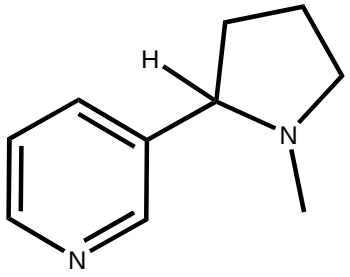
Claims:

1. A method of preparing a compound of Formula I-a, comprising



(I-a)

(i) reacting ethyl nicotinate and N-vinylpyrrolidone in the presence of an alcoholate base to 3-nicotinoyl-1-vinylpyrrolidin-2-one;

(ii) reacting the 3-nicotinoyl-1-vinylpyrrolidin-2-one with an acid to myosmine;

(iii) reducing the myosmine to nornicotine using a reducing agent; and

(iv) methylating the nornicotine to obtain the compound of formula Ia,

wherein the alcoholate base in step (i) is an alkali metal alcoholate chosen from sodium ethanolate, potassium ethanolate, and mixtures thereof, and

wherein the method is carried out in a one-pot process.

2. The method of claim 1, wherein step (i) is carried out in the presence of an aromatic solvent.

3. The method of claim 2, wherein the aromatic solvent is benzene, toluene, or a mixture thereof.

4. The method of any one of the preceding claims, wherein the alcoholate base is added in step (i) in an amount of between 1.4 and 2.0 equivalents, based on 1 equivalent of the ethyl nicotinate.

5. The method of any one of the preceding claims, wherein step (ii) is carried out using an inorganic acid at a temperature between 90 and 115°C, preferably between 100 and 105°C.

6. The method of claim 5, wherein the inorganic acid is HCl.

7. The method of any one of the preceding claims, wherein step (iv) is carried out using formic acid and paraformaldehyde, or formic acid and formaldehyde, preferably at a temperature between and including 40 to 95°C, further preferably between and including 60 to 85°C, even further preferably at a temperature from 60 to 70°C, even further preferably 65 ± 2°C.

8. The method of any one of the preceding claims, wherein step (iii) is carried out using $NaBH_4$ as reducing agent.

9. The method of any one of the preceding claims, further comprising reacting the compound of formula I-a with an organic base at a temperature between 140 and 160°C.

10. The method of any one of the preceding claims, further comprising separating enantiomers of the compound of formula I-a by addition of a chiral O,O'-disubstituted tartaric acid, preferably dibenzoyl tartaric acid.

11. The method of claim 10, wherein the dibenzoyl tartaric acid is O,O'-dibenzoyl-L-tartaric acid.

12. The method of claim 10, wherein the dibenzoyl tartaric acid is a mixture of O,O'-dibenzoyl-L-tartaric acid (L-DBTA) and O,O'-dibenzoyl-D-tartaric acid (D-DBTA) with a molar ratio of L-DBTA to D-DBTA of 80:20 or more.