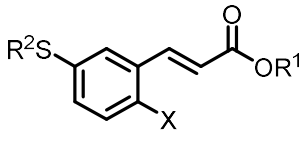
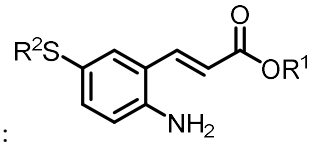
[0019] (b) introducing a halogenating agent (including fluorinating, chlorinating, brominating, or iodinating agent), a cyanating agent, a trifluoromethylation agent, or a hydroxylating agent, optionally in the presence of a solvent-2, to form said compound (1); wherein said solvent-1 and solvent-2 can be identical or different; and

[0020] Wherein said compound (2) is prepared in a process free of palladium catalyst.

[0020a] In one aspect, the present disclosure refers to a process for the preparation of a compound having formula (1), or a pharmaceutically acceptable salt thereof:


(1);

the process comprising:

(a) contacting a compound of formula (2):  (2);

with a first acid in a first solvent, and in the presence of a nitrous salt;

(b) introducing a halogenating agent, a cyanating agent, a trifluoromethylation agent, or a hydroxylating agent, optionally in the presence of a second solvent, to form said compound (1); wherein said first solvent and second solvent can be identical or different; and

wherein said compound (2) is prepared in a process free of palladium catalyst,

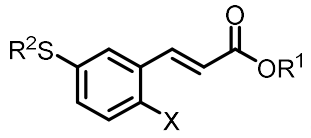
wherein: X is halo, CN, CF_3, or OH; R^1 is (C_1-C_6)alkyl; a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl; or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkyl or heterocycloalkyl group; and wherein the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group; and R^2 is selected from (C_1-C_6)alkyl or benzyl.

[0021] In a sub-example of example 1, in (a), said acid HA is HCl, HBr, HI, p-TsOH, or H_2SO_4. Preferably the acid HA is HCl.

[0022] In a further sub-example of example 1, in (a), said solvent-1 is water, THF, methyl THF, CH_3CN, or (C_1-C_6)alkyl acetate solvent, or mixtures thereof. Preferably, said solvent-1 is ethyl acetate or isopropyl acetate.p

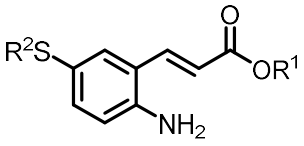
WE CLAIM:

1. A process for the preparation of a compound having formula (1), or a pharmaceutically acceptable salt thereof:



(1);

the process comprising:

(a) contacting a compound of formula (2): 

(2); with a first acid in a first solvent, and in the presence of a nitrous salt;

(b) introducing a halogenating agent, a cyanating agent, a trifluoromethylation agent, or a hydroxylating agent, optionally in the presence of a second solvent, to form said compound (1); wherein said first solvent and second solvent can be identical or different; and

wherein said compound (2) is prepared in a process free of palladium catalyst,

wherein:

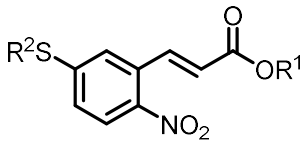
X is halo, CN, CF_3, or OH;

R^1 is $(C_1\text{-}C_6)$alkyl; a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl; or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkyl or heterocycloalkyl group; and

wherein the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group; and

R^2 is selected from $(C_1\text{-}C_6)$alkyl or benzyl.

2. The process according to claim 1, wherein said compound (2) is prepared by a process comprising:

(c1) activating a metal in the presence of a second acid in a polar solvent; and contacting a compound of formula (3): 

(3);

with said activated metal at an elevated temperature in a polar solvent to form said compound (2); or

(c2) reacting said compound of formula (3), optionally in the presence of a co-solvent, with an enzymatic reducing agent in an aqueous buffer solution, and in the presence of at least one catalyst and a co-factor, to form said compound of formula (2).

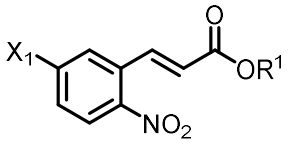
3. The process according to claim 2, comprising:

(c1) activating said metal in the presence of said second acid in a polar solvent; and contacting said compound of formula (3) with said activated metal at an elevated temperature in a polar solvent to form said compound (2).

4. The process according to claim 2, comprising:

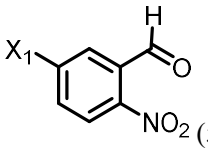
(c2) contacting said compound of formula (3), in the presence of a co-solvent, with said enzymatic reducing agent in an aqueous buffer, and in the presence of said metal catalyst, co-catalyst, and co-factor, to form said compound of formula (2).

5. The process according to any one of claims 1 to 4, wherein said compound (3) is prepared by a process comprising:

(d) contacting a compound of formula (4):  (4); with a thiol agent in the presence of a base, in an organic solvent, and at an elevated temperature; to form said compound (3),

wherein X_1 is halo.

6. The process according to claim 5, wherein said compound (4) is prepared by a process comprising:

(e) contacting a compound of formula (5):  (5); with an alkenating agent, in the presence of a base, in an organic solvent to form said compound (4).

7. The process according to any one of claims 1 to 6, wherein in step (a):

(i) said first acid is HCl, HBr, HI, p-TsOH, or H_2SO_4; and/or

(ii) said first solvent is water, THF, methyl THF, CH_3CN, (C_1-C_6)alkyl acetate, or any mixture thereof.

8. The process according to any one of claims 1 to 7, wherein in step (b):

(i) said halogenating agent is a metal halide salt; said cyanating agent is CuCN; said trifluoromethylation agent is $CuCF_3$; and said hydroxylating agent is Cu_2O/Cu(II); or

(ii) said second solvent is water, THF, methyl THF, CH_3CN, or (C_1-C_6)alkyl acetate solvent, or any mixture thereof.

9. The process according to any one of claims 2 to 3, or 5 to 8, wherein in step (c1):

(i) said metal is selected from Fe^0, Zn^0, Pt^0, Ru^0, or Rh^0; and/or

(ii) said polar solvent is water, (C_1-C_6)alkyl alcohol, or any mixture thereof.

10. The process according to any one of claims 2 to 3, or 5 to 9, wherein in step (c1) said activation is performed in the presence of ammonium chloride, acetic acid, or HCl.

11. The process according to any one of claims 2, or 4 to 8, wherein in step (c2):

(i) said co-solvent is selected from DMSO, or a water/DMSO mixture; and/or

(ii) said buffer is selected from phosphate, PIPES, TRICINE, BICINE, HEPES, TRIS, TES, CAPS, KPi, or CHES; and/or

(iii) said enzymatic reducing agent is a nitroreductase enzyme; and/or

(iv) said catalyst is a metal catalyst and a co-catalyst; wherein said metal catalyst is a vanadium catalyst selected from V_2O_5, NH_3VO_4, V(IV) oxide phthalocyanine, V(IV) oxide bis (2,4-pentanedionate), vanadyl sulfate hydrate, V(V)oxy triethoxide, 3% V/C, or V(III)2,4-pentanedionate; and/or

(v) said reaction is performed between pH 7 and pH 8.

12. The process according to any one of claims 5 to 11, wherein in step (d):

(i) said X_1 is fluoro or chloro; and/or

(ii) said base is a carbonate salt or phosphate salt; and/or

(iii) said organic solvent is selected from DMF, DMAc, or NMP; and/or

(iv) the reaction is performed under a low water content condition and no excess thiol agent is used.

13. The process according to any one of claims 6 to 12, wherein in step (e):

(i) said X_1 is F or Cl; and/or

(ii) said organic solvent is selected from DIPEA, CH_3CN, TEA, N-methyl morpholine, or any mixture thereof.

14. The process according to any one of claims 1 to 13, wherein X in compound (1) is iodo.

15. The process according to any one of claims 1 to 14, wherein R^1 is methyl or ethyl.

16. The process according to any one of claims 1 to 15, wherein R^2 is benzyl.

17. The process according to any one of claims 6 to 16, wherein the process is performed in the following order to form said compound of Formula (1):

A) Step (e); Step (d); Step (c1) or (c2); and followed by Steps (a) + (b);

B) Step (d); Step (e); Step (c1) or (c2); and followed by Steps (a) + (b); or

C) Step (d); Step (c1) or (c2); Step (e); and followed by Steps (a) + (b).