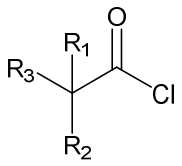
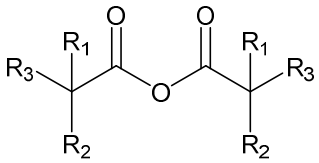
Claims

1. A method for the *in-situ* formation of a compound of formula (V) from pipecolic acid, wherein the *in-situ* method takes place in the presence of a solvent, wherein the solvent is an organic solvent having a boiling point ranging from 50°C to 160°C, water, or a mixture thereof, wherein the method comprises:

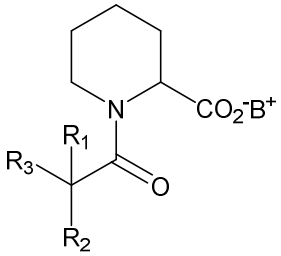
(a) reacting pipecolic acid with an acid chloride of formula (Ia) in the presence of a base, or reacting pipecolic acid with an acid anhydride of formula (Ib), optionally in the presence of a base, to form a compound of formula (II),



Formula (Ia)

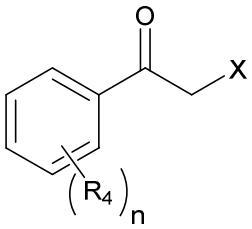


Formula (Ib)

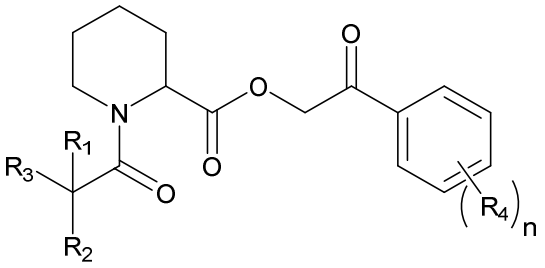


Formula (II)

(b) reacting the compound of formula (II) with a compound of formula (III) to form a compound of formula (IV),

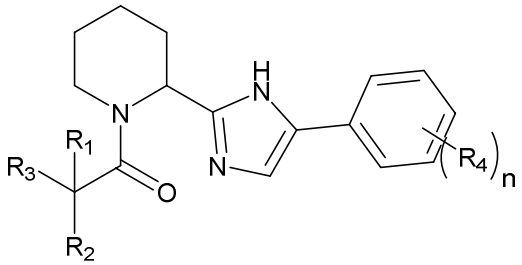


Formula (III)



Formula (IV)

(c) reacting the compound of formula (IV) with an ammonium source to form a compound of formula (V),



Formula (V)

wherein

R_1, R_2 and R_3 together with the carbon atom to which they are attached form a hydrocarbon group optionally comprising up to 3 heteroatoms independently selected from O, S, N and F;
the phenyl group of the compounds of formulas (III), (IV) and (V) is substituted with n R_4 substituents wherein n is zero, one, two, three, four, or five;
each R_4 is independently selected from halogen, cyano, nitro, C_1-C_6 alkyl optionally comprising up to 5 halogen atoms, C_2-C_6 alkenyl, C_1-C_6 alkoxy optionally comprising up to 3 halogen atoms, C_1-C_3-alkoxy-C_1-C_3-alkyl, and C_3-C_7 cycloalkyl;
B^+ is a cation provided by the base; and
X is a halogen.

2. The method of claim 1, wherein the base is a metal phosphate, a metal hydroxide, a metal carbonate, metal bicarbonate, or a combination thereof.

3. The method of claim 1 or 2, wherein the base is sodium hydroxide or potassium hydroxide.

4. The method of any preceding claim, wherein at least two equivalents of base to the acid chloride of formula (Ia) or acid anhydride of formula (Ib) or compound of formula (III) are used.

5. The method of any preceding claim, wherein the reaction of the pipecolic acid with the acid chloride of formula (Ia) or acid anhydride of formula (Ib) to form the compound of formula (II), and/or the reaction of the compound of formula (II) with the compound of formula (III) to form the compound of formula (IV), takes place in the presence of a phase transfer catalyst.

6. The method of claim 5, wherein the phase transfer catalyst is tetrabutylammonium bromide (TBAB).

7. The method of any preceding claim, wherein the solvent is an aromatic solvent, for example an alkylbenzene solvent such as toluene.

8. The method of any one of claim 1 to 6, wherein the solvent is a non-aromatic solvent solvent, for example 2-methyltetrahydrofuran.

9. The method of any preceding claim, wherein the reaction of the compound of formula (II) with the compound of formula (III) to form the compound of formula (IV) takes place at a temperature ranging from 50°C to 120°C.

10. The method of any preceding claim, wherein the ammonium source is ammonium acetate or a mixture of ammonia and acetic acid.

11. The method of any preceding claim, wherein the reaction of the compound of formula (IV) with the ammonium source to form a compound of formula (V) takes place at a temperature ranging from 90°C to 120°C.

12. The method of any preceding claim, wherein the carbon atom to which R_1, R_2 and R_3 are attached is a chiral center and the chirality remains unchanged throughout the reaction.

13. The method of any preceding claim, wherein:

R_1 is selected from hydrogen and methyl; and/or

R_2 is selected from hydrogen, C_1-C_2 alkyl and C_2-C_3 alkenyl; and/or

R_3 is selected from C_1-C_3 alkyl, C_2-C_5 alkenyl containing one or two double bonds, C_1-C_3 alkoxy, C_1-C_4 alkyl-C(O)-, C_1-C_4 alkyl-S-, C_1-C_4 alkyl-SCH_2-, C_1-C_4 alkenyl-S-, C_1-C_4 alkyl-S(O)-, C_1-C_4 alkyl-$S(O)_2$-, C_1-C_4 alkenyl-S(O)-, C_1-C_4 alkenyl-$S(O)_2$-, -SH, CF_3S-, cyclopropyl, cyclobutyl, furyl optionally substituted with methyl , and C_1-C_6 fluoro-alkyl.

14. The method of any preceding claim, wherein R_1, R_2 and R_3 together with the carbon atom to which they are attached form a hydrocarbon group selected from 3-thiabut-2-yl, 2-methyl-3-thiabut-2-yl, 3-thiapent-2-yl, 4-thiapent-2-yl, 2-thiaprop-1-yl, 2-methyl-3-thiapent-2-yl, 3-oxo-3-thiabut-2-yl, 3-oxo-2-methyl-3-thiabut-2-yl, 3-oxo-3-thiapent-2-yl, 4-oxo-4-thiapent-2-yl, 2-oxo-2-thiaprop-1-yl, 3-oxo-2-methyl-3-thiapent-2-yl, but-2-yl, pent-2-yl, but-3-en-2-yl, pent-3-en-2-yl, but-2-en-2-yl, pent-2-en-2-yl, but-1-en-2-yl, pent-1-en-2-yl, 2-methylbut-2-yl, 2-methylpent-2-yl, 2-methylbut-3-en-2-yl, 3-methylbut-2-yl, 3-methylbut-3-en-2-yl, 3-methylbut-2-en-2-yl, 2,3-dimethylbut-2-yl, 2,3-dimethylpent-2-yl, 2,3-dimethylbut-3-en-2-yl, 2,3-dimethylpent-3-en-2-yl, 2-methylpent-3-en-2-yl, prop-2-yl, prop-1-yl, ethyl, cyclopropyl, 1,1-dimethylcycloprop-2-yl, 1-methylcycloprop-2-yl, 1-methylcycloprop-1-yl, 3-thiahex-5-en-2-yl, 2-methyl-3-thiahex-5-en-2-yl, 1-mercaptoeth-1-yl, 2-mercaptoprop-2-yl, 3,3,3-trifluoroprop-2-yl, 2-methyl-3,3,3-

trifluoroprop-2-yl, 1-(2-furyl)eth-1-yl, 1-(5-methylfur-2-yl)eth-1-yl, 2-(2-furyl)prop-2-yl, 1-(3-furyl)eth-1-yl, 1-(5-methylfur-3-yl)eth-1-yl, 2-(3-furyl)prop-2-yl, 1-(2-tetrahydrofuryl)eth-1-yl, 2-(2-tetrahydrofuryl)prop-2-yl, 1-(3-tetrahydrofuryl)eth-1-yl, 2-(3-tetrahydrofuryl)prop-2-yl, 1-cyclopropyleth-1-yl, 2-cyclopropylprop-2-yl, 1-cyclobutyleth-1-yl, 2-cyclobutylprop-2-yl, cyclobutyl, cyclopentyl, pent-2-en-3-yl, 1-methoxyprop-1-yl, 1-methoxyeth-1-yl, 1,1,1-trifluorobut-3-yl, and 3-thiacyclobut-1-yl.

15. The method of any preceding claim, wherein the compound of formula (V) is 2-methyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)butan-1-one, 2-(methylthio)-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)propan-1-one, 2-methyl-2-(methylthio)-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)propan-1-one, or 2,2-dimethyl-1-(2-(5-(p-tolyl)-1H-imidazol-2-yl)piperidin-1-yl)but-3-en-1-one.