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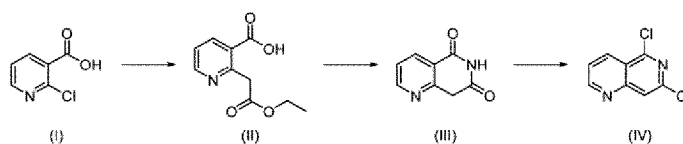
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(54) Title: SYNTHESIS OF 5, 7-DICHLORO-1, 6-NAPHTHYRIDINE



(57) Abstract: The present disclosure provides processes for preparing 5, 7-dichloro-1, 6-naphthyridine.



SYNTHESIS OF 5,7-DICHLORO-1,6-NAPHTHYRIDINE

FIELD

Provided herein are processes for preparing 5,7-dichloro-1,6-naphthyridine.

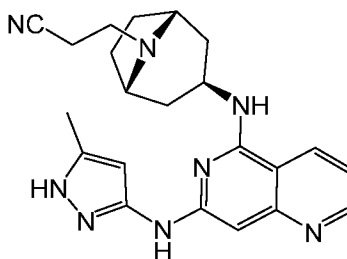
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BACKGROUND

The inflammatory bowel diseases (IBDs), such as ulcerative colitis (UC) and Crohn's disease (CD), adversely impact the quality of life of patients. The disorders are associated with rectal bleeding, diarrhea, abdominal pain, weight loss, nausea and vomiting, and also lead to an increased incidence of gastrointestinal cancers. The direct and indirect societal costs of IBD are substantial; 2014 estimates for the USA ranged from \$14.6 to \$31.6 billion, reflecting the deficiencies of available therapies.

Because inhibition of the Janus kinase ("JAK") family of enzymes could inhibit signaling of many key pro-inflammatory cytokines, JAK inhibitors may be useful in the treatment of UC and other inflammatory diseases such as CD, allergic rhinitis, asthma, and chronic obstructive pulmonary disease (COPD). However, due to the modulating effect of the JAK/STAT pathway on the immune system, systemic exposure to JAK inhibitors may have an adverse systemic immunosuppressive effect. Therefore, JAK inhibitors that are locally acting at the site of action without significant systemic effects would be particularly beneficial. Thus, for the treatment of gastrointestinal inflammatory diseases, such as UC and CD, it would be desirable to provide efficient, industrially scalable synthetic routes to JAK inhibitors which can be administered orally and achieve therapeutically relevant exposure in the gastrointestinal tract with minimal systemic exposure. It would also, accordingly, be desirable to provide efficient, industrially scalable synthetic routes to starting materials useful in the preparation of such JAK inhibitors.

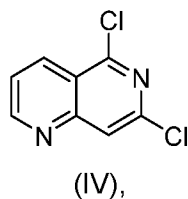
As discussed in U.S. Patent Nos. 9,725,470 and 10,072,026, 3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile is a potent gut-selective pan-JAK inhibitor. This compound has the following formula:



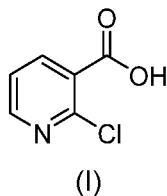
As discussed above, the ongoing need to treat UC and other inflammatory diseases such as CD demonstrates a need for an efficient, scalable synthetic route to the above-depicted pan-JAK inhibitor, including efficient and scalable processes for preparing starting materials used in its preparation. The processes disclosed herein meet this need by providing a concise, scalable synthetic route to 5,7-dichloro-1,6-naphthyridine, which is a starting material in an industrially scalable, efficient, and sustainable route to the pan-JAK inhibitor.

SUMMARY

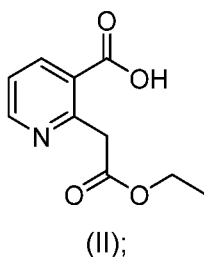
The present disclosure provides, inter alia, a process for preparing a compound of Formula (IV):



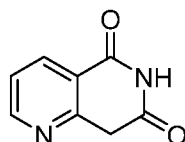
comprising: (a) combining a compound of Formula (I):



with ethyl acetoacetate, a copper catalyst, and an ethoxide base in ethanol to provide a compound of Formula (II):



(b) combining the compound of Formula (II) with carbonyldiimidazole and ammonium hydroxide to provide a compound of Formula (III):



(III); and

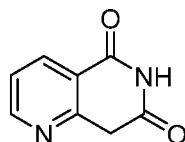
5 (c) combining the compound of Formula (III) with POCl_3 to provide the compound of Formula (IV).

In some embodiments, the copper catalyst is copper (II) acetate. In some embodiments, the ethoxide base of step (a) is sodium ethoxide or potassium ethoxide. In some embodiments, the ethoxide base is sodium ethoxide. In some embodiments, the molar ratio of the compound
10 of Formula (I) to the copper catalyst in step (a) is between about 15:1 and about 30:1. In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is about 20:1. In some embodiments, in step (a), between about 0.025 and about 0.075 molar equivalents of the copper catalyst are used with respect to the compound of Formula (I). In some embodiments, in step (a), about 0.05 molar equivalents of the copper catalyst are used
15 with respect to the compound of Formula (I).

In some embodiments, step (b) is performed in dichloromethane (DCM). In some embodiments, step (b) does not comprise the addition of a second base. In some embodiments, step (b) does not comprise the addition of an alkylamino base. In some embodiments, step (b) does not comprise the addition of triethylamine (TEA).

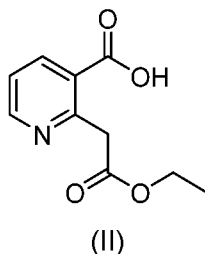
20 In some embodiments, step (c) further comprises the addition of Me_4NCl . In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) in step (c) is about 6:1.

The present disclosure also provides a process for preparing a compound of Formula (III):



(III),

25 comprising combining a compound of Formula (II):



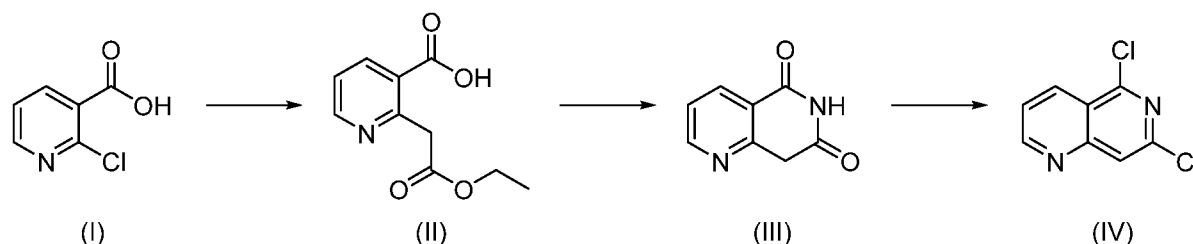
with carbonyldiimidazole and ammonium hydroxide to provide the compound of Formula (III).

In some embodiments, the carbonyldiimidazole and the ammonium hydroxide are combined in DCM. In some embodiments, the process does not comprise the addition of a further base. In some embodiments, the process does not comprise the addition of an alkylamino base. In some embodiments, the process does not comprise the addition of TEA.

DETAILED DESCRIPTION

1) General

Disclosed herein are processes for preparing the compound of Formula (IV) according to the following scheme:



The processes disclosed herein are suitable for performance at an industrial scale and proceed with high yield and purity of each intermediate.

2) Definitions

It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a solvent” includes a combination of two or more such solvents, reference to “a base” includes one or more bases, or mixtures of bases, and the like. Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive and covers both “or” and “and.”

Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard

deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from the context, all numerical values provided herein are modified by the term “about.”

Unless specifically stated or obvious from context, as used herein, the term “substantially”
5 is understood as within a narrow range of variation or otherwise normal tolerance in the art. Substantially can be understood as within 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, 0.01% or 0.001% of the stated value.

As used herein “substantially free of” refers to a compound of the disclosure or a composition comprising a compound of the disclosure containing no significant amount of such
10 other crystalline or amorphous solid forms identified herein. For example, an isolated compound of the disclosure can be substantially free of a given impurity when the isolated compound constitutes at least about 95% by weight of the compound, or at least about 96%, 97%, 98%, 99%, or at least about 99.5% by weight of the compound.

Unless defined otherwise, all technical and scientific terms used herein have the same
15 meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although other methods and materials similar, or equivalent, to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

As used herein, the term “solvate” refers to a complex formed by the combining of a
20 compound of the disclosure and a solvent. The term includes stoichiometric as well as non-stoichiometric solvates and includes hydrates.

As used herein, the term “hydrate” refers to a complex formed by the combining of a compound of the disclosure and water. The term includes stoichiometric as well as non-stoichiometric hydrates.

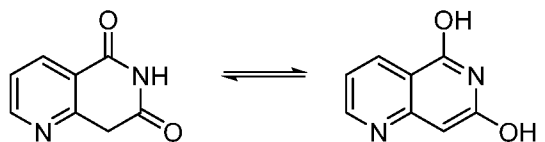
25 The present disclosure also includes salt forms of the compounds described herein. Examples of salts (or salt forms) include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is
30 hereby incorporated by reference in its entirety.

The compounds of the disclosure may, accordingly, be used or synthesized as free bases, solvates, hydrates, salts, or as combination salt–solvates or salt–hydrates.

The present disclosure also includes tautomeric forms of the compounds described herein. As used herein, “tautomers” or “tautomeric forms” refer to compounds that are

interchangeable forms of a particular compound structure and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and one or more atoms (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base.

- 5 Another example of tautomerism is the interchange between the dione and diol forms of the compound of Formula (III):



- The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.
- 15 some embodiments, reactions can be carried out in the absence of solvent, such as when at least one of the reagents is a liquid or gas.

- As used herein, "aprotic solvents" refer to any solvent that does not contain a labile hydrogen atom. Suitable aprotic solvents can include, by way of example and without limitation, tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), *N*-methylpyrrolidinone (NMP), formamide, *N*-methylacetamide, *N*-methylformamide, acetonitrile, dimethyl sulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, acetone, ethyl methyl ketone, ethyl acetate, dichloromethane (DCM), sulfolane, *N,N*-dimethylpropionamide, tetramethylurea, nitromethane, nitrobenzene, or
- 25 hexamethylphosphoramide.

- The reactions of the processes described herein can be carried out at appropriate temperatures which can be readily determined by the skilled artisan. Reaction temperatures will depend on, for example, the melting and boiling points of the reagents and solvent, if present; the thermodynamics of the reaction (e.g., vigorously exothermic reactions may need to be carried out at reduced temperatures); and the kinetics of the reaction (e.g., a high activation energy barrier may need elevated temperatures).
- 30

The reactions of the processes described herein can be carried out in air or under an inert atmosphere. Typically, reactions containing reagents or products that are substantially reactive with air can be carried out using air-sensitive synthetic techniques that are well known to the skilled artisan.

5 In some embodiments, preparation of compounds can involve the addition of acids or bases to effect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

Example acids can be inorganic or organic acids. Inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and nitric acid. Organic acids include
10 formic acid, acetic acid, propionic acid, butanoic acid, benzoic acid, 4-nitrobenzoic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, tartaric acid, trifluoroacetic acid, propiolic acid, butyric acid, 2-butyric acid, vinyl acetic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid and decanoic acid.

Example bases include lithium hydroxide, sodium hydroxide, potassium hydroxide,
15 lithium carbonate, sodium carbonate, and potassium carbonate. Some example strong bases include, but are not limited to, hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines, wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride, potassium hydride and lithium hydride;
20 and metal dialkylamides include sodium and potassium salts of methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, trimethylsilyl and cyclohexyl substituted amides.

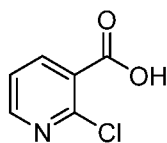
As used herein, the term "alkylamino base" refers to a base comprising a nitrogen atom covalently bound to three alkyl groups, wherein the alkyl groups may be straight- or branched-chain hydrocarbon groups having from 1 to 12 carbon atoms in the chain. Example alkylamino
25 bases include, but are not limited to, trimethylamine, triethylamine (TEA), and N, N-diisopropylethylamine (DIPEA).

Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of
30 protecting groups can be found, for example, in Greene, et al., Protective Groups in Organic Synthesis, 4d. Ed., Wiley & Sons, 2007, which is incorporated herein by reference in its entirety. Adjustments to the protecting groups and formation and cleavage methods described herein may be adjusted as necessary in light of the various substituents.

Upon carrying out preparation of compounds according to the processes described herein, isolation and purification operations such as concentration, filtration, extraction, solid-phase extraction, recrystallization, chromatography, and the like may be used, to isolate the desired products.

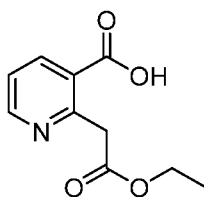
5 Specific compounds of the disclosure may be referred to by the following identifiers:

2-Chloronicotinic acid is referred to, alternately, as a compound of Formula (I) or Compound I:



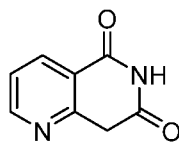
(I).

10 2-(2-Ethoxy-2-oxoethyl)nicotinic acid is referred to, alternately, as a compound of Formula (II) or Compound II:



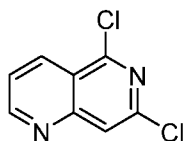
(II).

15 1,6-Naphthyridine-5,7(6*H*,8*H*)-dione is referred to, alternately, as a compound of Formula (III) or Compound III:



(III).

5,7-Dichloro-1,6-naphthyridine is referred to, alternately, as a compound of Formula (IV) or Compound IV:



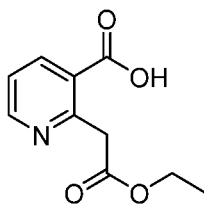
(IV).

3) Processes

The present disclosure provides, inter alia, processes for preparing a compound of Formula (IV), which is useful as a starting material in the synthesis of the pan-JAK inhibitor (3-((1*R*,3*S*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile). In one aspect, the the process comprises a copper-catalyzed alkylation. In another aspect, the process comprises an annulation. In yet another aspect, the process comprises a chlorination reaction.

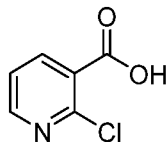
3.1) Copper-catalyzed alkylation

The compound of Formula (IV) may be formed via copper-catalyzed alkylation of a compound of Formula (I) to provide a compound of Formula (II), which can then be converted to a compound of Formula (IV) through additional steps (e.g., annulation and chlorination). Accordingly, in one aspect, the present disclosure provides a process of preparing a compound of Formula (II):



(II)

comprising combining a compound of Formula (I):



(I)

with ethyl acetoacetate, a copper catalyst, and a base in ethanol to provide a compound of Formula (II).

In some embodiments, the copper catalyst is copper (II) acetate.

In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is greater than 10:1 (e.g., 15:1, 20:1, 25:1). In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is between about 15:1 and about 30:1. In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is between about 15:1 and about 25:1. In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is between about 18:1 and about 22:1. In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is about 20:1.

In some embodiments, less than 0.1 molar equivalents (e.g., 0.075 molar equivalents, 0.05 molar equivalents, 0.025 molar equivalents) of the copper catalyst are used with respect to the compound of Formula (I). In some embodiments, between about 0.01 and about 0.09 molar equivalents of the copper catalyst are used with respect to the compound of Formula (I). In some embodiments, between about 0.025 and about 0.075 molar equivalents of the copper catalyst are used with respect to the compound of Formula (I). In some embodiments, between about 0.04 and about 0.06 molar equivalents of the copper catalyst are used with respect to the compound of Formula (I). In some embodiments, about 0.05 molar equivalents of the copper catalyst are used with respect to the compound of Formula (I).

In some embodiments, the base is an alkoxide base. In some embodiments, the base is an ethoxide base. In some embodiments, the ethoxide base is sodium ethoxide or potassium ethoxide. In some embodiments, the ethoxide base is sodium ethoxide.

In some embodiments, the copper catalyst is copper (II) acetate, and the base is sodium ethoxide.

In some embodiments, the process is performed at a temperature above about 10 °C.

In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol and then subsequently adding the compound of Formula (I) and the copper catalyst.

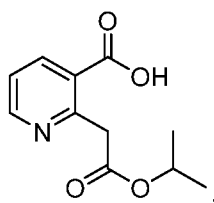
In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature above about 10 °C and then subsequently adding the compound of Formula (I) and the copper catalyst. In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature between about 10 °C and about 40 °C and then subsequently adding the compound of Formula (I) and the copper catalyst. In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature between about 10 °C and about 30 °C and then subsequently adding the compound of Formula (I) and the copper catalyst.

In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol and then subsequently adding the compound of Formula (I) and the copper catalyst at a temperature above about 10 °C. In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol and then subsequently adding the compound of Formula (I) and the copper catalyst at a temperature between about 20 °C and about 30 °C.

In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature above about 10 °C and then subsequently adding the

compound of Formula (I) and the copper catalyst at a temperature above about 10 °C. In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature between about 10 °C and about 40 °C and then subsequently adding the compound of Formula (I) and the copper catalyst at a temperature between about 20 °C and about 30 °C. In some embodiments, the process comprises combining the ethyl acetoacetate, the base, and ethanol at a temperature between about 10 °C and about 30 °C and then subsequently adding the compound of Formula (I) and the copper catalyst at a temperature between about 20 °C and about 30 °C.

The selection of an ethoxide base along with the use of ethanol as a solvent prevents the formation of mixed alkyl esters. Accordingly, in some embodiments, the compound of Formula (II) is produced substantially free of side products. In some embodiments, the compound of Formula (II) is produced substantially free of 2-(2-isopropoxy-2-oxoethyl)nicotinic acid, having the following structure:



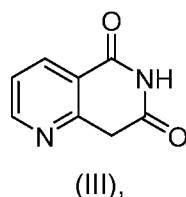
In some embodiments, the compound of Formula (II) is isolated by filtration. In some embodiments, the compound of Formula (II) is purified by washing with heptane.

In some embodiments, the compound of Formula (II) is isolated in high yield. In some embodiments, the compound of Formula (II) is isolated in at least about 90% yield. In some embodiments, the compound of Formula (II) is isolated in at least about 95% yield. In some embodiments, the compound of Formula (II) is isolated in at least about 96% yield. In some embodiments, the compound of Formula (II) is isolated in at least about 97% yield. In some embodiments, the compound of Formula (II) is isolated in at least about 98% yield.

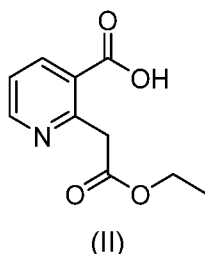
In some embodiments, the compound of Formula (II) is isolated with high purity. In some embodiments, the high purity is determined via HPLC. In some embodiments, the compound of Formula (II) is isolated with at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, or at least about 96% purity. In some embodiments, the compound of Formula (II) is isolated with at least about 90% purity. In some embodiments, the compound of Formula (II) is isolated with at least about 93% purity. In some embodiments, the compound of Formula (II) is isolated with at least about 95% purity.

3.2) Annulation

The compound of Formula (IV) may be formed via an annulation reaction of a compound of Formula (II) to provide a compound of Formula (III), which can then be converted to a compound of Formula (IV) through an additional step (e.g., chlorination). Accordingly, in one aspect, the present disclosure provides a process of preparing a compound of Formula (III):



comprising combining a compound of Formula (II):



with carbonyldiimidazole and ammonium hydroxide to provide the compound of Formula (III).

In some embodiments, the compound of Formula (II), the carbonyldiimidazole, and the ammonium hydroxide are combined in a solvent. In some embodiments, the solvent is an aprotic solvent. In some embodiments, the solvent is tetrahydrofuran or DCM. In some embodiments, the solvent is DCM.

In some embodiments, the process does not comprise the addition of a second base (i.e., another base beyond ammonium hydroxide). In some embodiments, the process does not comprise the addition of an alkylamino base. In some embodiments, the process does not comprise the addition of triethylamine (TEA).

In some embodiments, the carbonyldiimidazole is used in slight molar excess of the compound of Formula (II). In some embodiments, the molar ratio of the compound of Formula (II) to the carbonyldiimidazole is between about 1:1 and about 1:1.1. In some embodiments, the molar ratio of the compound of Formula (II) to the carbonyldiimidazole is about 1:1.05.

In some embodiments, the process for preparing the compound of Formula (III) is performed above 0 °C. In some embodiments, the process for preparing the compound of Formula (III) is performed at or above 5 °C. In some embodiments, the process for preparing the compound of Formula (III) is substantially performed at or above 10 °C.

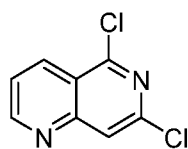
In some embodiments, the compound of Formula (III) was isolated by filtration. In some embodiments, the compound of Formula (III) is purified by washing with water.

In some embodiments, the compound of Formula (III) is isolated in high yield. In some embodiments, the compound of Formula (III) is isolated in at least about 80% yield. In some
5 embodiments, the compound of Formula (III) is isolated in at least about 85% yield, at least about 86% yield, at least about 87% yield, at least about 88% yield, at least about 89% yield, or at least about 90% yield. In some embodiments, the compound of Formula (III) is isolated in at least about 85% yield. In some embodiments, the compound of Formula (III) is isolated in at least about 87% yield.

10 In some embodiments, the compound of Formula (III) is isolated with high purity. In some embodiments, the high purity is determined via HPLC. In some embodiments, the compound of Formula (III) is isolated with at least about 90% purity. In some embodiments, the compound of Formula (III) is isolated with at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% purity. In some embodiments, the compound of
15 Formula (III) is isolated with at least about 95% purity. In some embodiments, the compound of Formula (III) is isolated with at least about 97% purity. In some embodiments, the compound of Formula (III) is isolated with at least about 99% purity.

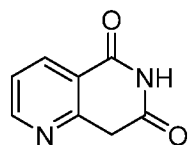
3.3) Chlorination reaction

20 The compound of Formula (IV) may be formed via a chlorination reaction of a compound of Formula (III). Accordingly, in one aspect, the present disclosure provides a process of preparing a compound of Formula (IV):



(IV),

25 comprising combining a compound of Formula (III):



(III)

with POCl₃ to provide the compound of Formula (IV).

In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is between about 2:1 and about 10:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is between about 4:1 and about 10:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is between about 5:1 and about 7:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is about 6:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is between about 2:1 and about 4:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is about 3:1. In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) is about 2.8:1.

In some embodiments, the process of preparing the compound of Formula (IV) further comprises the addition of Me_4NCl . In some embodiments, the Me_4NCl is used in slight molar excess of the compound of Formula (III). In some embodiments, the molar ratio of the compound of Formula (III) to the Me_4NCl is between about 1:1 and about 1:1.1. In some embodiments, the molar ratio of the compound of Formula (III) to the Me_4NCl is about 1:1.05.

In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held above 85 °C for at least 30 hours, at least 40 hours, at least 50 hours, at least 60 hours, or at least 70 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held above 85 °C for at least 60 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held above 85 °C for at least 65 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held above 85 °C for at least 70 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held above 85 °C for about 72 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held between about 85 °C and about 115 °C for about 72 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held between about 90 °C and about 110 °C for about 72 hours. In some embodiments, the compound of Formula (III), the POCl_3 , and the Me_4NCl are held between about 95 °C and about 105 °C for about 72 hours.

In some embodiments, the process of preparing the compound of Formula (IV) further comprises the addition of triethylamine (TEA). In some embodiments, the TEA is used in molar excess of the compound of Formula (III). In some embodiments, the molar ratio of the compound of Formula (III) to the TEA is between about 1:1 and about 1:3. In some embodiments, the molar ratio of the compound of Formula (III) to the TEA is between about 1:1.1 to 1:3. In some embodiments, the molar ratio of the compound of Formula (III) to the TEA is about 1:2.

In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held above 85 °C for at least 30 hours, at least 40 hours, at least 50 hours, at least 60 hours, at least 70 hours, at least 80 hours, or at least 90 hours. In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held above 85 °C for at least 50 hours. In some
5 embodiments, the compound of Formula (III), the POCl₃, and the TEA are held above 85 °C for at least 55 hours. In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held above 85 °C for at least 60 hours. In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held above 85 °C for at least 65 hours. In some
10 embodiments, the compound of Formula (III), the POCl₃, and the TEA are held between about 85 °C and about 115 °C for at least 65 hours. In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held between about 90 °C and about 110 °C for at least 65 hours. In some embodiments, the compound of Formula (III), the POCl₃, and the TEA are held between about 95 °C and about 100 °C for at least 65 hours.

In some embodiments, the compound of Formula (III) and the POCl₃ are combined in a
15 solvent. In some embodiments, the solvent is an aprotic solvent. In some embodiments, the solvent is toluene.

In some embodiments, the compound of Formula (IV) is isolated by filtration. In some
embodiments, the compound of Formula (IV) is purified by washing with water.

In some embodiments, the compound of Formula (IV) is isolated in high yield. In some
20 embodiments, the compound of Formula (IV) is isolated in at least about 80% yield. In some
embodiments, the compound of Formula (IV) is isolated in at least about 85% yield, at least
about 86% yield, at least about 87% yield, at least about 88% yield, at least about 89% yield, or
at least about 90% yield. In some embodiments, the compound of Formula (III) is isolated in at
least about 85% yield. In some embodiments, the compound of Formula (III) is isolated in at
25 least about 87% yield.

In some embodiments, the compound of Formula (IV) is isolated with high purity. In
some embodiments, the high purity is determined via HPLC. In some embodiments, the
compound of Formula (IV) is isolated with at least about 90% purity. In some embodiments, the
compound of Formula (IV) is isolated with at least about 95%, at least about 96%, at least about
30 97%, at least about 98%, or at least about 99% purity. In some embodiments, the compound of
Formula (IV) is isolated with at least about 95% purity. In some embodiments, the compound of
Formula (IV) is isolated with at least about 97% purity. In some embodiments, the compound of
Formula (IV) is isolated with at least about 99% purity.

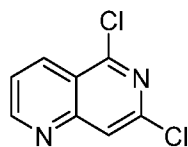
3.4) Stepwise Synthesis of the Compound of Formula (IV)

The compound of Formula (IV) can be provided by sequentially performing the processes disclosed herein. For example, the compound of Formula (IV) can be provided by sequentially performing the following three steps:

- A. copper-catalyzed alkylation of a compound of Formula (I) to provide a compound of Formula (II);
- B. annulation of the compound of Formula (II) to provide a compound of Formula (III); and
- C. chlorination of the compound of formula (III) to provide the compound of Formula (IV).

A process of preparing the compound of Formula (IV) may, alternately, comprise some, but not all, of the foregoing steps. In some embodiments, the process of preparing the compound of Formula (IV) comprises at least one of the foregoing steps. In some embodiments, the process of preparing the compound of Formula (IV) comprises at least two of the foregoing steps. In some embodiments, the process of preparing the compound of Formula (IV) comprises all three of the foregoing steps.

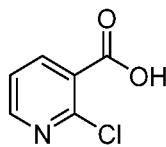
Accordingly, in an aspect, the present disclosure provides a process of preparing a compound of Formula (IV):



(IV),

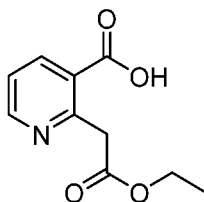
comprising

(a) combining a compound of Formula (I):



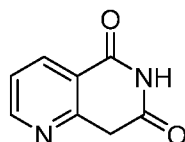
(I)

with ethyl acetoacetate, a copper catalyst, and an ethoxide base in ethanol to provide a compound of formula (II):



(II);

(b) combining the compound of Formula (II) with carbonyldiimidazole and ammonium hydroxide to provide a compound of Formula (III):



(III);

(c) combining the compound of Formula (III) with POCl_3 to provide the compound of Formula (IV).

Embodiments for the preparation of each of the compounds of Formulas (II), (III), and (IV) are as described and disclosed herein. Certain embodiments are described below:

In some embodiments, the copper catalyst is copper (II) acetate.

In some embodiments, the ethoxide base of step (a) is sodium ethoxide or potassium ethoxide. In some embodiments, the ethoxide base is sodium ethoxide.

In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst in step (a) is between about 15:1 and about 30:1. In some embodiments, the molar ratio of the compound of Formula (I) to the copper catalyst is about 20:1.

In some embodiments, step (b) is performed in dichloromethane (DCM).

In some embodiments, step (b) does not comprise the addition of a further base. In some embodiments, step (b) does not comprise the addition of an alkylamino base. In some embodiments, step (b) does not comprise the addition of triethylamine (TEA).

In some embodiments, step (c) further comprises the addition of Me_4NCl . In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) in step (c) is about 6:1.

In some embodiments, step (c) further comprises the addition of triethylamine (TEA). In some embodiments, the molar ratio of POCl_3 to the compound of Formula (III) in step (c) is about 2.8:1.

3.5) Exemplary advantages of the processes described herein

The processes described herein provide a concise, industrially scalable synthetic route to the compound of Formula (IV), a starting material in the synthesis of the pan-JAK inhibitor (3-((1*R*,3*s*,5*S*)-3-((7-((5-methyl-1*H*-pyrazol-3-yl)amino)-1,6-naphthyridin-5-yl)amino)-8-azabicyclo[3.2.1]octan-8-yl)propanenitrile). The processes proceed with high yield and produce the final product in high purity. In particular, it has been demonstrated that the processes described herein can be performed at the 100-gram scale and produce the compound of Formula (IV) with greater than 99% purity (as determined, for example, by HPLC) in at least 74% yield. The high purity and yield of the product ensures that the pan-JAK inhibitor would be produced in good quality.

Accordingly, in some embodiments, the processes described herein can be performed at the industrial scale. In some embodiments, the processes described herein can be performed at least at the 100-gram scale.

In some embodiments, the overall yield of the three-step process is at least about 65%. In some embodiments, the overall yield of the three-step process is at least about 70%. In some embodiments, the overall yield of the three-step process is at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, or at least about 75%. In some embodiments, the overall yield of the three-step process is about 74%.

In some embodiments, the compound of Formula (IV) afforded via the three-step process is at least about 90% pure. In some embodiments, the compound of Formula (IV) afforded via the three-step process is at least about 95% pure, at least about 96% pure, at least about 97% pure, at least about 98% pure, or at least about 99% pure. In some embodiments, the compound of Formula (IV) afforded via the three-step process is at least about 95% pure. In some embodiments, the compound of Formula (IV) afforded via the three-step process is at least about 97% pure. In some embodiments, the compound of Formula (IV) afforded via the three-step process is at least about 99% pure.

EXAMPLES

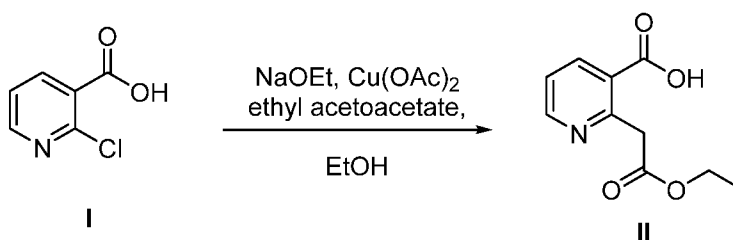
Abbreviations as used herein have respective meanings as follows:

aq.	Aqueous
Bu	Butyl
CD	Crohn's disease
CDI	Carbonyldiimidazole
DCM	Dichloromethane
equiv. or eq.	Equivalents

Et	Ethyl
g	Gram
h	Hour
HPLC	High-pressure liquid chromatography
kg	Kilogram
L	Liter
M	Molar
mg	Milligram
min	Minute
mL	Milliliter
mmol	Millimole
mol	Mole
MP	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance spectroscopy
RT	Room temperature
t-Bu	<i>tert</i> -Butyl
TEA	Triethylamine
vol	Volume
wt	Weight
μL	Microliter

Example 1: Synthesis of 2-(2-ethoxy-2-oxoethyl)nicotinic acid

Scheme 1

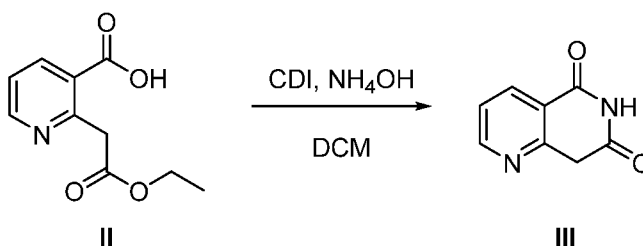


5 Compound II was synthesized according to the procedure depicted in Scheme 1. A flask was charged with ethanol (1170 mL, 923 g, 9V, 7.1X) at 20-30°C. Then, sodium ethoxide (146.0 g, 2.1 mol, 2.5 eq., 1.1X) was added at 20-40 °C, and the slurry was stirred for 20 min to dissolve. The solution was cooled to 10-30°C, and then ethyl acetoacetate (215 g, 1.65 mol, 2.0 eq., 1.65X) was added slowly under nitrogen atmosphere at 10-30 °C. The slurry was stirred for 10 0.5-1 h at 20-30°C followed by addition of Compound I (130 g, 0.83 mol, 1.0 eq., 1.0X), copper acetate (7.5 g, 41.3 mmol, 0.05 eq., 0.06X), and additional ethanol (130 mL, 103 g, 1.0V, 0.8X). The temperature was adjusted to 75-80°C, and the reaction mixture was stirred for 3-5 h. After

the reaction was complete (monitored by in-process liquid chromatography), H₂O (65.0 mL, 65.0 g, 0.5V, 0.5X) was added at 20 °C over the course of 10 minutes. The pH was adjusted to 6-7 at 20-30 °C by addition of a 20% oxalic acid aqueous solution (78.0 mL, 84.0 g, 0.6V, 0.65X). The slurry was concentrated by vacuum distillation at 40-45 °C to 2-4 V. The pH was adjusted to 4-5 at 20-50 °C by addition of a 20% oxalic acid aqueous solution (390 mL, 417 g, 3.0V, 3.2X). The temperature was adjusted to 50-55 °C, and the reaction mixture was stirred for 0.5 h. The organic layer and aqueous layer were separated. The aqueous layer was extracted twice with ethyl acetate (390 mL, 352g, 3.0V, 2.7X and 260.0 mL, 235g, , 2.0V, 1.8X) at 50-55 °C. The organic layers were combined and washed with brine (65.0 mL, 76.0 g, 0.5V, 0.6X), and stirred at 48-50 °C for 0.5 h. After phase separation, the organic layer was concentrated to about 4V at 40-45 °C, and a pale yellow slurry was formed. Heptane (390 mL, 267 g, 3.0V, 2.1X) was added at 40-45 °C. The temperature was adjusted to 15-25 °C, and the reaction mixture was stirred for 2-3 h. The solid was isolated via filtration. The resulting wet cake was washed with heptane (260 mL, 178 g, 2.0V, 1.4X) and dried at 50-55 °C under vacuum. 168 g (803.06 mmol) of Compound II was isolated as a yellow solid in 97.2% yield. Purity (HPLC): 96.25%; LC-MS: 210.2 [M+1]⁺.

Example 2: Synthesis of 1,6-naphthyridine-5,7(6H,8H)-dione

Scheme 2



Compound III was synthesized according to the procedure depicted in Scheme 2. A flask was charged with Compound II (230 g, 1.1 mol 1.0 eq., 1.0X) and DCM (850 mL, 1131 g, 3.7V, 4.9X). The suspension was first stirred for 10-15 min at 15-25 °C, then carbonyldiimidazole (187.3 g, 1.16 mol, 1.05 eq., 0.8X) was added in portions over a period of approximately 30 min under N₂ at 15-25 °C. Additional DCM was added (70 mL, 93 g, 0.3 V, 0.4 X) at 15-25 °C. The solution was stirred for 1.5-2.5 h at 15-25 °C. After the reaction was complete (monitored by in-process liquid chromatography), the reaction mixture solution was slowly added over 30 minutes at 10-25 °C to 25% ammonia hydroxide (508 mL, 2.2V, 462 g, 3.3 mol, 3.0 eq., 2.0X) precooled to 5-10 °C. The suspension was stirred at 15-25 °C for 1-2 h. The pH was slowly adjusted over approximately 40 min to 6.5-7.5 at 5-25 °C by addition of 4 M aq. HCl (1440 mL, 1512 g, 6.3V,

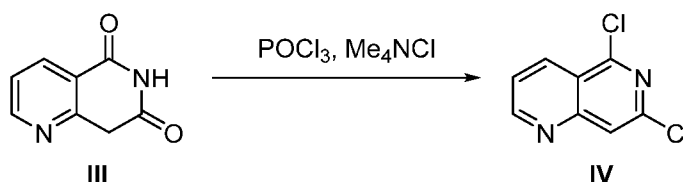
6.6X). The temperature was adjusted to 5-10 °C and the suspension stirred for 1-2 h. The solid was isolated by filtration. The resulting wet cake was washed with water (390 mL, 390 g, 1.7V, 3.0X) and dried at 75-80 °C under vacuum for 48 h. 158 g (974.41 mmol) of Compound III was isolated as a brown solid in 88.6% yield. Purity (HPLC): 99.92%; LC-MS: 163.1 [M+1]⁺.

5

Example 3: Synthesis of 5,7-dichloro-1,6-naphthyridine

Procedure 3(a)

Scheme 3



10

Compound IV was synthesized according to the procedure depicted in Scheme 3. A flask was charged with Compound III (100 g, 0.62 mol, 1.0 eq., 1.0X), phosphorus oxychloride (567 g, 3.7 mol, 6.0 eq., 5.7X), and MeN₄Cl (71.0 g, 0.65 mol, 1.05 eq., 0.7X) at 10-30 °C. The temperature was adjusted to 95-105 °C, and the reaction mixture was stirred for 72 h. After the reaction was complete (monitored by in-process liquid chromatography) the dark-colored suspension was cooled to 50-60 °C. Toluene (100 mL, 87 g, 1V, 0.9X) was added at 50-60 °C, and the slurry was concentrated by vacuum distillation to approximately 600 g (approximately 4V) to remove excess POCl₃ and other volatiles. Additional toluene (200 mL, 2V, 174 g, 1.7X) was added at 50-60 °C, and the slurry was concentrated by vacuum distillation to approximately 410 g (approximately 3V) to remove excess POCl₃ and other volatiles. THF was added (700 mL, 7.0V, 623 g, 6.2X), and the mixture was stirred for 0.5 h at 30-50 °C. Then, the mixture, precooled at 5-10 °C, was slowly added over 30 minutes to 25% aq. potassium carbonate (1200 mL, 1500 g, 12.0V, 15.0X) and ethyl acetate (700 mL, 630 g, 7.0V, 6.3X). The temperature was adjusted to 30-40 °C and the suspension stirred for 0.5 h. The insoluble material was removed over a diatomaceous earth (Celite®) pad (70 g, 0.7 X) by filtration and washed with THF (200 mL, 180 g, 2.0V, 1.8X) and ethyl acetate (300 mL, 270 g, 3.0V, 2.7X). After aqueous layer separation at 30-40 °C, the organic layers were combined and washed with brine (100.0 mL, 130 g, 1V, 1.3X). After aqueous layer separation the organic layer was treated with sodium sulfate (50 g, 0.5X) and activated carbon 783 (30 g, 0.3X, Sichuan Ebian Huatai Activated Carbon Co., Ltd) and stirred for 1h at 30-40 °C. After filtration of sodium sulfate and activated carbon and wash with ethyl acetate (400 mL, 360 g, 4.0V, 3.6X), the pale-yellow filtrated

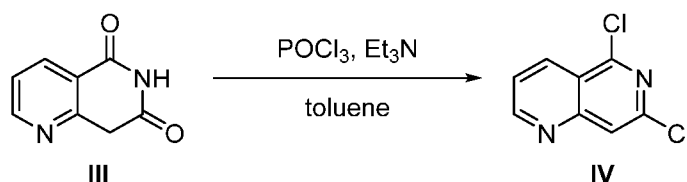
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30

solution was concentrated to 7-10V at 40-50 °C. Water was added (500 mL, 500 g, 5.0V, 5.0X) and the filtrate concentrated to 7-10V at 40-50 °C. Water was added (600 mL, 6.0V, 600 g, 6.0X) and the filtrate concentrated to approximately 13V at 40-50 °C. The temperature was adjusted to 10-20°C and the slurry was stirred for 1 h. The solid was isolated by filtration. The resulting wet cake was washed with water (200 mL, 200 g, 2.0V, 2.0X) and dried at 50-55 °C under vacuum for approximately 20 h. Compound IV was isolated as a pale-yellow solid (104.7 g) in 87.6% yield. Purity (HPLC): 99.97%; LC-MS: 200.9 [M+1]⁺.

Procedure 3(b)

Scheme 4



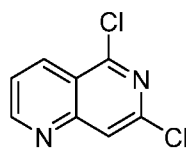
Alternatively, Compound IV can be synthesized according to the procedure depicted in Scheme 4. A flask was charged with Compound III (23.4 g, 144 mmol, 1.0 eq., 1.0X), toluene (117 mL), and phosphorus oxychloride (61.8 g, 400 mol, 2.78 eq., 2.64X) at 10-30 °C. The temperature was adjusted to 50-70°C. Et₃N (29.2 g, 289 mol, 2 eq., 0.7X) was added drop-wise over 2h at 50-70°C. The temperature was adjusted to 70-80°C, and the mixture was stirred for 1h. The temperature was adjusted to 95-100°C, and the reaction mixture was stirred for 64-96 h. After the reaction was complete (monitored by in-process liquid chromatography) the dark-colored suspension was cooled to room temperature and added drop-wise into another flask containing an aqueous potassium carbonate solution and ethyl acetate in order to quench excess POCl₃. To the solution was added THF (165 mL) and then diatomaceous earth (Celite®) (16.5 g). The temperature was adjusted to 35°C, and the mixture was stirred for 0.5h. Solids were removed by filtration and washed with ethyl acetate (70mL). The organic layers were then combined, separated from the aqueous phase, and washed with brine (25ml). After phase separation, sodium sulfate (20g) and activated carbon (7.0g) were added to the organic layer, and the mixture was stirred for at least 1h at 35 °C. After filtration of sodium sulfate and activated carbon and washing with ethyl acetate (95 mL), the filtered solution was concentrated to 200 mL at 40-50 °C. Water was added (120 mL) and the filtrate concentrated to 200 mL at 40-50 °C. Water was added (140mL) and the filtrate concentrated to approximately 280 mL at 40-50 °C. The temperature was adjusted to 10-20°C and the slurry was stirred for 1 h. The solid

was isolated by filtration. The resulting wet cake was washed with water and dried at 50-55 °C under vacuum for approximately 20 h. Compound IV was isolated in approximately 75% yield.

5 A number of embodiments have been described herein. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the disclosure. Accordingly, other embodiments are within the scope of the following claims:

CLAIMS

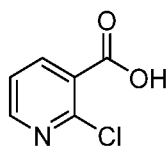
1. A process for preparing a compound of Formula (IV):



(IV),

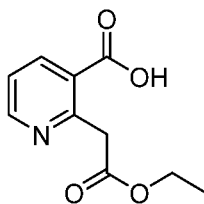
comprising

- (a) combining a compound of Formula (I):



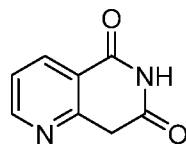
(I)

- with ethyl acetoacetate, a copper catalyst, and an ethoxide base in ethanol to provide a compound of Formula (II):



(II);

- (b) combining the compound of Formula (II) with carbonyldiimidazole and ammonium hydroxide to provide a compound of Formula (III):

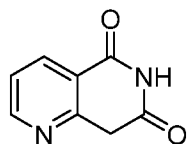


(III); and

- (c) combining the compound of Formula (III) with POCl_3 to provide the compound of Formula (IV).

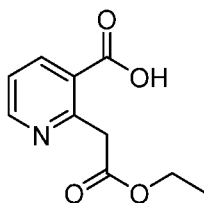
2. The process of claim 1, wherein the copper catalyst is copper (II) acetate.

3. The process of claim 1 or claim 2, wherein the ethoxide base of step (a) is sodium ethoxide or potassium ethoxide.
4. The process of any one of claims 1-3, wherein the ethoxide base is sodium ethoxide.
5. The process of any one of claims 1-4, wherein the molar ratio of the compound of Formula (I) to the copper catalyst in step (a) is between about 15:1 and about 30:1.
6. The process of any one of claims 1-5, wherein the molar ratio of the compound of Formula (I) to the copper catalyst is about 20:1.
7. The process of any one of claims 1-6, wherein step (b) is performed in dichloromethane (DCM).
8. The process of any one of claims 1-7, wherein step (b) does not comprise the addition of a second base.
9. The process of any one of claims 1-8, wherein step (b) does not comprise the addition of an alkylamino base.
10. The process of any one of claims 1-9, wherein step (b) does not comprise the addition of triethylamine (TEA).
11. The process of any one of claims 1-10, wherein step (c) further comprises the addition of Me_4NCl .
12. The process of any one of claims 1-11, wherein the molar ratio of POCl_3 to the compound of Formula (III) in step (c) is about 6:1.
13. The process of any one of claims 1-10, wherein step (c) further comprises the addition of triethylamine (TEA).
14. The process of any one of claims 1-10 or 13, wherein the molar ratio of POCl_3 to the compound of Formula (III) in step (c) is about 2.8:1.
15. A process for preparing a compound of Formula (III):



(III),

comprising combining a compound of Formula (II):



(II)

with carbonyldiimidazole and ammonium hydroxide to provide the compound of Formula (III).

16. The process of claim 15, wherein the compound of Formula (II), the carbonyldiimidazole and the ammonium hydroxide are combined in dichloromethane (DCM).
17. The process of claim 15 or claim 16, wherein the process does not comprise the addition of a second base.
18. The process of any one of claims 15-17, wherein the process does not comprise the addition of an alkylamino base.
19. The process of any one of claims 15-18, wherein the process does not comprise the addition of triethylamine (TEA).

INTERNATIONAL SEARCH REPORT

International application No

PCT/CN2021/136649

A. CLASSIFICATION OF SUBJECT MATTER**INV. C07D471/04****ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/134971 A1 (GLAXO GROUP LTD [GB]; ATKINSON FRANCIS LOUIS [GB] ET AL.) 3 November 2011 (2011-11-03) scheme 7; page 16 stages 7a to 7e; page 70 – page 71 scheme 4; page page 13 intermediate 7; page 53 – page 54	1-19
A	WO 2018/171602 A1 (CHIA TAI TIANQING PHARMACEUTICAL GROUP CO LTD [CN] ET AL.) 27 September 2018 (2018-09-27) steps 1 to 3; page 28	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

10 May 2022

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INTERNATIONAL SEARCH REPORT

International application No

PCT/CN2021/136649

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PETER NORMAN: "Evaluation of WO2011134971, chiral 1,6-napthyridine Syk kinase inhibitors", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 22, no. 3, March 2012 (2012-03), pages 335-339, XP055052846, DOI: 10.1517/13543776.2012.665878 scheme 1; page 337 -----	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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