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(54) Title: PROCESS FOR SYNTHESIZING 2-HYDROXY-6-((2-(1-ISOPROPYL-1H-PYRAZOL-5-YL)-PYRIDIN-3-YL)METHOXY)BENZALDEHYDE

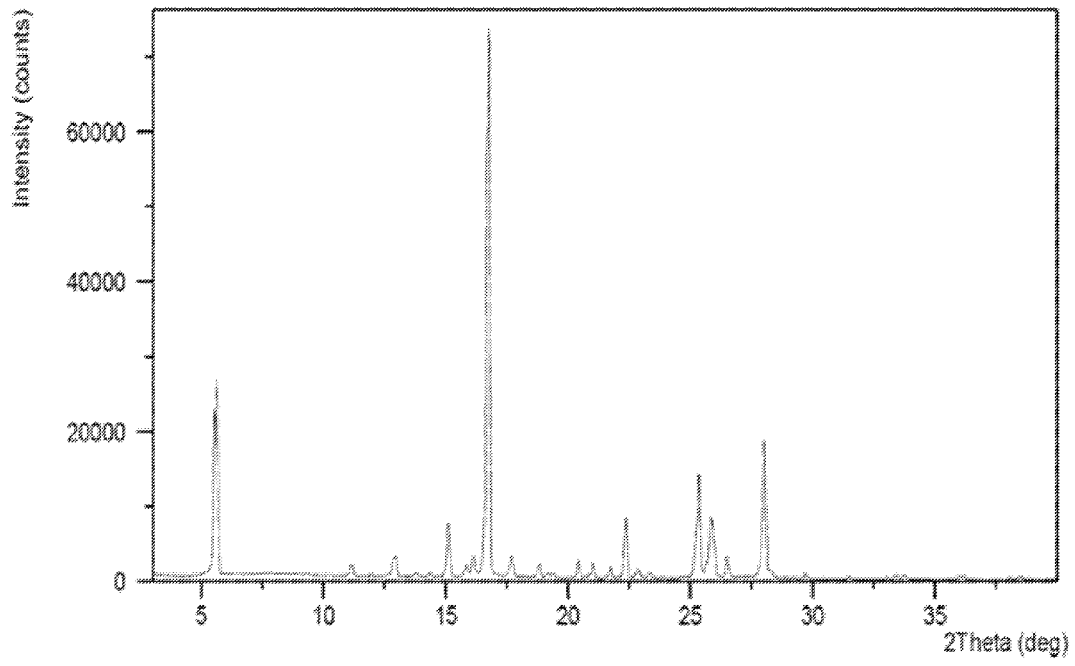

FIG. 1

(57) Abstract: Disclosed herein are processes for synthesizing 2-hydroxy-6-((2-(1-isopropyl-1H- pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde (also referred to herein as Compound (I)) and intermediates used in such processes. Compound (I) binds to hemoglobin and increases it oxygen affinity and hence can be useful for the treatment of diseases such as sickle cell disease.

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PROCESS FOR SYNTHESIZING 2-HYDROXY-6-((2-(1-ISOPROPYL-1H-PYRAZOL-5-YL)-PYRIDIN-3-YL)METHOXY)BENZALDEHYDE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/335,583, filed May 12, 2016, which is incorporated herein by reference in its entirety and for all purposes.

FIELD

Disclosed herein are processes for synthesizing 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde (Compound (I)) and intermediates used in such processes. Compound (I) binds to hemoglobin and increases it oxygen affinity and hence can be useful for the treatment of diseases such as sickle cell disease.

BACKGROUND

Compound (I) is disclosed in Example 17 of the International Publication No. WO2013/102142. Compound (I) binds to hemoglobin and increases it oxygen affinity and hence can be useful for the treatment of diseases such as sickle cell disease.

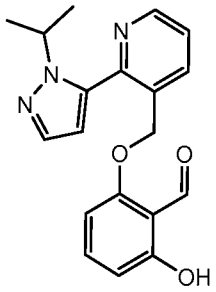
In general, for a compound to be suitable as a therapeutic agent or part of a therapeutic agent, the compound synthesis must be amendable to large scale manufacturing and isolation. The large scale manufacturing and isolation should not impact the physical properties and purity of the compound nor should it negatively impact cost or efficacy of a formulated active ingredient. Accordingly, scale up of manufacturing and isolation may require significant efforts to meet these goals.

SUMMARY

Compound (I) has been synthesized by certain methods starting with 2,6-dihydroxbenzaldehyde (compound 1) where each hydroxyl moiety is protected with an unbranched, straight-chain alkyl or alkoxyalkyl such as, for example, methyl or methoxymethyl. Following installation of the aldehyde group, various methods of deprotection of the hydroxyl group were employed to synthesize compound (1) used in the synthesis and production of Compound (I). However, the deprotection processes used lead to unwanted polymerization and decomposition reactions of compound (1) – attributed, in part, to the conditions used for

deprotection of the hydroxy groups. The undesired byproducts yield complex mixtures, lower yields of Compound (I), and require significant effort to purify Compound (I) to a degree acceptable for use as a part of a therapeutic agent, thus rendering the above processes impractical for commercial scale synthesis of Compound (I).

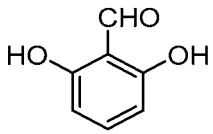
Provided herein are processes for the synthesis of Compound (I):



(I)

that employ a protecting group sequence and mild reaction conditions to obtain compound (1) in a manner that suppresses unwanted polymerization and decomposition reactions and enables commercial scale synthesis of Compound (I).

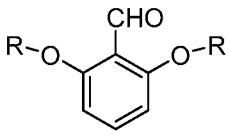
In one aspect, provided is a process of synthesizing compound (1):



(1)

the process comprising:

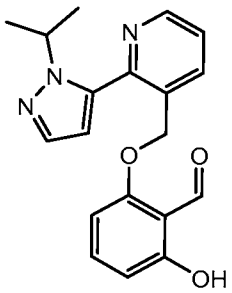
Step (i): treating a compound of formula (2):



(2)

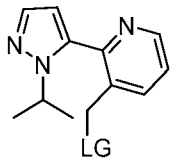
where each R is $–CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl with an acid to provide a compound (1) and wherein R^1 is hydrogen or alkyl and R^2 is alkyl;

Step (ii): optionally converting compound (1) to Compound (I):



(I)

by reacting compound (1) with a compound of formula (3):



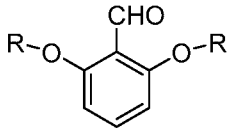
(3)

where LG is a leaving group under alkylation reacting conditions; and

Step (iii): optionally crystallizing Compound (I) from heptane and methyl *tert*-butyl ether at 40° +/-5 °C to 55 +/-5 °C, preferably at 45° +/-5 °C to 55 +/-5 °C.

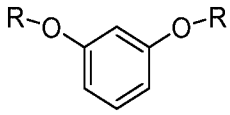
Further provided herein is a process for synthesizing Compound (I), the process comprising performing Steps (i) and (ii) of the first aspect in sequence, including embodiments and subembodiments of aspect 1 described herein, thereby synthesizing Compound (I). Further provided herein is a process for synthesizing Compound (I), the process comprising performing Steps (i), (ii), and (iii) of the first aspect in sequence, including embodiments and subembodiments of aspect 1 described herein, thereby obtaining Compound (I).

Provided herein in a second aspect, is a process of synthesizing a compound of formula (2):



(2)

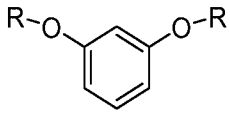
the process comprising formylating a compound of formula (4):



(4)

wherein each R in compounds of formulae (2) and (4) is $-CH(CH_2R^1)-OR^2$ (where R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl to provide a compound of formula (2) above.

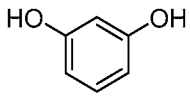
Provided herein in a third aspect, is a process of synthesizing a compound of formula (4):



(4)

wherein each R is $-CH(CH_2R^1)-OR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl, the process comprising:

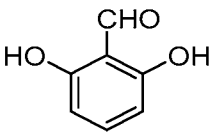
reacting compound (5):



(5)

with a vinyl ether of formula $CHR^1=CHOR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl) or 3,4-dihydro-2H-pyran optionally substituted with one, two or three alkyl, in the presence of a weak acid to provide a compound of formula (4) above.

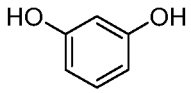
Provided in a fourth aspect is a process of synthesizing compound (1):



(1)

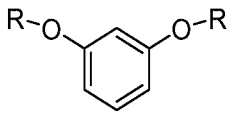
wherein each R is $-CH(CH_2R^1)-OR^2$ (where R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl, the process comprising:

Step (a): reacting compound (5):



(5)

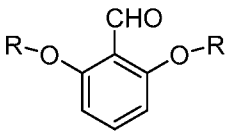
with a vinyl ether of formula $CHR^1=CHOR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl) or 3,4-dihydro-2H-pyran optionally substituted with one, two or three alkyl, in the presence of a weak acid to provide a compound of formula (4):



(4)

wherein each R is $–CH(CH_2R^1)-OR^2$ (where R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl;

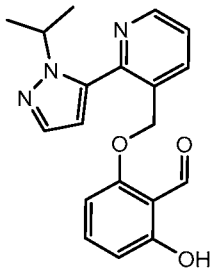
Step (b): treating compound (4) *in situ* with a formylating agent to provide a compound of formula (2):



(2)

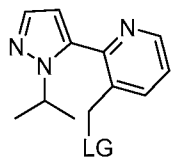
Step (c): treating the compound of formula (2) *in situ* with an acid to provide compound (1) above;

Step (d): optionally converting compound (1) to Compound (I):



(I)

by reacting compound (1) with a compound of formula (3)



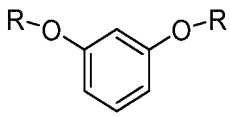
(3)

where LG is a leaving group under alkylation reacting conditions; and

Step (e): optionally crystallizing Compound (I) from heptane and methyl *tert*-butyl ether at 40° +/-5 °C to 55 +/-5 °C, preferably at 45° +/-5 °C to 55 +/-5 °C.

Further provided herein is a process of synthesizing Compound (I), the process comprising performing Steps (a), (b), and (c) or (b) and (c) of the fourth aspect in sequence, including embodiments and subembodiments of aspect 4 described herein,. Further provided herein is a process of synthesizing Compound (I), the process comprising performing Steps (a), (b), (c), and (d), or (b), (c), and (d) of the fourth aspect in sequence, including embodiments and subembodiments of aspect 4 described herein. Further provided herein is a process of synthesizing Compound (I), the process comprising performing Steps (a), (b), (c), (d), and (e), or (b), (c), and (d) and (e) of the fourth aspect in sequence, including embodiments and subembodiments of aspect 4 described herein. In one embodiment, the first and fourth aspects further include synthesizing compound (3) from the intermediate compound (6) as provided in the seventh aspect described herein.

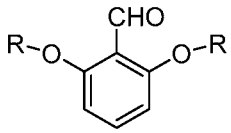
Further provided herein in a fifth aspect is an intermediate of the compound of formula (4):



(4)

where each R is tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.

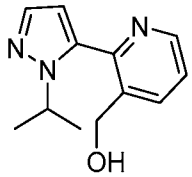
In a sixth aspect, provided is an intermediate of formula (2):



(2)

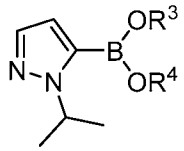
where each R is $-CH(CH_2R^1)-OR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.

In a seventh aspect, provided is a process of synthesizing compound (6):

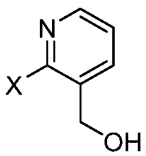


(6)

the process comprising reacting a boronic acid compound of formula:



where R^3 and R^4 are independently alkyl or together form $-(CR'R'')_2$ where R' and R'' are independently alkyl; with



where X is halo or triflate, in the presence of a palladium catalyst and a base in an organic/aqueous reaction mixture. Compound (6) can be used in the synthesis of Compound (3) as described herein.

The above aspects can be understood more fully by reference to the detailed description and examples below, which are intended to exemplify non-limiting embodiments.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a XRPD pattern for crystalline Form I of Compound (I).

FIG. 2 is a XRPD pattern for crystalline Form II of Compound (I).

DETAILED DESCRIPTION

Unless otherwise stated, the following terms as used in the specification and claims are defined for the purposes of this Application and have the following meaning:

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like.

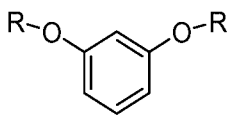
"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally crystallizing Compound (I) from heptane and methyl *tert*-butyl ethyl" means that the crystallization may but need not be done.

"About" as used herein means that a given amount or range includes deviations in range or amount that fall within experimental error unless indicated otherwise.

"Substantially pure" as used herein in connection with the polymorphic form refers to a compound such as Compound (I) wherein at least 70% by weight of the compound is present as the given polymorphic form. For example, the phrase "Compound (I) is substantially pure Form I or II" refers to a solid state form of Compound (I) wherein at least 70% by weight of Compound (I) is in Form I or II respectively. In one embodiment, at least 80% by weight of Compound (I) is in Form I or II respectively. In another embodiment, at least 85% by weight of Compound (I) is in Form I or II respectively. In yet another embodiment, at least 90% by weight of Compound (I) is in Form I or II respectively. In yet another embodiment, at least 95% by weight of Compound (I) is in Form I or II respectively. In yet another embodiment, at least 99% by weight of Compound (I) is in Form I or II respectively.

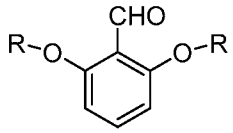
Embodiments:

(a) In embodiment (a), the process of the first aspect further comprises formylating a compound of formula (4):



(4)

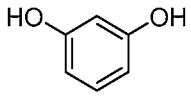
wherein each R is $-CH(CH_2R^1)-OR^2$ wherein R^1 is hydrogen or alkyl and R^2 is alkyl or R is tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl to provide a compound of formula (2).



(2)

In a first subembodiment of embodiment (a), each R is the same. In a second subembodiment, the tetrahydropyran-2-yl moiety is unsubstituted. In a third subembodiment of embodiment (a), the tetrahydropyran-2-yl moiety is substituted with one, two, or three alkyl.

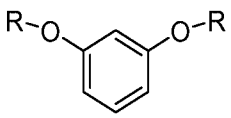
(b) In embodiment (b) the process of embodiment (a) further comprises reacting compound (5):



(5)

with a vinyl ether of formula $CHR^1=CHOR^2$, where R^1 is hydrogen or alkyl and R^2 is alkyl) or 3,4-dihydro-2H-pyran optionally substituted with one, two or three alkyl,

in the presence of a weak acid to provide a compound of formula (4):



(4)

wherein each R is $-CH(CH_2R^1)-OR^2$ (where R^1 is hydrogen or alkyl and R^2 is alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.

In one subembodiment of embodiment (b), the 3,4-dihydro-2H-pyran moiety is unsubstituted. In another subembodiment of embodiment (b), the 3,4-dihydro-2H-pyran moiety is substituted with one, two or three alkyl.

(c) In embodiment (c), the process of the first aspect, Step (i), fourth aspect, Step (c), and embodiments (a) and (b) is wherein the acid used in the removal of R group is an organic or inorganic acid. In a first subembodiment of embodiment (c), the acid is hydrochloric acid, sulfuric acid, trifluoroacetic acid, methanesulfonic acid, or ethanesulfonic acid. In a second subembodiment of embodiment (c), the acid is hydrochloric acid. In a third subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is performed at a pH of less than about: 4, 3, 2, or 1. In a fourth subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is performed at a pH of about 1 to about 3. In a fifth subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is performed at a pH greater than 1. In a sixth subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is performed at a pH less than 1. In a seventh subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the compound (2) is treated *in-situ* with the organic or inorganic acid to synthesize compound (1). In an eight subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is carried out in an organic solvent such as tetrahydrofuran, methyl tetrahydrofuran, ethyl ether, or dioxane. In a ninth subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is carried out in an organic solvent such as tetrahydrofuran. In a tenth subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the reaction is carried out at temperatures less than 30^{o}C +/-5 ^{o}C, preferably the reaction is carried out at temperatures less than about 20 ^{o}C. In an eleventh subembodiment of embodiment (c), including subembodiments and embodiments contained therein, the deprotection is performed in a shorter amount of time than previous synthetic routes. The shortened deprotection time can reduce polymerization or decomposition of the intermediate compound (1) and/or,(2) as described herein.

(d) In embodiment (d), the process of the first and fourth aspects, embodiments (a), (b) and (c) and subembodiments contained therein, is wherein LG is chloro, bromo, tosylate, mesylate, or triflate. LG can preferably be chloro. In a first subembodiment of embodiment (d), LG is chloro and the reaction is carried out in the presence of a non-nucleophilic organic base (such as pyridine, trimethylamine, N-methyl-2-pyrrolidone, and diisopropylethylamine in the presence of a weak inorganic base such as sodium bicarbonate, potassium bicarbonate, cesium

carbonate, and the like). In a second subembodiment of embodiment (d), the weak inorganic base is sodium bicarbonate. In a third subembodiment of embodiment (d), LG is chloro and the reaction is carried out in the presence of pyridine and a weak inorganic base such as sodium bicarbonate. In a fourth subembodiment of embodiment (d) and subembodiments and embodiments contained therein, the reaction is carried out in N-methyl-2-pyrrolidinone. In a fifth subembodiment of embodiment (d), LG is chloro and the reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and catalytic amount of NaI. In a sixth sub-embodiment of the embodiment (d) and sub-embodiments contained therein, the reaction is carried out at between 40 °C to 50 °C. In a seventh sub-embodiment of the embodiment (d) and sub-embodiments contained therein, the reaction is carried out at between 43 °C to 45 °C. In an eight sub-embodiment of the embodiment (d) and sub-embodiments contained therein, after the reaction is complete, the reaction mixture is treated with water and then seeded with Compound (I) Form I at 40 °C to 50 °C, preferably 40° to 46 °C to give Compound (I) as substantially pure Form I, preferably Compound (I) is at least 95% by weight pure Form I.

(e) In embodiment (e), the process of the first aspect, Step (iii), fourth aspect Step (e) and embodiments (a), (b), (c) and (d) and subembodiments contained therein is wherein-, the crystallization of Compound (I) is carried out at 45 +/-5 °C to 55 +/-5 °C or at 45 °C to 55 °C, and the solvent is n-heptane and methyl tert-butyl ether to provide substantially pure Compound (I) Form II. In one embodiment, at least 95% by wt of Compound (I) is Form II. In one embodiment, at least 98% by wt of Compound (I) is Form II. In one embodiment, at least 99% by wt of Compound (I) is Form II.

(f) In embodiment (f), the process of the first, second, third, fourth, fifth, and sixth aspects, embodiments (a)-(e), and subembodiments contained therein is wherein, each R is $-CH(CH_3)-O-CH_2CH_3$, $-CH(C_2H_5)-O-CH_2CH_3$. In one subembodiment of (g), each R is $-CH(CH_3)-O-CH_2CH_3$.

(g) In embodiment (g), the process of the first, second, third, fourth, fifth, and sixth aspects, embodiments (a)-(e), and subembodiments contained therein is wherein, each R is tetrahydropyran-2-yl optionally substituted with one or two methyl. In a first subembodiment of

(g), R is tetrahydrofuran-2-yl. In a second subembodiment of (g), each R is tetrahydropyran-2-yl is substituted with one methyl.

(h) In embodiment (h), the process of the third and fourth aspects, embodiments (a)-(e), and subembodiments contained therein is wherein, the acid used in the conversion of compound (5) to the compound of formula (4) is a weak acid such as p-toluenesulfonic acid or pyridinium tosylate. In a first subembodiment of embodiment (h), the acid is pyridinium tosylate.

(i) In embodiment (i) the process of second aspect and fourth aspect, Step (b), embodiments (a)-(i) and subembodiments contained therein, is wherein the formylating agent is n-BuLi and DMF, or n-formylmorpholine. In a first subembodiment of embodiment (i), the formylating agent is n-BuLi and DMF. In a second subembodiment of embodiment (i), including the first subembodiment of embodiment (i), the reaction is carried out in THF.

(j) In embodiment (j) the process of the seventh aspect, is wherein the palladium catalyst is dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) or its dichloromethane adduct. In a first subembodiment of embodiment (j), R^3 and R^4 together form $–C(CH_3)_2-C(CH_3)_2-$ and X is halo. In a second subembodiment of embodiment (j), including the first subembodiment of embodiment (j), R^3 and R^4 together form $–C(CH_3)_2-C(CH_3)_2-$ and X is chloro.

(k) In embodiment (j) the intermediate of the fifth and sixth aspects is wherein each R is $–CH(CH_3)-O-CH_2CH_3$.

(l) In embodiment (l) the intermediate of the fifth and sixth aspects is wherein, each R is tetrahydropyran-2-yl.

Form I of Compound (I) can be characterized by a XRPD pattern comprising X-ray powder diffraction peak (Cu Kα radiation) at one or more of 12.94°, 15.82°, 16.11°, 16.74°, 17.67°, 25.19°, 25.93° and 26.48° ±0.2 °2θ. In one embodiment, Form I of Compound (I) is characterized by an X-ray powder diffraction pattern (Cu Kα radiation) substantially similar to that of FIG. 1. In another embodiment, the Form I of the free base of Compound (I) is characterized by a XRPD pattern comprising at least two X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.94°, 15.82°, 16.11°, 16.74°, 17.67°, 25.19°, 25.93° and 26.48° (each ±0.2 °2θ). In another embodiment, the Form I of Compound (I) is characterized by a XRPD

pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.94°, 15.82°, 16.11°, 16.74°, 17.67°, 25.19°, 25.93° and 26.48° (each ±0.2 °2θ). In another embodiment, Form I is characterized by a XRPD pattern comprising 1, 2, 3, 4, or more peaks as tabulated below in Table 1 that lists the XRPD peak positions and relative intensities of major XRPD peaks for Form I of Compound (I).

Table 1: XRPD peaks for Form I of Compound (I).

°2θ	*d* space (Å)	Intensity (%)
5.51 ± 0.20	16.045	31.1
5.63 ± 0.20	15.696	35.5
11.17 ± 0.20	7.923	2.05
12.94 ± 0.20	6.841	3.7
15.09 ± 0.20	5.870	9.8
15.82 ± 0.20	5.600	2.3
16.11 ± 0.20	5.500	4.0
16.74 ± 0.20	5.295	100
17.67 ± 0.20	5.018	4.01
18.81 ± 0.20	4.716	2.8
19.13 ± 0.20	4.639	0.9
19.38 ± 0.20	4.581	1.0
20.41 ± 0.20	4.350	3.4
21.00 ± 0.20	4.230	2.9
21.72 ± 0.20	4.092	2.2
22.36 ± 0.20	3.976	10.6
22.86 ± 0.20	3.890	1.7
23.30 ± 0.20	3.817	1.2
25.19 ± 0.20	3.54	7.9

25.33 ± 0.20	3.516	19.1
25.93 ± 0.20	3.436	8.7
26.48 ± 0.20	3.366	3.6
28.01 ± 0.20	3.185	24.8
28.27 ± 0.20	3.157	1.49

Form II of Compound (I) can be characterized by a XRPD pattern comprising a X-ray powder diffraction peak (Cu Kα radiation at one or more of 13.44°, 14.43°, 19.76°, 23.97° ±0.2 °2θ. In another embodiment, Form II of Compound (I) is characterized by a XRPD pattern comprising a X-ray powder diffraction pattern (Cu Kα radiation) substantially similar to that of FIG. 2. In another embodiment, Form II of Compound (I) is characterized by a XRPD pattern comprising at least two X-ray powder diffraction peak (Cu Kα radiation) selected from 13.44°, 14.43°, 19.76°, 23.97° 2θ (each ±0.2 °2θ). In another embodiment, Form II of Compound (I) is characterized by a XRPD pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 13.44°, 14.43°, 19.76°, 23.97°2θ (each ±0.2 °2θ). In another embodiment, Form II of Compound (I) is characterized by a XRPD pattern comprising X-ray powder diffraction peaks (Cu Kα radiation) selected from 13.44°, 14.43°, 19.76°, 23.97°2θ (each ±0.2 °2θ).

In another embodiment, Form II is characterized by 1, 2, 3, 4, or more peaks as tabulated below in Table 2 that lists the XRPD peak positions and relative intensities of major XRPD peaks for Form II of Compound (I).

Table 2: Major XRPD peaks for Form II of Compound (I).

°2θ	*d* space (Å)	Intensity (%)
5.70 ± 0.20	15.494	24.8
9.64 ± 0.20	9.172	5.4
11.32 ± 0.20	7.812	12.2
11.52 ± 0.20	7.680	12.2
12.66 ± 0.20	6.992	10.3

12.90 ± 0.20	6.861	16.4
13.44 ± 0.20	6.587	28.5
14.43 ± 0.20	6.137	28.7
14.79 ± 0.20	5.991	18.3
15.38 ± 0.20	5.761	17.5
16.18 ± 0.20	5.477	16.4
16.51 ± 0.20	5.370	72.3
17.04 ± 0.20	5.205	100
18.56 ± 0.20	4.781	71.1
20.01 ± 0.20	4.437	22.5
20.31 ± 0.20	4.373	7.7
23.06 ± 0.20	3.858	16.3
23.97 ± 0.20	3.712	19.7
24.46 ± 0.20	3.639	34.1
25.06 ± 0.20	3.554	53.6
25.45 ± 0.20	3.500	88.0
26.29 ± 0.20	3.390	23.5
26.78 ± 0.20	3.329	12.6
27.07 ± 0.20	3.294	26.2
27.49 ± 0.20	3.245	5.4
28.09 ± 0.20	3.176	15.6
28.54 ± 0.20	3.128	13.44

The processes described herein can be used for synthesizing Compound (I) at a manufacturing scale synthesis (e.g., at least 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 10, 20, 25, 50, 100, or more kg amounts). The processes described herein can be useful for larger scale

syntheses (e.g., at least 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 10, 20, 25, 50, 100, or more kg amounts) which retain the physical properties, purity, efficacy, a combination thereof, or all thereof, of Compound (I).

The processes described herein surprisingly reduce polymerization of compound (1) and surprisingly reduce polymerization intermediates during the synthesis of Compound (I). In one embodiment, the polymerization can be reduced by at least 5%, 10%, 20%, 25%, 50%, 75%, 80%, 90%, 95% or more compared to previous synthesis routes as described herein.

The processes described herein surprisingly reduce decomposition reactions during the synthesis of (and deprotection of) compound (1). The decomposition reactions can be reduced by at least 5%, 10%, 20%, 25%, 50%, 75%, 80%, 90%, 95% or more compared to previous synthesis routes as described herein. The processes described herein can increase the purity of the final product of Compound (I) by at least 5%, 10%, 20%, 25%, 50%, 75%, 80%, 90%, 95%, 97%, 99% or more compared to previous synthesis routes as described herein.

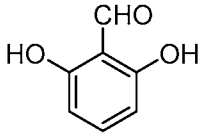
XRPD Analysis:

XRPD patterns were collected with a PANalytical X'Pert3 X-ray Powder Diffractometer using an incident beam of Cu Kα radiation (Kα1 (Å): 1.540598, Kα2 (Å): 1.544426 Kα2/Kα1 intensity ratio: 0.50, tube setting at 45 kV, 40 mA). A continuous scan mode between 3 and 40 (°2Θ) with a scan speed of 50 s per step and a step size of 0.0263 (°2Θ) in reflection mode was used. The diffractometer was configured using the symmetric Bragg-Brentano geometry. Data collection used Data Collector version® 4.3.0.161 and Highscore Plus® version 3.0.0.

Examples

Example 1

Synthesis of 2,6-dihydroxybenzaldehyde (Compound (1))



Step 1:

Tetrahydrofuran (700 mL) was added to resorcinol (170g, 1.54 mol, 1eq.) under inert gas protection, followed by addition of pyridinium tosylate (3.9 g, 15.4 mmol, 0.01eq.), THF 65 mL) and the reaction mixture was cooled down to 0 – 5 °C. Within 1 – 1.5 h ethylvinyl ether (444 mL, 4.63 mol, 3.0 eq.) was added while maintaining a temperature ≤5°C. After the addition was complete the reaction mixture was allowed to reach room temperature within 1.5 h. The reaction was stirred overnight, cooled down to 10-15 °C, and 510 mL of ½ sat. $NaHCO_3$ was added while maintaining the reaction solution below 20 °C. The phases were separated. The organic phase was washed once with 425 mL of water and once with 425 mL 12.5% NaCl solution and evaporated and azeotroped with THF to give bis-EOE-protected resorcinol (401.2 g, 1.55 mol, 102% uncorrected) as a clear colorless to yellowish oil.

Step 2:

Bis-EOE-protected resorcinol (390 g of, actual: 398.6g = 1.53 mol, 1 eq., corrected to 100% conversion) was added under inert gas protection to a 6 L glass vessel and THF (1170 mL) was added. The reaction mixture was cooled down to -10°C to -5°C and n-BuLi (625 mL, 2.7 M in heptane, 1.687 mol, 1.1 eq.) was added. The reaction mixture was agitated at -5°C – 0°C for 30-40 min and then DMF (153.4 mL, 1.99 mmol, 1.3 eq.) was added starting at -10°C to -5°C. The reaction mixture was stirred until complete and then quenched with 1N HCl/EtOAc. It was also discovered, *inter alia*, that protection with the EOE groups not only resulted in less byproducts but appeared to increase the speed of the formylation reaction to provide 2,6-bis(1-ethoxyethoxy)benzaldehyde (compound (2)).

The mixture was worked up, phase separated and the aqueous washed with MTBE. After aqueous wash to remove salts the organic phase was concentrated to the neat oil to obtain the compound (2) as yellow oil (almost quantitative).

A batch preparation was performed using solvent swap and was completed faster than other known methods for synthesizing Compound (I) with better purity and yield. The deprotection sequence allowed *in-situ* use of compound (2).

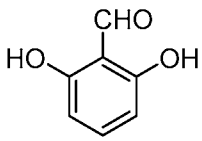
Step 3:

To the reaction solution of Step 2 was added 1N HCl (1755 mL) while maintaining the temperature < 20°C. The pH was of the solution was adjusted to pH = 0.7 – 0.8 with 6 M HCl.

The reaction mixture was stirred for 16 h. After the reaction was complete the organic phase was separated and 1560 mL of methyl *tert* butyl ether was added. The organic phase was washed once with 1170 mL of 1N HCl, once with 780 mL of ½ sat. NaCl solution and once with 780 mL of water and then concentrated to a volume of ~ 280mL. To the solution was added 780 mL of methyl *tert* butyl ether and concentrate again to 280 mL [temperature <45°C, *vacuo*]. To the slurry was added 780 mL of acetonitrile and the solution was concentrated in vacuo at T < 45°C to a final volume of ~ 280 mL. The slurry was heated to re-dissolve the solids. The solution was cooled slowly to RT and seeded at 60-65 °C to initiate crystallization of the product. The slurry was cooled down to -20°C to -15°C and agitated at this temperature for 1-2 h. The product was isolated by filtration and washed with DCM (pre-cooled to -20°C to -15°C) and dried under a stream of nitrogen to give 2,6-dihydroxybenzaldehyde as a yellow solid. Yield: 138.9 g (1.00 mol, 65.6%).

Example 1A

Alternate Synthesis of 2,6-dihydroxybenzaldehyde compound (1)



Step 1:

In a suitable reactor under nitrogen, tetrahydrofuran (207 L) was added to resorcinol (46 kg, 0.42 kmol, 1eq.) followed by addition of pyridinium tosylate (1.05 kg, 4.2 mol, 0.01eq.), and the reaction mixture was cooled down to 0 – 5 °C. Within 1 – 1.5 h ethylvinyl ether (90.4 kg, 120.5 L, 125 kmol, 3.0 eq.) was added while maintaining a temperature ≤5°C. After the addition was complete the reaction mixture was allowed to reach room temperature within 1.5 h. The reaction was stirred overnight, cooled down to 10-15 °C, and 138 L of aqueous 4% $NaHCO_3$ was added while maintaining the reaction solution below 20 °C. The phases were separated. The organic phase was washed once with 115 L of water and once with 125.2 kg of a 12.5% NaCl solution. The organic layer was dried by azeotropic distillation with THF to a water content value < 0.05% (by weight) to yield bis-EOE-protected resorcinol (106.2 kg, 0.42 kmol) as a solution in THF. An advantage over previously reported protection procedures is that the bis-EOE-protected resorcinol product does not need to be isolated as a neat product. The

product-containing THF solution can be used directly in the next reaction step thus increasing throughput and reducing impurity formation.

Step 2:

Bis-EOE-protected resorcinol solution (assumption is 100% conversion) was added under inert gas protection to suitable reactor. The reaction mixture was cooled down to -10°C to -5°C and n-BuLi (117.8 kg, 25% in heptane, 1.1 eq.) was added. The reaction mixture was agitated at -5°C – 0°C for 30-40 min and then DMF (39.7 kg, 0.54 kmol, 1.3 eq.) was added at -10°C to -5°C. The reaction mixture was stirred until complete and then quenched with aqueous HCl (1M, 488.8 kg) to give 2,6-bis(1-ethoxyethoxy)benzaldehyde. An advantage over previously reported procedures of using EOE protecting group is that the HCl quenched solution can be used directly in the deprotection step, and 2,6-bis(1-ethoxyethoxy)benzaldehyde does not need to be isolated as a neat oil.

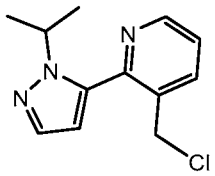
Step 3:

The pH of the quenched solution was adjusted to < 1 with aqueous HCl (6M, ca 95.9 kg) and the reaction mixture stirred at ambient temperature for 16 h. After the reaction was complete the organic phase was separated and 279.7 kg of methyl tert butyl ether was added. The organic phase was washed once with aqueous 1N HCl (299 kg), once with aqueous 12.5% NaCl (205.8 kg) and once with 189 kg of water and then concentrated to a volume of ca. 69 L. To the slurry was added 164 kg of acetonitrile and the solution was concentrated in vacuo at T < 45°C to a final volume of ca. 69 L. The slurry was heated to re-dissolve the solids. The solution was seeded at 60-65 °C to initiate crystallization of the product and cooled slowly to RT over 8 hrs. The slurry was cooled down to -20 °C to -15°C and agitated at this temperature for 1-2h. The product was isolated by filtration and washed with DCM (50.3 kg, pre-cooled to -20 °C to -15 °C) and dried under a stream of nitrogen to yield 2,6-dihydroxybenzaldehyde as a yellow solid. Yield: 37.8 kg (0.27 kmol, 65.4% Yield). The described telescoped approach from deprotection to crystallization increases the throughput and integrity of the product.

Example 2

Synthesis of 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine

dihydrochloride salt



Step 1:

An appropriately sized flask was purged with nitrogen and charged with (2-chloropyridin-3-yl)methanol (1.0 equiv), sodium bicarbonate (3.0 equiv), [1, 1′-bis(diphenyl-phosphino)-ferrocene]dichloropalladium (5 mol %), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.2 equiv), and a mixture of 2-MeTHF (17.4 vol) and deionized water (5.2 vol). The resulting solution was heated to 70°C to 75°C and conversion monitored by HPLC. Once the reaction was complete, the reaction mixture was cooled to room temperature, diluted with deionized water, and the phases were separated. The organic layer was extracted with 2 N HCl (10 vol) and the phases were separated. The aqueous phase was washed with MTBE. The pH of the aqueous phase was adjusted to 8–9 with 6 N NaOH. The product was extracted into EtOAc, treated with Darco G-60 for 30 to 60 min, dried over $MgSO_4$, filtered through Celite®, and concentrated to give (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methanol as a brown oil.

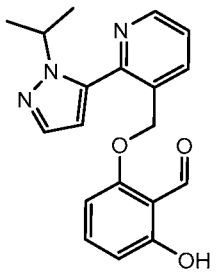
Step 2:

A suitably equipped reactor was charged with (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methanol hydrochloride salt (1 equivalent) and purified water. An aqueous sodium bicarbonate solution (8% $NaHCO_3$) was added slowly to maintain the solution temperature between 17 °C to 25 °C. After addition was complete, the reaction mixture was stirred at 17 °C to 25 °C and dichloromethane was added and the organic layer was separated. DCM solution was then distilled under atmospheric conditions at approximately 40°C and the volume was reduced. DCM was added the reactor and the contents of the reactor are stirred at 20°C to 30°C until a clear solution is formed. The contents of the reactor were cooled to 0°C to 5°C and thionyl chloride was charged to the reactor slowly to maintain a temperature of $\leq$ 5 °C. The reaction solution was stirred at 17 °C to 25 °C. When the reaction was complete, a solution of HCl (g) in 1,4-dioxane (ca. 4 N, 0.8 equiv.) was charged to the reactor slowly to maintain the solution temperature between 17 °C and 25 °C. The product 3-(chloromethyl)-2-(1-isopropyl-

1H-pyrazol-5-yl)pyridine dihydrochloride salt was filtered washed with dichloromethane and dried.

Example 3

Synthesis of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde Form I



(I)

A suitably equipped reactor was charged with 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine dihydrochloride salt (1 equivalent), sodium iodide (0.05 equivalent), sodium bicarbonate (4 equivalent), 1-methyl-2-pyrrolidinone (NMP), and 2,6-dihydroxy-benzaldehyde (1 to 1.05 equiv.). The reaction mixture was heated slowly to 40 °C to 50 °C and stirred until the reaction was complete. Water was then added and the reaction mixture was cooled and maintained at 17 °C to 25 °C. When the water addition was complete, the reaction mixture was stirred at 17 °C to 25 °C and slowly cooled to 0°C to 5°C and the resulting solids were collected by filtration. The solids were washed with a 0 °C to 5 °C 2:1 water/NMP solution, followed by 0 °C to 5 °C water. The solids were filtered and dried to give 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde as Form I or a mixture of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde as Form I Form I and NMP solvates.

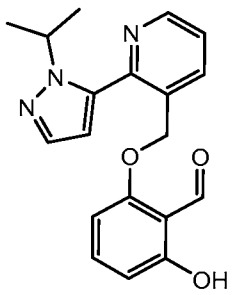
Alternative Synthesis:

A suitably equipped reactor was charged with 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine bishydrochloride salt (1 equivalent), sodium iodide (0.05 equivalent), sodium bicarbonate (3 to 4 equivalent), 1-methyl-2-pyrrolidinone (7 equivalent, NMP), and 2,6-dihydoxybenzaldehyde (1.05 equivalent). The reaction mixture was heated to 40 °C to 50° C and

stirred until the reaction was complete. Water (5 equivalent) was then added while maintaining the contents of the reactor at 40 °C to 46 ° C and the resulting clear solution seeded with 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde Form I. Additional water (5 equivalent) was added while maintaining the contents of the reactor at 40 °C to 50 ° C, the reactor contents cooled to 15 °C to 25 ° C, and the reactor contents stirred for at least 1 hour at 15 °C to 25 ° C. The solids were collected, washed twice with 1:2 NMP:water and twice with water, and dried to yield 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde Form I devoid of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde as NMP solvates.

Example 4

Preparation of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)-benzaldehyde Form II



Step 1:

A suitably equipped reactor with an inert atmosphere was charged with crude 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde (from Example 3 above) and MTBE and the contents stirred at 17°C to 25°C until dissolution was achieved. The reaction solution was passed through a 0.45 micron filter and MTBE solvent volume reduced using vacuum distillation at approximately 50 °C. The concentrated solution was heated to 55°C to 60°C to dissolve any crystallized product. When a clear solution was obtained, the solution was cooled to 50 °C to 55 °C and n-heptane was added. 2-Hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)benzaldehyde (e.g., Form II) seeds in a slurry of n-heptane were charged and the solution was stirred at 50°C to 55°C. The solution was cooled to 45 °C to 50 °C and n-heptane was added to the reactor slowly while maintaining a reaction solution temperature of 45°C to 50°C. The reaction solution are stirred at 45°C to 50°C and then slowly

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cooled to 17°C to 25°C. A sample was taken for FTIR analysis and the crystallization was considered complete when FTIR analysis confirmed 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)-pyridin-3-yl)methoxy)-benzaldehyde (Form II). The contents of the reactor were then cooled to 0°C to 5°C and the solids were isolated and washed with cold n-heptane and dried.

Reference to any prior art in the specification is not an acknowledgement or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be combined with any other piece of prior art by a skilled person in the art.

By way of clarification and for avoidance of doubt, as used herein and except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additions, components, integers or steps.

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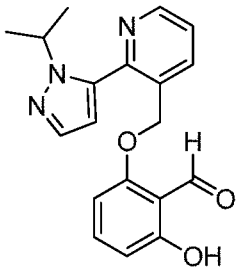
What is claimed is:

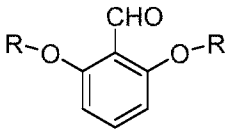
1. A process of synthesizing Compound (I):



(I)

the process comprising:

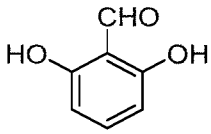
Step (i): treating a compound of formula (2):



(2)

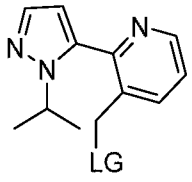
wherein each R is $–CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl; and wherein each R^1 is independently hydrogen or alkyl, and each R^2 is independently alkyl;

with an acid to provide compound (1):



(1)

Step (ii): reacting compound (1) with a compound of formula (3)



(3)

wherein LG is a leaving group under alkylation reaction conditions to provide Compound (I).

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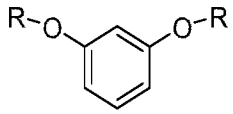
2. The process of claim 1 further comprising:

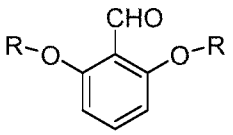
Step (iii): crystallizing Compound (I) from Step (ii) from heptane and methyl *tert*-butyl ether at 45° +/-5 °C to 55° +/-5 °C.

3. The process of claim 1 or 2 further comprising formylating a compound of formula (4):



(4)

to provide the compound of formula (2):

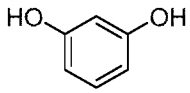


(2)

wherein each R in compound of formulae (2) and (4) is $-CH(CH_2R^1)-OR^2$ or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl; and

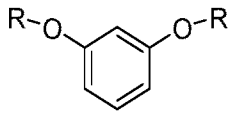
each R^1 is independently hydrogen or alkyl, and each R^2 is independently alkyl.

4. The process of claim 3 further comprising reacting compound (5):



(5)

with a vinyl ether of formula $CHR^1=CHOR^2$ (wherein R^1 is hydrogen or alkyl and R^2 is alkyl), or 3,4-dihydro-2H-pyran optionally substituted with one, two or three alkyl, in the presence of a weak acid to provide the compound of formula (4):



(4)

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wherein each R is $-CH(CH_2R^1)-OR^2$ (where each R^1 is independently hydrogen or alkyl and each R^2 is independently alkyl) or tetrahydropyran-2-yl optionally substituted with one, two, or three alkyl.

5. The process of claim 4 wherein compound (4) is treated *in situ* with a formylating agent to provide compound (2).

6. The process of any one of claims 1 to 3 wherein compound (2) is treated *in situ* with an acid to provide compound (1).

7. The process of any one of claims 1 to 6 wherein Compound (I) is crystallized from heptane and methyl *tert*-butyl ether at 45° +/-5 °C to 55 +/-5 °C to give Compound (I) in substantially pure Form II characterized by an XRPD pattern comprising X-ray powder diffraction peaks (Cu Kα radiation) at 13.37°, 14.37°, 19.95° and 23.92°2θ (each ±0.2 °2θ).

8. The process of claim 7 wherein Compound (I) is crystallized at 45 °C to 55 °C to give Compound (I) wherein at least 95% by wt of Compound (I) is Form II.

9. The process of any one of claims 1 to 8 wherein LG is chloro.

10. The process of any one of claims 1 to 9 wherein R is $-CH(CH_3)-O-CH_2CH_3$.

11. The process of any one of claims 1 to 10 wherein the acid for removal of the R groups is an inorganic acid.

12. The process of claim 11 wherein the acid is hydrochloric acid.

13. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI.

14. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI and Compound (I) is crystallized from the reaction mixture by addition of water at 40 °C to 50° C to give substantially pure Form I characterized by an XRPD pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44°°2θ (each ±0.2 °2θ).

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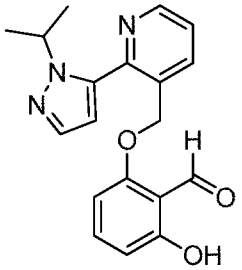
15. The process of any one of claims 1 to 12 wherein LG is chloro and the alkylation reaction is carried out in N-methyl-2-pyrrolidinone in the presence of sodium bicarbonate and a catalytic amount of NaI and Compound (I) is crystallized from the reaction mixture by addition of water at 40 °C to 46° C to give Compound (I) that at least 95% by weight Form I characterized by an XRPD pattern comprising at least three X-ray powder diffraction peaks (Cu Kα radiation) selected from 12.82°, 15.74°, 16.03°, 16.63°, 17.60°, 25.14°, 25.82° and 26.44°2θ (each ±0.2 °2θ).

16. The process of any one of claims 4 to 15 wherein the weak acid is pyridinium tosylate.

17. The process of any one of claims 3 to 16 wherein the formylating agent is n-BuLi and DMF.

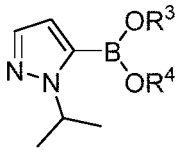
18. A process of synthesizing Compound (I):



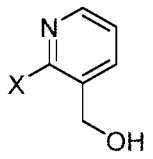
(I)

comprising:

(i) reacting a boronic acid compound of formula:



wherein R^3 and R^4 are each independently alkyl or together form $-(CR'R'')_2$ where R' and R" are each independently alkyl; with a compound of formula:



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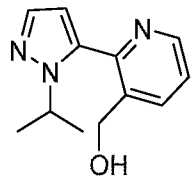
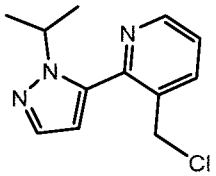
wherein X is halo or triflate, in the presence of a palladium catalyst and a base in an organic/aqueous reaction mixture to form compound (6):



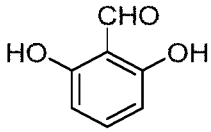
(6);

(ii) contacting compound (6) with sodium bicarbonate and a chlorinating agent to provide compound (3a):



(3a)

(iii) reacting compound (3a) with compound (1):



(1)

under alkylation reaction conditions to provide Compound (I).

19. The process of claim 18, further comprising crystallizing Compound (I) from heptane and methyl *tert*-butyl ether at 45° +/-5 °C to 55° +/-5 °C.

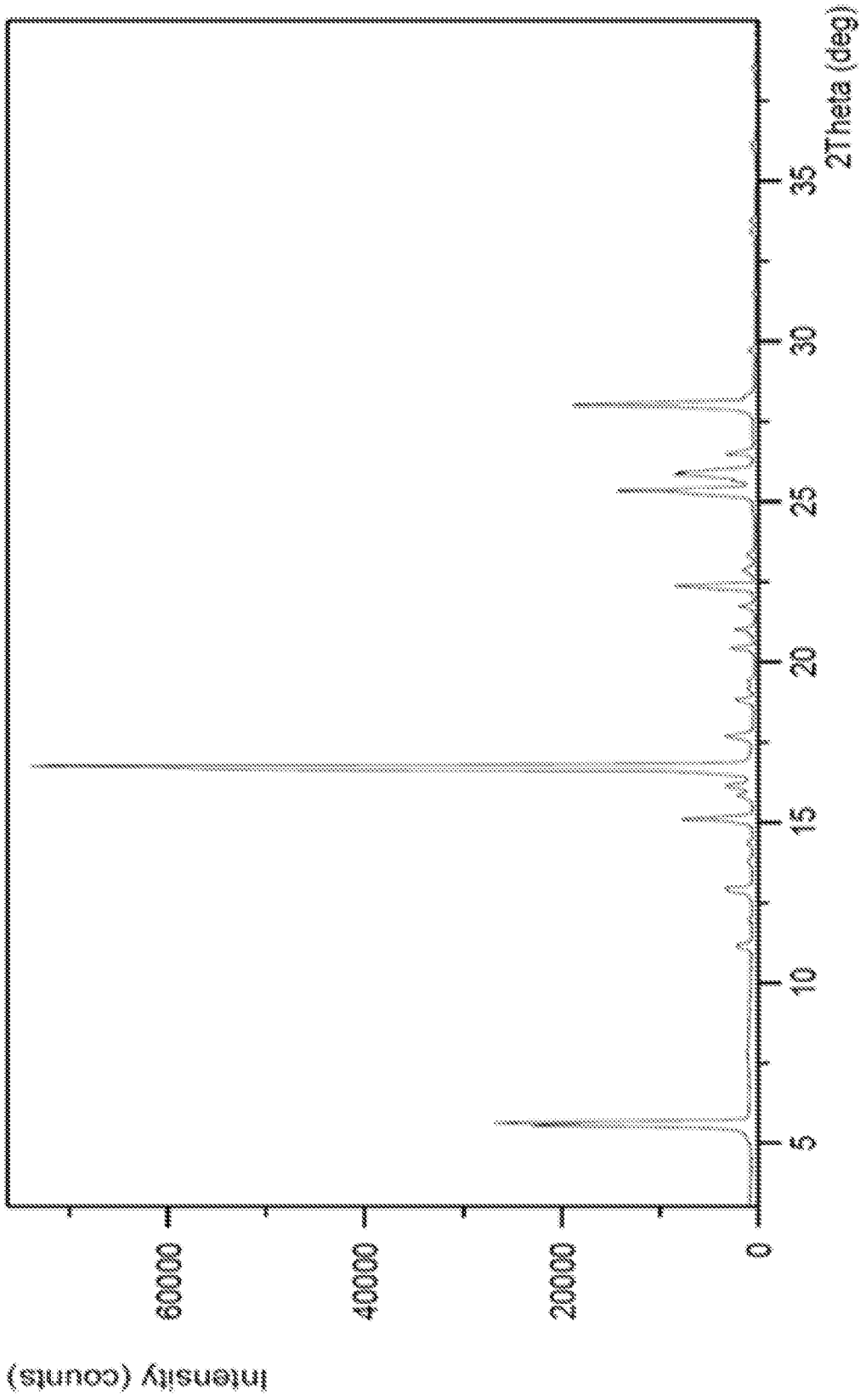

Intensity (counts)
60000
40000
20000
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 1

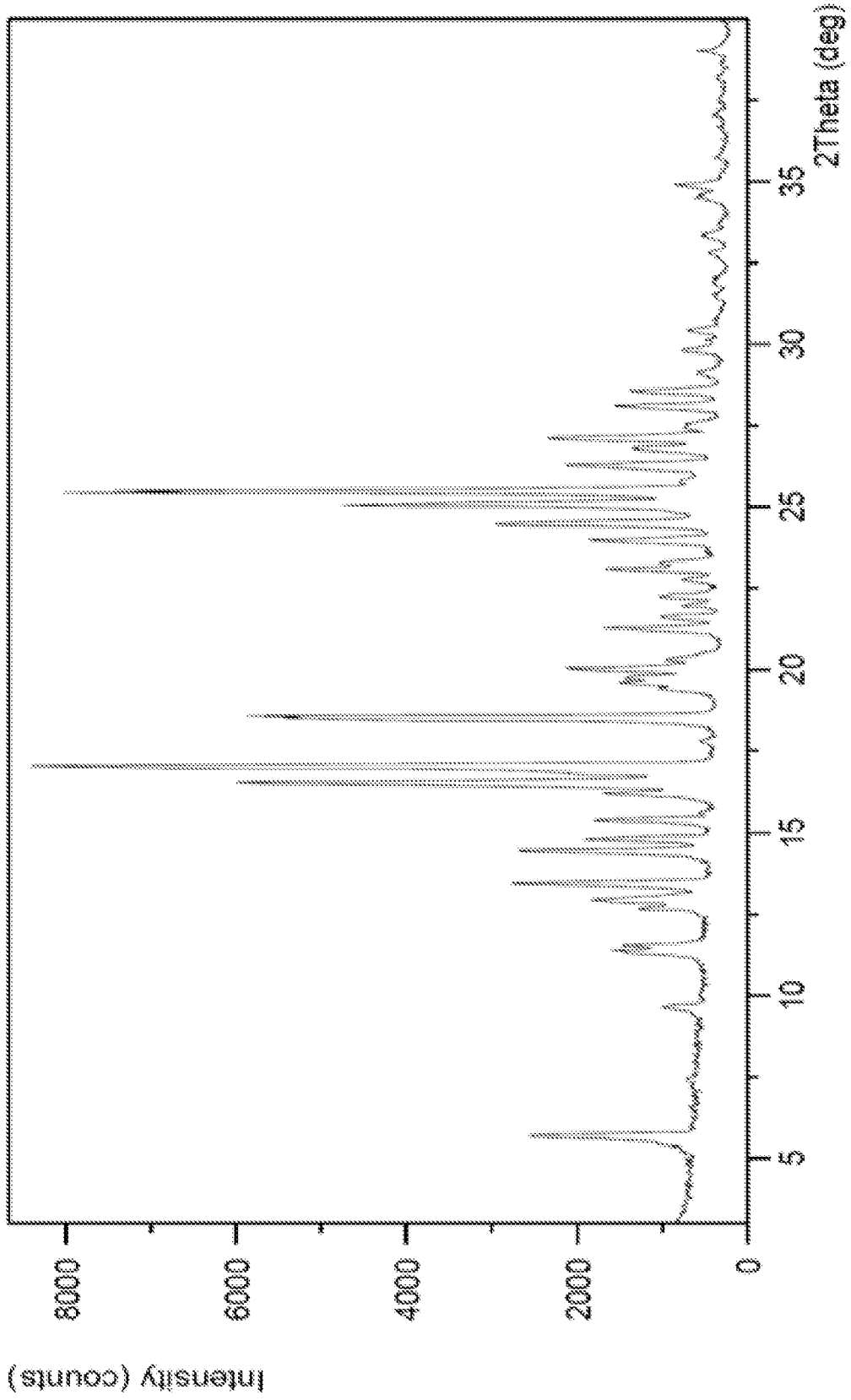

Intensity (counts)
8000
6000
4000
2000
0
5
10
15
20
25
30
35
2Theta (deg)

FIG. 2