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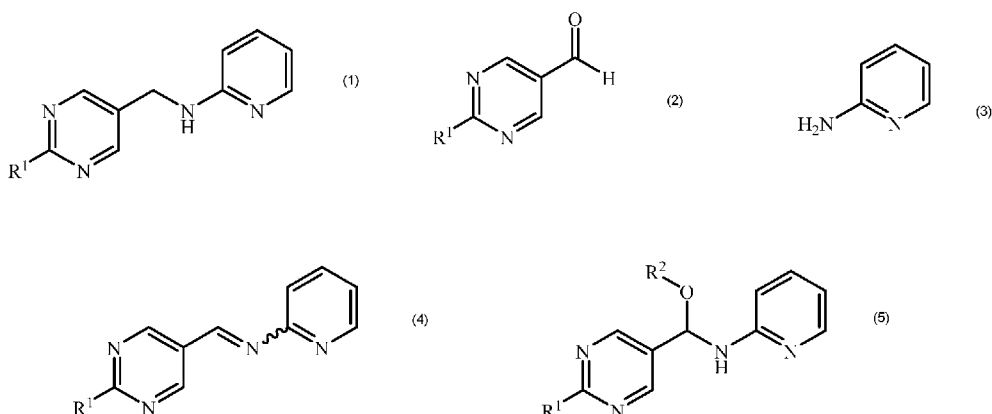
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(54) Title: PROCESS FOR THE PREPARATION OF *N*-[5-PYRIMIDINYL]METHYL-2-PYRIDINAMINES



(57) Abstract: Disclosed is a method for preparing a compound of Formula (1) wherein R^1 is H or C1-C3 alkyl, and the use of a compound of Formula (1) in a method for preparing mesoionic compounds, comprising: (A) contacting a compound of Formula (2) with 2-aminopyridine (3) in the presence of an inert solvent, optionally in the presence of an acid catalyst, to form a compound of Formula (4) (B) contacting the compound of Formula (4) with an alcohol R^2OH to form a compound of Formula (5) in the presence of an inert solvent wherein R^2 is C1-C4 alkyl; and (C) contacting the compound of Formula (5) with a borohydride reducing agent in the presence of an inert solvent to form a reaction mixture comprising the compound of Formula (1).

TITLEPROCESS FOR THE PREPARATION OF *N*-[(5-PYRIMIDINYL)METHYL]-2-PYRIDINAMINES

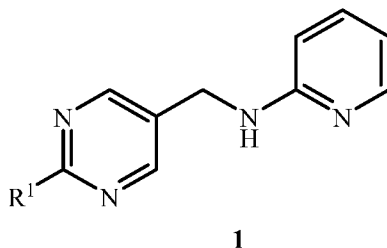
This invention relates to a method for preparing *N*-[(5-pyrimidinyl)methyl]-2-pyridinamines.

BACKGROUND OF THE INVENTION

A method for preparing *N*-[(5-pyrimidinyl)methyl]-2-pyridinamine and its utility as an intermediate for preparing the insecticide triflumezopyrim (2,4-dioxo-1-(5-pyrimidinylmethyl)-3-[3-(trifluoromethyl)phenyl]-2*H*-pyrido[1,2-*a*]pyrimidinium inner salt, CAS Registry No. 1263133-33-0) is described in PCT Patent Application Publication WO 2012/092115. There is a need for new or improved methods for the preparation of *N*-[(5-pyrimidinyl)methyl]-2-pyridinamines.

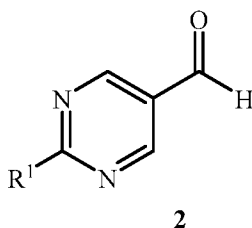
SUMMARY OF THE INVENTION

The present invention provides a method for preparing a compound of Formula 1

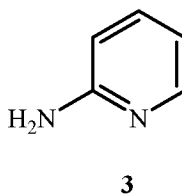


wherein R¹ is H or C₁-C₃ alkyl, comprising:

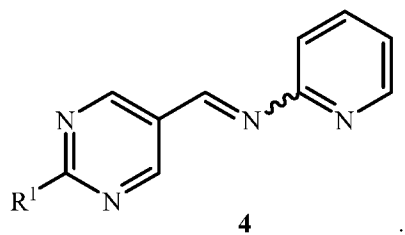
(A) contacting a compound of Formula 2



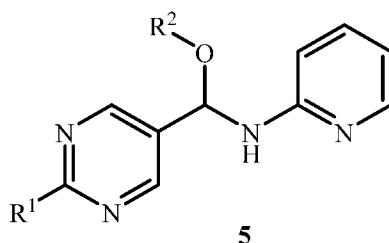
with 2-aminopyridine (3)



in the presence of an inert solvent S1, optionally in the presence of an acid catalyst, to form a compound of Formula 4



(B) contacting the compound of Formula 4 with an alcohol R²OH to form a compound of Formula 5 in the presence of an inert solvent S2

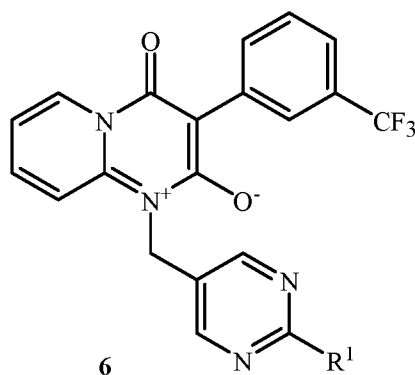


wherein R² is C₁-C₄ alkyl; and

(C) contacting the compound of Formula 5 with a borohydride reducing agent in the presence of an inert solvent S3 to form the compound of Formula 1.

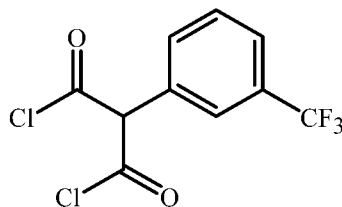
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This invention also relates to a method for preparing a compound of Formula 6



wherein R¹ is H or C₁-C₃ alkyl,

comprising contacting a compound of Formula 1 with the compound (7),



15

wherein the compound of Formula 1 is prepared by the method described above.

DETAILS OF THE INVENTION

As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,”
5 “having,” “contains,” “containing,” “characterized by” or any other variation thereof, are
intended to cover a non-exclusive inclusion, subject to any limitation explicitly indicated.
For example, a composition, mixture, process, method, article, or apparatus that comprises a
list of elements is not necessarily limited to only those elements but may include other
elements not expressly listed or inherent to such composition, mixture, process, method,
10 article, or apparatus.

The transitional phrase “consisting of” excludes any element, step, or ingredient not
specified. If in the claim, such phrase would close the claim to the inclusion of materials
other than those recited except for impurities ordinarily associated therewith. When the
phrase “consisting of” appears in a clause of the body of a claim, rather than immediately
15 following the preamble, it limits only the element set forth in that clause; other elements are
not excluded from the claim as a whole.

Where applicants have defined an invention or a portion thereof with an open-ended
term such as “comprising,” it should be readily understood that (unless otherwise stated) the
description should be interpreted to also describe such an invention using the terms
20 “consisting essentially of” or “consisting of.”

Further, unless expressly stated to the contrary, “or” refers to an inclusive or and not to
an exclusive or. For example, a condition A or B is satisfied by any one of the following: A
is true (or present) and B is false (or not present), A is false (or not present) and B is true (or
present), and both A and B are true (or present).

25 Also, the indefinite articles “a” and “an” preceding an element or component of the
invention are intended to be nonrestrictive regarding the number of instances (i.e.
occurrences) of the element or component. Therefore “a” or “an” should be read to include
one or at least one, and the singular word form of the element or component also includes the
plural unless the number is obviously meant to be singular.

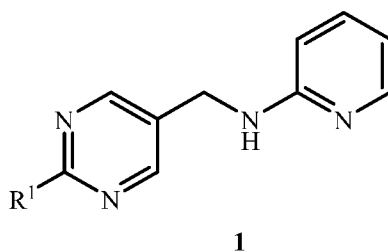
30 The term “ambient temperature” or “room temperature” as used in this disclosure
refers to a temperature between about 18 °C and about 28 °C.

In the above recitations, the term “alkyl”, includes straight-chain or branched alkyl,
such as, methyl, ethyl, *n*-propyl, *i*-propyl, or the different butyl isomers. As used herein,
haloalkanes are alkanes partially or fully substituted with halogen atoms (fluorine, chlorine,
35 bromine or iodine). Examples of haloalkanes include CH₂Cl₂, ClCH₂CH₂Cl,
ClCH₂CH₂CH₂CH₃, and CCl₃CH₃. Halogenated benzenes are benzenes partially or fully
substituted with halogen atoms (fluorine, chlorine, bromine or iodine). Examples of
halogenated benzenes include chlorobenzene, 1,2-dichlorobenzene and bromobenzene. C₇-

C₁₀ aromatic hydrocarbons are compounds containing one benzene ring which is substituted with alkyl groups. Examples of C₇-C₁₀ aromatic hydrocarbons include toluene, xylenes, ethyl benzene and cumene (*iso*-propylbenzene). C₅-C₁₀ aliphatic hydrocarbons are straight-chain or branched hydrocarbons. Examples of C₅-C₁₀ aliphatic hydrocarbons include *n*-hexane, mixed hexanes, *n*-heptane and mixed heptanes. C₅-C₁₀ cycloaliphatic hydrocarbons are cyclic hydrocarbons that can be substituted with straight-chain or branched alkyl groups. Examples of C₅-C₁₀ cycloaliphatic hydrocarbons include cyclopentane, methylcyclopentane, cyclohexane and methylcyclohexane.

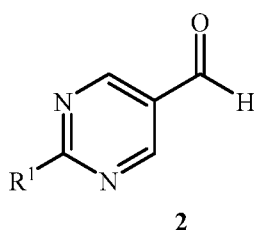
10 Embodiments of the present invention include:

Embodiment 1. A method of preparing a compound of Formula 1

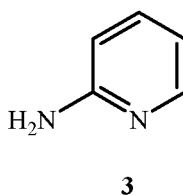


wherein R¹ is H,
comprising:

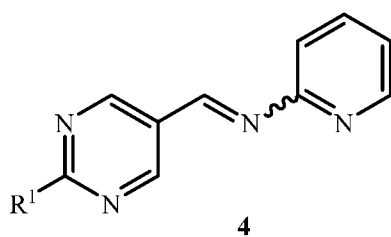
15 (A) contacting a compound of Formula 2



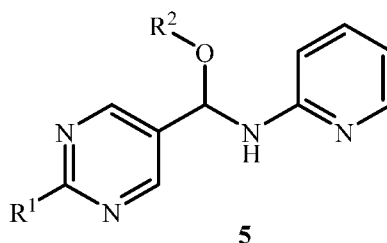
with 2-aminopyridine (3)



20 in the presence of an inert solvent S1, optionally in the presence of an acid catalyst, to form a compound of Formula 4



(B) contacting the compound of Formula **4** with an alcohol R^2OH to form a compound of Formula **5** in the presence of an inert solvent S2



5 wherein R^2 is C_1 - C_4 alkyl; and

(C) contacting the compound of Formula **5** with a borohydride reducing agent in the presence of an inert solvent S3 to form a reaction mixture comprising the compound of Formula **1**.

Embodiment 2. The method of Embodiment 1 wherein R^2 is CH_3 or CH_2CH_3 .

10 Embodiment 2a. The method of Embodiments 1 or 2 wherein Step (C) further comprises
 (i) contacting the reaction mixture with water and adjusting the pH of the reaction mixture with acid to pH less than 5, (ii) separating resulting aqueous and organic phases of the reaction mixture, (iii) adjusting the pH of the aqueous phase to pH 5 or greater with aqueous base, and (iv) extracting the compound of
 15 Formula **1** into an organic solvent S4.

Embodiment 3. The method of Embodiment 1 wherein the inert solvent S1 in Step A is toluene or xylenes.

Embodiment 4. The method of Embodiment 3 wherein the inert solvent S1 in Step A is toluene.

20 Embodiment 5. The method of any one of Embodiments 1 through 4 wherein an acid catalyst is present in Step A, and said acid catalyst is toluenesulfonic acid either as its *para*-isomer or as a mixture of isomers.

Embodiment 5A. The method of Embodiment 5 wherein the acid catalyst used is in an amount between 0.0001 and 0.01 molar equivalents of acid catalyst relative to
 25 the amount of the compound of Formula **2** used in Step A.

Embodiment 6. The method of Embodiment 1 wherein the alcohol in Step B is methanol.

Embodiment 6A. The method of Embodiment 6 wherein the methanol used is in an amount between 3 and 6 molar equivalents of methanol relative to the amount of the compound of Formula **2** used in Step A.

Embodiment 7. The method of Embodiment 1 wherein the inert solvent S2 in Step B is toluene or xylenes.

Embodiment 8. The method of Embodiment 7 wherein the inert solvent S2 in Step B is toluene.

Embodiment 9. The method of Embodiment 1 wherein the reaction temperature of Step B is between 10 and 30 °C.

Embodiment 10. The method of Embodiment 1 wherein the borohydride reducing agent in Step C is sodium borohydride, lithium borohydride or potassium borohydride.

Embodiment 11. The method of Embodiment 10 wherein the borohydride reducing agent is used in an amount of between 0.30 and 0.40 molar equivalents of the borohydride reducing agent relative to the amount of the compound of Formula **2** used in Step A.

Embodiment 12. The method of Embodiment 10 wherein the borohydride reducing agent in Step C is sodium borohydride.

Embodiment 13. The method of Embodiment 1 wherein the reaction time of Step C is between 1 and 6 hours.

Embodiment 14. The method of Embodiment 1 wherein the inert solvent S3 used in Step C is the same as the inert solvent S2 used in Step B.

Embodiment 15. The method of Embodiment 14 wherein the inert solvents S2 and S3 are both toluene or are both xylenes.

Embodiment 16. The method of Embodiment 15 wherein the inert solvents S2 and S3 are toluene.

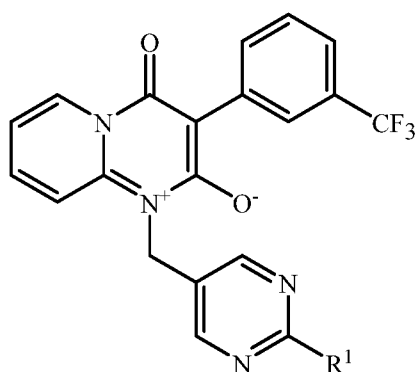
Embodiment 17. The method of Embodiment 1 wherein the inert solvents S1 of Step A, S2 of Step B, and S3 of Step C are the same.

Embodiment 18. The method of Embodiment 17 wherein the inert solvents S1 of Step A, S2 of Step B, and S3 of Step C are toluene or xylenes.

Embodiment 19. The method of Embodiment 18 wherein the inert solvents S1 of Step A, S2 of Step B, and S3 of Step C are toluene.

Embodiment 20. A method for preparing a compound of Formula **6**

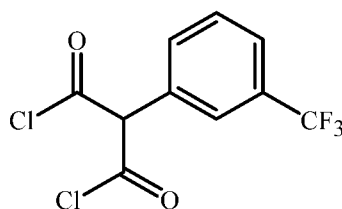
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6

wherein R^1 is H or C_1 - C_3 alkyl,

5 comprising contacting a compound of Formula 1 of Claim 1 with the compound (7),

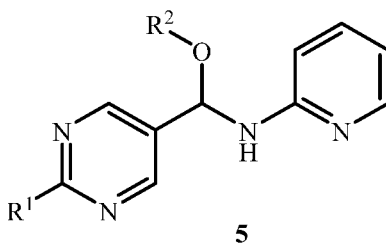


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wherein the compound of Formula 1 is prepared by the method of Claim 1.

Embodiment 21. The method Embodiment 20 wherein R^1 is H.

Embodiment 22. A compound of Formula 5



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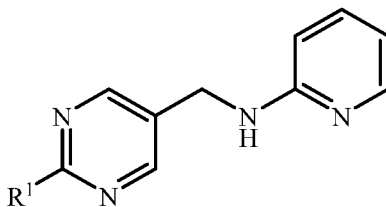
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wherein R^1 is H or C_1 - C_3 alkyl and R^2 is C_1 - C_4 alkyl.

Embodiment 23. The compound Embodiment 22 wherein R^1 is H and R^2 is CH_3 .

Combinations of Embodiments of the present invention include:

Embodiment A. A method of preparing a compound of Formula 1



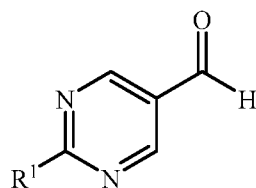
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wherein R^1 is H,

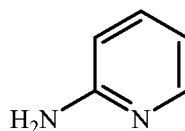
comprising:

(A) contacting a compound of Formula 2



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with 2-aminopyridine (3)

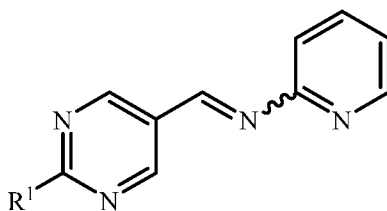


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in the presence of an inert solvent S1 and an acid catalyst which is toluenesulfonic acid

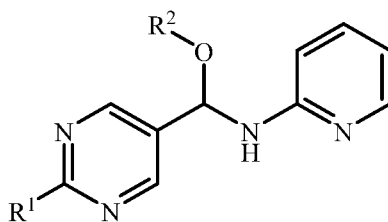
either as its *para*-isomer or as a mixture of isomers catalyst, to form a compound of Formula

4



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(B) contacting the compound of Formula 4 with an alcohol R^2OH to form a compound of Formula 5 in the presence of an inert solvent S2

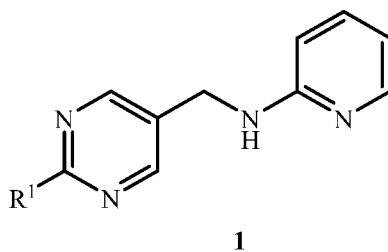


5

wherein R^2 is CH_3 or CH_2CH_3 ; and

(C) contacting the compound of Formula 5 with a sodium borohydride reducing agent in the presence of an inert solvent S3 to form the compound of Formula 1.

Embodiment B. A method of preparing a compound of Formula 1

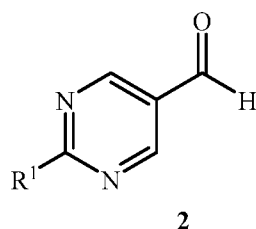


wherein R¹ is H,

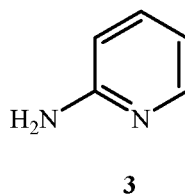
comprising:

(A) contacting a compound of Formula 2

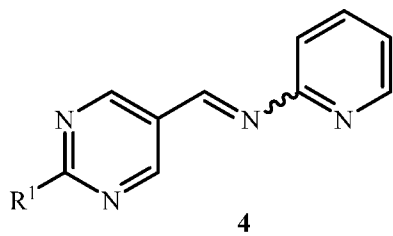
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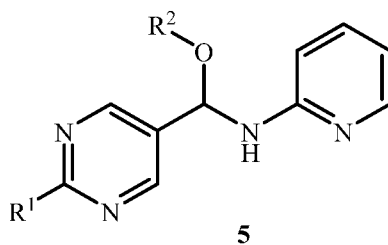
with 2-aminopyridine (**3**)



10 in the presence of a toluene solvent and an acid catalyst which is toluenesulfonic acid either as its *para*-isomer or as a mixture of isomers catalyst, to form a compound of Formula 4



(B) contacting the compound of Formula 4 with an alcohol R²OH to form a compound of Formula 5 in the presence of a toluene solvent



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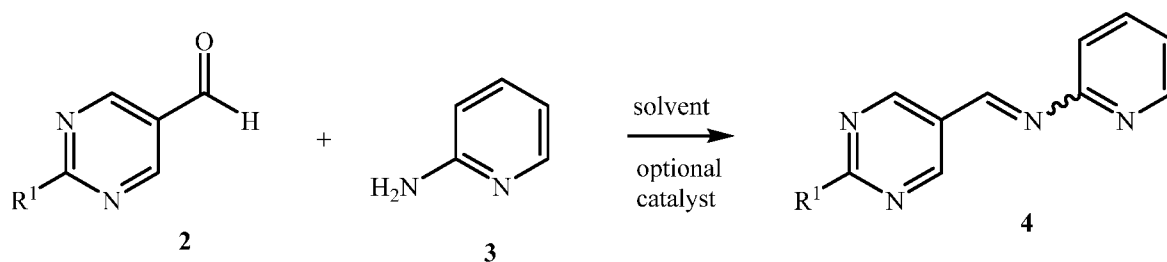
wherein R² is CH₃ or CH₂CH₃; and

(C) contacting the compound of Formula 5 with a sodium borohydride reducing agent in the presence of a toluene solvent to form the compound of Formula 1.

Embodiments of this invention, including Embodiments 1-23 above as well as any other embodiments described herein, can be combined in any manner, and the descriptions of variables in the embodiments pertain not only to the aforescribed method for preparing the compound of Formulae 1 and 6, but also to the starting compounds and intermediate compounds useful for preparing the compound of Formulae 1 and 6 by this method.

In the following Schemes, the definition of R¹ in the compounds of Formulae 1, 2, 4, 5 and 6, and of R² in the compounds of Formulae 5 are as defined above in the Summary of the Invention and description of Embodiments unless otherwise indicated.

Scheme 1



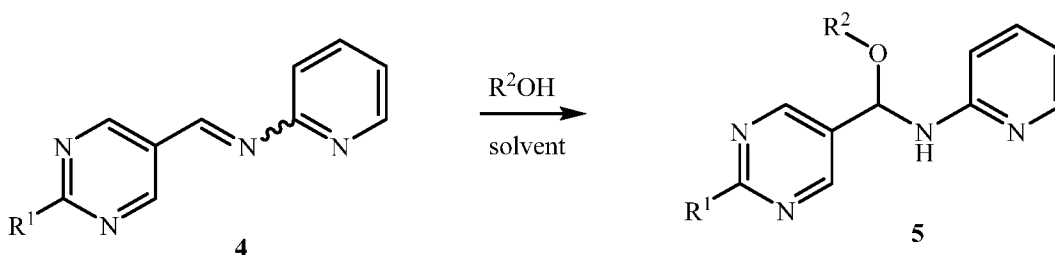
In Step A of the method of the invention, a compound of Formula 4 is prepared by treatment of a compound of Formula 2 with 2-aminopyridine (3) in the presence of an inert solvent S1, optionally in the presence of an acid catalyst, with azeotropic removal of water as shown in Scheme 1. While this reaction proceeds in the absence of added acid catalyst, it can be beneficial to add an acid catalyst to accelerate the rate of formation of the compound of Formula 4. While any amount of acid catalysts may be used, an amount between 0.0001 and 0.01 molar equivalents of acid catalyst relative to the amount of the compound of Formula 2 used in Step A is generally sufficient to provide a notable increase in reaction rate.

Examples of acid catalysts which can be used in Step A of this method include (a) sulfonic acids such as *para*-toluenesulfonic acid, toluenesulfonic acid as a mixture of isomers, and methanesulfonic acid, (b) inorganic acids such as hydrochloric acid, sulfuric acid, and phosphoric acid, and (c) organic acids such as acetic acid and propanoic acid. Since Step A involves azeotropic removal of water by distillation, the acid catalyst can be charged as a hydrate, as an aqueous solution, or in anhydrous form. A useful acid catalyst is toluenesulfonic acid either as its *para*-isomer or as a mixture of isomers. Inert solvents typically used in Step A of this method include (a) C₇-C₁₀ aromatic hydrocarbons (for

example, toluene, xylenes (as the pure *ortho*, *meta* and *para* isomers, as mixtures thereof, or as mixtures with ethylbenzene), ethyl benzene and cumene (*iso*-propylbenzene)), (b) halogenated benzenes (for example, chlorobenzene and 1,2-dichlorobenzene), and (c) haloalkanes (for example, 1,2-dichloroethane). Useful solvents are those that are suitable for use in all steps of the process, such as toluene and xylenes. In an embodiment of Step A of this method, the solvent is toluene.

The choice of reaction temperature, reaction pressure, and reaction time of the process of Step A is dependent on the reaction solvent. The process of Step A is conveniently carried out at the normal boiling point of the reaction solvent. Depending of the solvent employed, the reaction can be carried out at pressures above or below atmospheric pressure. The reaction time will depend on the desired level of conversion, whether or not a catalyst is used, and the choice of solvent. Typical reaction times range from 1 to 24 hours.

Scheme 2



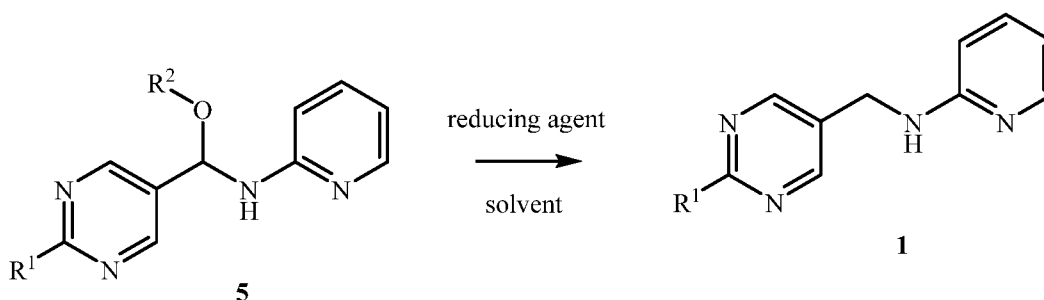
In Step B of the method of the invention, a compound of Formula 5 is prepared by treatment of a compound of Formula 4 with a C₁-C₄ alcohol in the presence of an inert solvent S2 as shown in Scheme 2. C₁-C₄ alcohols which can be used in Step B of this method include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, and 2-methyl-2-propanol. While any amount of C₁-C₄ alcohol may be used, it is generally more practical to use an amount between 1 and 10 molar equivalents of C₁-C₄ alcohol relative to the amount of the compound of Formula 2 used in Step A. In an embodiment of Step B, the alcohol is methanol. In a further embodiment of Step B, the methanol is in an amount between 3 and 6 molar equivalents of methanol relative to the amount of the compound of Formula 2 used in Step A. Inert solvents typically used in Step B of this method include (a) C₇-C₁₀ aromatic hydrocarbons (for example, toluene, xylenes (as the pure *ortho*, *meta* and *para* isomers, as mixtures thereof, or as mixtures with ethylbenzene), ethyl benzene and cumene (*iso*-propylbenzene)), (b) halogenated benzenes (for example, chlorobenzene and 1,2-dichlorobenzene), (c) haloalkanes (for example, dichloromethane, 1,2-dichloroethane and 1-chlorobutane), and (d) ethers (for example, tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butyl methyl ether, and dioxane). Mixtures of

these inert solvents may also be employed. In an embodiment of Step B, the inert solvent S2 is toluene or xylenes. In another embodiment of Step B, the inert solvent S2 is toluene.

In Step B of this method, the addition of the R²OH alcohol to the compound of Formula 5 can be performed at any temperature; for convenience, the reaction temperature is typically kept below the boiling point of the alcohol to avoid evaporative loss of the alcohol. In one embodiment of Step B, the reaction temperature is between 10 and 30 °C.

Compounds of Formula 5 are more stable than compounds of Formula 4, and are less prone than compounds of Formula 4 to break down to compounds of Formulae 2 and 3. Consequently, solutions of compounds of Formula 5 can be stored for extended periods of time prior to use in Step C of the process.

Scheme 3



In Step C of the method of the invention, a compound of Formula 1 is prepared by treatment of a compound of Formula 5 with a borohydride reducing agent in the presence of an inert solvent S3 as shown in Scheme 3. Borohydride reducing agents which can be used in Step C of this method include, but are not limited to, sodium borohydride, lithium borohydride, potassium borohydride, sodium triacetoxyborohydride and sodium trimethoxyborohydride. In an embodiment of Step C, the borohydride reducing agent is sodium borohydride.

In instances when the borohydride reducing agent is sodium triacetoxyborohydride or sodium trimethoxyborohydride, it is typical to use 1.0 to 1.5 molar equivalents of the borohydride reducing agent relative to the amount of the compound of Formula 2 charged in Step A. In instances when the borohydride reducing agent is sodium borohydride, lithium borohydride or potassium borohydride, typically 0.25 to 1.0 molar equivalents of the borohydride reducing agent relative to the amount of the compound of Formula 2 of Step A can be used. In an embodiment of Step C, the borohydride reducing agent is sodium borohydride, lithium borohydride or potassium borohydride, and is used in an amount of between 0.30 and 0.40 molar equivalents of the borohydride reducing agent relative to the amount of the compound of Formula 2 of Step A.

Inert solvents typically used in Step C of this method include (a) C₇-C₁₀ aromatic hydrocarbons (for example, toluene, xylenes (as the pure *ortho*, *meta* and *para* isomers, as mixtures thereof, or as mixtures with ethylbenzene), ethyl benzene and cumene (*iso*-propylbenzene)), (b) halogenated benzenes (for example, chlorobenzene and 1,2-dichlorobenzene), (c) haloalkanes (for example, dichloromethane, 1,2-dichloroethane and 1-chlorobutane), and (d) ethers (for example, tetrahydrofuran, 2-methyltetrahydrofuran, *tert*-butyl methyl ether, and dioxane). Mixtures of these inert solvents may also be employed. In an embodiment of Step C, the inert solvent S3 is toluene or xylenes. In another embodiment of Step C, the inert solvent S3 is toluene.

The reaction temperature in Step C of this method typically ranges from -10 to 50 °C. In one embodiment of Step C, the reaction temperature ranges from 0 to 30 °C. In another embodiment of Step C, the reaction temperature ranges from 5 to 15 °C. The reaction time in Step C of this method typically ranges from 1 hour to greater than 24 hours. In an embodiment of Step C, the reaction time is between 1 and 6 hours.

In an embodiment of this invention, the inert solvent S3 used in Step C is the same inert solvent S2 used in the preceding Step B. In an embodiment of this invention, the inert solvents S2 and S3 used in Steps B and C are both toluene or are both xylenes. In a further embodiment of this invention, the inert solvents S2 and S3 used in Steps B and C are both toluene.

In an embodiment of this invention, the inert solvents S2 used in Step B is the same inert solvent S1 used in the preceding Step A. In an embodiment of this invention, the inert solvents S1 and S2 used in Steps A and B are both toluene or are both xylenes. In a further embodiment of this invention, the inert solvents S1 and S2 used in Steps A and B are both toluene.

In an embodiment of this invention, the inert solvents S1 used in Step A, S2 used in Step B, and S3 used in Step C are the same. In an embodiment of this invention, the inert solvents S1 used in Step A, S2 used in Step B, and S3 used in Step C are toluene or xylenes. In a further embodiment of this invention, the inert solvents S1 used in Step A, S2 used in Step B, and S3 used in Step C are toluene.

The compound of Formula 1 can be isolated from the reaction mixture of Step C by standard techniques known in the art for the isolation of products from borohydride reductions. Typically, water is added to the reaction mixture or the reaction mixture is added to water to dissolve and/or digest boron complexes and/or any remaining borohydride reagent. The pH of the aqueous phase can optionally be raised by the addition of a base or lowered by the addition of an acid to facilitate digestion of any residual borohydride reagent and intermediate boron complexes. Suitable bases include alkali metal hydroxides, carbonates and bicarbonates. Suitable acids include mineral acids such as hydrochloric acid, sulfuric acid, and phosphoric acid and organic acids such as acetic acid.

Once the boron complexes and/or any remaining borohydride reagent are digested, the reaction mixture consists of either a single liquid phase or two liquid phases, depending on factors including the reaction solvent selected and the amount of water charged relative to the organic solvent.

5 If the reaction mixture consists of a single phase, the compound of Formula 1 can be extracted from this aqueous phase using a water immiscible organic solvent.

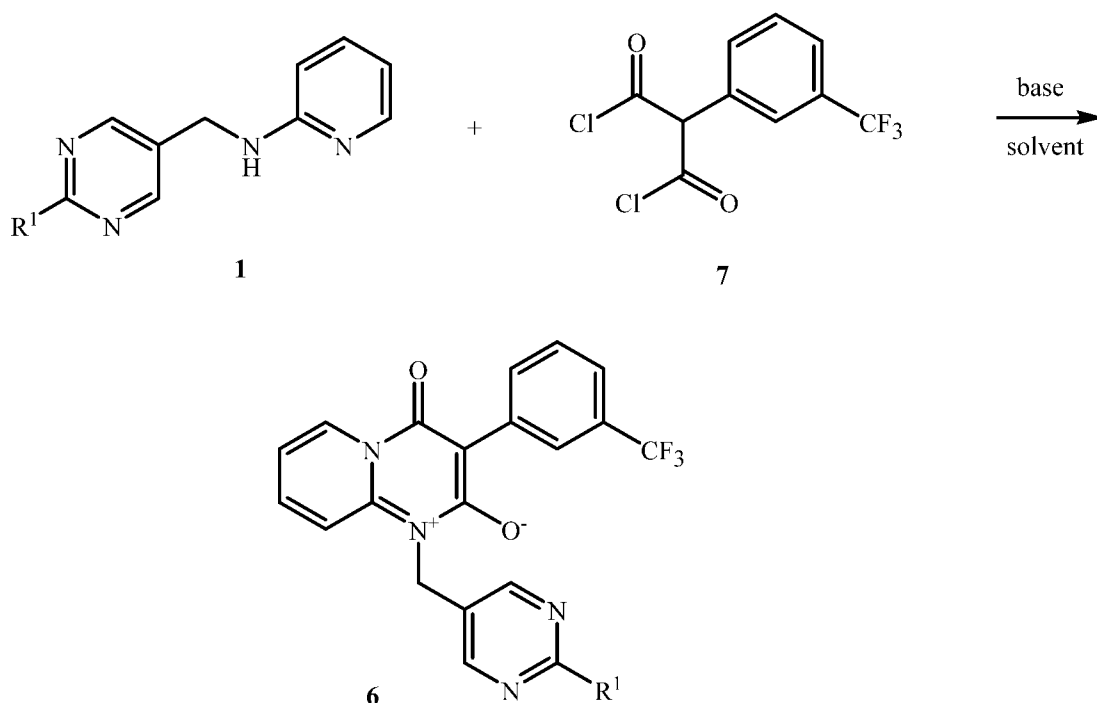
If the reaction mixture consists of two liquid phases, it can be advantageous to separate the organic phase from the reaction mixture at this point to remove any impurities that are present in the organic phase. Consequently, it can be advantageous to select an organic
10 solvent that gives a reaction mixture that consists of two liquid phases. In such cases, adjusting the pH of the aqueous phase to pH 5 or less minimizes loss of the product of Formula 1 to the organic phase, since at pH 5 or less, the compound of Formula 1 will partition into the aqueous layer. Once the organic phase is separated, the compound of Formula 1 can be isolated by extraction from the aqueous phase into a water immiscible
15 organic solvent. The ease of extraction of the compound of Formula 1 from the aqueous phase will be dependent on factors such as the pH of the aqueous phase, the amount of water charged relative the amount of the compound of Formula 1, and the solvent selected for the extraction. It is often advantageous at this point to maintain the pH of the aqueous phase at about 5 to 7 during the extraction so as to facilitate extraction of the compound of Formula 1
20 while suppressing the extraction of process impurities. Thus, the pH of the aqueous phase is adjusted with aqueous base to pH 5 or greater, and the compound of Formula 1 is extracted into an organic solvent S4. Typical organic solvents S4 include C₇-C₁₀ aromatic hydrocarbons and haloalkanes. In one embodiment, the organic solvent S4 is toluene, dichloromethane, 1,2-dichloroethane or 1-chlorobutane.

25 In an embodiment of this method, Step (C) further comprises (i) contacting the reaction mixture with water and adjusting the pH of the reaction mixture with acid to pH less than 5, (ii) separating resulting aqueous and organic phases of the reaction mixture, (iii) adjusting the pH of the aqueous phase to pH 5 or greater with an aqueous base, and (iv) extracting the compound of Formula 1 from the aqueous phase into an organic solvent S4.
30 In a further embodiment, the pH of the aqueous phase in (iii) above is adjusted with aqueous base to between pH 5 and 7. In a further embodiment, the pH of the aqueous phase in (iii) above is adjusted with aqueous base to between pH 5 and 6.

If the compound of Formula 1 is a solid at ambient temperature, it can be isolated from the organic layer and organic extracts by solvent exchange into a suitable crystallization
35 solvent. Subsequent cooling of the crystallization solvent, isolation of the solid product by filtration, and optional washing of the product with an appropriate organic solvent provides the purified compound of Formula 1.

Compounds of Formula **1** can be coupled with the compound (**7**) to provide the compounds of Formula **6** as shown in Scheme 4; such a coupling method is described in PCT Patent Application Publication WO 2013/090547. When R¹ in Formula **6** is H, the resulting compound is the insecticide triflumezopyrim (2,4-dioxo-1-(5-pyrimidinylmethyl)-3-[3-(trifluoromethyl)phenyl]-2*H*-pyrido[1,2-*a*]pyrimidinium inner salt, CAS Registry No. 1263133-33-0). Triflumezopyrim is described in PCT Patent Application Publications WO 2011/017351 and WO 2012/092115.

Scheme 4



The present method of preparing the compounds of Formula **1** thus can be used in the preparation of insecticidally active compounds of Formula **6**.

In the following Examples, Proton-NMR analysis was performed on a Varian VNMRS 300 MHz instrument. ¹H NMR spectra are reported in ppm downfield from tetramethylsilane; “s” means singlet, “br d” means broad doublet, and “m” means multiplet.

High pressure liquid chromatograph (HPLC) analysis was performed using a Hewlett Packard Series 1100 instrument equipped with a diode array UV detector (monitored at 230 nm) and fitted with a Zorbax Eclipse XDB C18 (150 mm x 4.6mm x 3.5μ) column. The column was maintained at 25 °C and the flow rate was 1 mL per minute. The mobile phase was composed of 46.2 mM ammonium bicarbonate in water (A) and acetonitrile (B). The mobile phase program was 85% A:15% B for 12 minutes, changed to 40% A:60% B over 4 minutes, and then changed to 20% A:80% B over four minutes.

PREPARATION EXAMPLE 1

Step A: Preparation of *N*-(5-pyrimidinylmethylene)-2-pyridinamine

To a 1L 3-neck round bottomed flask equipped with an overhead stirrer, a thermocouple, a Dean-Stark trap (about 25 mL total volume), and a condenser with a nitrogen inlet was added 400.0 g of a 2.1 weight % solution of pyrimidine-5-carboxaldehyde in dichloromethane (8.4 g, 77.7 mmole contained pyrimidine-5-carboxaldehyde) and 7.39 g of 99.0 weight % 2-aminopyridine (77.7 mmole). The reaction mixture was heated to reflux under a nitrogen blanket and 349 g of dichloromethane were removed via the Dean-Stark trap at 39-48 °C and atmospheric pressure. Toluene (126 mL) was added to the reaction mixture at about 48 °C, followed by 31 mg of 98.5 weight % *para*-toluenesulfonic acid monohydrate (0.16 mmol). The resulting reaction mixture was heated to reflux and distillate removed via the Dean-Stark trap until the temperature of the reaction mixture reached 110 °C, at which point an additional 40 g of distillate had been removed. 50 mL of toluene was added to the reactor and the reaction mixture was refluxed at 112-114 °C under atmospheric pressure for about 3.75 hours with removal of water via the Dean-Stark trap. HPLC analysis of the reaction mixture indicated 94.1 area % *N*-(5-pyrimidinylmethylene)-2-pyridinamine.

Step B: Preparation of *N*-[methoxy(5-pyrimidinyl)methyl]-2-pyridinamine

The reaction mixture from Step A was cooled to 21 °C and 7.5 g (234 mmol) of methanol was added. The reaction mixture was stirred at 16-24 °C for about 1 hour and then allowed to stand at room temperature overnight (about 16 hours) after which time HPLC analysis of the reaction mixture indicated 91.1 area % *N*-[methoxy(5-pyrimidinyl)methyl]-2-pyridinamine.

Step C: Preparation of *N*-[(5-pyrimidinyl)methyl]-2-pyridinamine

To a 500 mL jacketed resin kettle equipped with an overhead stirrer, a thermocouple, a recirculating heating and cooling bath, and a nitrogen inlet was added 1.05 g of 98% sodium borohydride powder (27.2 mmol) followed by 50 mL of toluene. The resulting slurry was blanketed with nitrogen, cooled to 9 °C, and the reaction mixture from Step B was added over 50 minutes using a metering pump while maintaining the temperature of the reaction mixture at 9 to 12 °C. Upon completion of the addition, the reactor used in Step B was rinsed with 10 mL of toluene, and this rinsate was added to the reaction mixture. The Step C reaction mixture was stirred at 11-12 °C for about 3 hours, after which time HPLC analysis of the reaction mixture indicated 92.7 area % *N*-[(5-pyrimidinyl)methyl]-2-pyridinamine. About 3.5 hours after the completion of the addition of the Step B solution, water (33.6 g) was added, followed by 11.2 g of 37 weight % HCl. The reaction mixture was allowed to warm to about 20 °C during the course of these additions and then stirred at room temperature (21-22 °C) for about one hour, after which time the pH of the aqueous layer was about 3.8. An additional 0.2 grams of 37 weight % HCl was added to adjust the pH of the aqueous layer to about 3.5. The reaction mixture was then stirred at room temperature

overnight (about 16 hours). The aqueous layer was then separated from the organic layer, and the pH of the aqueous layer adjusted to 6.0 by the addition of 4.0 g of 50% NaOH. The aqueous layer was then extracted with dichloromethane (5 X 34 mL), with the periodic addition of 50% NaOH to maintain the pH of the aqueous layer between about 5.4 and 6.0.

5 The combined dichloromethane extracts were concentrated to dryness using a rotary evaporator to give 11.1 g of solid.

The solid was transferred to a 250 mL jacketed resin kettle equipped with overhead stirrer, a thermocouple, a recirculating heating and cooling bath, and a nitrogen inlet, and 22.9 g of dichloromethane was added. The resulting solution was cooled to 5 °C and 51.5 mL of mixed heptanes was added with stirring while maintaining the temperature at 5-7 °C.

10 The heptanes were added slowly until a thick slurry formed, after which the rate of addition was increased to thin the slurry. The mixture was warmed to 14 °C over 15 minutes, and held at 14-15 °C for 15 minutes. The mixture was then cooled to 2 °C over one hour, and held at 2-3 °C for one hour, after which time the product was collected by filtration, washed

15 with 25 mL of cold heptanes, and dried in a vacuum oven at about 45 °C to leave 10.69 g of product. Analysis of the product by HPLC indicated 96.3 weight % (98.4 area %) *N*-[(5-pyrimidinyl)methyl]-2-pyridinamine (71% yield).

Characterization of *N*-[methoxy(5-pyrimidinyl)methyl]-2-pyridinamine by NMR

20 To a 250 mL 3-neck round bottomed flask equipped with a magnetic stirrer, a heating mantel, a thermocouple, a Dean-Stark trap, and a condenser with a nitrogen inlet was added 5.0 g of pyrimidine-5-carboxaldehyde and 75 mL of toluene. The reaction mixture was stirred at room temperature for about 10 minutes, and then 2-aminopyridine (4.35 g, 1.0 eq.) and *para*-toluenesulfonic acid monohydrate (20 mg, 0.2 mol%) were added at room

25 temperature. The Dean-Stark trap was filled with 20 mL toluene and the resulting reaction mixture heated to reflux (112-113 °C) for 3.5 hours under a nitrogen blanket. The reaction mixture was then concentrated by removal of 90 mL of distillate via the Dean-Stark trap. The reaction mixture was then transferred to a clean 1-neck round bottomed flask at which time a yellow solid crystallized out. The remaining solvent was removed using a rotatory

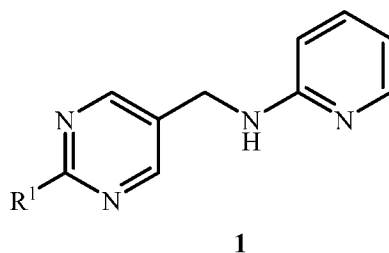
30 evaporator with a bath temperature of 60 °C, methanol (about 30 mL) was added to the residue, and the mixture stirred at room temperature overnight. On the following day, about 10 mL of the solution was concentrated to an oil using a rotary evaporator and analyzed by NMR (CDCl₃) which was consistent for *N*-[methoxy(5-pyrimidinyl)methyl]-2-pyridinamine containing methanol and a minor amount of *N*-(5-pyrimidinylmethylene)-2-pyridinamine.

35 The signals from *N*-[methoxy(5-pyrimidinyl)methyl]-2-pyridinamine were δ 9.15 (s, 1H), 8.87 (s, 2H), 8.11 (m, 1H), 7.47 (m, 1H), 6.72 (m, 1H), 6.54 (m, 1H), 6.40 (br d, 1H), 5.77 (br d, 1H), 3.48 (s, 3H).

CLAIMS

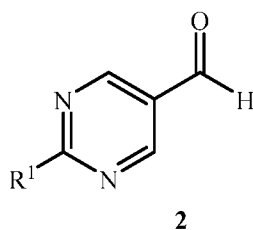
What is claimed is:

1. A method for preparing a compound of Formula 1

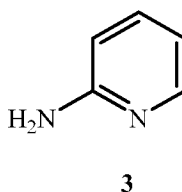


wherein R¹ is H or C₁-C₃ alkyl,
comprising:

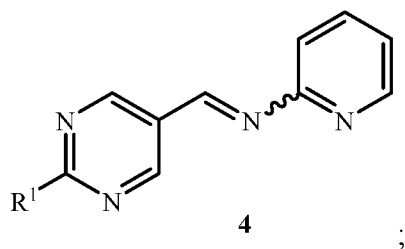
- (A) contacting a compound of Formula 2



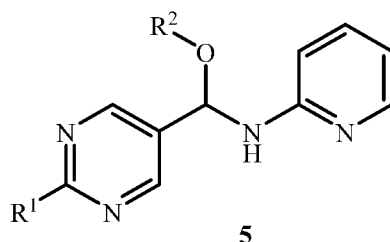
with 2-aminopyridine (**3**)



- 15 in the presence of an inert solvent S1, optionally in the presence of an acid catalyst, to form a compound of Formula 4



(B) contacting the compound of Formula 4 with an alcohol R^2OH to form a compound of Formula 5 in the presence of an inert solvent S2



5 wherein R^2 is C_1 - C_4 alkyl; and

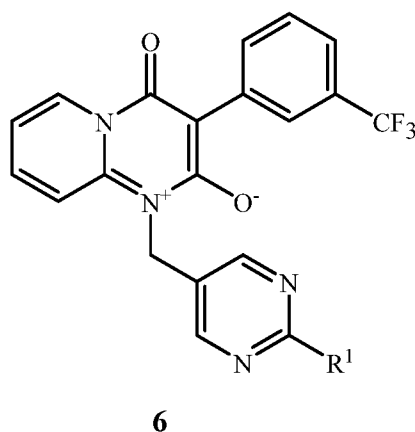
(C) contacting the compound of Formula 5 with a borohydride reducing agent in the presence of an inert solvent S3 to form a reaction mixture comprising the compound of Formula 1.

2. The method of Claim 1 wherein R^1 is H.

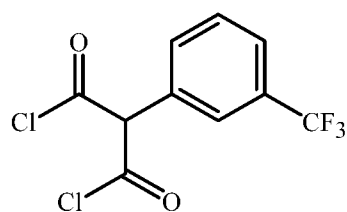
10 3. The method of Claim 2 wherein R^2 is CH_3 or CH_2CH_3 .

4. The method of any one of Claims 1-3 wherein Step (C) further comprises (i) contacting the reaction mixture with water and adjusting the pH of the reaction mixture with acid to pH less than 5, (ii) separating resulting aqueous and organic phases of the reaction mixture, (iii) adjusting the pH of the aqueous phase to pH 5 or greater with aqueous base,
15 and (iv) extracting the compound of Formula 1 into an organic solvent S4.

5. A method for preparing a compound of Formula 6



20 wherein R^1 is H or C_1 - C_3 alkyl,
comprising contacting a compound of Formula 1 of Claim 1 with the compound (7),

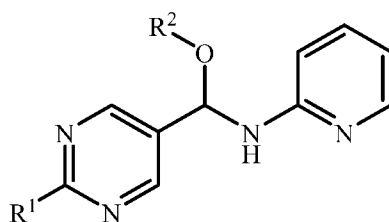


7

wherein the compound of Formula 1 is prepared by the method of Claim 1.

6. The method of Claim 5 wherein R^1 is H.

7. A compound of Formula 5



5

wherein R^1 is H or C_1 - C_3 alkyl and R^2 is C_1 - C_4 alkyl.

8. The compound of Claim 7 wherein R^1 is H and R^2 is CH_3 .

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/028703

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 C07D471/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/092115 A1 (DU PONT [US]; PAHUTSKI THOMAS FRANCIS JR [US]) 5 July 2012 (2012-07-05) cited in the application Schemes 4 and 13 on pages 15 and 20. Synthesis Example 1 on pages 54-56.; claim 1 -----	1-8
X	WO 2013/090547 A1 (DU PONT [US]) 20 June 2013 (2013-06-20) cited in the application Example 3, pages 38-41. -----	1-8
A	WO 2011/017351 A2 (DU PONT [US]; HOLYOKE JR CALEB WILLIAM [US]; ZHANG WENMING [US]; TONG) 10 February 2011 (2011-02-10) cited in the application Schemes 4 and 10 on pages 22 and 26. -----	1-8

☐ 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

17 July 2017

Date of mailing of the international search report

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Authorized officer

Gettins, Marc

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/028703

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/028703

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2011017351 A2	10-02-2011
