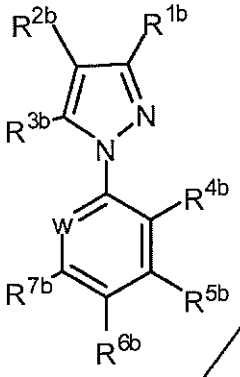
CLAIMS

We claim:

1. A process for preparing a 1-aryl-5-alkyl pyrazole compound of formula (IB):



(IB)

wherein:

R^{1b} is hydrogen, cyano, halogen, R^{8b}, formyl, $-CO_2H$, $-C(O)R^{8b}$, $-C(O)OR^{8b}$, $-C(O)NR^{9b}R^{10b}$ or $-C(S)NH_2$;

R^{2b} is R^{8b} or $-S(O)_mR^{11b}$;

R^{3b} is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, $R^{8b}NH$, $(R^{8b})_2N$, $R^{8b}O$, $R^{8b}S$ or $R^{8b}C(O)CH_2$- wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl or heteroaryl group may optionally be substituted by one or more of halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, nitro, cyano or $-C(S)NH_2$;

R^{4b}, R^{5b}, R^{7b} and R^{13b} are each independently hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{6b} is halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, $-C(O)R^{12b}$, $-S(O)_nR^{12b}$ or SF_5;

W is nitrogen or C-R^{13b};

R^{8b} is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heterocyclyl or heteroaryl;

R^{9b} and R^{10b} are independently hydrogen, alkyl, haloalkyl, hydroxy or alkoxy;

R^{11b} is alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl or halocycloalkyl;

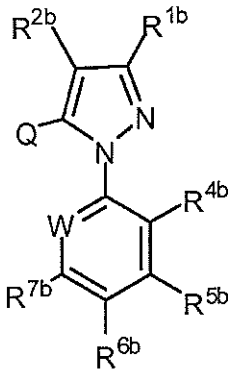
R^{12b} is alkyl or haloalkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2;

which comprises:

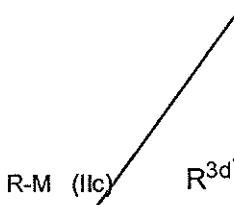
(i) reacting a compound of formula (IIB):



(IIB)

wherein R^{1b}, R^{2b}, R^{4b}, R^{5b}, R^{6b}, R^{7b} and W are as defined above for the compound of formula (IB) and Q is iodo, bromo, chloro or a haloalkylsulfonate group;

with a compound of formula (IIc) or (IId):



R-M (IIc) (IId)

wherein R, R^{1d}, R^{2d} and R^{3d} are independently alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl, wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl group may optionally be substituted with one or more halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, nitro, cyano or $-C(S)NH_2$ groups; M is MgX, ZnX, RZn, BY_2, BF_3 or SnR'_3; X is iodo, bromo or chloro; Y is OH or alkoxy, or each Y may be an alkoxy group which is part of a glycol derivative $Y-(CR''R''')_a-Y$ where R'' and R''' are independently hydrogen or C_1-C_3 alkyl and a is 2, 3 or 4; and R' is alkyl or haloalkyl;

or

reacting the compound of formula (IIB) with $R^{8b}NH_2$, $(R^{6b})_2NH$, $R^{8b}OH$, $R^{8b}SH$ or an enolate anion $R^{6b}C(O)CH_2^-$, wherein R^{8b} is as defined above for the compound of formula (IB);

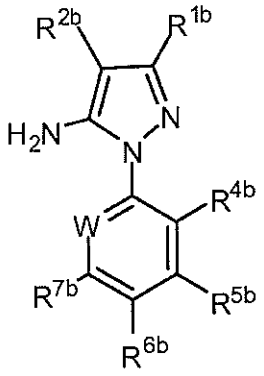
in the presence of a transition metal catalyst to form the compound of formula (IB);

(ii) wherein if R^{1b} in the compound of formula (IB) is $-C(O)OR^{8b}$ or $-C(O)NR^{9b}R^{10b}$, optionally converting the $-C(O)OR^{8b}$ or $-C(O)NR^{9b}R^{10b}$ groups to cyano, hydroxyalkyl, aminoalkyl, dialkylaminoalkyl, formyl, $-C(O)R^{6b}$ or $-C(S)NH_2$, wherein R^{8b}, R^{9b} and R^{10b} are as defined above for the compound of formula (IB), via functional group modification; and

(iii) wherein if R^{2b} is $-S(O)_mR^{11b}$, optionally oxidizing the group $-S(O)_mR^{11b}$ where m is 0 or 1, to form the compound of formula (IB);

wherein the sequence of steps ii) and iii) may be interchanged.

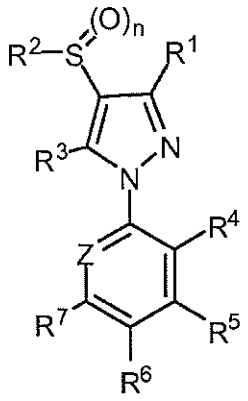
2. The process of claim 1, wherein the compound of formula (IIB) wherein Q is I, Br or Cl is prepared by reacting a compound of formula (IIIB):



(IIIB)

wherein R^{1b}, R^{2b}, R^{4b}, R^{5b}, R^{6b}, R^{7b} and W are as defined in claim 1 for the compound of formula (IB), with a source of Br, Cl or I and a nitrite compound T-ONO, where T is hydrogen or alkyl, or a salt thereof.

3. The process of claim 1, wherein the transition metal catalyst is a palladium catalyst.
4. The process of claim 2, wherein T-ONO is sodium nitrite, isopentyl nitrite, or *tert*-Butyl nitrite.
5. The process of claim 1, wherein Q is bromo.
6. The process of claim 1, wherein M is ZnX or RZn.
7. The process of claim 1, wherein M is BY_2.
8. The process of claim 7, wherein Y is hydroxy.
9. The process of claim 1, wherein the compound of formula (IIB) is reacted with the compound of formula (IId).
10. The process of claim 9, wherein the compound of formula (IId) is trimethylboroxine.
11. The process of claim 1, wherein in step (i) the compound of (IIB) is reacted with a compound of (IIc) wherein M is BY_2 or a compound of formula (IId), and wherein the process further comprises addition of a base to the reaction mixture.
12. The process of claim 11, wherein the base is an alkali metal hydroxide or an alkali metal carbonate.
13. The process of claim 3, wherein the palladium catalyst is selected from $(Ph_3P)_4Pd$, $(Ph_3P)_2PdCl_2$, $(CH_3CN)_2PdCl_2$, $Pd_2(dba)_3$ or $(dppf)PdCl_2$.
14. The process of claim 1, wherein in step (i), the compound of formula (IIB) is reacted with a compound of formula (IId) in the presence of $Pd_2(dba)_3$ and potassium carbonate.
15. The process of claim 2, wherein the compound of formula (IIIB) is fipronil.
16. The process of claim 4, wherein T-ONO is sodium nitrite and the source of Br is HBr.
17. A process for preparing a 1-aryl-5-alkyl pyrazole compound of formula (I):



(I)

wherein:

R^1 and R^3 are each independently hydrogen, cyano, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, formyl, aryl, heterocyclyl, heteroaryl, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$ or $-C(S)NH_2$, wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl or heteroaryl group may optionally be substituted by one or more of halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, alkyl or haloalkylthio; alkyl or haloalkyl sulfinyl; alkyl or haloalkyl sulfonyl; nitro, cyano and $-C(S)NH_2$;

R^2 is alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl or halocycloalkyl;

R^4, R^5, R^7 and R^{12} are each independently hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^6 is halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, $-C(O)R^{11}$, $-S(O)_mR^{11}$ or SF_5;

Z is nitrogen or C-R^{12};

R^8 is alkyl, haloalkyl, cycloalkyl or halocycloalkyl;

R^9 and R^{10} are independently hydrogen, alkyl, haloalkyl, hydroxy or alkoxy;

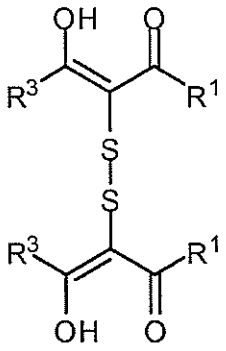
R^{11} is alkyl or haloalkyl;

n is 0, 1 or 2; and

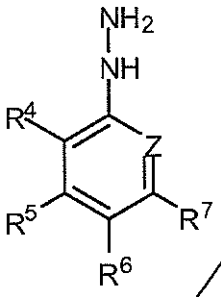
m is 0, 1 or 2;

which comprises:

(i) reacting a disulfide compound of formula (II) with an arylhydrazine of formula (III)

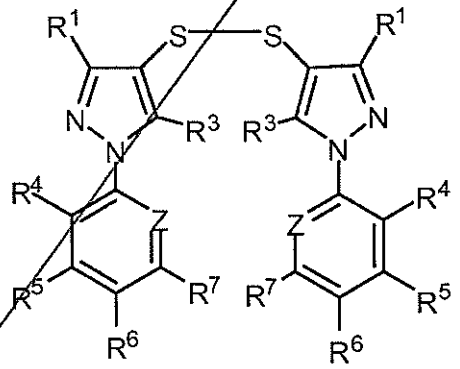


(II)



(III)

wherein R^1 and R^3 are each independently hydrogen, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, formyl, aryl, heteroaryl, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$ or $-C(S)NH_2$, wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl or heteroaryl group may optionally be substituted by one or more of halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, alkyl or haloalkylthio; alkyl or haloalkyl sulfinyl; alkyl or haloalkyl sulfonyl; nitro, cyano and $-C(S)NH_2$; and R^4, R^5, R^6, R^7 and Z are as defined for the compound of formula (I), to form a pyrazole disulfide of formula (IV)



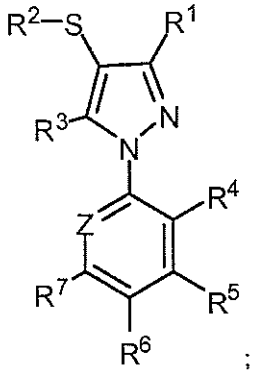
(IV)

wherein R^1, R^3 R^4, R^5, R^6, R^7 and Z are as defined for the compound of formula (I);

(ii) reacting the compound of formula (IV) with a compound of formula (V)

R^2-LG (V)

wherein R^2 is as defined above for the compound of formula (I) and LG is a leaving group to form a compound of formula (VI)



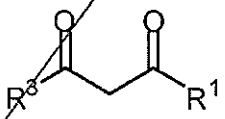
(VI)

(iii) wherein if in the compound of formula (VI), R^1 or R^3 are -C(O)OR^8 or -C(O)NR^9R^{10}, optionally converting the -C(O)OR^8 or -C(O)NR^9R^{10} groups in the compound of formula (VI) to cyano, hydroxyalkyl, aminoalkyl, dialkylaminoalkyl, formyl, -C(O)R^8 or –C(S)NH_2; and

(iv) optionally oxidizing the –SR^2 to form the compound of formula (I);

wherein the sequence of steps iii) and iv) may be interchanged.

18. The process of claim 17, wherein the disulfide of formula (II) is formed by reaction of the -diketone of formula (VII)



(VII)

with a disulfide dihalide reagent.

19. The process of claim 17, wherein in step ii) the reaction of the compound of formula (IV) with the compound of formula (V) is carried out in the presence of a reducing agent.

20. The process of claim 19, wherein the reducing agent is tetrakis(dimethylamino)ethylene, sodium borohydride, sodium dithionite, sodium hydroxymethanesulfinate, zinc hydroxymethanesulfonate, formic acid or sodium formate.

21. The process of claim 17, wherein R_2 is alkyl or haloalkyl;

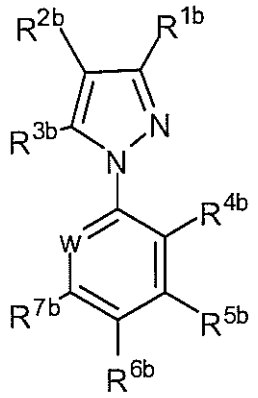
R_1 is –C(O)OR^8 or –C(O)NR^9R^{10}; and

R^3 is alkyl.

22. The process of claim 17, wherein in step ii) the leaving group LG is iodide.

Claims

1. A process for preparing a 1-aryl-5-alkyl pyrazole compound of formula (IB):



(IB)

wherein:

R^{1b} is hydrogen, cyano, halogen, R^{8b}, formyl, $-CO_2H$, $-C(O)R^{8b}$, $-C(O)OR^{8b}$, $-C(O)NR^{9b}R^{10b}$ or $-C(S)NH_2$;

R^{2b} is $-S(O)_mR^{11b}$;

R^{3b} is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, heteroaryl, wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl or heteroaryl group may optionally be substituted by one or more of halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, nitro, cyano or $-C(S)NH_2$;

R^{4b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{5b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{7b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{13b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{6b} is halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, $-C(O)R^{12b}$, $-S(O)_nR^{12b}$ or SF_5;

W is nitrogen or $C-R^{13b}$;

R^{8b} is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heterocyclyl or heteroaryl;

R^{9b} and R^{10b} are independently hydrogen, alkyl, haloalkyl, hydroxy or alkoxy;

R^{11b} is alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl or halocycloalkyl;

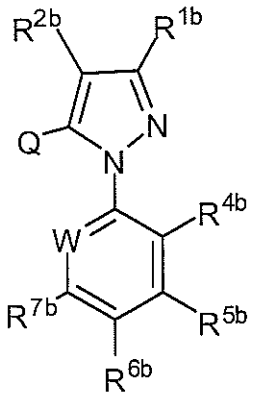
R^{12b} is alkyl or haloalkyl;

m is 0, 1 or 2; and

n is 0, 1 or 2;

which comprises:

(i) reacting a compound of formula (IIB):



(IIB)

wherein

R^{1b} is hydrogen, cyano, halogen, R^{8b}, formyl, $-CO_2H$, $-C(O)R^{8b}$, $-C(O)OR^{8b}$, $-C(O)NR^{9b}R^{10b}$ or $-C(S)NH_2$;

R^{2b} is $-S(O)_mR^{11b}$

R^{4b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{5b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{6b} is halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, $-C(O)R^{12b}$, $-S(O)_nR^{12b}$ or SF_5;

R^{7b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

R^{8b} is alkyl, haloalkyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heterocyclyl or heteroaryl

R^{11b} is alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl or halocycloalkyl;

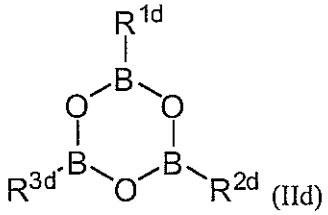
W is nitrogen or C-R^{13b};

R^{13b} is hydrogen, halogen, alkyl, haloalkyl, cyano or nitro;

and

Q is iodo, bromo, chloro or a haloalkylsulfonate group;

with a compound of formula (IId):



(IId)

wherein R^{1d}, R^{2d} and R^{3d} are independently alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl, wherein each alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl or heterocyclyl group may optionally be substituted with one or more halogen, hydroxy, alkoxy, alkoxyalkoxy, amino, alkylamino, dialkylamino, nitro, cyano or $-C(S)NH_2$ groups;

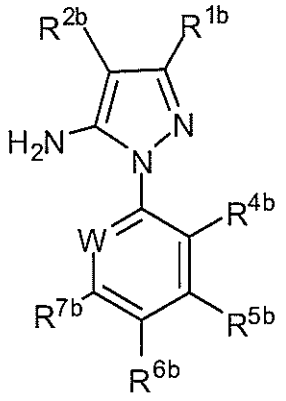
in the presence of a transition metal catalyst to form the compound of formula (IB);

(ii) wherein if R^{1b} in the compound of formula (IB) is -C(O)OR^{8b} or -C(O)$NR^{9b}R^{10b}$, optionally converting the -C(O)OR^{8b} or -C(O)$NR^{9b}R^{10b}$ groups to cyano, hydroxyalkyl, aminoalkyl, dialkylaminoalkyl, formyl, -C(O)R^{8b} or $-C(S)NH_2$, wherein R^{8b}, R^{9b} and R^{10b} are as defined above for the compound of formula (IB), via functional group modification; and

(iii) optionally oxidizing the group $-S(O)_mR^{11b}$ where m is 0 or 1, to form the compound of formula (IB);

wherein the sequence of steps ii) and iii) may be interchanged.

2. The process of claim 1, wherein the compound of formula (IIB) wherein Q is I, Br or Cl is prepared by reacting a compound of formula (IIIB):



(IIIB)

wherein R^{1b}, R^{2b}, R^{4b}, R^{5b}, R^{6b}, R^{7b} and W are as defined in claim 1 for the compound of formula (IB), with a source of Br, Cl or I and a nitrite compound T-ONO, where T is hydrogen or alkyl, or a salt thereof.

3. The process of claim 1, wherein the transition metal catalyst is a palladium catalyst.
4. The process of claim 2, wherein T-ONO is sodium nitrite, isopentyl nitrite, or *tert*-Butyl nitrite.
5. The process of claim 1, wherein Q is bromo.
6. The process of claim 1, wherein the compound of formula (IId) is trimethylboroxine and R^{3b} is methyl.
7. The process of claim 1, wherein in step (i) the compound of (IIB) is reacted with a compound of formula (IId), and wherein the process further comprises addition of a base to the reaction mixture.
8. The process of claim 7, wherein the base is an alkali metal hydroxide or an alkali metal carbonate.
9. The process of claim 3, wherein the palladium catalyst is selected from $(Ph_3P)_4Pd$, $(Ph_3P)_2PdCl_2$, $(CH_3CN)_2PdCl_2$, $Pd_2(dba)_3$, $(dppf)PdCl_2$, or a palladium metal catalyst covalently linked to a polymer chain.
10. The process of claim 2, wherein the compound of formula (IIIB) is fipronil.
11. The process of claim 4, wherein T-ONO is sodium nitrite and the source of Br is HBr.
12. The process of claim 1, wherein in step (i), the compound of formula (IIB) is reacted with a compound of formula (IId) in the presence of potassium carbonate.
13. The process of claim 1, wherein in step (i), the compound of formula (IIB) is reacted with a compound of formula (IId) in the presence of n-butyl acetate.
14. The process of claim 1, wherein:

    R^{4b} is halogen, haloalkyl, cyano or nitro.

15. The process of claim 1, wherein:

    W is C-R^{13b}.

16. The process of claim 1, wherein:

W is C-R^{13b}; and

R^{13b} is halogen, haloalkyl, cyano or nitro.

17. The process of claim 1, wherein:

R^{4b} is halogen;

W is C-R^{13b}; and

R^{13b} is halogen.

18. The process of claim 1, wherein:

R^{4b} is halogen;

W is C-R^{13b};

R^{13b} is halogen; and

R^{6b} is haloalkyl.

19. The process of claim 1, wherein in step (i), the compound of formula (IIB) is reacted with a compound of formula (IId) in the presence of $Pd_2(dba)_3$ and potassium carbonate.