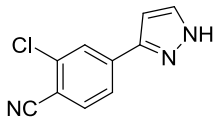
Claims

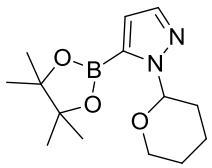
1. A process for the preparation of 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)



(V)

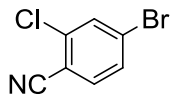
comprising the steps of

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)



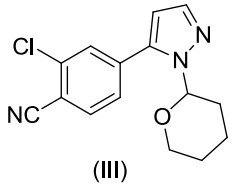
(I)

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)

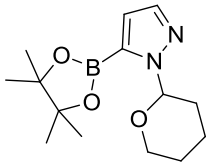
b) treating the compound of formula (III) in a methanol solvent with a catalytic amount of HCl;

c) adding a base to neutralize the mixture; and

d) isolating the compound of formula (V).

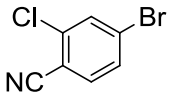
2. A process according to claim 1 comprising the steps of

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)



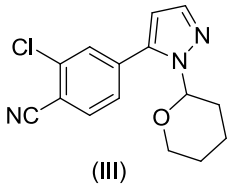
(II)

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

b) isolating the acetonitrile phase;

c) adding water to the cooled acetonitrile phase;

d) isolating the precipitated 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)benzonitrile of formula (III)



(III)

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

f) adding a base to neutralize the mixture;

g) adding water to the mixture; and

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

3. A process according to claim 1 or 2, 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, preferably from about 0.6 to about 0.8, mol-%.

4. A process according to claim 1, 2 or 3, wherein the molar ratio of the $Pd(OAc)_2$ to triphenylphosphine is 1:3.

5. A process according to any of the previous claims, wherein the

base is potassium carbonate.

6. A process according to any of the previous claims, wherein the reaction temperature at step a) is from about 60 to about 75 °C, preferably 70 ± 3 °C.

7. A process according to any of the previous claims, wherein step a) is carried out under nitrogen flow.

8. A process according to any of claims 2 to 7, wherein a base is added to the isolated acetonitrile phase before step c).

9. A process according to claim 8, wherein the base is ammonia water.

10. A process according to any of claims 2 to 9, wherein the temperature of the mixture after step c) is 10 – 40 °C, preferably 20 ± 5 °C.

11. A process according to any of the previous claims, wherein the reaction time at step a) is 1 – 8 h, preferably 2 – 4 h.

12. A process according to any of claims 2 to 11, wherein the amount of HCl used per amount of compound of formula (III) in step e) is from 0.05 to 0.2, preferably from 0.07 to 0.10, molar equivalents.

13. A process according to any of claims 2 to 12, wherein the reaction temperature at step e) is 0 - 20 °C, preferably 10 ± 5 °C.

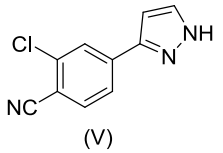
14. A process according to any of claims 2 to 13, wherein the reaction time at step e) is 1 – 8 h, preferably 2 – 4 h.

15. A process according to any of claims 2 to 14, wherein the base used at step f) is ammonia water.

16. A process according to any of claims 2 to 15, wherein the temperature of the mixture after step g) is 10 – 20 °C.

17. A process according to any of claims 2 to 16, wherein the isolation at step h) is carried out at 0 – 5 °C.

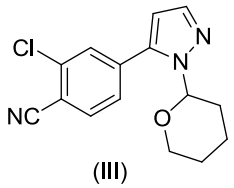
18. A process for the preparation of 2-chloro-4-(1H-pyrazol-3-yl)benzonitrile of formula (V)



(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)

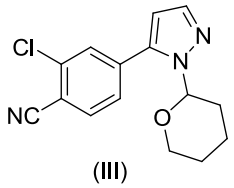
in a methanol solvent with a catalytic amount of HCl;

b) adding a base to neutralize the mixture;

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

19. A process according to claim 18 comprising the steps of

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



(III)

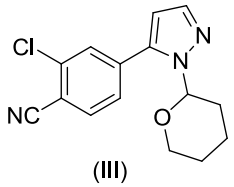
in a methanol solvent with a catalytic amount of HCl;

b) adding a base to neutralize the mixture;

c) adding water to the mixture; and

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

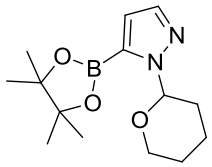
20. A process for the preparation of 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)benzonitrile of formula (III)



(III)

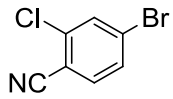
comprising the steps of

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)

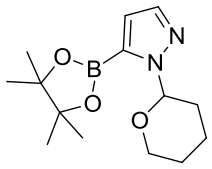


(II)

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

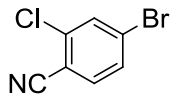
21. A process according to claim 20 comprising the steps of

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;

b) isolating the acetonitrile phase;

c) adding water to the cooled acetonitrile phase;

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