

-1-

PROCESSES FOR THE PREPARATION OF SUBSTITUTED
PHENYLACETONITRILES AND SUBSTITUTED PHENYLACETIC ACIDS

TECHNICAL BACKGROUND

[0001] The present invention relates to processes for the preparation of substituted phenylacetone nitriles and substituted phenylacetic acids. These compounds are intermediates in the preparation of certain glucagon-like peptide-1 (GLP-1) receptor agonists.

BACKGROUND

[0002] Substituted phenylacetone nitriles and substituted phenylacetic acids are intermediates in the preparation of certain GLP-1 receptor agonists, including the benzimidazole compounds disclosed in WO2020/263695. The process disclosed in WO2020/263695 for preparing the substituted phenylacetone nitrile and phenylacetic acid intermediates is cumbersome because it involves multiple time-consuming purification and isolation steps. The previously disclosed process also involves the use of toxic reagents such as dichloromethane (DCM).

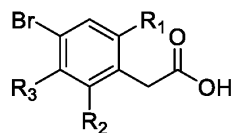
[0003] There is a need for an improved process which is less-resource intensive, cheaper, more environmentally friendly, and/or facilitates more efficient production. More particularly, there is a need for a process which reduces waste of materials, such as solvents; reduces or avoids the use of toxic and hazardous reagents and solvents; improves atom economy to improve yields and/or reduces energy and time demand.

BRIEF SUMMARY

[0004] The telescoped process of the present invention addresses one of more of these needs. Subsequent organic reactions are combined without isolation of intermediates, which prevents waste in the form of materials and solvents needed for isolation, results in increased yields and/or reduces the time and energy burden. In the present process, non-hazardous solvents such as non-halogenated solvents are used.

-2-

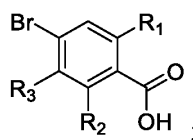
[0005] In a first aspect, the present disclosure provides a process for preparing a compound of the formula:



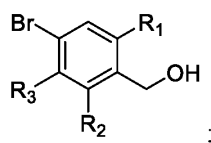
or salt thereof, wherein R₁ is selected from H, F, and CH₃, R₂ is selected from H, F, and CH₃, R₃ is selected from H, F and CH₃, and R₁, R₂, and R₃ are not the same.

[0006] In one embodiment, the process includes:

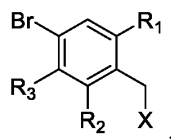
- i. combining a non-halogenated solvent with a benzoic acid of the formula:



- ii. adding a reducing agent to form a benzyl alcohol of the formula:

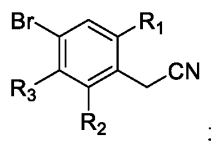


- iii. combining the benzyl alcohol with a reagent in a second non-halogenated solvent to form a first intermediate of the formula:



wherein X is selected from Cl, Br, I, a sulfonate, and a tosylate;

- iv. combining the first intermediate with a cyanide to form a benzyl nitrile of the formula



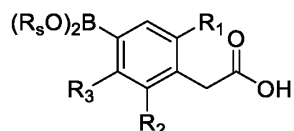
- v. combining the benzyl nitrile with a hydroxide;

wherein one or more of the following is not isolated prior to the next step: the benzyl alcohol of step (ii), the first intermediate of step (iii) and the benzyl nitrile of step (iv).

[0007] In a particular embodiment, X is Br.

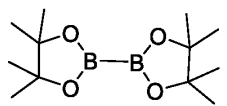
-3-

[0008] In one embodiment, the process according to the first aspect can further comprise (step vi) combining the phenylacetic acid resulting from step v with a borane reagent and a catalyst to form a boronate of the formula

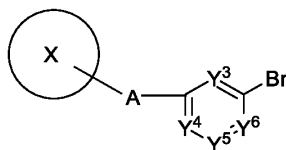


wherein R_s is a C_1 - C_6 alkyl, or a C_2 - C_6 alkylene forming a cyclic boronate. In a particular embodiment, R_s is C_6 alkylene.

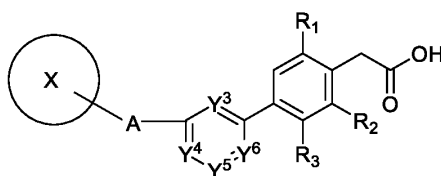
[0009] In one embodiment, the borane reagent is 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (or *bis*(pinacolato)diboron):



[0010] In yet another embodiment, the process can further include (step vii) combining the boronate with a compound of the formula



to arrive at a compound of the formula



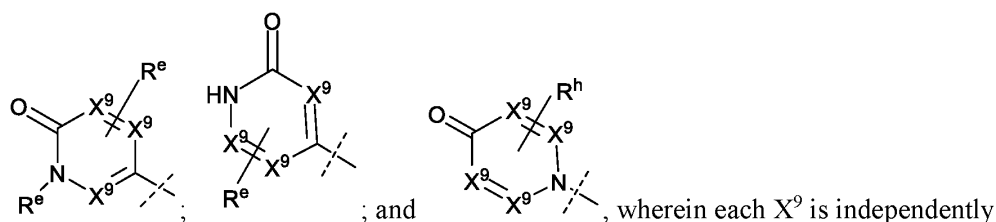
wherein R_1 , R_2 and R_3 are as defined above, and



is phenyl; a 5 or 6-membered heteroaryl; or pyridone; which phenyl, 5 or 6-membered heteroaryl or pyridone is optionally substituted with one or two R^{1a} ;

R^{1a} is at each occurrence independently selected from: CN; halo; C_1 - C_3 alkyl, which can be optionally substituted with OH; C_1 - C_3 haloalkyl; C_1 - C_3 alkoxy; C_3 - C_5 cycloalkyl; - SO_2C_1 - C_3 alkyl; - $C(O)NH_2$;

-4-



CH or N and no more than one X^9 in the ring is N, each R^e is independently selected from: H, C₁-C₃ haloalkyl, halo, C₃-C₅ cycloalkyl and C₁-C₃ alkyl optionally substituted with OH, R^h is H, C₁-C₃ haloalkyl, halo, C₃-C₅ cycloalkyl, OH, -NR^cR^d or C₁-C₃ alkyl optionally substituted with OH;

5- or 6- membered heteroaryl or phenyl, wherein the heteroaryl or phenyl is optionally substituted with one or two substituents independently selected from: C₁-C₃ alkoxy, C₃-C₅ cycloalkyl, -CH₂-C₃-C₅ cycloalkyl, -SO₂C₁-C₃ alkyl, C₄-C₅ heterocyclyl, -CH₂-C₄-C₅ heterocyclyl, halo, C₁-C₃ haloalkyl, C₁-C₃ haloalkoxy, CN, -CONR^cR^d, -NR^cR^d and C₁-C₃ alkyl optionally substituted with OH;

-A- is -CH₂O-; -OCH₂-; or -CH₂NH-;

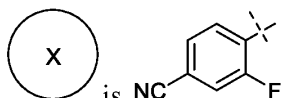
Y^3 , Y^4 , Y^5 and Y^6 are independently N; CH; or CR^{2a}; wherein no more than two of Y^3 , Y^4 , Y^5 and Y^6 are N and no more than two of Y^3 , Y^4 , Y^5 and Y^6 are CR^{2a};

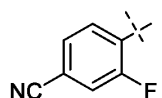
R^{2a} at each occurrence is independently halo or methyl; and

R^c and R^d are each independently H or C₁-C₃alkyl.



[0011] In an embodiment,  is phenyl substituted with halo, preferably F, and CN.



[0012] In a particular embodiment,  is .

[0013] In an embodiment, -A- is -CH₂O-.

[0014] In an embodiment, Y^3 is N and Y^4 , Y^5 and Y^6 are all CH.

[0015] In an embodiment of the above compounds, R₁ is F, R₂ is H and R₃ is CH₃.

[0016] In one embodiment, the non-halogenated solvent and the second non-halogenated solvent of the process according to the first aspect can be different or the same. In an embodiment, the non-halogenated solvent and the second non-halogenated solvent can independently be selected from acetone, acetonitrile, anisole, butyl acetate, *t*-butylmethyl ether, cumene, cyclohexane, dimethylformamide (DMF), dimethylsulfoxide, ethanol, ethyl acetate (EtOAc), ethyl ether, heptane, hexane, isopropanol, methanol (MeOH), methylbutylketone, methylethylketone, pentane, pyridine, tetrahydrofuran (THF), toluene, and xylenes, or a combination thereof. In a particular embodiment, the non-halogenated solvents are independently selected from: THF and toluene.

[0017] In yet another embodiment, the reducing agent of the process according to the first aspect can be selected from diborane, lithium borohydride, sodium triacetoxymethylborohydride, sodium cyanoborohydride, sodium borohydride, lithium aluminum hydride, and hydrogen, or a combination thereof. In one embodiment, the reducing agent is sodium borohydride. In a particular embodiment, sodium borohydride is used with boron trifluoride etherate.

[0018] In one further embodiment, the reagent in step iii of the process of the first aspect can be selected from HBr, aqueous HBr, alcoholic HBr, PBr₃, dibromodimethylhydantoin, N-bromosuccinimide, HI, aqueous HI, PCl₃, and tosylchloride, or a combination thereof. In one embodiment, the reagent is aqueous HBr.

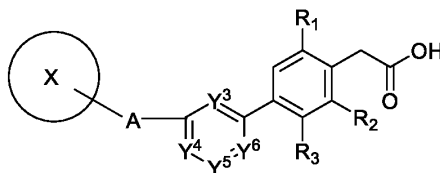
[0019] In one embodiment, the cyanide of the process according to the first aspect can be selected from LiCN, NH₄CN, N(CH₃)₄CN, N(Et)₄CN, N(n-Pr)₄CN, N(i-Pr)₄CN, N(n-Bu)₄CN, N(t-Bu)₄CN, HCN, NaCN, KCN, Zn(CN)₂, and (CH₃)₃SiCN, or a combination thereof. In one embodiment, the cyanide is selected from N(t-Bu)₄CN, NaCN, Zn(CN)₂, and (CH₃)₃SiCN. In a particular embodiment, the cyanide is NaCN.

[0020] In one embodiment, the hydroxide according to the process of the first aspect can be selected from LiOH, NaOH, KOH, Mg(OH)₂, Ca(OH)₂, or Sr(OH)₂, or a combination thereof. In a particular embodiment, the hydroxide is KOH.

[0021] In one embodiment, the process according to the first aspect provides a yield of the phenylacetic acid (step v) of at least 70 wt%, at least 75 wt%, at least 78 wt%, at least 80 wt%, at least 82 wt%, or at least 85 wt% as calculated from the benzoic acid (step i).

-6-

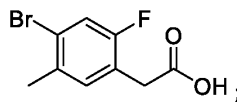
[0022] In another embodiment, the process according to first aspect provides a yield of



the compound of the formula of at least 60 wt%, at least 65 wt%, at least 70 wt% or at least 72 wt% as calculated from the compound resulting from the phenylacetic acid (step v).

[0023] In another embodiment, in the process according to the first aspect the benzyl alcohol (resulting from step ii) is not isolated prior to combining with the reagent in the second non-halogenated solvent. In yet another embodiment, in the process according to the first aspect the benzyl alcohol (resulting from step ii) is not isolated prior to combining with the reagent in the second non-halogenated solvent and the first intermediate (resulting from step iii) is not isolated prior to combining with the cyanide. In one further embodiment, in the process according to the first aspect the benzyl alcohol (resulting from step ii) is not isolated prior to combining with the reagent in the second non-halogenated solvent and the first intermediate (resulting from step iii) is not isolated prior to combining with the cyanide and the benzyl nitrile (resulting from step iv) is not isolated prior to combining with the hydroxide. In yet another embodiment, the process for preparing the compound is chromatography-free. In yet another embodiment, the process for preparing the compound includes at least one, at least two, or at least three process steps, such as step ii, step iii, step iv, or any combination thereof, that are chromatography-free.

[0024] In a second aspect, the present disclosure provides a process for preparing a compound of the formula:



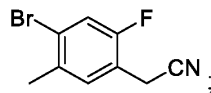
or salt thereof.

[0025] In one embodiment, the process according to the second aspect includes:

- i. combining 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene with a cyanide in a non-halogenated solvent to form a benzyl nitrile of the

-7-

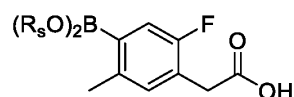
formula



- ii. combining the benzyl nitrile with a hydroxide to produce the compound, wherein the benzyl nitrile is not isolated prior to step (ii).

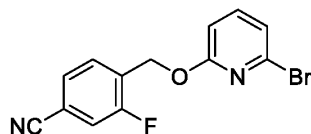
[0026] In one embodiment, the process according to the second aspect further comprises

- iii. combining the compound resulting from step (ii) with a borane reagent and a catalyst to form a boronate of the formula

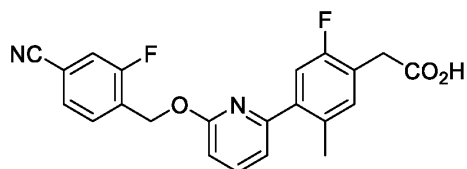


wherein R_s is a C_1 - C_6 alkyl, or a C_2 - C_6 alkylene forming a cyclic boronate;

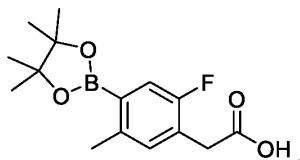
- iv. combining the boronate of step (iii) with a pyridine of the formula:



to arrive at a compound of the formula:



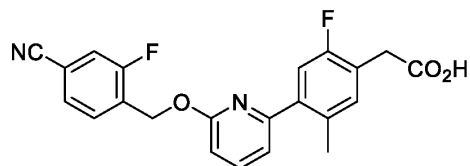
[0027] In one embodiment, the borane reagent is 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (or *bis*(pinacolato)diboron). In one embodiment, the boronate according to the process of the second aspect is



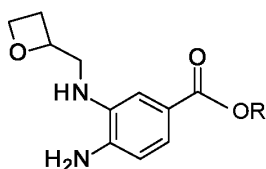
[0028] In another embodiment, the process according to the second aspect further comprises the steps of:

-8-

- a. carrying out an amide coupling reaction with a compound of the formula:

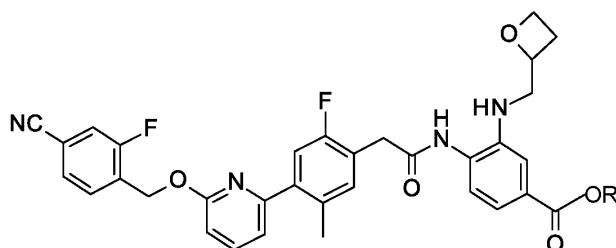


and a compound of the formula:



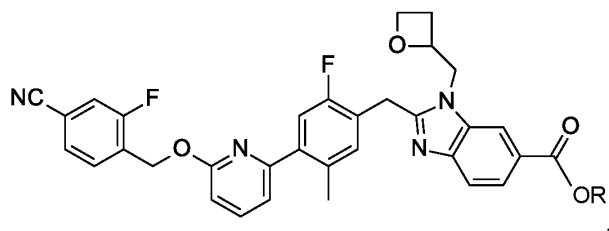
wherein R is H or an acid protecting group;

to produce a compound of the formula:



or salt thereof;

- b. performing a cyclisation reaction on the compound resulting from step (a) to produce a compound of the formula:

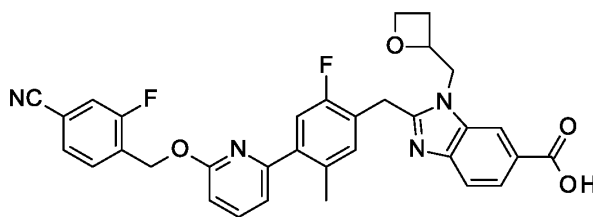


and optionally reacting to form a pharmaceutically acceptable salt thereof.

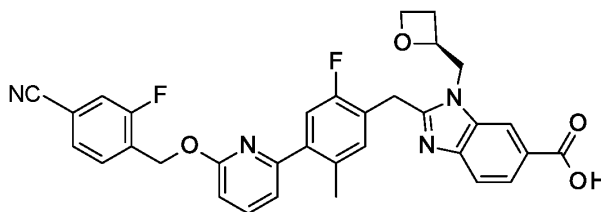
-9-

[0029] In a particular embodiment, R is H or C₁-C₄ alkyl.

[0030] In a further embodiment, where R is an acid protecting group the process further comprises the step of hydrolyzing the ester compound to produce the acid compound of the formula:



and optionally reacting to form a pharmaceutically acceptable salt thereof. In a preferred embodiment, the acid compound is of the formula:



and the salt is the *tert*-butylamine salt.

[0031] In one embodiment, in the process according to the second aspect the boronate is not isolated prior to combining with the pyridine.

[0032] In another embodiment, the non-halogenated solvent can be selected from acetone, acetonitrile, anisole, butyl acetate, *t*-butylmethyl ether, cumene, cyclohexane, DMF, dimethylsulfoxide, ethanol, EtOAc, ethyl ether, heptane, hexane, isopropanol, MeOH, methylbutylketone, methylethylketone, pentane, pyridine, THF, toluene, and xylenes, or a combination thereof. In a particular embodiment, the non-halogenated solvents are independently selected from: THF and toluene.

[0033] In another embodiment, the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene of the process according to the second aspect is obtained by combining 4-bromo-2-fluoro-5-methyl-benzyl alcohol with a bromination agent. In another embodiment, the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene obtained from 4-bromo-2-fluoro-5-methyl-benzyl alcohol is not isolated prior to combining with the

-10-

cyanide. In one embodiment, the bromination agent according to the foregoing step can be selected from HBr, aqueous HBr, alcoholic HBr, PBr₃, dibromodimethylhydantoin, and N-bromosuccinimide, or a combination thereof. In one embodiment, the bromination agent is aqueous HBr.

[0034] In another embodiment, the 4-bromo-2-fluoro-5-methyl-benzyl alcohol of the process according to the second aspect is obtained by combining 4-bromo-2-fluoro-5-methyl-benzoic acid or a salt or an ester thereof with a reducing agent in a non-halogenated solvent. In another embodiment, the 4-bromo-2-fluoro-5-methyl-benzyl alcohol obtained from 4-bromo-2-fluoro-5-methyl-benzoic acid, salt, or ester is not isolated prior to combining with the bromination agent.

[0035] In one embodiment, the cyanide of the process according to the second aspect can be selected from LiCN, NH₄CN, N(CH₃)₄CN, N(Et)₄CN, N(n-Pr)₄CN, N(i-Pr)₄CN, N(n-Bu)₄CN, N(t-Bu)₄CN, HCN, NaCN, KCN, Zn(CN)₂, and (CH₃)₃SiCN, or a combination thereof. In one embodiment, the cyanide is selected from N(t-Bu)₄CN, NaCN, Zn(CN)₂, or (CH₃)₃SiCN. In a particular embodiment, the cyanide is NaCN.

[0036] In one embodiment, the reducing agent of the process according to the second aspect can be selected from diborane, lithium borohydride, sodium triacetoxymborohydride, sodium cyanoborohydride, sodium borohydride, lithium aluminum hydride, and hydrogen, or a combination thereof. In one embodiment, the reducing agent is sodium borohydride. In a particular embodiment, sodium borohydride is used with boron trifluoride etherate.

[0037] In one embodiment, the hydroxide according to the process of the second aspect can be selected from LiOH, NaOH, KOH, Mg(OH)₂, Ca(OH)₂, and Sr(OH)₂, or a combination thereof. In a particular embodiment, the hydroxide is KOH.

DETAILED DESCRIPTION

[0038] It is understood in this disclosure that isolating or being isolated means the compound resulting from a synthetic step is separated and purified prior to being used in the subsequent synthetic step. In practice, a compound is considered isolated when a compound is at least 80 wt% pure, such as at least 85 wt% pure, at least 87 wt% pure, at least 90 wt% pure, at least 92 wt% pure, at least 95 wt% pure, at least 96 wt% pure, at least 97 wt% pure, at least 98 wt% pure or at least 99 wt% pure.

-11-

[0039] As is well known in the art, isolating or being isolated includes organic chemical separation and purification methods including but not limited to distillation, precipitation, crystallization, chromatography, or any combination thereof. A compound is not isolated if a reaction mixture is used for the next step in its crude form. A purification step to remove a side product or solvent, e.g., the distillation of a solvent to concentrate a reaction mixture or product mixture does not constitute isolation.

[0040] It is further well known in the art that a process or a process step is chromatography-free when no chromatography is utilized for purification during the process or process step. This excludes utilizing of chromatography for analytical purpose such as monitoring product formation and completion of reaction.

[0041] The term “halo” refers to fluorine, chlorine, bromine, or iodine.

[0042] The term “C₁-C_n alkyl” refers to a straight, or branched chain saturated hydrocarbon containing 1 to n carbon atoms. Examples of a C₁-C₃ alkyl group include, but are not limited to, methyl, ethyl and propyl.

[0043] The term “C₂-C₆ alkylene” refers to a bivalent C₂-C₆ alkyl group.

[0044] The term “C₁-C₃ haloalkyl” refers to a C₁-C₃ alkyl group, as defined herein, which is substituted with one, or more halo. Examples of C₁-C₃ haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl and pentafluoroethyl.

[0045] The term “C₁-C₃ alkoxy” refers to a straight, or branched chain saturated hydrocarbon containing 1 to 3 carbon atoms which is linked via an oxygen atom to the rest of the compound, i.e., -O(alkyl). Examples of C₁-C₃ alkoxy groups include, but are not limited to, methoxy, ethoxy and propoxy.

[0046] The term “C₁-C₃ haloalkoxy” refers to a C₁-C₃alkoxy group, as defined herein, which is substituted with one, or more halo. Examples of C₁-C₃ haloalkoxy groups include, but are not limited to, trifluoromethoxy, difluoromethoxy and pentafluoroethoxy.

[0047] The term “C₃-C₅ cycloalkyl” refers to a monocyclic saturated carbon ring containing between 3 and 5 carbon atoms. Specifically, it refers to cyclopropyl, cyclobutyl or cyclopentyl.

[0048] The term “5 or 6-membered heteroaryl” refers to a 5 or 6 membered monocyclic aromatic ring containing one or more heteroatoms, preferably selected from: N, S and O. Examples of 5-membered heteroaryls include, but are not limited to,

-12-

pyrazole, triazole and thiazole. Examples of 6-membered heteroaryls include, but are not limited to, pyridine and pyridazine.

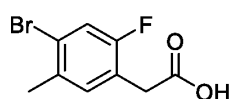
[0049] The term “C₄-C₅ heterocyclyl” refers to a 4 or 5 membered monocyclic saturated ring containing one or more heteroatoms, for example, oxetane.

[0050] The term “pharmaceutically acceptable salt” as used herein refers a salt of a compound that is acceptable for clinical and/or veterinary use. Examples of pharmaceutically acceptable salts and common methodology for preparing them can be found in “Handbook of Pharmaceutical Salts: Properties, Selection and Use” P. Stahl, *et al.*, 2nd Revised Edition, Wiley-VCH, 2011 and S.M. Berge, *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Sciences*, 1977, 66(1), 1-19.

[0051] Certain abbreviations are defined as follows: “DCM” refers to dichloromethane; “DMF” refers to N,N-dimethylformamide; “DMSO” refers to dimethyl sulfoxide; “Et” refers to ethyl; “EtOAc” refers to ethyl acetate; “h” refers to hours or hour, respectively; “i-Pr” refers to i-propyl, isopropyl or -CH(CH₃)₂; “KOAc” refers to potassium acetate; “MeOH” refers to methanol or methyl alcohol; “min” refers to minute or minutes; “MTBE” refers to methyl tert-butyl ether; “n-Bu” refers to n-butyl or -CH₂CH₂CH₂CH₃; “n-Pr” refers to n-propyl or -CH₂CH₂CH₃; “t-Bu” refers to t-butyl, tert-butyl or -C(CH₃)₃; and “THF” refers to tetrahydrofuran.

EXPERIMENTAL

Example 1



2-(4-Bromo-2-fluoro-5-methylphenyl)acetic acid

[0052] [Step 1] 4-Bromo-2-fluoro-5-methylbenzoic acid (200 g, 0.858 mol, 1 eq) was dissolved in THF (600 mL). Sodium borohydride (52 g, 1.375 mol, 1.6 eq) was added to a reactor followed by THF (1.1 L). The mixture was stirred at 27 °C for at least 30 min then cooled to 5 °C. The benzoic acid in THF was then added slowly to the reactor, keeping the temperature <25 °C. The mixture was held at 10 °C, then boron trifluoride etherate (256 g, 1.80 mol, 2.1 eq) was added, keeping the temperature <30 °C. The mixture was stirred at 25 °C until the reaction was complete (approximately 2 h, no more

-13-

than 5.0% starting material remaining). Toluene (1 L) was added and the mixture was cooled to 5 °C. Toluene (300 mL) and MeOH (300 mL) were added slowly, keeping the temperature <30 °C, then 1 M hydrochloric acid (2 L) was added, continuing to keep the temperature <30 °C. Toluene (1 L) was then added and the layers were separated. The organic layer was washed with a solution of aqueous NaHCO₃ (50 g NaHCO₃ in 1 L water) and then with water (1 L). The organic layer was concentrated under reduced pressure to a final volume of 800 mL and the product, (4-bromo-2-fluoro-5-methylphenyl)methanol, was carried forward in solution (the solution contains 183 g, 97% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 (d, *J* = 9.4 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 5.30 (t, *J* = 5.7 Hz, 1H), 4.47 (d, *J* = 5.7 Hz, 2H), 2.31 (s, 3H).

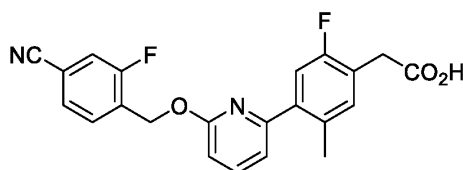
[0053] [Step 2] The toluene solution of (4-bromo-2-fluoro-5-methylphenyl)methanol (containing 183 g, 0.835 mol, 1.0 eq) from Step 1 was added to a reaction vessel. 48% HBr in water (640 mL) was added to the reactor and the mixture was heated to 90 °C. After the reaction was complete (approximately 3 h), the mixture was cooled to 27 °C. The layers were separated, and the organic layer was washed with water (915 mL) followed by two washes with aqueous NaHCO₃ in water (46 g NaHCO₃ in 915 mL, twice) to give the product, 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene, dissolved in the organic layer. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 (d, *J* = 9.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 4.64 (d, *J* = 1.0 Hz, 2H), 2.31 (s, 3H).

[0054] [Step 3] Water (457 mL) was added to a reaction vessel, followed by sodium cyanide (45 g, 0.918 moles, 1.1 eq). The mixture was stirred at 27 °C to dissolve, then cooled to 10 °C. DMSO (915 mL) was added followed by the solution of 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene solution in toluene prepared in Step 2, and the resulting mixture was heated to 35 °C. Upon reaction completion (approximately 24 h), water (457 mL) and toluene (1.1 L) were added, and the temperature lowered to 27 °C. The layers were separated, and the organic layer was washed three times with water (732 mL, then 549 mL, then 549 mL). The layers were separated and the organic layer was concentrated under reduced pressure to provide the product, 2-(4-bromo-2-fluoro-5-methylphenyl)acetonitrile (183 g, 0.802 mol, 96 % yield for two steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 (d, *J* = 9.4 Hz, 1H), 7.44 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.01 (d, *J* = 1.0 Hz, 2H), 2.33 (s, 3H).

-14-

[0055] [Step 4] Water (732 mL) was added to a reaction vessel, then KOH (140 g, 3.0 eq) was added. Ethanol (640 mL) was added to 2-(4-bromo-2-fluoro-5-methylphenyl)acetonitrile prepared in Step 3, then the resulting solution was added to the reactor with the aqueous KOH. The mixture was heated to 80 °C. Upon reaction completion (approximately 4 h), the mixture was cooled to 27 °C, then water (2.0 L) and MTBE (915 mL) were added. The layers were separated, and the aqueous layer was treated with concentrated HCl until the pH of the mixture was <4.00. The aqueous layer was then extracted twice with MTBE (2.2 L, then 732 mL). The two MTBE layers were combined and washed with water (915 mL). The layers were separated, and the organic layer was concentrated under reduced pressure until it reached approximately 732 mL volume. Heptane (1.1 L) was added, and the mixture was again distilled under reduced pressure until the volume was approximately 732 mL. Heptane (1.1 L) was added again, and the mixture was again distilled under reduced pressure until the volume was approximately 732 mL. Heptane (1.1 L) was added again, and the mixture was again distilled under reduced pressure until the volume was approximately 732 mL. The mixture was heated to 85 °C to dissolve the contents, then cooled to 20 °C, during which time the product crystallized. The product was isolated by filtration, then rinsed with heptane (183 mL), and dried under vacuum to yield 2-(4-bromo-2-fluoro-5-methylphenyl)acetic acid as a nearly white solid (170 g, 0.688 mol, 86% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.52 (s, 1H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 3.57 (d, *J* = 1.4 Hz, 2H), 2.29 (s, 3H).

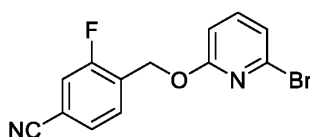
Example 2



2-(4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-fluoro-5-methylphenyl)acetic acid

Preparation of 4-(((6-Bromopyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile

-15-



[0056] 2-Bromo-6-fluoropyridine (100 g, 0.568 mol, 1 eq) was added to a reaction vessel followed by 3-fluoro-4-(hydroxymethyl)benzonitrile (90 g, 0.596 moles, 1.05 eq), and THF (600 mL). The mixture was cooled to 0 °C, then a solution of potassium tert-butoxide in THF (1.0 M, 568 mL, 0.568 mol, 1.0 eq) was added, keeping the temperature below 10 °C. The mixture was stirred at 5 °C for approximately 1 h. In a separate reactor, water (2 L) and concentrated aqueous HCl (10 mL) were added, and the mixture cooled to 5 °C. The reaction mixture from the first reaction vessel was added slowly, keeping the temperature below 10 °C. The mixture was stirred at 2.5 °C for at least 1 h, then the mixture was filtered and rinsed with water (300 mL). The solids were charged to a reaction vessel, followed by isopropanol (500 mL). The mixture was heated to 65 °C for a least 30 min, then cooled to 10 °C. The mixture was stirred for at least 1 h, then filtered and rinsed with water (200 mL). The solids were dried under vacuum to give the product, 4-(((6-bromopyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile, as a white solid (165 g, 0.537 mol, 95% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 7.92 (d, J = 10.0 Hz, 1H), 7.75 (t, J = 1.6 Hz, 1H), 7.74 (d, J = 0.9 Hz, 1H), 7.70 (dd, J = 7.7, 8.1 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 5.43 (d, J = 1.1 Hz, 2H).

[0057] Alternative Method for the Preparation of 4-(((6-Bromopyridine-2-yl)oxy)methyl)-3-fluorobenzonitrile: 3-Fluoro-4-(hydroxymethyl)benzonitrile (36 kg, 240 mmol), 2-methyltetrahydrofuran (324 L), 2-bromo-6-fluoropyridine (43.2 kg, 245 mmol) and 1,2-dimethoxyethane (108 L) were charged into a reactor under argon. The solution was heated to 29 °C and powdered KOH (20.16 kg, 359.3 mmol) was charged in two portions to the solution. The mixture was then heated to 45 °C until content of 3-fluoro-4-(hydroxymethyl)benzonitrile was <3.0 area% by HPLC (5 h). The reaction mixture was allowed to cool to 27 °C then adjusted to pH 5.50 -7.50 using aqueous acetic acid solution (made from 6.84 L acetic acid diluted with 180 L water) at 27 °C. The reaction mixture was stirred and then the layers were allowed to settle. The bottom aqueous layer was separated from the top organic product-containing layer. The lower aqueous layer was back-extracted with 108 L 2-methyltetrahydrofuran, and the organic layers were combined. The combined organic layers were washed with aqueous NaCl solution (made

-16-

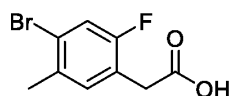
from 18 kg NaCl and 180 L water). The resulting organic product solution was concentrated under reduced pressure below 55 °C to a volume of 180 L. Isopropanol (180 L) was charged to the contents while under 55 °C then concentration was continued under reduced pressure and below 60 °C to 5 ± 1 volumes. Addition of isopropanol (180 L) and concentration again to 5 ± 1 volumes was repeated twice to give a white heterogeneous mixture. The temperature was raised to 65 °C and water (72 L) was slowly added while maintaining temperature at 65 °C, followed by stirring for 1 h after completed addition. The reaction was cooled to 10 °C over a period of 6 h and then stirred for 2 h at 5 to 10 °C. Solids were collected and washed with water, then dried under reduced pressure with heating to 55 °C to give 4-(((6-bromopyridine-2-yl)oxy)methyl)-3-fluorobenzonitrile (62.55 kg, 203.7 mmol, 85% yield) as a light yellow solid in 99.4% purity (HPLC area%).

[0058] 2-(4-Bromo-2-fluoro-5-methylphenyl)acetic acid (50 g, 0.202 mol, 1 eq) was added to a reaction vessel, followed by isopropanol (450 mL). The mixture was stirred at 30 °C, then bis(pinacolato)diboron (56.5 g, 0.222 moles, 1.1 eq) was added, followed by KOAc (61.5 g, 0.626 moles, 3.1 eq). The mixture was sparged with inert gas for at least 30 min, then 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II).DCM complex (2.5 g, 0.003 moles, 0.015 eq) was added. The mixture was heated to 80 °C for approximately 10 h. The mixture was cooled to 30 °C, then 4-(((6-bromopyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile (62.1 g, 0.202 moles, 1.0 eq) was added. A solution of potassium carbonate in water (56 g K₂CO₃ in 200 mL water) was added, and the reactor purged with inert gas. The mixture was heated to 80 °C. After approximately 3 h, the mixture was cooled to 60 °C, then concentrated under reduced pressure until the remaining volume was approximately 300 mL. The mixture was cooled to 27 °C, then water (850 mL) was added. Concentrated HCl in water (30 mL) was added, followed by MTBE (1 L), then additional concentrated HCl in water (55 mL). Once the pH reached <4.00, the mixture was heated to 45 °C. The layers were separated, and the organic layer was washed with water (250 mL). The organic layer was treated with activated charcoal (7.5 g), then filtered through Celite® Hyflo Super Cel® filter aid and rinsed with MTBE (200 mL). The filtrate was concentrated under reduced pressure until the remaining volume was approximately 250 mL. Heptane (500 mL) was added, and the mixture was stirred at 45 °C for at least 1 h, then cooled to 25 °C. The resulting mixture was filtered

-17-

and the filter cake was rinsed with heptane (50 mL). The crude solid was added to a reaction vessel, followed by isopropanol (200 mL) and water (200 mL). The mixture was heated to 75 °C, then cooled to 20 °C. The mixture was filtered and the filter cake was rinsed with water (50 mL). The solids were added to a reaction vessel, followed by water (300 mL). The mixture was heated to 40 °C, stirred at least 30 min, then filtered at 40 °C and the filter cake was rinsed with water (50 mL). The resulting solids were dried under vacuum to provide the product, 2-(4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-fluoro-5-methylphenyl)acetic acid, as a white solid (58 g, 0.147 mol, 73% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.50 (s, 1H), 7.89 (d, *J* = 10.6 Hz, 1H), 7.85 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.72 (s, 1H), 7.71 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.21 (dd, *J* = 7.4, 6.7 Hz, 1H), 7.17 (d, *J* = 10.6 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.51 (s, 2H), 3.63 (s, 2H), 2.23 (s, 3H).

Comparative Example 3



2-(4-Bromo-2-fluoro-5-methylphenyl)acetic acid

[0059] [Step 1] 4-Bromo-2-fluoro-5-methylbenzoic acid (2.0 g, 8.4 mmol, 1 eq) was added to a reactor. THF (20 mL) was added, followed by a solution of borane.dimethyl sulfide complex (2 M solution in THF, 5 mL, 10 mmol). The mixture was stirred at 25 °C. Upon reaction completion, MeOH (5 mL) was added. The mixture was concentrated, then EtOAc (40 mL) and 1 M HCl in water (20 mL) was added. The layers were separated, and the organic layer was washed with saturated aqueous NaCl (40 mL). The organics were dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was purified by silica gel chromatography with EtOAc/hexanes (10-35% EtOAc over 15 min) to provide the product, (4-bromo-2-fluoro-5-methylphenyl)methanol, as a solid (97wt%, 1.9 g, 8.4 mmol, quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 (d, *J* = 9.4 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 5.30 (t, *J* = 5.7 Hz, 1H), 4.47 (d, *J* = 5.7 Hz, 2H), 2.31 (s, 3H).

[0060] [Step 2] (4-Bromo-2-fluoro-5-methylphenyl)methanol (97 wt%, 1.9 g, 8.4 mmol 1 eq) was added to a reaction vessel. DCM (20 mL) was added. The mixture was

-18-

cooled to 0 °C, then phosphorus tribromide (1.0 mL, 2.85 g, 10.5 mmol, 1.25 eq) was added slowly. The mixture was stirred at 0 °C for 15 min, then saturated aqueous NaHCO₃ (30 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (40 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), then dried over Na₂SO₄, filtered, and concentrated to give 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene as a solid which was used in its entirety in Step 3. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 (d, *J* = 9.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 4.64 (d, *J* = 1.0 Hz, 2H), 2.31 (s, 3H).

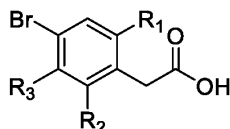
[0061] [Step 3] 1-Bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene (as prepared in Step 2) was dissolved in DMSO (10 mL), then sodium cyanide (0.6 g, 12.2 mmoles, 1.45 eq) was added. The mixture was stirred at 25 °C for approximately 1 h. EtOAc (50 mL) was added, followed by water (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous NaCl (50 mL). The organic layer was dried over Na₂SO₄ and concentrated to dryness to provide the product, 2-(4-bromo-2-fluoro-5-methylphenyl)acetonitrile, as a solid (1.3 g, 5.7 mmol, 68% yield over Steps 2 and 3). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.62 (d, *J* = 9.4 Hz, 1H), 7.44 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.01 (d, *J* = 1.0 Hz, 2H), 2.33 (s, 3H).

[0062] [Step 4] 2-(4-Bromo-2-fluoro-5-methylphenyl)acetonitrile (1.2 g, 5.1 mmol, 1 eq) was added to a reaction vessel. Ethanol (5 mL) and water (3 mL) were added, followed by KOH (0.9 g). The mixture was heated to 90 °C and stirred overnight. The mixture was cooled to 5 °C, then 1 M HCl was added until the pH was between 4-5. EtOAc (30 mL) and water (30 mL) are added. The layers were separated and the organic layer was washed with saturated aqueous NaCl (30 mL). The layers were separated, and the organic layer was dried over Na₂SO₄, then concentrated to provide the product, 2-(4-bromo-2-fluoro-5-methylphenyl)acetic acid, as a solid (1.0 g, 4.1 mmol, 80% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.52 (s, 1H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 3.57 (d, *J* = 1.4 Hz, 2H), 2.29 (s, 3H).

-19-

WE CLAIM:

1. A process for preparing a compound of the formula:



or salt thereof, wherein

R₁ is selected from H, F, and CH₃,

R₂ is selected from H, F, and CH₃,

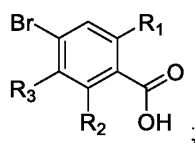
R₃ is selected from H, F and CH₃,

and

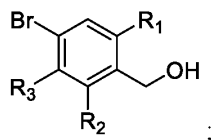
R₁, R₂, and R₃ are not the same;

comprising the steps of:

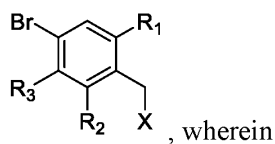
- i. combining a non-halogenated solvent with a benzoic acid of the formula:



- ii. adding a reducing agent to form a benzyl alcohol of the formula:



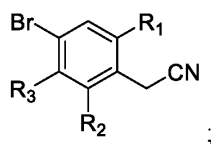
- iii. combining the benzyl alcohol with a reagent in a second non-halogenated solvent to form a first intermediate of the formula:



X is selected from Cl, Br, I, a sulfonate, and a tosylate;

-20-

- iv. combining the first intermediate with a cyanide to form a benzyl nitrile of the formula

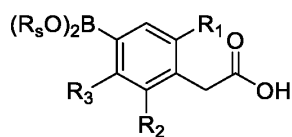


- v. combining the benzyl nitrile with a hydroxide;

wherein one or more of the following is not isolated prior to the next step: the benzyl alcohol of step (ii), the first intermediate of step (iii), and the benzyl nitrile of step (iv).

2. The process according to claim 1 further comprising the steps of:

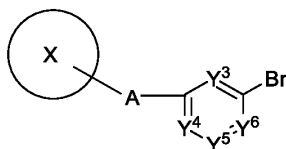
- vi. combining the compound resulting from step (v) with a borane reagent and a catalyst to form a boronate of the formula



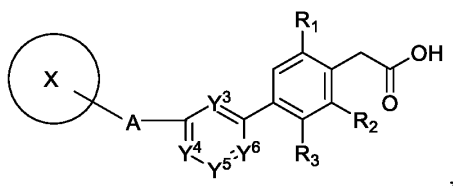
, wherein R_s is a C_1 - C_6 alkyl, or a C_2 - C_6 alkylene

forming a cyclic boronate;

- vii. combining the boronate with a compound of the formula



to arrive at a compound of the formula



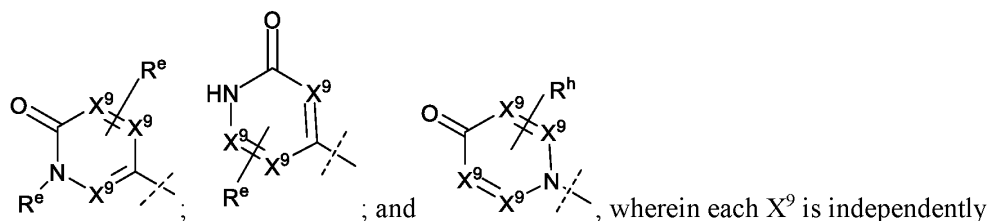
wherein R_1 , R_2 and R_3 are as defined in claim 1 and



is phenyl; a 5 or 6-membered heteroaryl; or pyridone; which phenyl, 5 or 6-membered heteroaryl or pyridone is optionally substituted with one or two R^{1a} ;

-21-

R^{1a} is at each occurrence independently selected from: CN; halo; C₁-C₃ alkyl, which can be optionally substituted with OH; C₁-C₃ haloalkyl; C₁-C₃ alkoxy; C₃-C₅ cycloalkyl; -SO₂C₁-C₃ alkyl; -C(O)NH₂;



wherein each X⁹ is independently CH or N and no more than one X⁹ in the ring is N, each R^e is independently selected from: H, C₁-C₃ haloalkyl, halo, C₃-C₅ cycloalkyl and C₁-C₃ alkyl optionally substituted with OH, R^h is H, C₁-C₃ haloalkyl, halo, C₃-C₅ cycloalkyl, OH, -NR^cR^d or C₁-C₃ alkyl optionally substituted with OH;

5- or 6- membered heteroaryl or phenyl, wherein the heteroaryl or phenyl is optionally substituted with one or two substituents independently selected from: C₁-C₃ alkoxy, C₃-C₅ cycloalkyl, -CH₂-C₃-C₅ cycloalkyl, -SO₂C₁-C₃ alkyl, C₄-C₅ heterocyclyl, -CH₂-C₄-C₅ heterocyclyl, halo, C₁-C₃ haloalkyl, C₁-C₃ haloalkoxy, CN, -CONR^cR^d, -NR^cR^d and C₁-C₃ alkyl optionally substituted with OH;

-A- is -CH₂O-; -OCH₂-; or -CH₂NH-;

Y³, Y⁴, Y⁵ and Y⁶ are independently N; CH; or CR^{2a}; wherein no more than two of Y³, Y⁴, Y⁵ and Y⁶ are N and no more than two of Y³, Y⁴, Y⁵ and Y⁶ are CR^{2a};

R^{2a} at each occurrence is independently halo or methyl; and

R^c and R^d are each independently H or C₁-C₃alkyl.

3. The process according to claim 1 or claim 2, wherein the non-halogenated solvent and the second non-halogenated solvent can be independently selected from acetone, acetonitrile, anisole, butyl acetate, *t*-butylmethyl ether, cumene, cyclohexane, dimethylformamide, dimethylsulfoxide, ethanol, ethyl acetate, ethyl ether, heptane,

-22-

hexane, isopropanol, methanol, methylbutylketone, methylethylketone, pentane, pyridine, tetrahydrofuran, toluene, and xylenes, or a combination thereof.

4. The process according to any one of claims 1 to 3, wherein the reducing agent is selected from diborane, lithium borohydride, sodium triacetoxymethylborohydride, sodium cyanoborohydride, sodium borohydride, lithium aluminum hydride, and hydrogen, or a combination thereof.

5. The process according to any one of claims 1 to 4, wherein the reagent in step iii is selected from HBr, aqueous HBr, alcoholic HBr, PBr₃, dibromodimethylhydantoin, N-bromosuccinimide, HI, aqueous HI, PCl₃, and tosylchloride, or a combination thereof.

6. The process according to any one of claims 1 to 5, wherein the cyanide is selected from LiCN, NH₄CN, N(CH₃)₄CN, N(Et)₄CN, N(n-Pr)₄CN, N(i-Pr)₄CN, N(n-Bu)₄CN, N(t-Bu)₄CN, HCN, NaCN, KCN, Zn(CN)₂, and (CH₃)₃SiCN, or a combination thereof.

7. The process according to any one of claims 1 to 6, wherein the hydroxide is selected from LiOH, NaOH, KOH, Mg(OH)₂, Ca(OH)₂, or Sr(OH)₂, or a combination thereof.

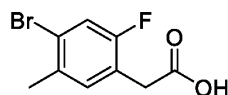
8. The process according to claim 1 wherein the yield of the compound resulting from step (v) is at least 70 wt%, at least 75 wt%, at least 78 wt%, at least 80 wt%, at least 82 wt%, or at least 85 wt% as calculated from the benzoic acid of step (i).

9. The process according to claim 2 wherein the yield of the compound resulting from step (vii) is at least 60 wt%, at least 65 wt%, at least 70 wt% or at least 72 wt% as calculated from the compound resulting from step (v).

10. The process according to any one of the preceding claims, wherein the benzyl alcohol of step (ii) is not isolated prior to step (iii), and the first intermediate of step (iii) is not isolated prior to step (iv), and the benzyl nitrile of step (iv) is not isolated prior to step (v).

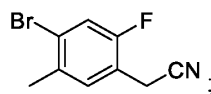
-23-

11. A process for preparing a compound of the formula:



or salt thereof, comprising the steps of:

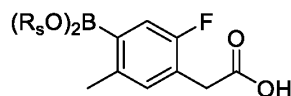
- i. combining 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene with a cyanide in a non-halogenated solvent to form a benzyl nitrile of the formula



- ii. combining the benzyl nitrile with a hydroxide to produce the compound, wherein the benzyl nitrile is not isolated prior to step (ii).

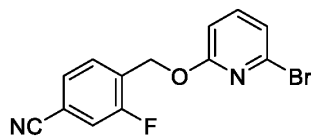
12. The process according to claim 11 further comprising:

- iii. combining the compound resulting from step (ii) with a borane reagent and a catalyst to form a boronate of the formula

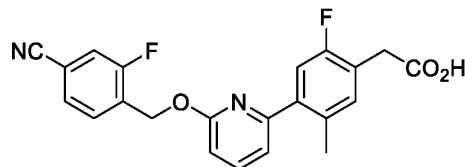


wherein R_s is a C_1 - C_6 alkyl, or a C_2 - C_6 alkylene forming a cyclic boronate;

- iv. combining the boronate of step (iii) with a pyridine of the formula:



to arrive at a compound of the formula

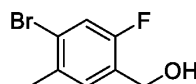


13. The process according to claim 12 wherein the boronate is not isolated prior to combining with the pyridine.

-24-

14. The process according to any one claim of claims 11 to 13, wherein the non-halogenated solvent is selected from acetone, acetonitrile, anisole, butyl acetate, *t*-butylmethyl ether, cumene, cyclohexane, dimethylformamide, dimethylsulfoxide, ethanol, ethyl acetate, ethyl ether, isopropanol, methanol, heptane, hexane, methylbutylketone, methylethylketone, pentane, pyridine, tetrahydrofuran, toluene, and xylenes, or a combination thereof.

15. The process according to any one of claims 11 to 13, wherein the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene is obtained by combining a benzyl alcohol of the formula

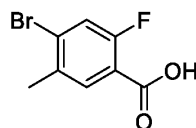


with a bromination agent.

16. The process according to claim 15 wherein the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene is not isolated prior to combining with the cyanide.

17. The process according to claim 15 or claim 16, wherein the bromination agent is selected from HBr, aqueous HBr, alcoholic HBr, PBr₃, dibromodimethylhydantoin, and N-bromosuccinimide, or a combination thereof.

18. The process according to any one claim of claims 15 to 17, wherein the benzyl alcohol is obtained by combining a benzoic acid of the formula



with a reducing agent in a non-halogenated solvent.

19. The process according to claim 18, wherein the benzyl alcohol is not isolated prior combining with the bromination agent.

20. The process according to claim 18 or claim 19, wherein the reducing agent is selected from a diborane, lithium borohydride, sodium triacetoxyborohydride, sodium

-25-

cyanoborohydride, sodium borohydride, lithium aluminum hydride, and hydrogen, or a combination thereof.

21. The process according to any one claim of claims 11 to 20, wherein the cyanide is selected from LiCN, NH₄CN, N(CH₃)₄CN, N(Et)₄CN, N(n-Pr)₄CN, N(i-Pr)₄CN, N(n-Bu)₄CN, N(t-Bu)₄CN, HCN, NaCN, KCN, Zn(CN)₂, and (CH₃)₃SiCN, or a combination thereof.

22. The process according to any one claim of claims 11 to 21, wherein the hydroxide is selected from LiOH, NaOH, KOH, Mg(OH)₂, Ca(OH)₂, and Sr(OH)₂, or a combination thereof.