METHODS FOR PREPARING OXAZOLIDINONES AND COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

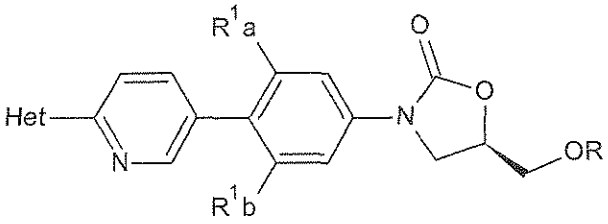
[0001] Oxazolidinones as a chemical class find widespread use as pharmaceutical agents for the therapy and prophylaxis of such medical conditions as bacterial infections and atherosclerosis. The utility of these compounds has spurred efforts to find efficient routes to synthesize them, such as the copper-catalyzed cross coupling disclosed in US 20070049759. US 20070155798, which is hereby incorporated by reference in its entirety, recently disclosed potently anti-bacterial oxazolidinones that feature substituted pyridinyl phenyl moieties. These moieties were initially incorporated by synthetic routes involving tin-based couplings, which because of the toxicity of any residual tin compounds is not desirable for pharmaceutical use. Accordingly, a need exists for synthetic routes to substituted (pyridinyl)phenyl oxazolidinones that does not involve use of tin reagents.

Field of the Invention

[0002] Novel methods are useful in the preparation of oxazolidinone-containing compounds.

SUMMARY

[0003] A method of synthesizing a compound of the structure



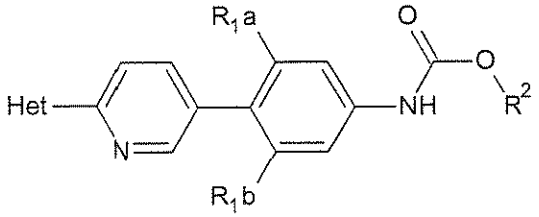
wherein

R is H,

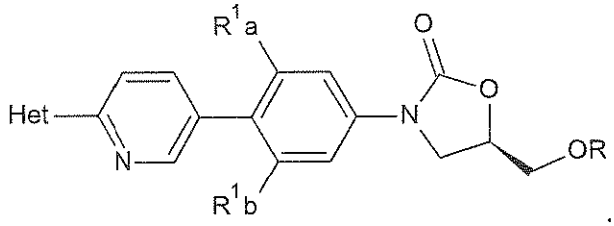
R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a and R^1b is F,

Het is an optionally-substituted five- or six-membered heterocycle comprising at least one N, O, or S atom,

comprises treating a compound having the structure

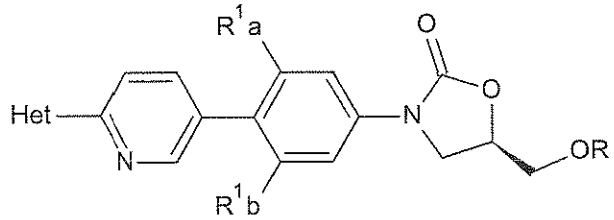


wherein R^2 is selected from the group consisting of optionally substituted benzyl and optionally substituted C_1-C_6 alkyl, with a strong base or an organolitihium salt and then addition of glycidyl butyrate to the resulting anion under conditions to make

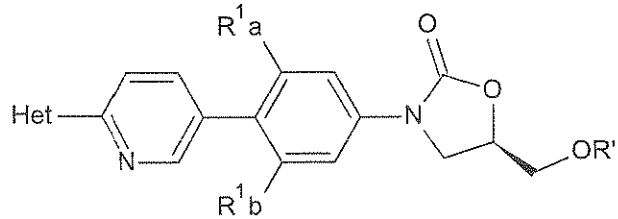


[0004] As provided herein, the treating step is performed in the presence of a facilitating compound, such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

[0005] In some embodiments, the method includes an additional step comprising reacting

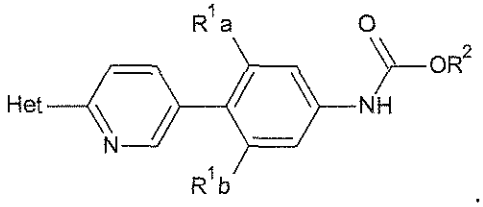


with $POCl_3$, $POCl(OBn)_2$, or $P(N\text{-}iPr_2)(O\text{-}tBu)_2$ under conditions form



wherein R' is $PO(OH)_2$.

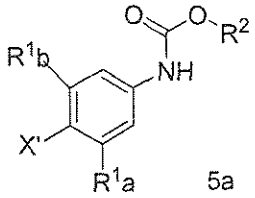
[0006] The method may also comprise treating the compound of the structure



[0008] As provided herein, the coupling is carried out in the presence of a palladium complex such as phosphine ligand bound to palladium, for example, dichloro-bis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), or $Pd_2(dba)_3$.

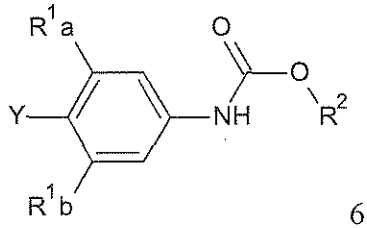
[0009] A separate method of making an intermediate, or an additional step before the coupling step above, comprises

a) treating an aryl halide of structure 5a



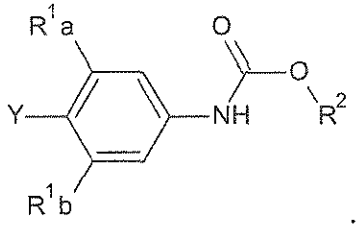
5a

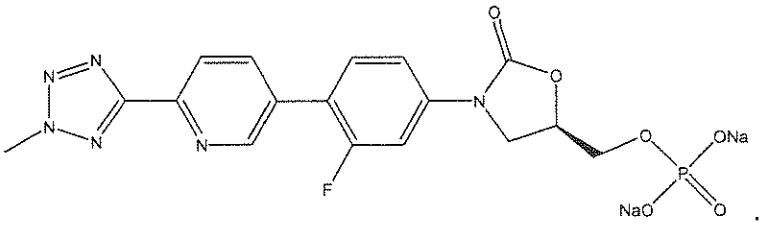
wherein X^1 is leaving group, with a strong base such as n-butyl lithium and then reacting a resulting anion with a trialkylboric acid ester under conditions to form



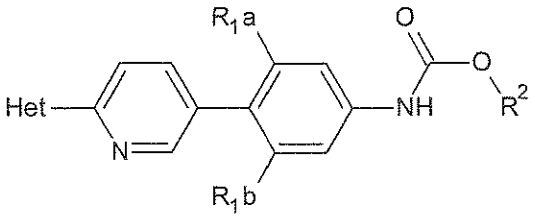
6; or

b) treating the aryl halide of structure 5a with a palladium catalyst such as $PdCl_2(dppf)_2$ and a dipinacolate ester of diboronic acid under conditions to form





[0014] In some embodiments, a compound of the formula has the structure:



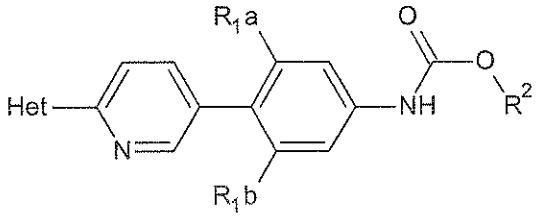
wherein;

R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a and R^1b is F,

R^2 is selected from the group consisting of optionally substituted benzyl and optionally substituted C_1-C_6 alkyl, and

Het is an optionally-substituted five- or six-membered heterocycle comprising at least one N, O, or S atom.

[0014a] According to a first aspect, there is provided a compound of the formula:



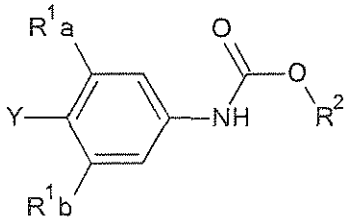
wherein

R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a and R^1b is F,

R^2 is selected from the group consisting of optionally substituted benzyl and optionally substituted C_1-C_6 alkyl, and

Het is tetrazolyl optionally substituted with methyl.

[0015] In some embodiments, a compound of the formula has the following structure:



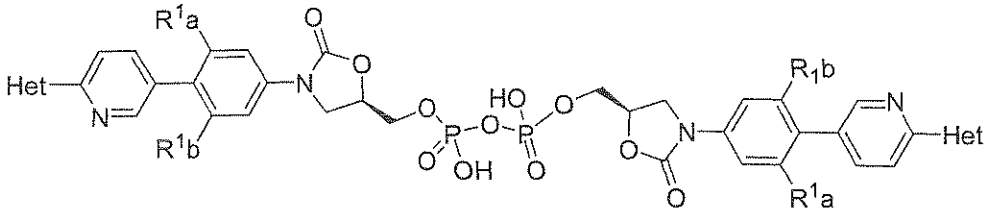
wherein

R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a *and* R^1b *is F*,

R^2 is selected from the group consisting of optionally substituted benzyl and optionally substituted C_1-C_6 alkyl, and

Y is selected from the group consisting of ZnCl, BF_3, and BR^3R^4, wherein R^3 and R^4 are independently selected from the group consisting of OH and optionally-substituted C_1-C_6 mono and dihydric alcohols, and wherein R^3 and R^4 together may form a ring.

[0016] As provided herein, a composition comprises the compound herein such as prepared in accordance with the processes herein and a dimer having the following structure or a pharmaceutically acceptable salt of the dimer



wherein R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a and R^1b is F,

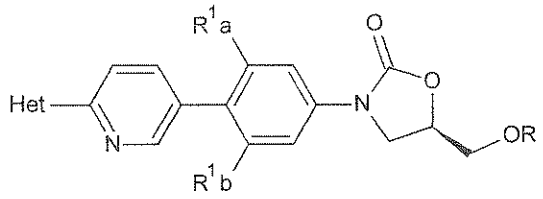
Het is an optionally-substituted five- or six-membered heterocycle comprising at least one N, O, or S atom.

[0017] As provided herein, R^1a is F and R^1b is H and Het is 2-methyl-tetrazol-5-yl.

[0018] In further embodiments a composition comprises the compound herein such as prepared in accordance with the processes above, wherein the composition lacks tin impurities.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0019] Methods are provided for synthesizing substituted (pyridinyl)phenyl-oxazolidinones



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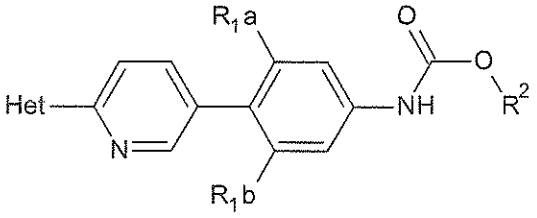
Claims

1. A compound of the formula:



wherein

R^1a and R^1b are independently selected from H and F, provided that at least one of R^1a and R^1b is F,

R^2 is selected from the group consisting of optionally substituted benzyl and optionally substituted C_1-C_6 alkyl, and

Het is tetrazolyl optionally substituted with methyl.

2. The compound of claim 1 wherein R^1a is F and R^1b is H.

3. The compound of claim 1 wherein Het is substituted with methyl.

4. The compound of claim 3 wherein Het is 2-methyl-tetrazol-5-yl.

5. The compound of claim 1 wherein R^2 is benzyl.

6. The compound of claim 1 wherein R^1a is F, R^1b is H, R^2 is benzyl, and Het is 2-methyl-tetrazol-5-yl.

7. The compound of claim 1 wherein the optionally substituted benzyl and the optionally substituted C_1-C_6 alkyl are independently unsubstituted or substituted with halogen or C_1-C_4 alkyloxy.