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 phenylacetonitriles and substituted phenylacetic acids. These compounds are intermediates in the preparation of certain glucagon-like peptide-1 (GLP-1) receptor agonists.

BACKGROUND

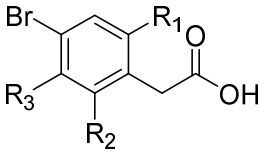
[0002] Substituted phenylacetonitriles and substituted phenylacetic acids are intermediates in the preparation of certain GLP-1 receptor agonists, including the benzimidazole compounds disclosed in WO2020/263695. The process disclosed in WO2020/263695 for preparing the substituted phenylacetonitrile 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 disclosure 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.

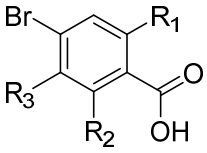
[0005] In a first item, the present disclosure provides a process for preparing a compound of the formula:



or salt thereof, wherein R_1 is selected from H, F, and CH_3, R_2 is selected from H, F, and CH_3, R_3 is selected from H, F and CH_3, and R_1, R_2, and R_3 are not the same.

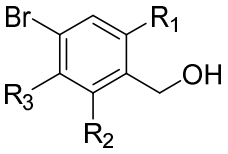
[0006] In one example, the process includes:

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



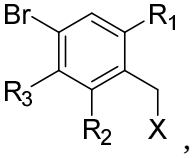
;

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



;

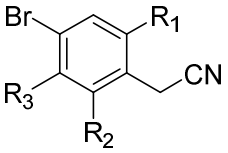
iii. combining the benzyl alcohol with a reagent in a second non-halogenated solvent to form a first intermediate of the formula:



,

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

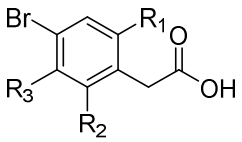


;

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).

[0006a] In an aspect, the present disclosure provides a process for preparing a compound of the formula:



or salt thereof, wherein

R_1 is selected from H, F, and CH_3,

R_2 is selected from H, F, and CH_3,

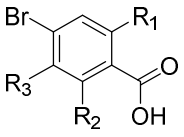
R_3 is selected from H, F and CH_3,

and

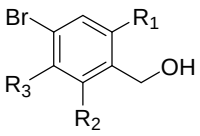
R_1, R_2, and R_3 are not the same;

comprising the steps of:

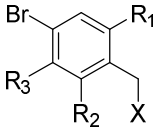
i. combining a non-halogenated solvent with a benzoic acid of the formula:


;

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

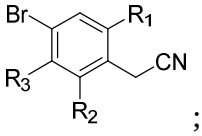

;

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


, 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

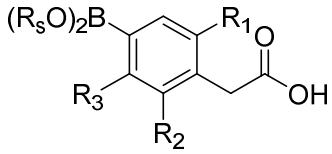

;

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).

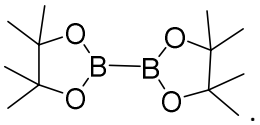
[0007] In a particular example, X is Br.

[0008] In one example, the process according to the first item 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

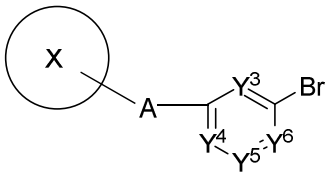


wherein R_s is a C_1-C_6 alkyl, or a C_2-C_6 alkylene forming a cyclic boronate. In a particular example, R_s is C_6 alkylene.

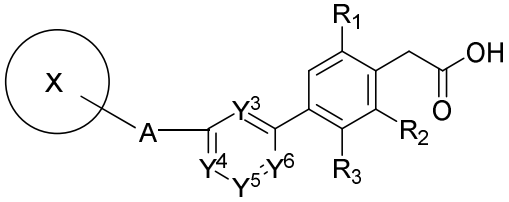
[0009] In one example, the borane reagent is 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (or *bis*(pinacolato)diboron):



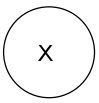
[0010] In yet another example, the process can further include (step vii) combining the boronate with a compound of the formula



to arrive at a compound of the formula

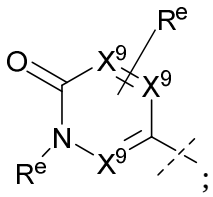
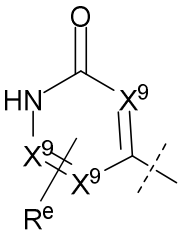
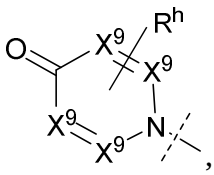


wherein R_1, R_2 and R_3 are as defined above, and



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; -$C(O)NH_2$;


; 
; and , wherein each X^9 is independently CH or N and no more than one X^9 in the ring is N, each R^e is independently selected from: H, C_1-C_3 haloalkyl, halo, C_3-C_5 cycloalkyl and C_1-C_3 alkyl optionally substituted with OH, R^h is H, C_1-C_3 haloalkyl, halo, C_3-C_5 cycloalkyl, OH, -NR^cR^d or C_1-C_3 alkyl optionally substituted with OH;

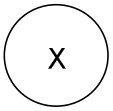
5- or 6- membered heteroaryl or phenyl, wherein the heteroaryl or phenyl is optionally substituted with one or two substituents independently selected from: C_1-C_3 alkoxy, C_3-C_5 cycloalkyl, -CH_2-C_3-C_5 cycloalkyl, -SO_2C_1-C_3 alkyl, C_4-C_5 heterocyclyl, -CH_2-C_4-C_5 heterocyclyl, halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, CN, -$CONR^cR^d$, -NR^cR^d and C_1-C_3 alkyl optionally substituted with OH;

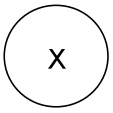
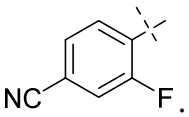
-A- is -CH_2O-; -OCH_2-; or -CH_2NH-;

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 C_1-C_3alkyl.

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

[0012] In a particular example,  is .

[0013] In an example, -A- is -CH_2O-.

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

[0015] In an example of the above compounds, R_1 is F, R_2 is H and R_3 is CH_3.

[0016] In one example, the non-halogenated solvent and the second non-halogenated solvent of the process according to the first item can be different or the same. In an example, 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 example, the non-halogenated solvents are independently selected from: THF and toluene.

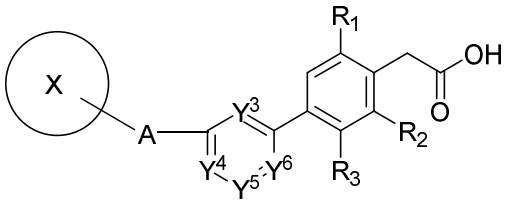
[0017] In yet another example, the reducing agent of the process according to the first item can be selected from diborane, lithium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, sodium borohydride, lithium aluminum hydride, and hydrogen, or a combination thereof. In one example,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

[0018] In one further example, the reagent in step iii of the process of the first item can be selected from HBr, aqueous HBr, alcoholic HBr, PBr_3, dibromodimethylhydantoin, N-bromosuccinimide, HI, aqueous HI, PCl_3, and tosylchloride, or a combination thereof. In one example, the reagent is aqueous HBr.

[0019] In one example, the cyanide of the process according to the first item can be selected from LiCN, NH_4CN, $N(CH_3)_4CN$, $N(Et)_4CN$, $N(n\text{-}Pr)_4CN$, $N(i\text{-}Pr)_4CN$, $N(n\text{-}Bu)_4CN$, $N(t\text{-}Bu)_4CN$, HCN, NaCN, KCN, $Zn(CN)_2$, and $(CH_3)_3SiCN$, or a combination thereof. In one example, the cyanide is selected from $N(t\text{-}Bu)_4CN$, NaCN, $Zn(CN)_2$, and $(CH_3)_3SiCN$. In a particular example, the cyanide is NaCN.

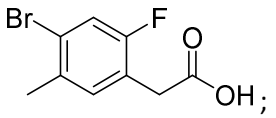
[0020] In one example, the hydroxide according to the process of the first item can be selected from LiOH, NaOH, KOH, $Mg(OH)_2$, $Ca(OH)_2$, or $Sr(OH)_2$, or a combination thereof. In a particular example, the hydroxide is KOH.

[0021] In one example, the process according to the first item 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).

[0022] In another example, the process according to first item 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 example, in the process according to the first item 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 example, in the process according to the first item 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 example, in the process according to the first item 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 example, the process for preparing the compound is chromatography-free. In yet another example, 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 item, the present disclosure provides a process for preparing a compound of the formula:

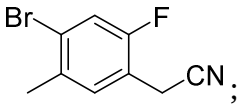


or salt thereof.

[0025] In one example, the process according to the second item includes:

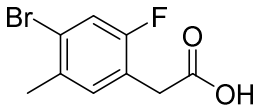
i. combining 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene with a cyanide in a non-halogenated solvent to form a benzyl nitrile of the

formula



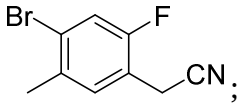
ii. combining the benzyl nitrile with a hydroxide to produce the compound, wherein the benzyl nitrile is not isolated prior to step (ii).

[0025a] In another aspect, the present disclosure provides a process for preparing a compound of the formula:



or salt thereof, comprising the steps of:

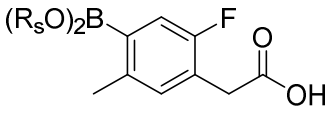
i. combining 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene with a cyanide in a non-halogenated solvent to form a benzyl nitrile of the formula



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

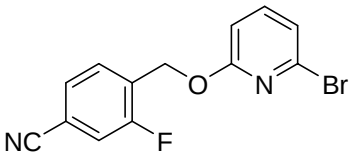
[0026] In one example, the process according to the second item further comprises

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

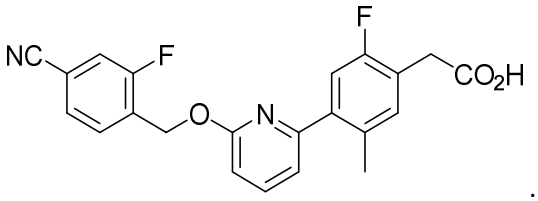


wherein R_s is a C_1-C_6 alkyl, or a C_2-C_6 alkylene forming a cyclic boronate;

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

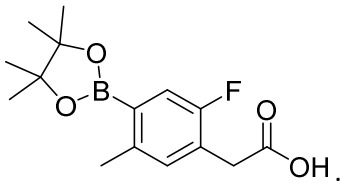


to arrive at a compound of the formula:



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[0027] In one example, 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 example, the boronate according to the process of the second item is

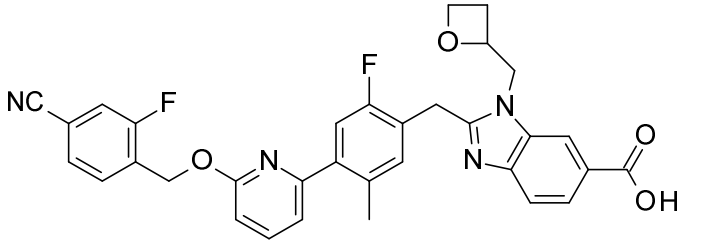


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[0028] In another example, the process according to the second item further comprises the steps of:

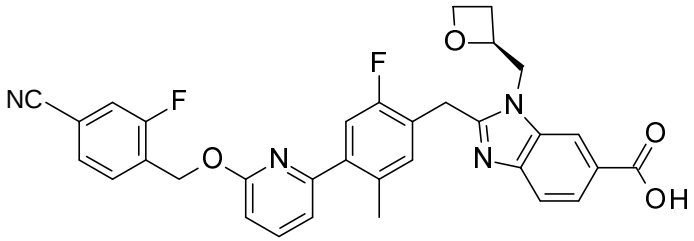
[0029] In a particular example, R is H or C_1-C_4 alkyl.

[0030] In a further example, 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:



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



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

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

[0032] In another example, 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 example, the non-halogenated solvents are independently selected from: THF and toluene.

[0033] In another example, the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene of the process according to the second item is obtained by combining 4-bromo-2-fluoro-5-methyl-benzyl alcohol with a bromination agent. In another example, 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

cyanide. In one example, the bromination agent according to the foregoing step can be selected from HBr, aqueous HBr, alcoholic HBr, PBr_3, dibromodimethylhydantoin, and N-bromosuccinimide, or a combination thereof. In one example, the bromination agent is aqueous HBr.

[0034] In another example, the 4-bromo-2-fluoro-5-methyl-benzyl alcohol of the process according to the second item 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 example, 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 example, the cyanide of the process according to the second item can be selected from LiCN, NH_4CN, $N(CH_3)_4CN$, $N(Et)_4CN$, $N(n\text{-}Pr)_4CN$, $N(i\text{-}Pr)_4CN$, $N(n\text{-}Bu)_4CN$, $N(t\text{-}Bu)_4CN$, HCN, NaCN, KCN, $Zn(CN)_2$, and $(CH_3)_3SiCN$, or a combination thereof. In one example, the cyanide is selected from $N(t\text{-}Bu)_4CN$, NaCN, $Zn(CN)_2$, or $(CH_3)_3SiCN$. In a particular example, the cyanide is NaCN.

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

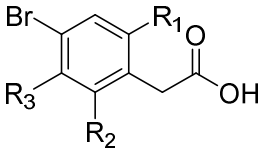
[0037] In one example, the hydroxide according to the process of the second item can be selected from LiOH, NaOH, KOH, $Mg(OH)_2$,$Ca(OH)_2$, and $Sr(OH)_2$, or a combination thereof. In a particular example, the hydroxide is KOH.

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.

WE CLAIM:

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



or salt thereof, wherein

R_1 is selected from H, F, and CH_3,

R_2 is selected from H, F, and CH_3,

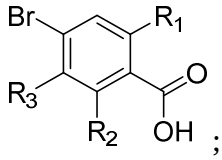
R_3 is selected from H, F and CH_3,

and

R_1, R_2, and R_3 are not the same;

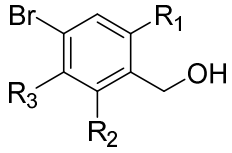
comprising the steps of:

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



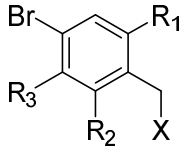
;

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



;

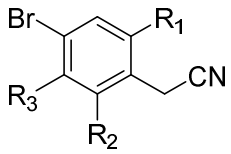
iii. combining the benzyl alcohol with a reagent in a second non-halogenated solvent to form a first intermediate of the formula:



, 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



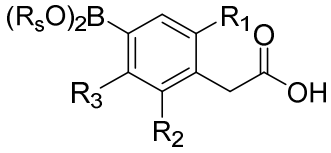
;

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).

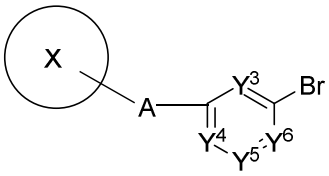
2. The process according to claim 1 further comprising the steps of:

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

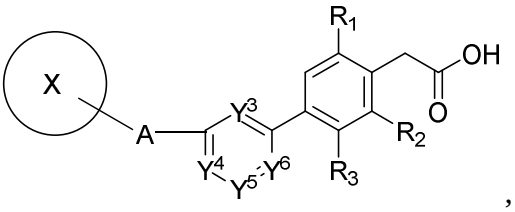


, wherein R_s is a C_1-C_6 alkyl, or a C_2-C_6 alkylene forming a cyclic boronate;

vii. combining the boronate with a compound of the formula

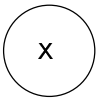


to arrive at a compound of the formula



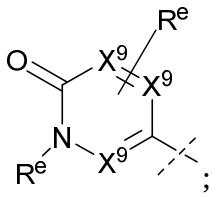
,

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

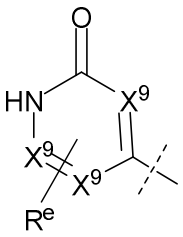


is phenyl; a 5 or 6-membered heteroaryl; or pyridone; which phenyl, 5 or 6-membered heteroaryl or pyridone is optionally substituted with one or two R^{1a};

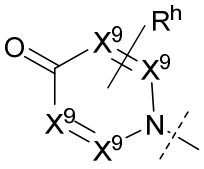
R^{1a} is at each occurrence independently selected from: CN; halo; C_1-C_3 alkyl, which can be optionally substituted with OH; C_1-C_3 haloalkyl; C_1-C_3 alkoxy; C_3-C_5 cycloalkyl; -SO_2C_1-C_3 alkyl; -$C(O)NH_2$;



;



; and



, wherein each X^9 is independently CH or N and no more than one X^9 in the ring is N, each R^e is independently selected from: H, C_1-C_3 haloalkyl, halo, C_3-C_5 cycloalkyl and C_1-C_3 alkyl optionally substituted with OH, R^h is H, C_1-C_3 haloalkyl, halo, C_3-C_5 cycloalkyl, OH, -NR^cR^d or C_1-C_3 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: C_1-C_3 alkoxy, C_3-C_5 cycloalkyl, -CH_2-C_3-C_5 cycloalkyl, -SO_2C_1-C_3 alkyl, C_4-C_5 heterocyclyl, -CH_2-C_4-C_5 heterocyclyl, halo, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, CN, -$CONR^cR^d$, -NR^cR^d and C_1-C_3 alkyl optionally substituted with OH;

-A- is -CH_2O-; -OCH_2-; or -CH_2NH-;

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 C_1-C_3alkyl.

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,

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

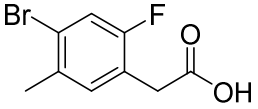
5. The process according to any one of claims 1 to 4, wherein the reagent in step iii is selected from HBr, aqueous HBr, alcoholic HBr, PBr_3, dibromodimethylhydantoin, N-bromosuccinimide, HI, aqueous HI, PCl_3, and tosylchloride, or a combination thereof.

6. The process according to any one of claims 1 to 5, wherein the cyanide is selected from LiCN, NH_4CN, $N(CH_3)_4CN$, $N(Et)_4CN$, $N(n\text{-}Pr)_4CN$, $N(i\text{-}Pr)_4CN$, $N(n\text{-}Bu)_4CN$, $N(t\text{-}Bu)_4CN$, HCN, NaCN, KCN, $Zn(CN)_2$, and $(CH_3)_3SiCN$, 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.

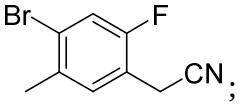
8. The process according to any one of the preceding claims, wherein
the benzyl alcohol of step (ii) is not isolated prior to step (iii), and
the first intermediate of step (iii) is not isolated prior to step (iv), and
the benzyl nitrile of step (iv) is not isolated prior to step (v).

9. 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

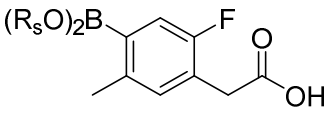


;

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

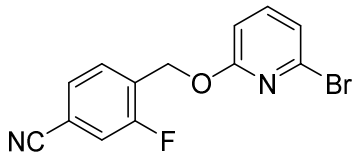
10. The process according to claim 9 further comprising:

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

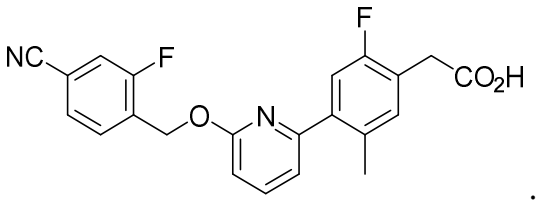


wherein R_s is a C_1-C_6 alkyl, or a C_2-C_6 alkylene forming a cyclic boronate;

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



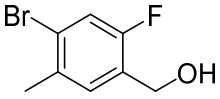
to arrive at a compound of the formula



.

11. The process according to claim 10 wherein the boronate is not isolated prior to combining with the pyridine.

12. The process according to any one of claims 9 to 11, wherein the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene is obtained by combining a benzyl alcohol of the formula

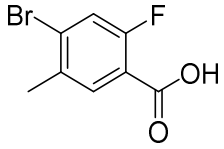


with a bromination agent.

13. The process according to claim 12 wherein the 1-bromo-4-(bromomethyl)-5-fluoro-2-methylbenzene is not isolated prior to combining with the cyanide.

14. The process according to claim 12 or claim 13, wherein the bromination agent is selected from HBr, aqueous HBr, alcoholic HBr, PBr_3, dibromodimethylhydantoin, and N-bromosuccinimide, or a combination thereof.

15. The process according to any one claim of claims 12 to 14, wherein the benzyl alcohol is obtained by combining a benzoic acid of the formula



with a reducing agent in a non-halogenated solvent.

16. The process according to claim 15, wherein the benzyl alcohol is not isolated prior combining with the bromination agent.