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(54) Title: PROCESS FOR THE PREPARATION OF 4-ALKOXY-3-HYDROXYPICOLINIC ACIDS

(57) Abstract: 4-Alkoxy-3-hydroxypicolinic acids may be conveniently prepared from 4,6-dibromo-3-hydroxypicolonitrile in a series of chemical steps selected from bromo substitution, nitrile hydrolysis and halogen reduction that are conducted as a single pot process. 4,6-Dibromo-3-hydroxypicolonitrile may be prepared from furfural in a series of chemical steps selected from cyano-am-
ination, amine salt formation and bromination-rearrangement.



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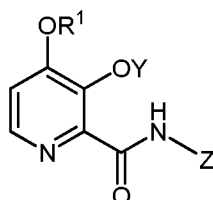
PROCESS FOR THE PREPARATION OF 4-ALKOXY-3-HYDROXYPICOLINIC ACIDS

Field

The present disclosure concerns processes for the preparation of 4-alkoxy-3-hydroxypicolinic acids. More particularly, the present disclosure concerns a process for the preparation of 4-alkoxy-3-hydroxypicolinic acids from furfural.

Background

U.S. Patent 6,521,622 B1 and U.S. Application Serial Number 61/747,723 describe *inter alia* certain heterocyclic aromatic amide compounds of general Formula

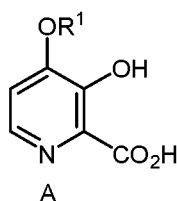


and their use as fungicides.

These disclosures also describe the preparation of 4-alkoxy-3-hydroxypicolinic acids and derivatives thereof as key intermediates in the preparation of these heterocyclic aromatic amide compounds. It would be useful to have an efficient and scalable process route to 4-alkoxy-3-hydroxypicolinic acids from inexpensive raw materials.

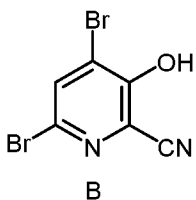
Summary

The present disclosure concerns processes for the preparation of 4-alkoxy-3-hydroxypicolinic acids of Formula A



wherein R¹ is a C₁-C₃ alkyl;

from the compound of Formula B



The compound of Formula A may be prepared in a one-pot process that comprises the following steps:

- 5 a) creating a first mixture containing an alkali metal alkoxide of Formula C



wherein M is Na or K, and R¹ is a C₁-C₃ alkyl;

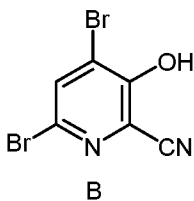
and the compound of Formula B and heating the first mixture;

- 10 b) creating a second mixture by adding water, a strong base, and zinc metal to the first mixture;

c) heating the second mixture; and

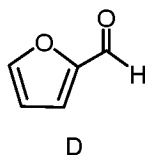
d) isolating the compound of Formula A.

The present disclosure also concerns a process for the preparation of the compound of Formula B



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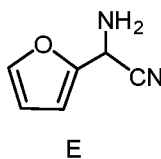
from the compound of Formula D



The compound of Formula B may be prepared in a process that comprises the following steps:

5 a) creating a first mixture by combining together a 2-phase water-organic solvent system, an ammonia source, a cyanide source and the compound of Formula D;

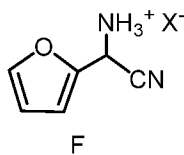
b) separating a second mixture from the first mixture containing the compound of Formula E as a solution in the organic solvent;



10 c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture;

wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄;

d) separating a fourth mixture from the third mixture that is an aqueous mixture containing the compound of formula F;



wherein X is Cl, Br, HSO₄, NO₃ or H₂PO₄;

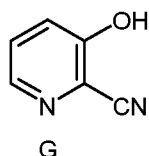
e) adding a brominating agent, selected from the group including:

i) bromine and a bromide compound with an oxidant; and

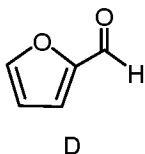
ii) a bromide compound with an oxidant,
to the fourth mixture to form a fifth mixture; and

f) isolating the compound of Formula B from the fifth mixture.

The present disclosure also concerns a process for the preparation of the compound of
5 Formula G



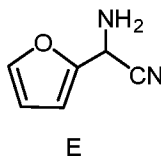
from the compound of Formula D



The compound of Formula G may be prepared in a process that comprises the
10 following steps:

a) creating a first mixture by combining together water, an organic solvent, an ammonia source, a cyanide source and the compound of Formula D;

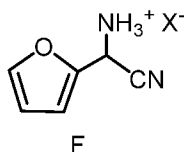
b) separating a second mixture from the first mixture containing the compound of Formula E as a solution in the organic solvent;



c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture;

wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄;

d) separating a fourth mixture from the third mixture that is an aqueous mixture containing the compound of formula F;



wherein X is Cl, Br, HSO₄, NO₃ or H₂PO₄;

5 e) adding a brominating agent that is a bromide compound with an oxidant to the fourth mixture to form a fifth mixture; and

f) isolating the compound of Formula G from the fifth mixture.

Detailed Description

The terms “isolate,” “isolating,” or “isolation” as used herein mean to partially or
10 completely remove or separate the desired product from the other components of a finished chemical process mixture using standard methods such as, but not limited to, filtration, extraction, distillation, crystallization, centrifugation, trituration, liquid-liquid phase separation or other methods known to those of ordinary skill in the art. The isolated product may have a purity that ranges from <50% to > 50%, and may be purified to a higher purity
15 level using standard purification methods. The isolated product may also be used in a subsequent process step with or without purification.

In the process described herein 4-alkoxy-3-hydroxypicolinic acids are prepared from 4,6-dibromo-3-hydroxypicolinonitrile in a series of chemical steps involving bromo
substitution, nitrile hydrolysis, and halogen reduction. The current disclosure describes an
20 improved process for the preparation of 4-alkoxy-3-hydroxypicolinic acids from 4,6-dibromo-3-hydroxypicolinonitrile utilizing a more efficient “one-pot” process.

Also described herein are improved processes for the preparation of 4,6-dibromo-3-hydroxypicolinonitrile from furfural. The processes utilize partial or complete replacement of bromine with a bromide/oxidant pair of reagents that produce bromine *in situ*. Such a process

improvement decreases the need to handle elemental bromine and improves the efficiency of bromine atom utilization.

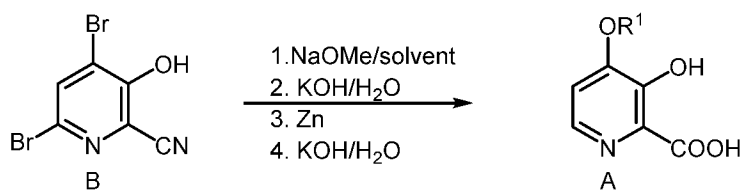
The *in situ* generation of bromine in the preparation of 4,6-dibromo-3-hydroxypicolinonitrile from furfural described herein is equivalent to using elemental bromine and surprisingly, the presence of the oxidant does not negatively impact the Strecker or rearrangement reactions. In addition, it was also surprising that the oxidant did not lead to degradation or oxidation of the pyridine ring or the nitrile group of the 4,6-dibromo-3-hydroxypicolinonitrile.

A. Preparation of Compound of Formula A

An improved process for the preparation of 4-alkoxy-3-hydroxypicolinic acids of Formula A from 4,6-dibromo-3-hydroxypicolinonitrile (compound B) utilizing a more efficient “one-pot” process is described. The process involves treating the compound of Formula B first with a sodium alkoxide, and then with zinc metal, aqueous strong base, and optionally, adding additional aqueous strong base, and finally acidifying the final reaction mixture with aqueous strong acid to produce the compound of Formula A (wherein R¹ is a C₁-C₃ alkyl).

In one embodiment of this process, the reaction of the compound of Formula B with sodium methoxide can be conducted in a dipolar, aprotic solvent such as DMSO or sulfolane, optionally with added methanol, or in methanol as the solvent. Utilizing at least 2 molar equivalents of sodium methoxide, preferably 2.5-3 molar equivalents, and heating at from about 50 to about 80 °C for about 1 hour to about 24 hours the displacement of the 4-bromo group with methoxide is complete. The resulting reaction mixture can then be diluted

Scheme I



with water and a strong, aqueous base, such as potassium hydroxide or sodium hydroxide (2-3 molar equivalents), treated with from about 1 to about 3 molar equivalents of zinc metal (i.e., Zn dust with a particle size of < 10 μm, Zn powder with a particle size of < 150 μm, or

another high surface area Zn solid) and stirred at from about 20 °C to about 70 °C until reduction of the 6-bromo group is complete. Additional strong aqueous base (2-3 molar equivalents) can then be added and the resulting mixture heated at from about 80 °C to about 95 °C for from about 4 to about 24 hours. The desired compound of Formula A (wherein R¹ is methyl) may be isolated by acidifying the reaction mixture and employing standard isolation and purification techniques.

In another embodiment of this process, after the reaction of the compound of Formula B with sodium methoxide is complete, the resulting reaction mixture can then be diluted with water, a strong aqueous base (4-6 molar equivalents), and zinc metal, and then maintained at temperatures ranging from about 20 °C to about 95 °C for from about 2 to about 48 hours. Following completion of the zinc reduction and base hydrolysis reactions, the desired product can be isolated by acidifying the reaction mixture and employing standard isolation and purification techniques.

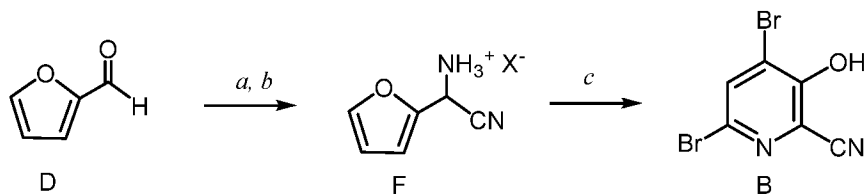
In another embodiment of this process, after the reaction of the compound of Formula B with sodium methoxide is complete, the resulting reaction mixture can then be diluted with water and strong aqueous base (4-6 molar equivalents), and the resulting mixture heated at from about 80 °C to about 95 °C for from about 4 to about 24 hours to complete hydrolysis of the nitrile group. The resulting mixture can then be treated with zinc metal and then maintained at temperatures ranging from about 20 °C to about 70 °C until reduction of the 6-bromo group is complete. Following completion of the zinc reduction and base hydrolysis reactions, the desired product can be isolated by acidifying the reaction mixture and employing standard isolation and purification techniques.

In another embodiment of this process, after the reaction of the compound of Formula B with sodium methoxide is complete, the hydrolysis of the nitrile group and the reduction of the 6-bromo group may be carried out concurrently by adding the water, the strong aqueous base, and the zinc metal (in one portion or by addition over a period of time) to the reaction vessel and heating it from about 80 °C to about 95 °C for the time needed to complete the hydrolysis of the nitrile group and the reduction of the 6-bromo group.

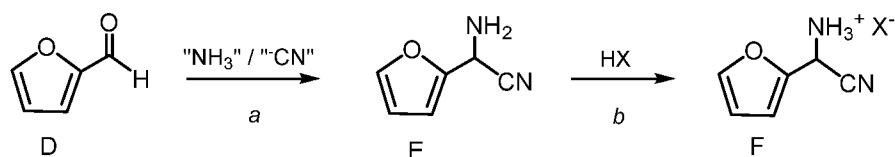
B. Preparation of Compound of Formula B

As shown in Scheme II, furfural (Formula D) can be converted in a process using chemical steps *a*, *b* and *c* into 4,6-dibromo-3-hydroxypicolinonitrile (Formula B). The

Scheme II



cyano(furan-2-yl)methanaminium halide salt of Formula F is prepared in a biphasic process (organic-aqueous, 2-phase solvent system) by first reacting furfural (Formula D) with at least one equivalent each of an ammonia source and a cyanide source (Step *a*) in a reaction

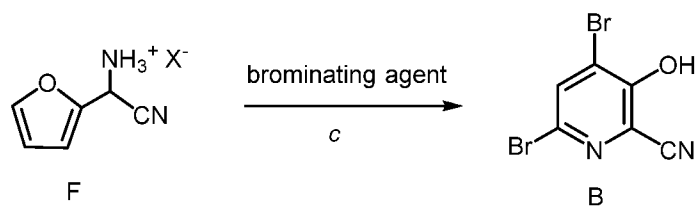


- 10 known in the art as the Strecker synthesis of α -aminonitriles, which is described in *Organic Syntheses*, Coll. Vol. I, page 21 and Coll. Vol. III, pages 84 and 88, to provide the amino(furan-2-yl)acetonitrile of Formula E. Suitable ammonia sources include: ammonium salts such as, but not limited to, ammonium acetate, ammonium bromide, ammonium chloride, ammonium formate, ammonium sulfate and ammonium cyanide; ammonia dissolved in an organic solvent such as, for example, ammonia in methanol, ammonia in ethanol and ammonia in dioxane; ammonia in water (i.e., ammonium hydroxide); and liquid, anhydrous ammonia or gaseous ammonia. Suitable cyanide sources include: cyanide salts such as, but not limited to, sodium cyanide, potassium cyanide and ammonium cyanide; and hydrogen cyanide which may be added in a continuous-addition manner with ammonia to the
- 15 furfural. The reaction (Step *a*) is carried out in a 2-phase solvent system consisting of water and a water immiscible solvent selected from: ethers, such as diethyl ether, methyl t-butyl ether (MTBE), tetrahydrofuran (THF), and 2-methyltetrahydrofuran (2-MeTHF); esters, such as ethyl acetate, and isopropyl acetate; alkanes, such as hexane, cyclohexane, heptane, and
- 20

octane; aromatics, such as anisole, toluene and a xylene or a mixture of xylenes, and mixtures thereof. Such a reaction has been described in WO Application 2000049008, page 55. The present reaction is typically conducted with agitation sufficient to maintain an essentially uniform mixture of the reactants. Such a reaction may be conducted for about 1 to about 50
5 hours at between about 15 °C and about 30 °C.

After the reaction to prepare the amino(furan-2-yl)acetonitrile of Formula E is complete, the organic phase of the 2-phase solvent system containing the compound of Formula E is easily separated from the aqueous phase by standard phase separation and extraction methods. The compound of Formula E, as a solution in the organic phase, is then
10 converted into the salt of Formula F by treatment with an aqueous solution of a mineral acid. Suitable mineral acids include, but are not limited to, hydrobromic acid (HBr), hydrochloric acid (HCl), nitric acid (HNO₃), sulfuric acid (H₂SO₄), and phosphoric acid (H₃PO₄). The present reaction may be conducted at from about 0 °C to about 25 °C. After suitable mixing of the organic phase containing the compound of Formula E and the aqueous solution of the
15 mineral acid, the aqueous acid solution containing the cyano(furan-2-yl)methanaminium halide salt of Formula F is separated from the organic phase by standard phase separation and extraction methods and is ready for the final bromination/rearrangement reaction (Scheme II, Step c) to prepare the compound of Formula B.

In the bromination/rearrangement reaction step of the process, the cyano(furan-2-yl)methanaminium salt of Formula F is treated with a brominating agent, such as bromine, to
20 provide the product of Formula B. The starting material of Formula F, wherein X is Br, Cl,



NO₃, HSO₄, or H₂PO₄, may be treated with a suitable brominating agent. From about 3 to about 6 molar equivalents of bromine may be used. The reaction is preferably conducted
25 using about 3-5 molar equivalents of bromine and the bromide salt of the compound of Formula F (X = Br). It is often convenient to use an excess of the brominating agent such as a 5%, 10% or 15% molar excess, to insure the reaction proceeds to completion. The reaction

is preferably carried out in a protic solvent or reaction medium such as water, or mixtures of water and a water soluble, organic solvent such as, for example, methanol, ethanol, tetrahydrofuran, dioxane or acetonitrile. The temperature at which the reaction is conducted is generally between about 10 °C and about 25 °C. Upon completion of the addition of the
5 bromine, the reaction mixture may be allowed to warm slowly to room temperature and stir for 10-48 hours or the reaction may be heated at about 30-40 °C to complete the reaction. Optionally, the reaction time may be shortened by adding a base, such as, for example, 2-4 molar equivalents of sodium acetate, to the reaction. After the reaction is complete the desired product is recovered by employing standard isolation and purification techniques.

10 In some embodiments of the present disclosure, bromination/rearrangement of the compound of Formula F may involve the use of one or more brominating agents selected from: (1) bromine, and (2) a bromide compound paired with an oxidant. It is known in the literature that bromide compounds such as, for example, HBr, KBr, and NaBr, when combined with an oxidant such as, for example, hydrogen peroxide, potassium
15 peroxymonosulfate (i.e., Oxone®), DMSO or t-butyl hydroperoxide, under appropriate reaction conditions, can produce bromine (this is referred to herein as *in situ* generation of bromine). Use of a bromide compound that is a salt such as, for example, NaBr or KBr, for the *in situ* generation of bromine, also requires the use of an acid for bromine formation). The acid may be selected from the group including HBr, HCl, H₂SO₄, HNO₃, H₃PO₄, acetic
20 acid and mixtures thereof. Such an approach that involves the *in situ* generation of bromine offers the advantage of: limiting or eliminating the use of elemental bromine, improving the bromine atom efficiency of the process, and reducing the formation and disposal of bromide waste streams.

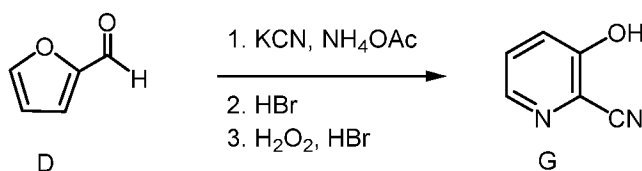
In some embodiments of the present disclosure, use of a bromide compound such as,
25 for example, HBr, KBr, or NaBr paired with an oxidant such as hydrogen peroxide in the process to prepare the compound of Formula B from the compound of Formula F (X = Br) can be conducted by slowly adding the hydrogen peroxide (the oxidant) to the compound of Formula F and the bromide compound (i.e., KBr or NaBr as the bromide compound which requires the use of an acid for *in situ* bromine formation) at ambient temperature and
30 maintaining the temperature at less than about 50 °C during the addition. From about 3-5 molar equivalents of hydrogen peroxide relative to the compound of Formula B may be used

in the presence of a sufficient amount of the bromide compound (2-5 molar equivalents) and an acid in the process.

Chemical literature describing the use of bromide compounds with oxidants to conduct bromination chemistry include: a) "Simple and Practical Halogenation of Arenes, Alkenes, and Alkynes with Hydrohalic Acid/H₂O₂ (or TBHP)," *Tetrahedron*, 55, (1999) 1127-1142, b) "Oxidative Halogenation with "Green" Oxidants: Oxygen and Hydrogen Peroxide," *Angew. Chem. Int. Ed.*, **2009**, 48, 8424, and references therein. Patents describing the generation of bromine from the reaction of bromide salts or HBr with hydrogen peroxide include U.S. 5,266,295, U.S. 4,029,732 and U.S. 2,772,302.

10 C. Preparation of Compound of Formula G

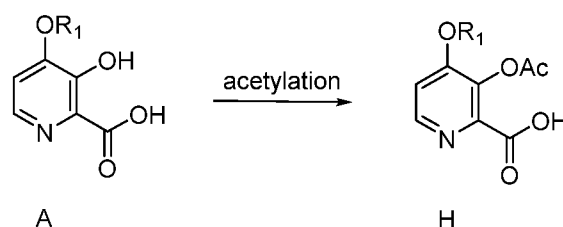
Another embodiment of the present disclosure involves a process for the preparation of the compound of Formula G from furfural. In the first part of this process, furfural is converted into the cyano(furan-2-yl)methanaminium bromide salt of Formula F (X is Br), using the biphasic process as described herein. In the next step of the process, the bromide salt of Formula F is combined with additional aqueous HBr (1.5 equivalents) and then reacted with from about 3 to about 4 molar equivalents of hydrogen peroxide (relative to the bromide salt of Formula F) to provide 3-hydroxy-picolinonitrile (Formula G). The temperature at



which the hydrogen peroxide addition may be conducted is between about 0 °C and about 50 °C. Upon completion of the addition of the hydrogen peroxide, the reaction mixture is allowed to stir at room temperature for about one to about 24 hours. After the reaction is complete, the desired product is recovered by employing standard isolation and purification techniques.

D. Preparation of Compound of Formula H

The conversion of the 4-alkoxy-3-hydroxypicolinic acid of Formula A to the 3-acetoxy compound of Formula H, may be accomplished by acetylating the compound of Formula A with one or more acetylation reagents selected from acetic anhydride and acetyl chloride, bases selected from pyridine, alkyl substituted pyridines, and trialkylamines, or utilization of Schotten-Baumann reaction conditions.

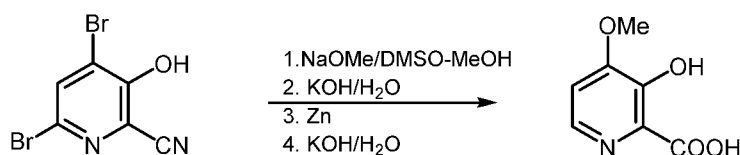


The product obtained by any of these processes, can be recovered by conventional means, such as evaporation, filtration or extraction, and can be purified by standard procedures, such as by recrystallization or chromatography.

The following examples are presented to illustrate the disclosure.

Examples

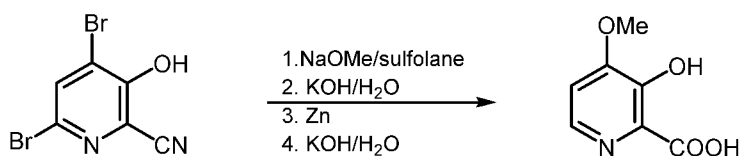
Example 1a. 3-Hydroxy-4-methoxypicolinic acid



A slurry of sodium methoxide (25 g, 0.45 mol) was prepared with 50 mL of anhydrous DMSO and 1 mL of MeOH. To this slurry was added a solution of 4,6-dibromo-3-hydroxy-2-picolonitrile (50 grams, 0.181 mol) and about 50 mL of anhydrous DMSO, which was added over 30 minutes. The reaction was maintained between 50-65 °C during the addition. After the addition was complete, the reaction was allowed to stir for an additional hour at >50 °C. The reaction was determined to be complete by ¹H NMR analysis. The reaction was allowed to cool to 35 °C, and then 100 mL of water, followed by 45 % KOH (40 mL, 468 mmol) were added to the reaction solution. Zinc dust (15.4 g 234 mmol; < 10 micron particle

size) was then added in 5 gram portions at 15 min intervals, which led to a temp rise to about 45 °C. The reaction was allowed to stir overnight at ambient temperature. The reaction was not complete, so the reaction was heated to 50 °C, and then additional Zn dust (4.8 grams, 74 mmol) was added. The reaction was complete after 3 hours. Additional KOH (45 % aqueous, 40 mL, 468 mmol) was added to the reaction mixture. The reaction was then heated at 94 °C for 12 hours to complete the hydrolysis. The reaction was cooled to ambient, and then filtered to remove solids. The solids were washed with about 100 mL of water into the reaction solution. The pH of the combined filtrate and wash solution was then adjusted to 0.4 with 12N HCl. The resulting mixture was allowed to stir for about 1 hour to ensure the pH was stable, and then the solids were collected by filtration. The resulting off-white solids were washed with acetone. The material was dried in a vacuum oven at 50 °C to afford 4-methoxy-3-hydroxypicolinic acid as a very pale yellow powder (19.22 g, 63.2% yield with 96 % purity, which equates to 60.7 % yield). The organic purity was 99.75% as determined by HPLC. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.03 (d, *J* = 6.4 Hz, 1H), 7.39 (d, *J* = 6.4 Hz, 1H), 4.04 (s, 3H).

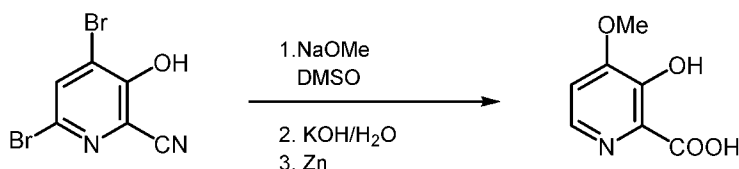
Example 1b. 3-Hydroxy-4-methoxypicolinic acid



Neat sodium methoxide (14.7 g, 271 mmol) was added to a solution of 4,6-dibromo-3-hydroxypicolinonitrile (30.2 g, 109 mmol) and sulfolane (120 g) over a 30 minute period, which led to a temperature rise to 50 °C. The reaction was then heated at 60 °C for 18 hours. The reaction solution was allowed to cool to ambient temperatures, and then 150 mL of DI water was added to the reaction, followed by 50 mL of 45 wt % KOH (5.4 equiv, 586mmol). Zn dust (113 mmol, 7.5grams) was added, and then the reaction was heated to 40 °C. After 2 hours, additional Zn dust (2.5 grams, 38 mmol) was added, and then the reaction was heated to 60 °C for an additional 2 hours. The reaction was allowed to stir overnight at ambient. ¹H NMR analysis of the reaction mixture indicated that the debromination was complete. The reaction was filtered to remove solids, 45 % KOH (50 mL, 596 mmol) was added to the filtrate, and then the resulting solution was heated to about 90 °C. The reaction

was allowed to stir at about 90 °C for 5.5 h, which resulted in near complete conversion. The reaction was allowed to stir at about 90 °C overnight. The reaction mixture was cooled to < 30 °C, and then the pH was adjusted to 0.8 with 40 % sulfuric acid, which led to the formation of solids. The solids were isolated by filtration and then dried to yield a solid, which was greater than a 100 % yield. The material was slurried overnight in 0.5 pH hydrochloric acid. The material was then isolated by filtration and drying to afford 10.3 grams of 4-methoxy-3-hydroxypicolinic acid as an off-white powder, which was determined to be 94 % pure by HPLC (53 % yield).

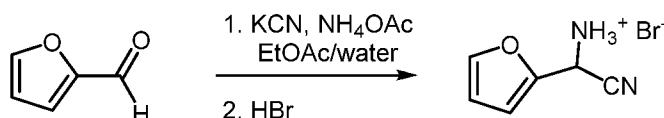
Example 1c. 3-Hydroxy-4-methoxypicolinic acid



A 500 mL 3-neck flask was charged with sodium methoxide (25 g, 0.462 mol) and 25 mL of dimethyl sulfoxide. The sodium methoxide/DMSO mixture was placed under inert gas and mechanically stirring to create a free flowing slurry. A solution of 4,6-dibromo-3-hydroxypicolinonitrile (50.3 grams, 0.181 mol, DBHP, 96.2 wt % purity) in about 25 mL of anhydrous DMSO was prepared in a separate vessel. The DBHP solution was added to the sodium methoxide/DMSO mixture over 50 minutes *via* a syringe pump. The temperature was maintained below 60 °C during the addition. After the addition was complete, the reaction was allowed to stir for an additional hour. During that time the reaction mixture solidified. 100 mL of water followed by 50 % KOH (50 mL, 941 mmol) were added to the solidified reaction mixture. The resulting mixture was stirred for about 1.5 hours to break up the solids into a thick slurry. Zn dust (14.8 g, 226 mmol) was then added in about 5 gram portions about 20 minutes apart, which led to a temperature rise to about 40 °C. Over the course of the Zn digestion, the reaction thinned into an easily mixed slurry. The reaction was allowed to stir overnight at ambient temperature. The reaction was then heated up to 95 °C for 24 hours. The reaction was cooled to <20 °C, and then the pH of the solution was adjusted to 0.6 with aqueous HCl (12 N), which resulted in the precipitation of the product. The solids were isolated by filtration, washing with about 50 mL of water, and then

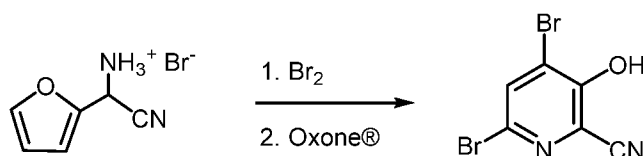
washed with about 25 mL of acetone. The resulting slightly yellow powder was allowed to dry in the hood, which led to 23.3 grams of product. The product was 96 % pure as determined by ^1H NMR (versus internal standard), which equated to a 76 % yield of the desired product based on the purity of the starting material and final product. ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 (d, J = 6.4 Hz, 1H), 7.39 (d, J = 6.4 Hz, 1H), 4.04 (s, 3H).

Example 1d. Cyano(furan-2-yl)methanaminium bromide

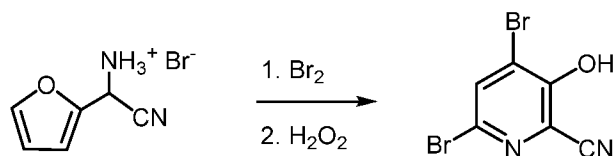


To an 500 mL flask outfitted with a stir bar was added 33.65 grams of ammonium acetate (436 mmol), 150 mL of ethyl acetate, 30 mL of DI water, and 10 grams of KCN (154 mmol). Furfural (14 g, 145 mmol) was then added to the reactor via syringe. The temperature in the reactor increased from about 15 °C to 24 °C. The reaction was allowed to stir overnight at ambient. ^1H NMR analysis of the ethyl acetate phase showed that the conversion was > 95 % complete. 75 mL of 20 % aqueous sodium carbonate was added to the reactor and allowed to stir for 10 minutes. The sodium carbonate solution was removed and then the reaction mixture was washed with 40 mL of saturated brine. ^1H NMR (400 MHz, DMSO- d_6) δ 7.53 (dd, J = 2.0, 1.0 Hz, 1H), 6.47 (dd, J = 3.4, 1.1 Hz, 1H), 6.42 (dd, J = 3.3, 1.7 Hz, 1H), 5.08 (s, 1H).

After removal of the brine phase, 24.5 mL of aqueous 48% HBr (1 equiv., 145 mmol) diluted in about 130 ml of DI water was added to the reaction. The reaction was mixed for 15 minutes. The aqueous layer was removed and placed in a separate vessel. The organic layer was then washed with 2 x 25 mL of DI water. Each wash was added to the holding vessel with the initial HBr extracted phase. A total of 210.5 grams of aqueous phase was obtained containing about 14.06 wt % of cyano(furan-2-yl)methanaminium bromide.

Example 1e. 4,6-Dibromo-3-hydroxypicolinonitrile

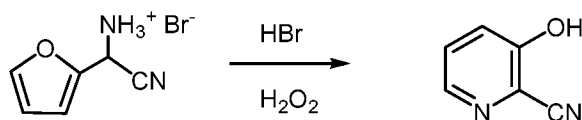
52.5 g of the aqueous phase containing 7.38 g (36 mmol) of cyano(furan-2-yl)methanaminium bromide (14.06 wt% in water) was placed into a 250 mL flask outfitted with a stir bar. The flask was then placed in an ice bath. After cooling to <10 °C, 5.8 g of bromine (36 mmol) was then added to the reaction drop wise over 15 minutes resulting in the formation of solids. After stirring for 1 h the reaction was allowed to warm to ambient temperature. Oxone® (27 g, 87.8 mmol) was added to the reaction in portions resulting in the dissolution of the solids and a reddish brown liquid phase, which slowly converted to round pellet-like material after stirring for 1 h. The reaction was quenched with saturated, aqueous sodium bisulfite. The solids were then isolated by filtration, washed with DI water, and then dried overnight to yield 6.25 grams of a tan powder. ¹H NMR analysis indicated that the product consisted of 4,6-dibromo-3-hydroxypicolinonitrile (96.6 mol %, 60.3 % yield) and 6-bromo-3-hydroxypicolinonitrile (3.4 mol %, 2.2 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 1.00H), 7.75 (d, *J* = 8.9 Hz, 0.034H), 7.44 (d, *J* = 8.9 Hz, 0.034H). HRMS (*m/z*) Positive Ion mode [*M*+1] calcd for C₆H₃Br₂N₂O 276.8612; found 276.8611.

Example 1f. 4,6-Dibromo-3-hydroxypicolinonitrile

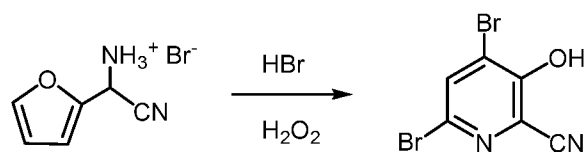
52.5 g of the aqueous phase containing 7.38 g (36 mmol) of cyano(furan-2-yl)methanaminium bromide (14.06 wt% in water) was placed into a 250 mL flask outfitted with a stir bar. The flask was then placed in an ice bath. After cooling to <10 °C, 5.8 g of bromine (36 mmol) was then added to the reaction drop wise over about 15 minutes resulting in the formation of solids. After stirring for 1 h, 30% hydrogen peroxide (9.4 mL) was added to the reaction via syringe over 20-30 minutes. This resulted in the dissolution of the solids and then precipitation of a fine powder over a 1-2 hour period. The reaction was quenched

with saturated sodium bisulfite. The solids were then isolated by filtration, washed with DI water, and then dried overnight to yield 6.03 grams of a tan powder. ^1H NMR analysis indicated that the product consisted of 4,6-dibromo-3-hydroxypicolinonitrile (94.5 mol %, 57.3 % yield) and 6-bromo-3-hydroxypicolinonitrile (5.5 mol %, 3.2 % yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.27 (s, 1.00H), 7.75 (d, J = 8.9 Hz, 0.075H), 7.44 (d, J = 8.9 Hz, 0.075H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 157.65, 141.95, 135.55, 128.76, 124.37, 120.34, 115.97. HRMS (m/z) Positive Ion mode $[\text{M}+1]$ calcd for $\text{C}_6\text{H}_3\text{Br}_2\text{N}_2\text{O}^+$ 276.8612; found 276.8609.

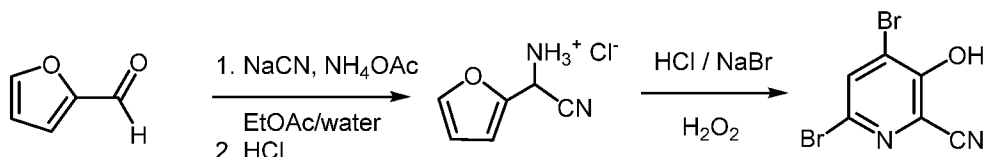
Example 1g. 3-Hydroxypicolinonitrile



52.5 g of the aqueous phase containing 7.38 g (36 mmol) of cyano(furan-2-yl)methanaminium bromide (14.06 wt% in water) was placed into a 250 mL flask outfitted with a stir bar. 48 % HBr (6.2 mL, 55 mmol) was added to the flask with stirring. The flask was then placed in an ice bath. After cooling to $<5^\circ\text{C}$, about 7 mL of 30% hydrogen peroxide was added to the reaction *via* syringe over 20-30 minutes. This resulted in very little heat evolution. The reaction was allowed to warm to ambient temperature, at which point the reaction started to self heat to about 50°C . The reaction was cooled to 20°C , and then 7 mL of 30 % peroxide was added, which resulted in the formation of a precipitate. The reaction was allowed to stir for about 20 min and then the reaction was quenched with saturated sodium bisulfite, which resulted in a temperature rise to about 40°C . During the temp rise, the solids dissolved. The reaction was then placed in an ice bath. After stirring for about 45 minutes, solids developed. The solids were collected by filtration and washed with DI water. 3-Hydroxypicolinonitrile (1.63 grams) was isolated as a tan crystalline solid (37.3 % yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 11.67 (s, 1H), 8.19 (dd, J = 4.4, 1.3 Hz, 1H), 7.56 (dd, J = 8.6, 4.4 Hz, 1H), 7.47 (dd, J = 8.7, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 157.67, 141.93, 135.56, 128.75, 125.99, 124.37, 120.34, 115.97. HRMS (m/z) Negative Ion mode $[\text{M}-1]$ calcd for $\text{C}_6\text{H}_4\text{N}_2\text{O}$ 119.0246; found 119.0240.

Example 1h. 4,6-Dibromo-3-hydroxypicolinonitrile

53 g of the aqueous phase containing 7.45 g (37 mmol) of cyano(furan-2-yl)methanaminium bromide (14.06 wt% in water) was placed into a 250 mL flask outfitted with a stir bar. 48 % HBr (8.2 mL, 73 mmol) was added to the flask with stirring. The flask was placed in an ice bath. After cooling to <5 °C, 6 to 7 mL of 30% hydrogen peroxide was added to the reaction via syringe over 20-30 minutes. This resulted in very little heat evolution. The reaction was allowed to warm to ambient temperature, at which point the reaction started to self heat to about 46-48 °C and became yellow orange in color (homogeneous). The reaction was cooled to 20 °C, and then another 7 mL of the 30 % hydrogen peroxide was added via syringe over 15-20 minutes, which resulted in the formation of a precipitate. The reaction was allowed to stir overnight. The reaction was quenched with sodium bisulfite to yield a slightly yellow solution with solids. Peroxide test strips indicated no residual peroxides. The solids were collected by filtration, washed with water, and dried to yield 6.22 grams of a light tan powder. ¹H NMR analysis indicated that the product consisted of 4,6-dibromo-3-hydroxypicolinonitrile (58.1 % yield) and 6-bromo-3-hydroxypicolinonitrile (3.8 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 1.00H), 7.75 (d, *J* = 8.9 Hz, 0.064H), 7.44 (d, *J* = 8.9 Hz, 0.064H).

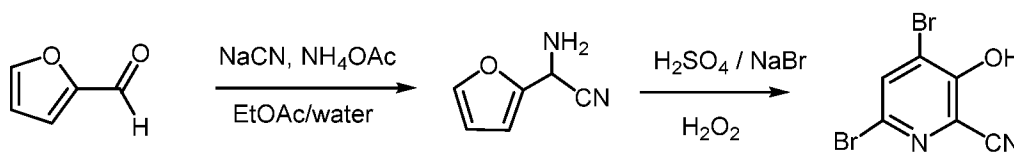
Example 1i. 4,6-Dibromo-3-hydroxypicolinonitrile

A stock solution of cyano(furan-2-yl)methanaminium chloride was prepared using 39.21 grams of furfural, 20 grams of sodium cyanide, 96 grams of ammonium acetate in 300 mL of ethyl acetate and 260 mL of water. After formation of the α-aminonitrile, 75 mL of saturated sodium carbonate was added to the mixture and allowed to mix for 20-30 minutes. The aqueous phase was removed and then the organic phase was subsequently washed with 2

x 50 mL of saturated aqueous brine. 34 mL of aqueous 12 N HCl (1 equiv., 408 mmol) diluted in about 260 ml of DI water was added to the organic phase. The resulting mixture was mixed (>500 rpm) for 15 minutes. After settling, the aqueous layer containing the cyano(furan-2-yl)methanaminium chloride was removed and placed in a plastic holding
 5 vessel to form a stock solution. The organic layer was then extracted with 44 mL of DI water, followed by 46 mL of DI water. Each aqueous extract was placed in the holding vessel resulting in about 460 g of aqueous phase. The aqueous phase was diluted to a total of 480 grams which contained about 64.70 g (13.5 wt%) of the cyano(furan-2-yl)methanaminium chloride.

10 60 grams of the stock solution containing about 8.1 g (51 mmol of cyano(furan-2-yl)methanaminium chloride) was placed into a 250 mL RB flask with a stir bar. About 4.2 mL (50.4 mmol) of 12N HCl and 10.4 g (101 mmol) of NaBr were added to the flask. 30 % hydrogen peroxide (20 g, 176 mmol) was added dropwise over 50 minutes to the flask. Over a 25 min period during the addition (about 7.5 g of peroxide had been added), the reaction
 15 self heated to 56 °C, at which point the reaction was cooled to about 36 °C. After 40 minutes, solids began to form. The reaction was allowed to stir for an additional 6 hours. The solids were collected by filtration, washed with DI water, and then dried. 6.28 grams of a free flowing, light tan powder was obtained as a mixture of 4,6-dibromo-3-hydroxypicolinonitrile (39.1 wt % yield), 6-bromo-3-hydroxypicolinonitrile (3.0 wt % yield), 6-chloro-3-hydroxy-
 20 picolinonitrile (6.23 wt % yield), and one of the 4/6-chloro/bromo-3-hydroxypicolinonitrile isomers (0.4 wt % yield) as determined by ¹H NMR. A total yield of 51 % was observed. ¹H NMR (400 MHz, DMSO-*d*₆) of the desired product: δ 8.27 (s, 1.00H), δ 8.18 (s, 0.11H), δ 7.75 (d, *J* = 8.9 Hz, 0.64H), 7.65 (d, *J* = 8.9 Hz, 0.01H), 7.53 (d, *J* = 8.9 Hz, 0.01H), 7.44 (d, *J* = 8.9 Hz, 0.064H).

25 Example 1j. 4,6-Dibromo-3-hydroxypicolinonitrile

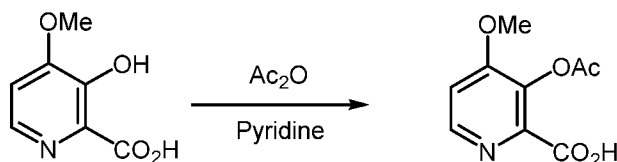


To a 500 mL flask outfitted with a stir bar was added 36 grams of ammonium acetate (467 mmol), 200 mL of ethyl acetate, and 7.5 grams of NaCN (153 mmol). 75 mL of water

was utilized to wash the residual sodium cyanide into the flask and out of the funnel. Furfural (12.7 mL, 14.7 grams, 153 mmol) was then quickly added to the reactor *via* syringe. The temperature in the reactor increased from about 15 °C to 24 °C. The reaction was allowed to stir overnight at ambient temperature (18 °C). The agitation was turned off to allow the two liquid phases to separate. The organic phase was then sampled for ¹H NMR analysis and the reaction was determined to be only about 80 % complete. The reaction was then stirred at 25 °C (using a water bath) for an additional 6 hours. The reaction was shown to be about 90 % complete by ¹H NMR. 75 mL of 20 % aqueous sodium carbonate was added to the reactor and allowed to stir for 30 minutes, and then the mixture was allowed to sit without stirring for 20-30 min. The aqueous phase was removed and then the organic phase containing the α-aminonitrile of furfural in ethyl acetate was washed with 2x50 mL of saturated brine.

10 N sulfuric acid (15 mL, 1 equivalent, 153 mmol) was diluted in about 225 ml of DI water. The ethyl acetate solution containing the α-aminonitrile of furfural was extracted with the diluted sulfuric acid solution in about 1/3 portions. Each extraction was placed into a 500 mL RB with a stir bar. The organic solution was extracted with an additional 5 mL of DI water. To the combined aqueous acid extracts was added 47 g of sodium bromide (459 mmol) and then hydrogen peroxide (30 %, 360 mmol) was added over a 2 hour period, which resulted in a temperature rise from 19 °C to about 50 °C. The reaction was allowed to stir overnight. ¹H NMR analysis indicated that the reaction was a 1:1 mixture of 6-bromo-3-hydroxypicolinonitrile and 4,6-dibromo-3-hydroxypicolinonitrile. An additional 15 mL of 10 N sulfuric acid and 13.5 grams of 30 % peroxide (107 mmol) was added to the reaction solution and the reaction was heated to 45 °C. After 2 hours, the reaction was complete as indicated by ¹H NMR analysis. The solids were collected by filtration, washed with water, and dried to yield 21.9 grams of a light tan powder. ¹H NMR analysis indicated that the powder consisted of 4,6-dibromo-3-hydroxypicolinonitrile (49.8 % yield) and 6-bromo-3-hydroxypicolinonitrile (2.4 % yield).

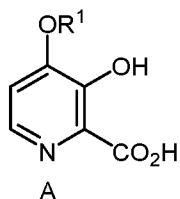
Example 1k. 3-(Acetyloxy)-4-methoxypicolinic acid



3-Hydroxy-4-methoxypicolinic acid (5.0 g, 29.6 mmol) was slurried in 50 mL of pyridine and 50 mL of acetic anhydride at ambient temperature. After 1h, a yellow solution had formed which was then stirred overnight. The solution was evaporated at 45 °C (2 mm Hg) to give 6.28 g of tan solid (99% yield, mp = 132 – 134 °C). ¹H NMR (400 MHz, DMSO-
5 *d*₆) δ 13.32 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H), 7.40 (d, J = 5.5 Hz, 1H), 3.91 (s, 3H), 2.27 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.95, 164.81, 158.34, 147.87, 142.77, 136.18, 110.87, 56.59, 20.27. HRMS (*m/z*) calcd for C₉H₉NO₅ 211.0478, found 211.0481 ([M]⁺).

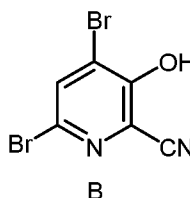
WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of Formula A



wherein R¹ is a C₁-C₃ alkyl;

- 5 from a compound of Formula B



which comprises the following steps:

- a) creating a first mixture containing an alkali metal alkoxide of Formula C



- 10 wherein M is Na or K, and R¹ is C₁-C₃ alkyl;

and the compound of Formula B and heating the first mixture;

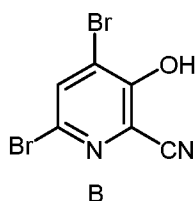
- b) creating a second mixture by adding water, a strong base, and zinc metal to the first mixture;

- c) heating the second mixture; and

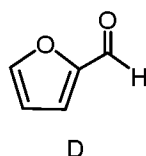
- 15 d) isolating the compound of Formula A.

2. The process of Claim 1 wherein M is Na and R¹ is methyl.

3. The process of Claim 1 wherein the first mixture further comprises a solvent selected from the group including DMSO, methanol, sulfolane, and mixtures thereof.
4. The process of Claim 1 wherein the strong base is selected from sodium hydroxide or potassium hydroxide.
- 5 5. The process of Claim 1 further including a step for removing zinc salts or zinc metal from the second mixture prior to heating the second mixture.
6. A process for the preparation of a compound of Formula B



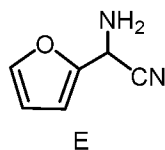
from a compound of Formula D



which comprises the following steps:

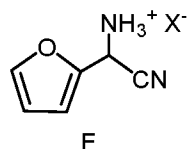
a) creating a first mixture by combining together a 2-phase water-organic solvent system, an ammonia source, a cyanide source and the compound of Formula D;

b) separating a second mixture from the first mixture containing a compound of Formula E as a solution in the organic solvent;



c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄;

d) separating a fourth mixture from the third mixture that is an aqueous mixture containing a compound of Formula F;



wherein X is Cl, Br, HSO₄, NO₃ or H₂PO₄;

5 e) adding a brominating agent including bromine, a bromide compound with an oxidant, and mixtures thereof to the fourth mixture to form a fifth mixture; and

f) isolating the compound of Formula B from the fifth mixture.

7. The process of Claim 6 wherein the organic solvent is selected from the group including, MTBE, ethyl acetate, isopropyl acetate, THF, 2-MeTHF, toluene, a xylene or a
10 mixture of xylenes, and mixtures thereof.

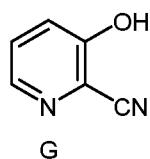
8. The process of Claim 6 wherein the mineral acid is hydrobromic acid.

9. The process of Claim 6 wherein X is Br.

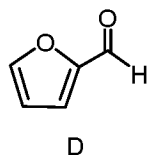
10. The process of Claim 6 wherein the bromide compound is hydrobromic acid or a bromide salt selected from NaBr and KBr in combination with an acid.

15 11. The process of Claim 6 wherein the oxidant is selected from hydrogen peroxide and potassium peroxymonosulfate.

12. A process for the preparation of a compound of Formula G



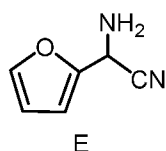
from a compound of Formula D



which comprises the following steps:

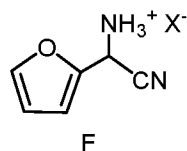
5 a) creating a first mixture by combining together a 2-phase water-organic solvent system, an ammonia source, a cyanide source and the compound of Formula D;

b) separating a second mixture from the first mixture containing the compound of Formula E as a solution in the organic solvent;



10 c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄;

d) separating a fourth mixture from the third mixture that is an aqueous mixture containing a compound of Formula F;



wherein X is Cl, Br, HSO₄, NO₃ or H₂PO₄;

15 e) adding a brominating agent including a bromide compound with an oxidant to the fourth mixture to form a fifth mixture; and

f) isolating the compound of Formula G from the fifth mixture.

13. The process of Claim 12 wherein the organic solvent is selected from the group including MTBE, ethyl acetate, isopropyl acetate, THF, 2-MeTHF, toluene, a xylene or a mixture of xylenes, and mixtures thereof.

14. The process of Claim 12 wherein the mineral acid is hydrobromic acid.

5 15. The process of Claim 12 wherein X is Br.

16. The process of Claim 12 wherein the bromide compound is hydrobromic acid or a bromide salt selected from NaBr and KBr in combination with an acid.

17. The process of Claim 12 wherein the oxidant is selected from hydrogen peroxide and potassium peroxymonosulfate.

10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/014532

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/40; A01N 37/34; C07D 213/00; C07D 213/84; C07D 405/00 (2017.01)

CPC - C07D 213/803; A01N 37/34; A61K 31/44; C07D 213/79; C07D 307/54 (2017.02)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0009649 A1 (DOW AGROSCIENCES LLC) 14 January 2016 (14.01.2016) entire document	1-4
A	US 2016/0009647 A1 (DOW AGROSCIENCES LLC) 14 January 2016 (14.01.2016) entire document	1-5

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2017

Date of mailing of the international search report

19 MAY 2017

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/014532

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2017/014532

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-5 are drawn to processes for the preparation of a compound of Formula A.

Group II: claims 6-11 are drawn to processes for the preparation of a compound of Formula B.

Group III: claims 12-17 are drawn to processes for the preparation of a compound of Formula G.

The inventions listed in Groups I, II, and III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, processes for the preparation of a compound of Formula A, are not present in Groups II and III; the special technical features of Group II, processes for the preparation of a compound of Formula B, are not present in Groups I and III; and the special technical features of Group III, processes for the preparation of a compound of Formula G, are not present in Groups I and II.

The Groups I, II, and III share the technical features of a compound of Formula B; and a process for the preparation of a compound of Formula G from a compound of Formula D; which comprises the following steps: a) creating a first mixture by combining together a 2-phase water-organic solvent system, an ammonia source, a cyanide source and the compound of Formula D; b) separating a second mixture from the first mixture containing the compound of Formula E as a solution in the organic solvent; c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄; d) separating a fourth mixture from the third mixture that is an aqueous mixture containing a compound of Formula F; e) adding a brominating agent including a bromide compound with an oxidant to the fourth mixture to form a fifth mixture; and f) isolating the compound of Formula G or a compound of Formula B from the fifth mixture. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2016/0009649 A1 to Dow Agrosciences LLC teaches a compound of Formula B (Para. [0005], Compound A;...see shown structure...); and a process for the preparation of a compound of Formula G from a compound of Formula D (Para. [0006]); which comprises the following steps: a) creating a first mixture by combining together a 2-phase water-organic solvent system, an ammonia source, a cyanide source and the compound of Formula D (Para. [0006]); b) separating a second mixture from the first mixture containing the compound of Formula E as a solution in the organic solvent (Paras. [0006] and [0010]); c) adding an aqueous solution of a mineral acid to the second mixture to form a third mixture wherein the mineral acid is HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄ (Paras. [0006] and [0010]); d) separating a fourth mixture from the third mixture that is an aqueous mixture containing a compound of Formula F (Paras. [0006] and [0010]); e) adding a brominating agent including a bromide compound with an oxidant to the fourth mixture to form a fifth mixture F (Paras. [0006], [0010], [0023], and [0026]); and f) isolating the compound of Formula G or a compound of Formula B from the fifth mixture (Paras. [0006], [0010], [0023], [0026]; Paras. [0046] through [0048]).

The inventions listed in Groups I, II, and III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.