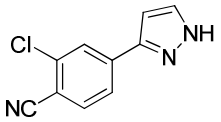
Claims

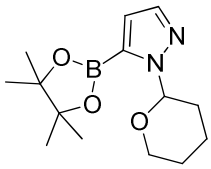
1. A method for preparing 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)



(V)

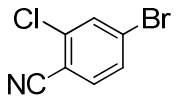
comprising the steps of

a) reacting 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of formula (I)



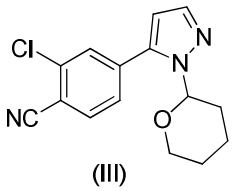
(I)

with 4-bromo-2-chlorobenzonitrile of formula (II)



(II)

at an elevated temperature in the presence of $Pd(OAc)_2$, triphenylphosphine and a base in an acetonitrile-water solvent to form 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)benzonitrile of formula (III)



(III) ;

b) treating the compound of formula (III) with a catalytic amount of HCl in a methanol solvent;

c) adding a base to neutralize the mixture; and

d) isolating the compound of formula (V).

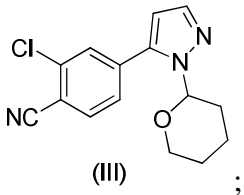
2. The method according to claim 1, wherein step a) further comprises

i) isolating the acetonitrile phase;

ii) cooling the acetonitrile phase;

iii) adding water to the cooled acetonitrile phase; and

iv) precipitating 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)--benzonitrile of formula (III)



(III) ;

and

wherein step c) further comprises

i) adding water to the mixture; and

ii) precipitating the compound of formula (V).

3. The method according to claim 1, wherein the amount of $Pd(OAc)_2$ used per amount of compound of formula (II) in step a) is from about 0.5 to about 2 mol-%.

4. The method according to claim 3, wherein the amount of $Pd(OAc)_2$ used per amount of compound of formula (II) in step a) is from about 0.6 to about 0.8 mol-%.

5. The method according to claim 1, wherein the molar ratio of the $Pd(OAc)_2$ to triphenylphosphine is 1:3.

6. The method according to claim 1, wherein the base is potassium carbonate.

7. The method according to claim 1, wherein the reaction temperature at step a) is from about 60° C. to about 75° C.

8. The method according to claim 7, wherein the reaction temperature at step a) is from 67° C. to 73° C.

9. The method according to claim 1, wherein step a) is carried out under nitrogen flow.

10. The method according to claim 2, wherein step a) further comprises adding a base to the isolated acetonitrile phase after step ai) and before step aii).

11. The method according to claim 10, wherein the base is ammonia water.

12. The method according to claim 2, wherein the temperature of the mixture after step aiii) is 10° C. to 40° C.

13. The method according to claim 12, wherein the temperature of the mixture after step aiii) is 20° C. to 25° C.

14. The method according to claim 1, wherein the reaction time at step a) is 1 hour to 8 hours.

15. The method according to claim 14, wherein the reaction time at step a) is 2 hours to 4 hours.

16. The method according to claim 1, wherein the amount of HCl used per amount of compound of formula (III) in step b) is from about 0.05 to about 0.2 molar equivalents.

17. The method according to claim 16, wherein the amount of HCl used per amount of compound of formula (III) in step b) is from 0.07 to 0.10 molar equivalents.

18. The method according to claim 1, wherein the reaction temperature at step b) is 0° C. to 20° C.

19. The method according to claim 18, wherein the reaction temperature at step b) is 5° C. to 15° C.

20. The method according to claim 1, wherein the reaction time at step b) is 1 hour to 8 hours.

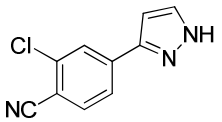
21. The method according to claim 20, wherein the reaction time at step b) is 2 hours to 4 hours.

22. The method according to claim 1, wherein the base used at step c) is ammonia water.

23. The method according to claim 2, wherein the temperature of the mixture after step ci) is 10° C. to 20° C.

24. The method according to claim 2, wherein the isolation at step d) is carried out at 0° C. to 5° C.

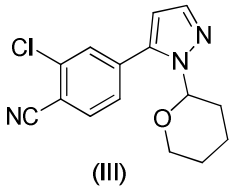
25. A method for preparing 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)



(V)

comprising the steps of

a) treating 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)benzonitrile of formula (III)



(III)

with a catalytic amount of HCl in a methanol solvent;

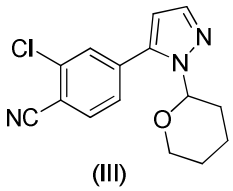
b) adding a base to neutralize the mixture;

c) precipitating the compound of formula (V); and

d) isolating the precipitated compound of formula (V).

26. The method according to claim 25, wherein step b) further comprises adding water to the mixture after step b) and before step c).

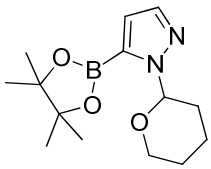
27. A method for preparing 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)benzonitrile of formula (III)



(III)

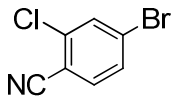
comprising the steps of

a) reacting 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole of formula (I)



(I)

with 4-bromo-2-chlorobenzonitrile of formula (II)



(II)

at an elevated temperature in the presence of $Pd(OAc)_2$, triphenylphosphine and a base in an acetonitrile-water solvent.

28. The method according to claim 27, further comprising the steps of

b) isolating the acetonitrile phase;

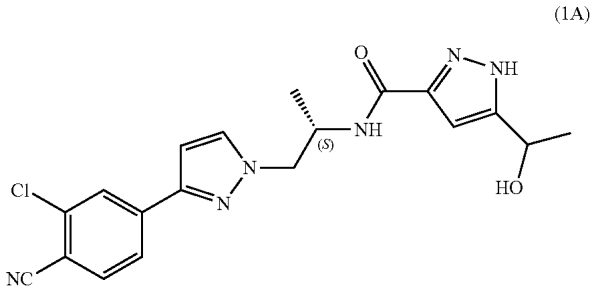
c) cooling the acetonitrile phase;

d) adding water to the cooled acetonitrile phase;

e) precipitating the compound of formula (III); and

f) isolating the precipitated compound of formula (III).

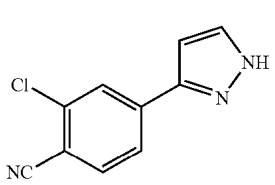
29. A method for preparing the compound of formula(1A)



(1A)

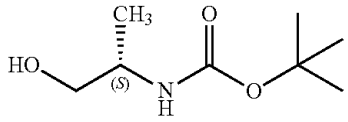
comprising the steps of

a) reacting a compound of formula (V)



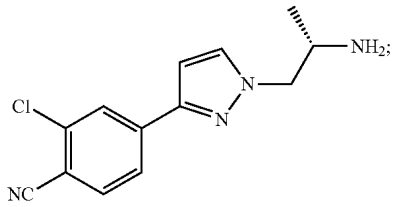
(V)

with a compound of formula (VI)



(VI)

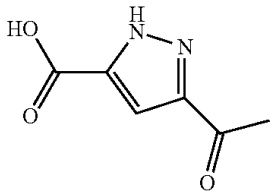
to produce a compound of formula (VII)



(VII)

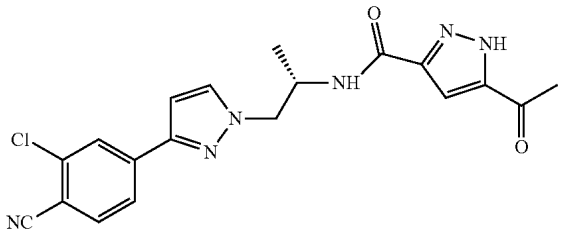
and

b) reacting the compound of formula (VII) with a compound of formula (VIII)



(VIII)

to produce a compound of formula (IX)



(IX)

and

c) reducing the compound of formula (IX) to produce the compound of formula (1A);

wherein the compound of formula (V) is prepared according to claim 1.