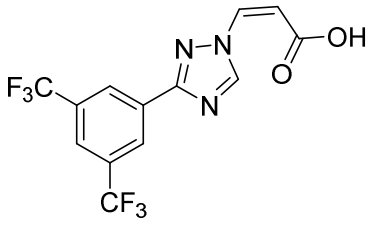
CLAIMS

~~What is claimed is:~~

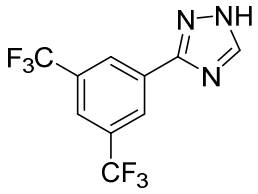
1. A process of making a compound represented by structural formula **III**,



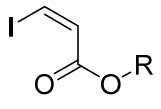
(**III**),

the process comprising:

reacting a compound represented by structural formula (**I**) with a compound represented by structural formula (**II**),

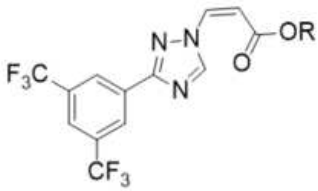


(**I**),



(**II**)

in the presence of a catalyst, an organic base, and an ether-containing solvent under the conditions suitable to produce a compound represented by structural formula (**IIIa**),



(**IIIa**); and

<u>wherein the catalyst is present in an amount from 0.05 to 0.2 molar equivalents based on the amount of the compound represented by structural formula **I**;</u>

without isolating, reacting the compound represented by structural formula (**IIIa**) with an inorganic base in the presence of isopropyl alcohol (IPA) under conditions suitable to produce a compound represented by structural formula (**III**);

<u>wherein the inorganic base is a metal hydroxide selected from LiOH, NaOH, KOH, CsOH, $Ca(OH)_2$, $Mg(OH)_2$, and $Ba(OH)_2$;</u> and

isolating the compound represented by structural formula (**III**),

wherein R is a C_2-C_5 alkyl, a C_6-C_{18} aryl, a 5-18 member heteroaryl, a C_3-C_{12} cycloalkyl, or a 3-12 member heterocycloalkyl, each of which is optionally and independently substituted with one or more substituents selected from halo, CN, OH,

C_1-C_3 alkyl, C_1-C_3 haloalkyl, -NO_2, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, and C_1-C_3 alkoxy.

2. The process of Claim 1, wherein R is a C_2-C_5 alkyl or a C_6-C_{18} aryl~~.~~,

~~3. The process of Claim 1 or 2, wherein R is a C_2-C_5 alkyl.~~

~~4. The process of any one of Claims 1-3,~~ optionally wherein R is isopropyl~~.~~ or

~~5. The process of Claim 1 or 2, wherein R is~~ a phenyl.

~~6~~3. The process of ~~any one of~~ Claim~~s~~ 1~~-5~~ or 2, wherein the catalyst and the organic base are present in a combined amount of less than 1 molar equivalent of the compound represented by structural formula **II**.

~~7. The process of any one of Claims 1-6, wherein the catalyst is present in an amount from 0.05 to 0.2 molar equivalents based on the amount of the compound represented by structural formula **I**.~~

~~8~~4. The process of any one of Claims 1-~~7~~3, wherein the catalyst is present in an amount of 0.1 molar equivalents based on the amount of the compound represented by structural formula **I**.

~~9~~5. The process of any one of Claims 1-~~8~~4, wherein the catalyst is:

(a) selected from the group consisting of 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene~~.~~; or

(b)~~10. The process of any one of Claims 1-9, wherein the catalyst is~~ DABCO.

~~11~~6. The process of any one of Claims 1-~~10~~5, wherein the organic base is present in the amount:

(a) from 0.5 to 2 molar equivalents based on the amount of the compound represented by structural formula **I**~~.~~; or

(b)~~12. The process of any one of Claims 1-11, wherein the organic base is present in the amount of~~ 1.0 molar equivalents based on the amount of the compound represented by structural formula **I**.

~~13~~7. The process of any one of Claims 1-~~12~~6, wherein the organic base is:

(a) selected from the group consisting of DIPEA, Et_3N, piperidine, pyridine, and 4-(dimethylamino)pyridine~~.~~; or

(b)~~14. The process of any one of Claims 1-13, wherein the organic base is~~ DIPEA.

~~15~~8. The process of any one of Claims 1-~~14~~7, wherein the ether-containing solvent is:

(a) selected from the group consisting of MeTHF, CPME, and MTBE~~.~~; or

(b)~~16. The process of any one of Claims 1-15, wherein the ether-containing solvent is~~ MeTHF.

~~17~~9. The process of any one of Claims 1-~~16~~8, wherein the amount of the compound of structural formula **II** is from 1.0 to 1.5 molar equivalents based on the amount of compound of structural formula **I**.

~~18~~10. The process of any one of Claims 1-~~17~~9, wherein the inorganic base is:

(a) LiOH, NaOH or KOH~~.~~;

(b)~~19. The process of any one of Claims 1-18, wherein the inorganic base is~~ KOH or NaOH~~.~~; or

(c)~~20. The process of any one of Claims 1-19, wherein the inorganic base is~~ KOH.

~~21~~11. The process of any one of Claims 1-~~20~~10, wherein:

(a) the conditions suitable to produce the compound represented by structural formula **IIIa** include reacting the compound represented by structural formula **I** with the compound represented by structural formula **II** at a temperature from 5°C to 55°C~~.~~;

(b)~~22. The process of any one of Claims 1-21, wherein~~ the conditions suitable to produce the compound represented by structural formula **IIIa** include reacting the compound represented by structural formula **I** with the compound represented by structural formula **II** for a period of time from 5 h to 30 h~~.~~;

(c)~~23. The process of any one of Claims 1-22,~~ wherein the conditions suitable to produce the compound represented by structural formula **III** include reacting the compound represented by structural formula **IIIa** with an inorganic base at a temperature from 5°C to 55°C~~.~~; and/or

(d)~~24. The process of any one of Claims 1-23, wherein~~ the conditions suitable to produce the compound represented by structural formula **III** include reacting the compound represented by structural formula **IIIa** with an inorganic base for a period of time from 1 h to 10 h.

~~25~~12. The process of any one of Claims 1-~~24~~11, further including isolating the compound represented by structural formula **III** from a reaction mixture

~~26. The process of any one of Claim 25~~, wherein isolating the compound represented by structural formula **III** comprises:

(i) adding water and HCl to the the reaction mixture comprising the compound represented by structural formula **III**, thereby generating an aqueous phase and an organic phase;

(ii) separating and, optionally, concentrating the organic phase, thereby generating a final organic phase;

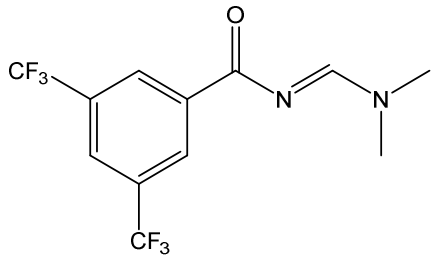
(iii) adding a C_5-C_{12} hydrocarbon solvent to the final organic phase, thereby generating a precipitate of the compound represented by structural formula **III**; and

(iv) isolating the precipitate of the compound represented by structural formula **III**~~.~~; and/or

~~27. The process of Claim 26,~~ optionally wherein the C_5-C_{12} hydrocarbon solvent is heptane~~.~~ or

~~28. The process of any one of Claims 26, wherein the C_5-C_{12} hydrocarbon solvent is~~ isooctane.

~~29~~13. The process of any one of Claims 1-~~28~~12, further comprising reacting a compound represented by structural formula (IV)

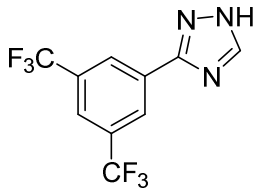


(IV),

with a hydrazine represented by structural formula (V)

H_2NNH_2 (V),

under the conditions suitable to produce a compound represented by structural formula (I),



(I); and

isolating the compound represented by structural formula (I).

~~30~~14. The process of Claim ~~29~~13, wherein reacting the compound represented by structural formula (IV) with the hydrazine represented by structural formula (V) is performed in the presence of an organic acid~~.~~;

~~31. The process of Claim 30,~~optionally wherein the organic acid is:

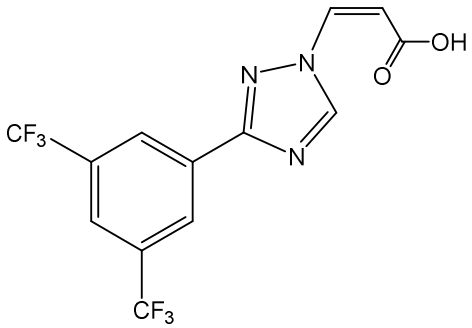
(a) a formic acid, acetic acid, or propionic acid~~.~~; or

(b)~~32. The process of Claim 31, wherein the organic acid is~~ acetic acid.

~~33~~15. The process of ~~any one of~~ Claim~~s~~ ~~29~~13~~–32~~ or 14, wherein the conditions suitable to produce the compound represented by structural formula (I) include reacting the compound represented by structural formula (IV) with the hydrazine represented by structural formula (V) at a temperature from 50 °C to 60 °C.

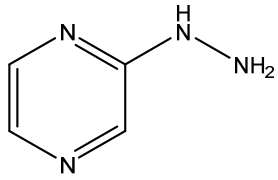
~~34~~16. The process of any one of Claims 1-~~28~~12, further comprising:

reacting a compound represented by structural formula (III)



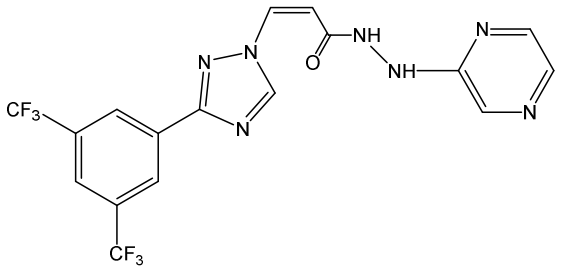
(III),

with a hydrazine represented by structural formula (VI)



(VI),

in the presence of a polar solvent, a second organic base, and a coupling agent under the conditions suitable to produce a compound represented by structural formula (VII),



(VII);

exchanging the polar solvent for acetonitrile (ACN); and

crystallizing the compound represented by structural formula (VII) from the ACN as crystalline Form D, wherein Form D is characterized by at least three X-ray powder diffraction peaks at 2θ angles selected from 3.7°, 7.3°, 10.9°, 18.3° and 21.9°.

3517. The process of Claim 3416, wherein the second organic base is:

(a) selected from the group consisting of DIPEA, Et_3N, piperidine, pyridine, and 4-(dimethylamino)pyridine.; or

(b)36. The process of Claim 35, wherein the second organic base is DIPEA.

3718. The process of any one of Claims 3416 36 or 17, wherein the polar solvent is:

(a) selected from the group consisting of a C_1-C_6 alcohol, MeTHF, CPME, and MTBE.; or

38.(b) The process of Claim 37, wherein the polar solvent is MeTHF.

3919. The process of any one of Claims 3416-3818, wherein the coupling agent is:

(a) selected from the group consisting of propylphosphonic anhydride (T3P), 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).; or

40.(b) The process of Claim 39, wherein the coupling agent is the T3P.

4120. The process of any one of Claims 3416-4019, wherein the conditions suitable to produce the compound represented by structural formula (VII) include reacting the compound represented by structural formula (III) with the hydrazine represented by structural formula (VI) at a temperature from -25 °C to -15 °C.,

42. Tthe process of any one of Claims 34-41, further comprising recrystallizing Form D of the compound represented by structural formula (VII) in an aqueous isopropyl alcohol (IPA) under the conditions suitable to produce the crystalline Form A of the compound represented by structural formula (VII).;

~~43. The process of Claim 42,~~optionally wherein the conditions suitable for producing Form A of the compound represented by structiural formula (VII) comprise:

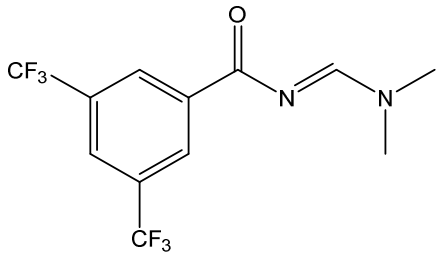
dissolving Form D in the aqueous IPA, thereby producing a slurry; and

holding the slurry at a temperature from 38 °C to 42°C for a time from 5 hours to 12 hours

wherein Form A is characterized by at least three X-ray powder diffraction peaks at 2θ angles selected from 4.4°, 19.9°, 21.3° and 22.0°.

~~44~~21. The process of any one of Claims 1-~~28~~12, further comprising:

reacting a compound represented by structural formula (IV)

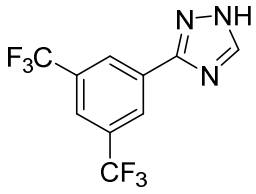


(IV),

with a hydrazine represented by structural formula (V)

H_2NNH_2 (V),

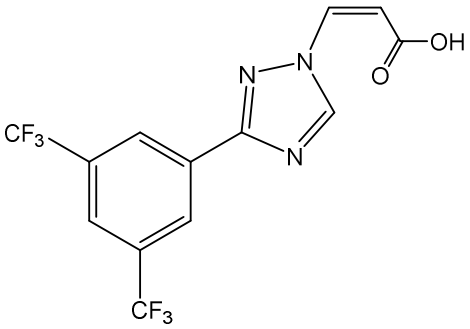
under the conditions suitable to produce a compound represented by structural formula (I),



(I)

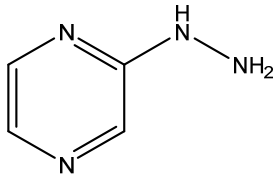
isolating the compound represented by structural formula (I);

reacting a compound represented by structural formula (III)



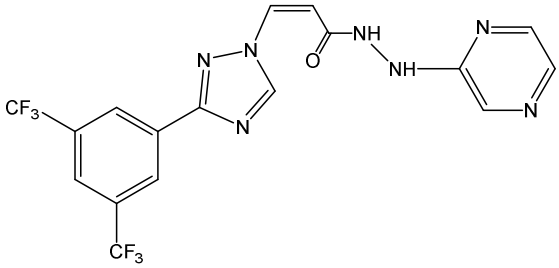
(III),

with a hydrazine represented by structural formula (VI)



(VI),

in the presence of a polar solvent, a second organic base, and a coupling agent under the conditions suitable to produce a compound represented by structural formula (VII),



(VII);

exchanging the polar solvent for acetonitrile (ACN);

crystallizing the compound represented by structural formula (VII) from the ACN as a crystalline Form D; and

recrystallizing Form D of the compound represented by structural formula (VII) in an aqueous isopropyl alcohol (IPA) under the conditions suitable to produce the crystalline Form A of the compound represented by structural formula (VII)

wherein:

Form D is characterized by at least three X-ray powder diffraction peaks at 2θ angles selected from 3.7°, 7.3°, 10.9°, 18.3° and 21.9° and

Form A is characterized by at least three X-ray powder diffraction peaks at 2θ angles selected from 4.4°, 19.9°, 21.3° and 22.0°.