US$8,000/Kg.

[0005] Furthermore, the use of back-to-back Pd transformations leads to robustness challenges, such as the need for high Pd loading (6 mol% and 5 mol%), and difficulties in Pd-removal downstream.

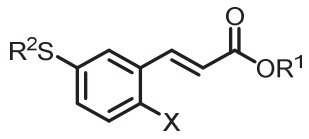
[0006] In order to drive cost down and to improve overall process robustness, there is a need to develop an improved novel synthetic technology to prepare compound (2a) which will serve as a key intermediate compound to prepare compound (1a) or analogs thereof.

[0007] The present inventors have developed a novel synthetic route which eliminates all use of expensive precious metals, including Pd, to address these cost and robustness challenges. In the improved process of preparation of compound (2) and (2a) of the invention, the amino group is prepared through a reduction of a nitro group with Iron, an inexpensive base metal. The present inventors have further developed an alternative novel bio-catalytic nitroreduction with nitroreductase enzyme, which improved the yield of compound (2a).

SUMMARY

[0008] The present disclosure provides a precious metal catalyst free, preferably palladium metal catalyst free, improved, safer, cost-effective and easy to operate on plant scale process for synthesis of acrylate compounds, including halo acrylate compounds.

[0009] In example 1, the present disclosure provides a process for the preparation of a compound having formula (1):



[0010] (1); or a salt thereof:

[0011] wherein:

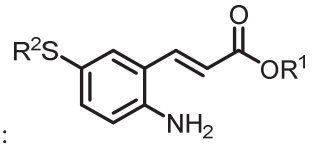
[0012] X is halo, CN, CF_3, or OH;

[0013] 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;

[0014] wherein the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S;

[0015] or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group;

[0016] R^2 is selected from (C_1-C_6)alkyl or benzyl; comprising:



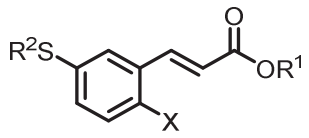
[0017] (a) contacting a compound of formula (2): (2);

[0018] wherein said R^1 and R^2 are as defined above in compound (1); with an acid HA in a solvent-1, and in the presence of a nitrous salt;

[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);

wherein:

X is halo, CN, CF_3, or OH;

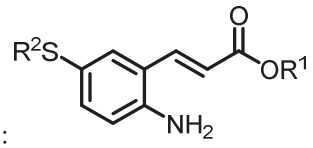
R^1 is (C_1-C_6)alkyl; a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl; or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- membered cycloalkyl or heterocycloalkyl group;

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;

R^2 is selected from (C_1-C_6)alkyl or benzyl;

comprising:

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

(2);

wherein said R^1 and R^2 are as defined above in compound (1); with an acid HA in a solvent-1, 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 solvent-2, to form said compound (1); wherein said solvent-1 and solvent-2 can be identical or different; and

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

[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.

[0023] In a further sub-example of example 1, in (a), said nitrous salt is $NaNO_2$.

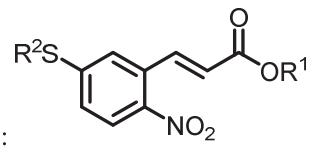
[0024] In a further sub-example of example 1, in (a), said low temperature is between -10°C to 10°C; or between 0°C to 5°C. Preferably, between 0°C to 5°C.

[0025] In a further sub-example of example 1, in (b), 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). Preferably, in (b), a halogenating agent is used, more preferably said halogenating agent is a KI or CuI.

[0026] In a further sub-example of example 1, in (b), said solvent-2 is water, THF, methyl THF, CH_3CN, or (C_1-C_6)alkyl acetate solvent, or mixtures thereof. Preferably, in (b), said solvent-2 is (C_1-C_6)alkyl; more preferably, isopropyl acetate.

[0027] In example 2, the present disclosure provides a process according to example 1, further comprising preparing said compound (2) comprising:

[0028] (c1) activating a metal in the presence of an acidic salt HA^1 in a polar solvent; and

contacting a compound of formula (3):  (3);

[0029] wherein said R^1 and R^2 are as defined above in compound (1);

[0030] with said activated metal at an elevated temperature in a polar solvent to form said compound (2) or a salt thereof;

[0031] or alternatively, the process further comprising preparing said compound (2) comprising:

[0032] (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), or a salt thereof.

[0033] In example 3, the present disclosure provides a process according to example 2, further comprising preparing said compound (2) comprising:

[0034] (c1) activating a metal in the presence of an acidic salt HA^1 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) or a salt thereof.

[0035] In example 4, the present disclosure provides a process according to example 2, further comprising preparing compound (2) comprising:

[0036] (c2) contacting said compound of formula (3), in the presence of a co-solvent, with an enzymatic reducing agent in an aqueous buffer, and in the presence of a metal catalyst, a co-catalyst, and a co-factor, to form said compound of formula (2), or a salt thereof.

[0037] In a sub-example of any of examples 2 or 3, in (c1), said metal is selected from Fe^o, Zn^o, Pd^o, Pt^o, Ru^o, or Rh^o. Preferably, said metal is Fe^o.

[0038] In a further sub-example of any of examples 2 or 3, in (c1), said acidic salt HA^1 is ammonium chloride, acetic acid, or HCl. Preferably, said acidic salt HA^1 is ammonium chloride.

[0039] In a further sub-example of any of examples 2 or 3, in (c1), said polar solvent is water, $(C_1$-$C_6)$alkyl alcohol, or mixture thereof. Preferably, said polar solvent is water and ethanol mixture.

[0040] In a further sub-example of any of examples 2 or 3, in (c1), said elevated temperature is between 50°C to 90°C; or 75°C to 80°C. Preferably, said temperature is 75°C to 80°C.

[0041] In a further sub-example of any of examples 2 or 4, in (c2), said co-solvent is selected from DMSO, or water/DMSO mixture. Preferably, the co-solvent is 20 vol% to 30 vol% DMSO. More preferably, the co-solvent is 30 vol% DMSO.

[0042] In a further sub-example of any of examples 2 or 4, in (c2), said buffer is selected from phosphate, PIPES, TRICINE, BICINE, HEPES, TRIS, TES, CAPS, Kpi, or CHES. Preferably, the buffer is TRICINE.

[0043] In a further sub-example of any of examples 2 or 4, in (c2), said enzymatic reducing agent is a nitroreductase (NR) enzyme. Preferably the enzyme is NR-55.

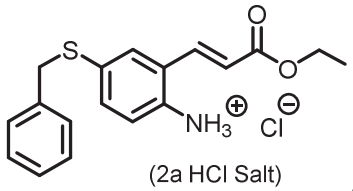
[0044] In a further sub-example of any of examples 2 or 4, in (c2), said catalyst is a metal catalyst and a co-catalyst; wherein said metal catalyst is a vanadium catalyst selected from V_20_5, NH_3VO_4, V(IV) oxide phthalocyanine, V(IV) oxide bis (2,4-pentanedionate), vanadyl sulfate hydrate, V(V)oxy triethoxide, 3% V/C, or V(III)2,4-pentanedionate.

[0045] In a further sub-example of any of examples 2 or 4, in (c2), said catalyst is a metal catalyst and a co-catalyst; wherein said metal catalyst is V_20_5 or NH_3VO_4, and said co-catalyst is GDH-101 and sugar, and wherein said co-factor is NADP+. Preferably, the sugar is dextrose or glucose.

[0046] In a further sub-example of any of examples 2 or 4, in (c2), said reaction is performed at between pH 7 or 8.

[0047] In a further sub-example of any of examples 2 or 4, in (c2), said compound of formula (3), which is dissolved in said co-solvent, is slowly added to the enzymatic reducing agent in said aqueous buffer solution and in the presence of a metal catalyst, a co-catalyst, and co-factor. Preferably, said metal catalyst is vanadium metal, more preferably, V_20_5 or NH_3VO_4. Preferably, said co-catalyst is GDH-101 and sugar. Preferably, the sugar is dextrose or glucose. Preferably, said co-factor is NADP+.

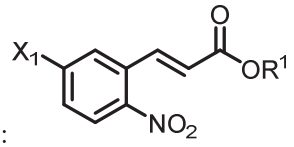
[0048] In a further sub-example of any of examples 2 or 4, the product of (c2) is a salt selected from a halide salt, selected from HCl salt or HBr salt, or a sulphonic acid salt, selected from mesylate salt, tosylate salt, or aryl sulphonate salt. Preferably, the salt is a halide salt, more preferably HCl salt.

A more preferred product of (c2) is 

(2a HCl Salt) .

[0049] In a further sub-example of any of examples 2 or 4, in (c2), more preferably, the reaction is performed at an elevated temperature. Preferably, the temperature ranges from 40°C to 50°C. More preferably, between 43°C to 47°C. Most preferably 45°C.

[0050] In example 5, the present disclosure provides a process according to example 2, further comprising preparing said compound (3) comprising:

[0051] (d) contacting a compound of formula (4): 

(4); wherein X_1 is halo; and said R^1 is as defined above in compound (3);

[0052] with a thiol agent in the presence of a base, in an organic solvent, and at an elevated temperature; to form said compound (3), or a salt thereof.

[0053] In a sub-example of example 5, in (d), said X_1 in each of Compound (4) and (5) is fluoro or chloro. Preferably, X_1 is fluoro.

[0054] In a further sub-example of example 5, in (d), said base is a carbonate salt or phosphate salt. Preferably, said base is Cs_2CO_3 or K_3PO_4.

[0055] In a further sub-example of example 5, in (d), said organic solvent is selected from DMF, DMAc, or NMP.

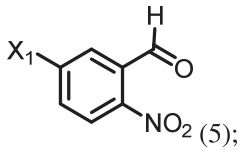
[0056] In a further sub-example of example 5, in (d), said elevated temperature is between 50°C to 85°C; or between 65°C to 80°C. Preferably said temperature is 70°C.

[0057] In a further sub-example of example 5, in (d), said thiol agent is $C_6H_5CH_2SH$ or (C_1-C_6)alkyl-SH, such as CH_3SH. Preferably, said thiol agent is $C_6H_5CH_2SH$.

[0058] In a further sub-example of example 5, in (d), said reaction is performed under a low water content condition and no excess thiol agent is used to avoid any sulfur generation in the work up. Preferably, the water content concentration is kept below 1000 ppm. Preferably, the thiol agent is within 0.90 equivalent to 1.1 equivalent. In a preferred sub-example, no sulfur was generated in the work up.

[0059] In example 6, the present disclosure provides a process according to example 5, further comprising preparation of said compound (4), or a salt thereof, comprising:

[0060] (e) contacting a compound of formula (5):



(5);

[0061] wherein X_1 is halo as defined in compound (4); with an alkenating agent, in the presence of a base, in an organic solvent to form said compound (4), or a salt thereof.

[0062] In a sub-example of example 6, in (e), said X_1 in each of Compound (4) and (5) is F or Cl.

[0063] In a further sub-example of example 6, in (e), said alkenylating agent is Wittig reagent (including triphenyl phosphonium ylide or ethyl 2-(diethoxyphosphoryl)acetate), or Horner-Wadsworth-Emmons (HWE) reagent. Preferably, the alkenylating agent is Wittig reagent. More preferably, ethyl 2-(diethoxyphosphoryl)acetate.

[0064] In a further sub-example of example 6, in (e), said organic solvent is selected from DIPEA, CH_3CN, TEA, N-methyl morpholine, or mixtures thereof. Preferably, the solvent is CH_3CN.

[0065] In a further sub-example of example 6, in (e), said halide salt is selected from LiCl or LiBr. Preferably the halide salt is LiCl.

[0066] In example 7, the present disclosure provides a process according to any of the above examples 1, 2, 3, 4, 5, or 6, or any sub-examples thereof, wherein X in compound (1) is iodo.

[0067] In example 8, the present disclosure provides a process according to any of the above examples 1, 2, 3, 4, 5, 6, or 7, or any sub-examples thereof, wherein X_1 in each of compounds (1) and (2) is fluoro or chloro.

[0068] In example 9, the present disclosure provides a process according to any of the above examples 1, 2, 3, 4, 5, 6, 7, or 8, or any sub-examples thereof, wherein R^1 in each of compounds (1), (2), (3), and (4) is methoxy or ethoxy.

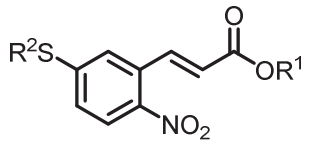
[0069] In example 10, the present disclosure provides a process according to any of the above examples 1, 2, 3, 4, 5, 6, 7, 8, or 9, or any sub-examples thereof, wherein R^2 in each of compounds (1), (2), and (3) is benzyl.

[0070] In example 11, the present disclosure provides a process according to any of the above examples 1, 2, 3, 4, 5, 6, 7, 8, or 9, or any sub-examples thereof, wherein said compound (1) is obtained via the following order of reactions: (e), (d), (c1), then (a) and (b); or (e), (d), (c2), then (a) and (b).

[0071] Alternatively, in a sub-example, said compound (1) is obtained via the following order of reactions: (d), (e), (c1), then (a) and (b); or (d), (e), (c2), then (a) and (b).

[0072] Yet alternatively, in another sub-example, said compound (1) is obtained via the following order of reactions: (d), (c1), (e), then (a) and (b); or (d), (c2), (e), then (a) and (b).

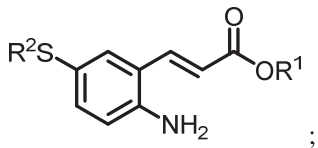
[0073] In example 11, the present disclosure provides a compound, which is:



(3);

wherein R^1 is ethyl; and R^2 is benzyl; or a salt thereof.

[0073a] In another aspect, the present disclosure refers to a compound, which is:



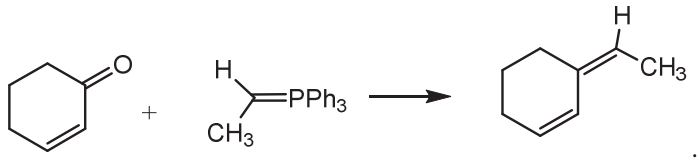
;

wherein R^1 is ethyl; and R^2 is benzyl; or a salt thereof.

DETAILED DESCRIPTION

[0074] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

[0075] "Alkenating agent" means an agent that converts a carbonyl group to alkene group. Two examples of such alkenating agent are "Horner-Wadsworth-Emmons (HWE) agent" and "Wittig agent". For example, the Wittig reaction uses phosphoranes to convert an α,β-unsaturated ketone to a conjugated alkene as follows:



.

The Wittig reaction produces *Z* alkenes. Horner-Wadsworth-Emmons (HWE) reaction is a variation of the Wittig reaction, which gives *E* alkenes. The *Z* and *E* alkenes refer to the relative position of the two higher priority groups in an alkene group as widely understood by those skilled in the art. If the higher priority groups are on the same side of the alkene group, then the alkene is called a *Z*-alkene (German;

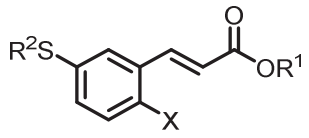
zusammen = together). If the higher priority groups are on the opposite sides of the alkene group, then the alkene is called an *E*-alkene (German; entgegen = opposite).

[0076] "(C_α-C_β)Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), pentyl (including all isomeric forms), and the like.

[0077] "Amino" means -NH_2.

WE CLAIM:

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



(1);

wherein:

X is halo, CN, CF_3, or OH;

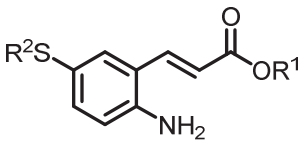
R^1 is (C_1-C_6)alkyl; a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl; or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- membered cycloalkyl or heterocycloalkyl group;

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;

R^2 is selected from (C_1-C_6)alkyl or benzyl;

comprising:

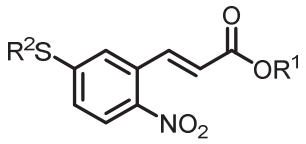
(a) contacting a compound of formula (2): 

(2);

wherein said R^1 and R^2 are as defined above in compound (1); with an acid HA in a solvent-1, 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 solvent-2, to form said compound (1); wherein said solvent-1 and solvent-2 can be identical or different; and

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

2. The process according to claim 1, further comprising preparing said compound (2) comprising: (c1) activating a metal in the presence of an acidic salt HA^1 in a polar solvent; and contacting a compound of formula (3): 

(3);

wherein said R^1 and R^2 are as defined above in compound (1);

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

or alternatively, the process further comprising preparing said compound (2) comprising:

(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), or a salt thereof.

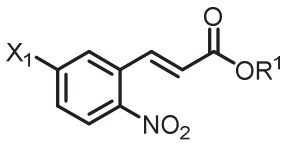
3. The process according to claim 2, comprising:

(c1) activating a metal in the presence of an acidic salt HA^1 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) or a salt thereof.

4. The process according to claim 2, comprising:

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

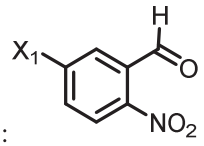
5. The process according to claim 2, further comprising preparing said compound (3), or a salt thereof, comprising:

(d) contacting a compound of formula (4):  (4);

wherein X_1 is halo; and said R^1 is as defined above in compound (3);

with a thiol agent in the presence of a base, in an organic solvent, and at an elevated temperature; to form said compound (3), or a salt thereof.

6. The process according to claim 5, further comprising preparation of said compound (4) comprising:

(e) contacting a compound of formula (5):  (5);

wherein X_1 is halo as defined in compound (4); with an alkenating agent, in the presence of a base, in an organic solvent to form said compound (4), or a salt thereof.

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

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

(ii) said solvent-1 is water, THF, methyl THF, CH_3CN, or (C_1-C_6)alkyl acetate solvent, or mixtures thereof.

8. The process according to any one of claims 1 to 7, wherein in (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 solvent-2 is water, THF, methyl THF, CH_3CN, or (C_1-C_6)alkyl acetate solvent, or mixtures thereof.

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

(i) said metal is selected from Fe^o, Zn^o, Pd^o, Pt^o, Ru^o, or Rh^o;

(ii) said acidic salt HA^1 is ammonium chloride, acetic acid, or HCl; or

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

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

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

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

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

(iv) said catalyst is a metal catalyst and a co-catalyst; wherein said metal catalyst is a vanadium catalyst selected from V_20_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;

(v) said reaction is performed at between pH 7 or pH 8; or

(vi) wherein the product of (c2) is a salt selected from a halide salt, selected from HCl salt or HBr salt, or a sulphonic acid salt, selected from mesylate salt, tosylate salt, or aryl sulphonate salt.

11. The process according to any one of claims 5 to 10, wherein in (d):

(i) said X_1 in each of Compound (4) and (5) is fluoro or chloro;

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

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

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

12. The process according to any one of claims 6 to 11, wherein in (e):

(i) said X_1 in each of Compound (4) and (5) is F or Cl; or

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

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

14. The process according to any one of the above claims, wherein X_1 in each of compounds (1) and (2) is fluoro or chloro.

15. The process according to any one of the above claims, wherein R^1 in each of compounds (1), (2), (3), and (4) is methoxy or ethoxy.

16. The process according to any one of the above claims, wherein R^2 in each of compounds (1), (2), and (3) is benzyl.

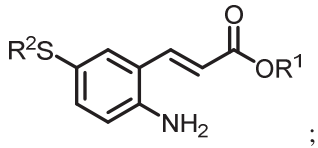
17. The process according to any one of the above claims, wherein the process is performed in the following order to form said compound of Formula (1):

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).

18. A compound, which is:



;

wherein R^1 is ethyl; and R^2 is benzyl; or a salt thereof.