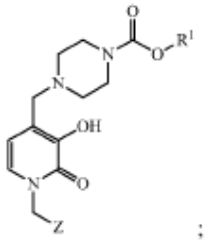


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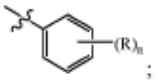
in the presence of a source of formaldehyde and an acid to form a product comprising a compound having the formula of Formula (I):



;

(I)

wherein Z is a substituted or unsubstituted phenyl ring having the formula:



;

the index n is an integer from 0 to 5;

each R is independently:

i) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy;

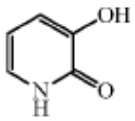
iii) halogen; or

iv) cyano; and

R^1 is $C_1 - C_4$ linear or $C_3 - C_4$ branched alkyl.

The present disclosure also provides a process for preparing tert-butyl 4-((1-(4-chlorobenzy1)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-l-carboxylate, comprising,

A) reacting 3-hydroxypyridin-2(1*H*)-one having the formula:

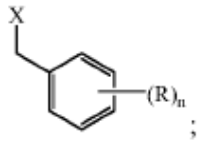


with 4-chlorobenzyl chloride having the formula:

What is claimed is:

1. A process for preparing a compound, the process comprising:

A) reacting 3-hydroxypyridin-2(1*H*)-one with a benzylating agent having the formula:



;

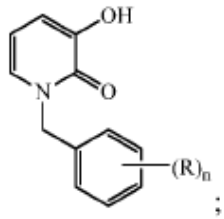
wherein X is a leaving group;

in the presence of:

i) an amount of a silylating reagent that provides at least 2 equivalents of a silyl protecting group; and

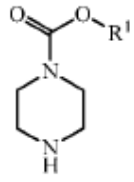
ii) a proton source;

to form a N-benzy1-3-hydroxypyridin-2(1H)-one having the formula:



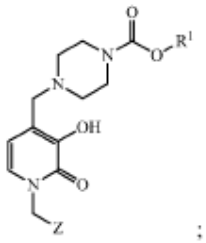
; and

B) reacting the N-benzy1-3-hydroxypyridin-2(1*H*)-one formed in Step (A) with a compound having the formula:



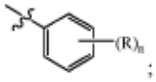
;

in the presence of a source of formaldehyde and an acid to form a product comprising a compound having the formula of Formula (I):



(I)

wherein Z is a substituted or unsubstituted phenyl ring having the formula:



the index n is an integer from 0 to 5;

each R is independently:

i) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl;

ii) C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy;

iii) halogen; or

iv) cyano; and

R^1 is C_1 – C_4 linear or C_3 – C_4 branched alkyl.

2. The process according to Claim 1, wherein R^1 is chosen from methyl, ethyl and *tert*-butyl.

3. The process according to Claim 1, wherein R^1 is *tert*-butyl.

4. The process according to Claim 1, wherein R is halogen.

5. The process according to Claim 1, wherein Z is chosen from 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 3-iodophenyl, and 4-iodophenyl.

6. The process according to Claim 1, wherein Z is 4-chlorophenyl.

7. The process according to Claim 1, wherein R is C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkyl.

8. The process according to Claim 1, wherein Z is chosen from 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-(n-propyl)phenyl, 3-(n-propyl)phenyl, 4-(n-propyl)phenyl, 2-(n-butyl)phenyl, 3-(n-butyl)phenyl, 4-(n-butyl)phenyl, 2-(n-pentyl)phenyl, 3-(n-pentyl)phenyl, 4-(n-pentyl)phenyl, 2-(n-hexyl)phenyl, 3-(n-hexyl)phenyl, 4-(n-hexyl)phenyl, *2-(iso*-propyl)phenyl*,* 3-(*iso*-propyl)phenyl, 4-(*iso*-propyl)phenyl, 2-(*iso*-butyl)phenyl, 3-(*iso*-butyl)phenyl, 4-(*iso*-butyl)phenyl, 2-(*sec*-butyl)phenyl, 3-(*sec*-butyl)phenyl, 4-(*sec*-butyl)phenyl, 2-(*tert*-butyl)phenyl, 3-(*tert*-butyl)phenyl, 4-(*tert*-butyl)phenyl, 2-(*iso*-pentyl)phenyl, 3-(*iso*-pentyl)phenyl, 4-(*iso*-pentyl)phenyl, 2-(*iso*-hexyl)phenyl, 3-(*iso*-hexyl)phenyl, and 4-(*iso*-hexyl)phenyl.

9. The process according to Claim 1, wherein R is C_1-C_6 linear, C_3-C_6 branched or C_3-C_6 cyclic alkoxy.

10. The process according to Claim 1, wherein Z is chosen from 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2-(n-propoxy)phenyl, 3-(n-propoxy)phenyl, 4-(n-propoxy)phenyl, 2-(n-butoxy)phenyl, 3-(n-butoxy)phenyl, 4-(n-butoxy)phenyl, 2-(n-pentyloxy)phenyl, 3-(n-pentyloxy)phenyl, 4-(n-pentyloxy)phenyl, 2-(n-hexyloxy)phenyl, 3-(n-hexyloxy)phenyl, 4-(n-hexyloxy)phenyl, 2-(*iso*-propoxy)phenyl, 3-(*iso*-propoxy)phenyl, 4-(*iso*-propoxy)phenyl, 2-(*iso*-butoxy)phenyl, 3-(*iso*-butoxy)phenyl, 4-(*iso*-butoxy)phenyl, 2-(*sec*-butoxy)phenyl, 3-(*sec*-butoxy)phenyl, 4-(*sec*-butoxy)phenyl, 2-(*tert*-butoxy)phenyl, 3-(*tert*-butoxy)phenyl, *4-(tert*-butoxy)phenyl*,* 2-(*iso*-pentyloxy)phenyl, 3-(*iso*-pentyloxy)phenyl, *4-(iso*-pentyloxy)phenyl*,* 2-(*iso*-hexyloxy)phenyl, 3-(*iso*-hexyloxy)phenyl, *4-(iso*-hexyloxy)phenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,3,5-trifluorophenyl, 2,4,6-trifluorophenyl, 3,4,5-trifluorophenyl, 2,3,4,5-tetrafluorophenyl, 2,3,4,6-tetra-fluorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,3,4-trichlorophenyl, 2,3,5-trichlorophenyl, 2,4,6-trichlorophenyl, 3,4,5-trichlorophenyl, 2,3,4,5-tetrachlorophenyl, 2,3,4,6-tetra-chlorophenyl, 2,3,4,5,6-pentachlorophenyl, 2,3-dibromophenyl, 2,4-dibromophenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tribromophenyl, 2,3,5-tribromophenyl, 2,4,6-tribromophenyl, 3,4,5-tribromophenyl, 2,3,4,5-tetrabromophenyl, 2,3,4,6-tetra-bromophenyl, 2,3,4,5,6-pentabromophenyl, 2,3-diiodophenyl, 2,4-diiodophenyl, 2,5-diiodophenyl, 2,6-diiodophenyl,

3,4-diiodophenyl, 3,5-diiodophenyl, 2,3,4-triiodophenyl, 2,3,5-triiodophenyl, 2,4,6-triiodophenyl, 3,4,5-triiodophenyl, 2,3,4,5-tetraiodophenyl, 2,3,4,6-tetraiodophenyl, 2,3,4,5,6-pentaiodophenyl, 2,3-dimethylphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2,6-dimethyl-phenyl, 3,4-dimethylphenyl, 3,5-dimethylphenyl, 2,3,4-trimethylphenyl, 2,3,5-trimethyl-phenyl, 2,4,6-trimethylphenyl, 3,4,5-trimethylphenyl, 2,3,4,5-tetramethylphenyl, 2,3,4,6-tetra-methylphenyl, 2,3,4,5,6-pentamethylphenyl, 2,3-diethylphenyl, 2,4-diethylphenyl, 2,5-diethylphenyl, 2,6-diethylphenyl, 3,4-diethylphenyl, 3,5-diethylphenyl, 2,3,4-triethylphenyl, 2,3,5-triethylphenyl, 2,4,6-triethylphenyl, 3,4,5-triethylphenyl, 2,3,4,5-tetraethylphenyl, 2,3,4,6-tetra-ethylphenyl, 2,3,4,5,6-pentaethylphenyl, 2,3-dibromophenyl, 2,4-dibromo-phenyl, 2,5-dibromophenyl, 2,6-dibromophenyl, 3,4-dibromophenyl, 3,5-dibromophenyl, 2,3,4-tribromophenyl, 2,3,5-tri(n-propyl)phenyl, 2,4,6-tri(n-propyl)phenyl, 3,4,5-tri(n-propyl)phenyl, 2,3,4,5-tetra(n-propyl)phenyl, 2,3,4,6-tetra-(n-propyl)phenyl, 2,3,4,5,6-penta(n-propyl)phenyl, 2,3-di(n-butyl)phenyl, 2,4-di(n-butyl)phenyl, 2,5-di(n-butyl)phenyl, 2,6-di(n-butyl)phenyl, 3,4-di(n-butyl)phenyl, 3,5-di(n-butyl)phenyl, 2,3,4-tri(n-butyl)-phenyl, 2,3,5-tri(n-butyl)phenyl, 2,4,6-tri(n-butyl)phenyl, 3,4,5-tri(n-butyl)phenyl, 2,3,4,5-tetra(n-butyl)phenyl, 2,3,4,6-tetra(n-butyl)phenyl, and 2,3,4,5,6-penta(n-butyl)phenyl.

11. The process according to Claim 1, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched and C_3-C_6 cyclic alkyl and at least one R is halogen.

12. The process according to Claim 1, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched and C_3-C_6 cyclic alkoxy and at least one R is halogen.

13. The process according to Claim 1, wherein at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched and C_3-C_6 cyclic alkyl and at least one R is chosen from C_1-C_6 linear, C_3-C_6 branched and C_3-C_6 cyclic alkoxy.

14. The process according to Claim 1, wherein the benzylating agent has the formula:

;

wherein the leaving group X is chosen from chloro, bromo, iodo, tosyl, and mesyl.

15. The process according Claim 14, wherein the leaving group X is chloro.

16. The process according Claim 14, wherein the leaving group X is iodo.

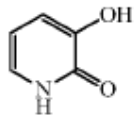
17. The process according to Claim 1, wherein the number of equivalents of silylating reagent in Step (A) is from 2 to about 4.

18. The process according to Claim 1, wherein the proton source in Step (A) is ammonium sulfate.

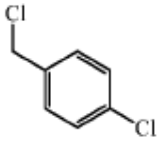
19. The process according to Claim 1, wherein the source of formaldehyde is an aqueous solution of formaldehyde.

20. A process for preparing tert-butyl 4-((1-(4-chlorobenzy1)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine-l-carboxylate, comprising,

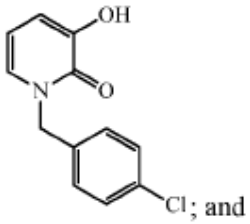
A) reacting 3-hydroxypyridin-2(1*H*)-one having the formula:



with 4-chlorobenzyl chloride having the formula:

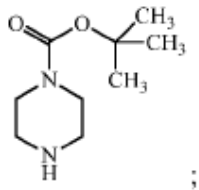


in the presence of two equivalents of a silylating reagent, a proton source and a salt of a mineral acid to form 1-(4-chlorobenzy1)-3-hydroxypyridin-2(1*H*)-one having the formula:

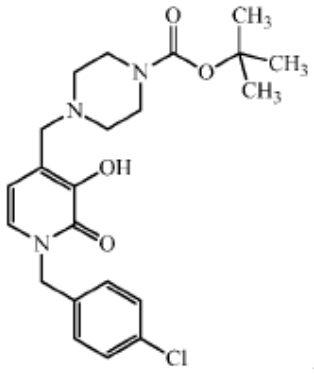


; and

B) reacting 1-(4-chlorobenzy1)-3-hydroxypyridin-2(1*H*)-one with *tert*-butyl piperazine-l-carboxylate having the formula:


;

in the presence of aqueous formaldehyde and a protic acid to form a product comprising *tert*-butyl 4-((1-(4-chlorobenzy1)-3-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)methyl)piperazine- 1 -carboxylate having the formula:


.

21. The process according to Claim 20, wherein the silylating reagent is hexamethyldisilazane.

22. The process according to Claim 20, wherein the proton source in Step (A) is ammonium sulfate.

23. The process according to Claim 20, wherein the protic acid in Step (B) is acetic acid.

24. The process according to claim 20, wherein the salt of a mineral acid is potassium iodide.

25. The process according to claim 20, wherein the product further comprises acetate.

26. The process according to claim 1, wherein R^1 is C_1-C_4 linear or C_3-C_4 branched alkyl.

27. The process according to claim 1, wherein the product further comprises acetate.

28. The process according to claim 1, wherein the silylating reagent is hexamethyldisilazane.

29. The process according to claim 1, wherein the acid in Step (B) is acetic acid.