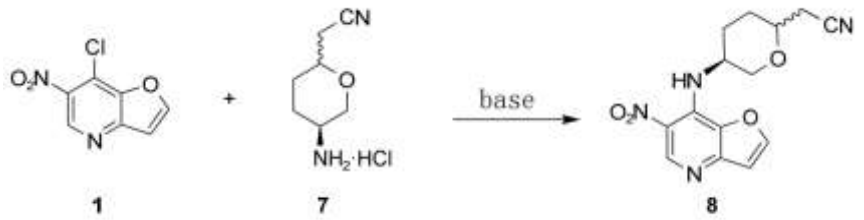


subjecting the mixture 10 or the hydrates of the mixture 10 to an isomerization reaction under basic condition to obtain compound 6 or a hydrate of the compound 6.

According to the examples of the present disclosure, in the synthesis route 2, the steps 1A, 2A and 3A are in accordance with the steps 1, 2 and 3 of the synthesis route 1. In the step 4A, the reaction is carried out under basic condition, and the base is alkoxide base, preferably alkali metal C_{1-6} alkoxide, more preferably, potassium tert-butoxide.

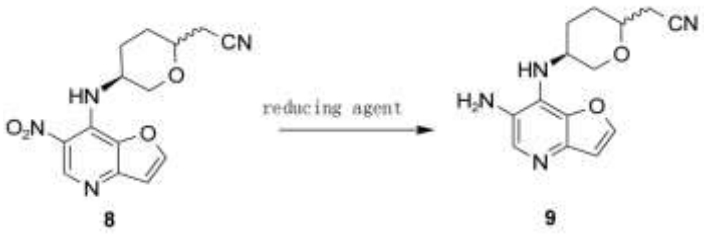
According to the examples of the present disclosure, the present disclosure provides another method for synthesizing the compound 6A, comprising step 1A, step 2A, step 3A and step 4A, wherein the steps 1A, 2A and 3A are in accordance with the methods described in the steps 1, 2 and 3 for preparing the compound 6A (synthesis route 1) above, wherein:

step 1A:



reacting compound 1 with cis-trans isomer mixture 7 in a solvent in the presence of a base to obtain cis-trans isomer mixture 8;

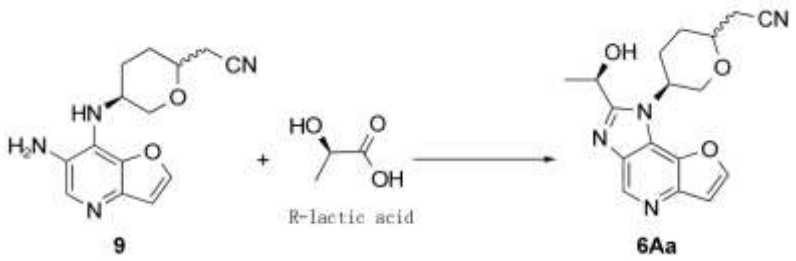
step 2A:



8 9

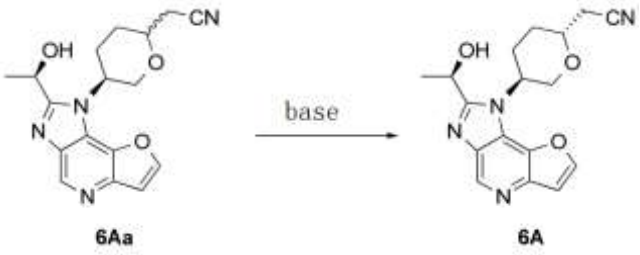
subjecting the cis-trans isomer mixture 8 to a reduction reaction to obtain cis-trans isomer mixture 9 or the mixture 9 hydrochlorides;

step 3A:



subjecting the cis-trans isomer mixture 9 or the mixture 9 hydrochlorides to a ring-closing reaction with R-lactic acid to obtain mixture 6Aa or hydrates of the mixture 6Aa; and

step 4A:



subjecting the mixture 6Aa or the hydrates of the mixture 6Aa to an isomer transformation reaction under basic condition to obtain a hydrate of compound 6A. The base is alkoxide base, preferably alkali metal C_{1-6} alkoxide, and more preferably, potassium tert-butoxide; and the hydrate of the compound 6A is preferably a monohydrate of compound 6A.

According to the examples of the present disclosure, in the method for synthesizing the compound 6A through steps 1A to 4A, in the step 4A,

the reaction is carried out in a solvent, wherein the solvent is preferably tetrahydrofuran;

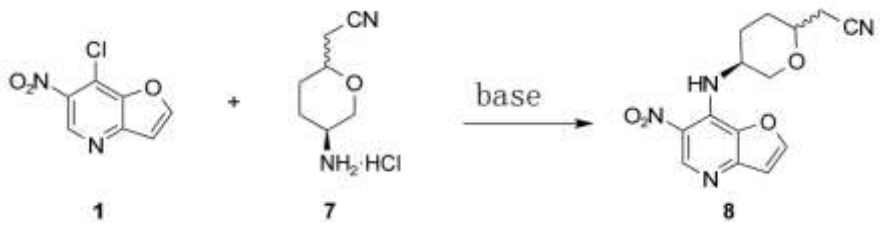
the molar ratio of mixture 6Aa to the base is from 1:0.05 to 1:0.2, and preferably from 1:0.1 to 1:0.2;

the reaction is carried out at room temperature; and

after the reaction is completed, dilute hydrochloric acid is added to adjust the pH to 6-7, the solvent is removed by rotary evaporation. Water is added to the reaction solution, the obtained system is stirred, filtered, and washed with water. The filter cake is collected and dried at 50°C to obtain the hydrate of the compound 6A.

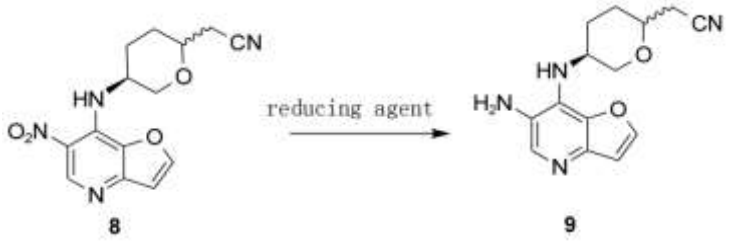
According to the examples of the present disclosure, the present disclosure provides another method for synthesizing the compound 6B, comprising step 1A, step 2A, step 3A and step 4A, wherein the steps 1A, 2A and 3A are in accordance with the methods described in the steps 1, 2 and 3 for preparing the compound 6B (synthesis route 1) above, wherein:

step 1A:



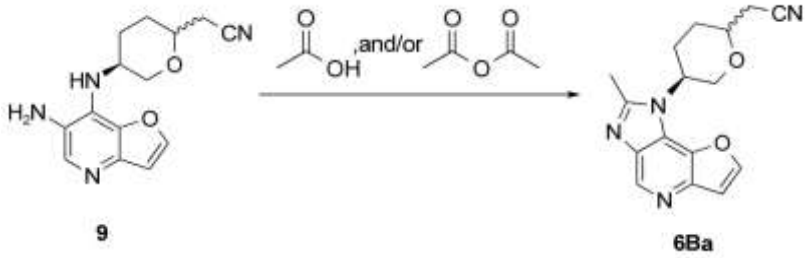
reacting compound 1 with cis-trans isomer mixture 7 in a solvent in the presence of a base to obtain cis-trans isomer mixture 8;

step 2A:



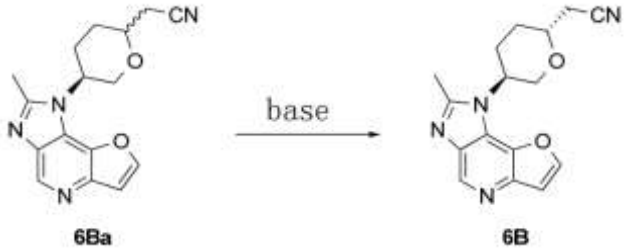
subjecting the cis-trans isomer mixture 8 to a reduction reaction to obtain cis-trans isomer mixture 9 or the mixture 9 hydrochlorides;

step 3A:



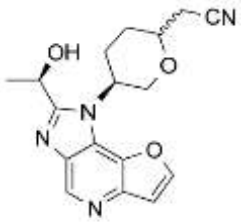
subjecting the cis-trans isomer mixture 9 or the mixture 9 hydrochlorides to a ring-closing reaction with acetic anhydride and/or acetic acid to obtain mixture 6Ba; and

step 4A:



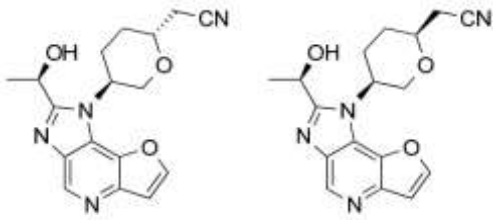
the mixture 6Ba is subjected to an isomer transformation reaction under basic condition to obtain the compound 6B. The base is alkoxide base, preferably alkali metal C_{1-6} alkoxide, and more preferably, potassium tert-butoxide.

According to the examples of the present disclosure, in the method for synthesizing compound 6B through steps 1A to 4A, in step 4A,



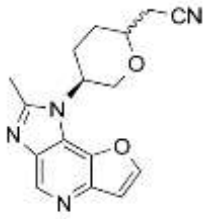
6Aa ,

or hydrates of the mixture of formula 6Aa, or salts of the mixture of formula 6Aa, wherein the mixture of formula 6Aa comprises a compound of formula 6A and a compound of formula 6Ab:



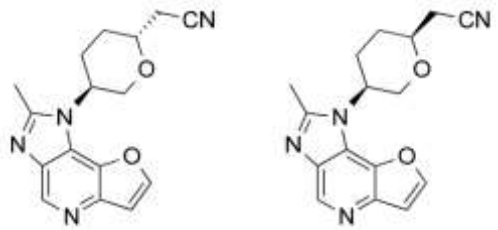
6A 6Ab .

The present application further provides a mixture of formula 6Ba (mixture 6Ba):



6Ba ,

or salts of the mixture of formula 6Ba, wherein the mixture of formula 6Ba comprises a compound of formula 6B and a compound of formula 6Bb:



6B 6Bb .

Beneficial effects

The methods for synthesizing the 1H-furo[3,2-b]imidazo[4,5-d]pyridine compounds of the present disclosure have the advantages of high yield, less impurities and are easy to control, save the cost. The methods are simple, convenient to operate, and are suitable for industrial scale.

DESCRIPTION OF THE DRAWINGS