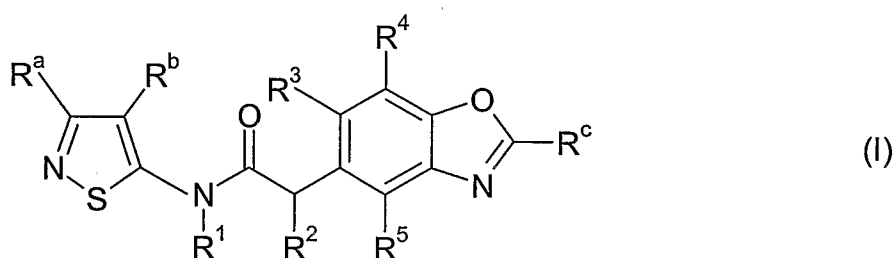


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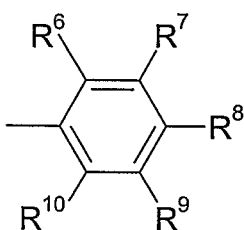
CHEMICAL PROCESS FOR THE PREPARATION OF BENZOXAZOLE DERIVATIVES USED AS PESTICIDES

The present invention relates to an improved process for making azole derivatives useful as insecticidal, acaricidal, molluscicidal and nematocidal compounds.

5 Azole derivatives with useful insecticidal properties are disclosed in WO00/06566, WO00/63207, WO01/55144 and WO03/011861. The applicants have found a method of making the compounds in improved yield and purity. There is therefore provided a process for the preparation of compounds of formula (I)



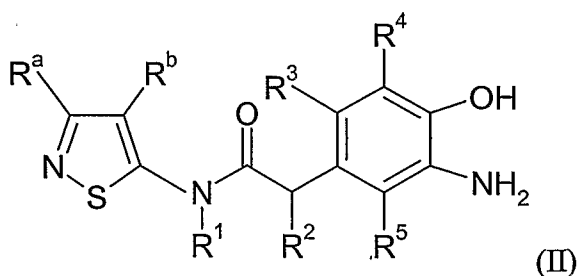
10 wherein R^a is C_{1-3} alkyl; R^b is halogen; R^c is C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} alkoxy, furfuryl or is a group



15 R^1 is hydrogen, C_{1-2} alkyl, (C_{1-6})alkoxymethyl or propargyl; R^2 is hydrogen, methyl or fluoro; R^3 , R^4 and R^5 are, independently, hydrogen, halogen, C_{1-2} alkyl, C_{1-2} alkoxy or C_{1-2} haloalkyl; R^6 and R^{10} are, independently, hydrogen, halogen, C_{1-3} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, nitro, cyano, C_{1-2} haloalkoxy, C_{1-8} alkylthio, C_{1-6} alkylsulfinyl,

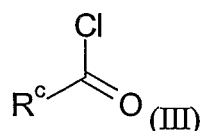
- 2 -

C_{1-6} alkylsulfonyl, amino, C_{1-3} alkylamino or di(C_{1-3})alkylamino; R^7 , R^8 and R^9 are, independently, hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{2-6} alkynyloxy, C_{3-6} cycloalkyl, nitro, cyano, C_{1-6} haloalkoxy, C_{2-6} haloalkenyloxy, $S(O)_pR^{11}$, OSO_2R^{12} , $NR^{13}SO_2R^{14}$, $NR^{15}R^{16}$, $NR^{17}COR^{18}$, COR^{19} , $SiR^{20}R^{21}R^{22}$, SCN , optionally substituted aryl or optionally substituted heteroaryl or optionally substituted heterocyclyl; R^{11} , R^{12} and R^{14} are, independently, C_{1-6} alkyl, C_{1-6} haloalkyl or optionally substituted aryl; R^{13} and R^{17} are, independently, hydrogen or C_{1-2} alkyl; R^{15} and R^{16} are, independently, hydrogen or C_{1-3} alkyl; or R^{15} and R^{16} together with the N atom to which they are attached form a five or six-membered optionally substituted heterocyclic ring which may contain a further heteroatom selected from O and S; R^{18} and R^{19} are, independently, hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted aryl, optionally substituted heteroaryl or $NR^{23}R^{24}$; R^{20} , R^{21} and R^{22} are, independently, C_{1-4} alkyl or aryl; R^{23} and R^{24} are, independently, hydrogen or C_{1-3} alkyl; or R^{23} and R^{24} together with the N atom to which they are attached form a five or six-membered optionally substituted heterocyclic ring which may contain a further heteroatom selected from O and S; and p is 0, 1 or 2, the process comprising reacting a formula of compound II



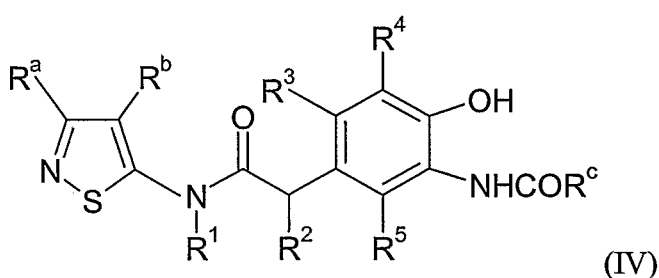
where R^a , R^b , R^1 , R^2 , R^3 , R^4 and R^5 are as defined in relation to formula (I) with a compound of formula III

- 3 -



where R^c is as defined in relation to formula (I) followed by treatment with a base and cyclising the resulting adduct.

The reaction proceeds via an adduct of formula IV



The intermediate of formula (IV) may be isolated or the process can be performed without isolation of the intermediate.

Certain compounds of formula (IV) are novel and as such form a further aspect of the invention.

Suitable conditions for the reactions are described in WO03/011861

The coupling reaction is preferably carried out at -20°C to 30°C .

The reaction is preferably performed in a solvent. A very wide range of solvents may be used, for example suitable solvents include dimethylacetamide, THF, DMF or DCM.

The preferred molar ratio of acid chloride to aminophenol is from 1:1 to 1:2.

The coupling reaction is preferably carried out in the presence of a base, especially a tertiary amine.

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The further treatment with a base may be with any suitable base such as an amine, preferably a primary amine or inorganic bases. A preferred base is ammonia.

Suitable conditions for the cyclisation reaction are described in WO03/011861.

Suitable solvents are chloralkanes such as 1,1,2,2-tetrachlorethane or aromatic

5 hydrocarbons such as toluene or xylene.

The acylation reaction reaction between II and III is very difficult to control in order to avoid diacylation i.e. there is an undesirable acylation of the hydroxy group of II as well as the desired acylation of the amino group of II. The applicants have surprisingly found that the further treatment with bases produces compounds of sufficiently high

10 purity such that no further purification is required.

Each alkyl moiety is a straight or branched chain and is, for example, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl or *neo*-pentyl.

Halogen is fluorine, chlorine, bromine or iodine.

15 Haloalkyl groups are alkyl groups which are substituted with one or more of the same or different halogen atoms and are, for example, CF₃, CF₂Cl, CF₃CH₂ or CHF₂CH₂.

Alkenyl and alkynyl moieties can be in the form of straight or branched chains. The alkenyl moieties, where appropriate, can be of either the (*E*)- or (*Z*)-configuration. Examples are vinyl, allyl, ethynyl and propargyl.

20 Haloalkenyl moieties are alkyl moieties which are substituted with one or more of the same or different halogen atoms, an example being CH₂CH=CCl₂.

Aryl includes naphthyl, anthracyl, fluorenyl and indenyl but is preferably phenyl.

The term heteroaryl refers to an aromatic ring containing up to 10 atoms including one or more heteroatoms (preferably one or two heteroatoms) selected from O, S and N.

25 Examples of such rings include pyridine, pyrimidine, furan, quinoline, quinazoline, pyrazole, thiophene, thiazole, oxazole and isoxazole.

- 5 -

The terms heterocycle and heterocyclyl refer to a non-aromatic ring containing up to 10 atoms including one or more (preferably one or two) heteroatoms selected from O, S and N. Examples of such rings include 1,3-dioxolane, tetrahydrofuran and morpholine.

5 Cycloalkyl includes cyclopropyl, cyclopentyl and cyclohexyl.

When present, the optional substituents on aryl, heteroaryl or heterocyclyl are selected, independently, from hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, nitro, cyano, C₁₋₆ haloalkoxy, C₁₋₂ alkylthio, SO₂CH₃, SO₂CH₂CH₃, OSO₂CH₃ and SCN.

10 It is to be understood that dialkylamino substituents include those where the dialkyl groups together with the N atom to which they are attached form a five, six or seven-membered heterocyclic ring which may contain one or two further heteroatoms selected from O, N or S and which is optionally substituted by one or two independently selected (C₁₋₆)alkyl groups. When heterocyclic rings are formed by joining two groups on
15 an N atom, the resulting rings are suitably pyrrolidine, piperidine, thiomorpholine and morpholine each of which may be substituted by one or two independently selected (C₁₋₆) alkyl groups.

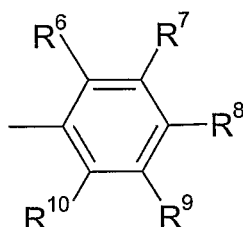
Preferred groups for R^a, R^b, R^c, R¹, R², R³, R⁴ and R⁵ in any combination thereof are set out below.

20 Preferably R^a is methyl or ethyl.

It is preferred that R^b is bromo or chloro, especially chloro.

The group R^c is preferably is a group

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or is C₁₋₆ alkyl or is C₁₋₆ haloalkyl.

More preferably R^c is C₁₋₆ alkyl or C₁₋₆ haloalkyl, more especially C₁₋₃ haloalkyl.

Preferably R¹ is hydrogen, C₁₋₂ alkyl or (C₁₋₆) alkoxyethyl.

5 It is more preferred that R¹ is hydrogen, ethyl, CH₂OCH₃ or CH₂OC₂H₅.

Yet more preferably R¹ is hydrogen, ethyl or CH₂OC₂H₅.

It is even more preferred that R¹ is hydrogen or CH₂OC₂H₅, especially hydrogen.

Preferably R² is hydrogen or fluoro.

In one aspect of the invention, it is preferred that R² is fluoro.

10 Preferably R³, R⁴ and R⁵ are each, independently, hydrogen or halogen.

It is preferred that R³ is hydrogen or fluorine.

More preferably R³ is hydrogen.

It is preferred that R⁴ is hydrogen or fluorine.

More preferably R⁴ is hydrogen.

15 It is preferred that R⁵ is hydrogen or fluorine.

More preferably R⁵ is hydrogen.

It is preferred that R⁷, R⁸ and R⁹ are each, independently, hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy(C₁₋₆)alkoxy, C₂₋₆ alkynyloxy, nitro, cyano, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl or C₂₋₆ haloalkenyloxy.

20 It is preferred that R⁷ is hydrogen, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy(C₁₋₆)alkoxy, nitro or cyano.

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More preferably R^7 is hydrogen, chlorine, fluorine, methyl, $OC_2H_4OCH_3$, nitro or cyano.

It is even more preferred that R^7 is hydrogen or chlorine.

It is yet more preferred that R^7 is hydrogen.

- 5 It is preferred that R^8 is hydrogen, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkoxy, C_{2-6} alkynyloxy, cyano, C_{1-6} alkylsulfonyl or C_{2-6} haloalkenyloxy.

More preferably R^8 is hydrogen, chlorine, fluorine, bromine, CF_3 , ethoxy, $OC_2H_4OCH_3$, $OCH_2C\equiv CH$, cyano, SO_2CH_3 or $OCH_2CH=CCl_2$.

It is even more preferred that R^8 is hydrogen, chlorine, CN, CF_3 or SO_2CH_3 .

- 10 Yet more preferably R^8 is hydrogen.

It is preferred that R^9 is hydrogen, halogen or C_{1-6} alkylthio.

More preferably R^9 is hydrogen, chlorine, fluorine, iodine or SCH_3 .

It is even more preferred that R^9 is hydrogen, chlorine or fluorine.

Yet more preferably R^9 is hydrogen.

- 15 It is preferred that R^6 and R^{10} are, independently, hydrogen, halogen, C_{1-3} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, nitro, cyano, C_{1-2} haloalkoxy, C_{1-8} alkylthio or C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl; provided that at least one of R^6 and R^{10} is not hydrogen.

- 20 In one aspect of the invention, it is preferred that R^6 and R^{10} are, independently, hydrogen, halogen, C_{1-3} alkyl, C_{1-2} haloalkyl, C_{1-2} alkoxy, nitro, cyano, C_{1-2} haloalkoxy or C_{1-2} alkylthio, provided that at least one of R^6 and R^{10} is not hydrogen.

It is more preferred that R^6 is hydrogen, methyl, chlorine, fluorine or bromine and R^{10} is hydrogen, methyl, chlorine, fluorine, OCH_3 , SCH_3 , CF_3 or nitro, provided that at least one of R^6 and R^{10} is not hydrogen.

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It is still more preferred that R⁶ is hydrogen, chlorine, fluorine or bromine and R¹⁰ is hydrogen, chlorine, fluorine, OCH₃, SCH₃, CF₃ or nitro, provided that at least one of R⁶ and R¹⁰ is not hydrogen.

Even more preferably R⁶ is hydrogen, chlorine, fluorine or bromine and R¹⁰ is
5 chlorine, fluorine or bromine.

It is most preferred that when R⁶ is hydrogen, R¹⁰ is fluorine, chlorine or bromine and that when R⁶ is chlorine or fluorine, R¹⁰ is fluorine.

The invention is illustrated by the following Example:

10

EXAMPLE 1

Step1:

311 mg (1 mmol) of 2-(3-Amino-4-hydroxy-phenyl)-N-(4-chloro-3-ethyl-isothiazol-5-yl)-acetamide was dissolved in 4.5 ml of THF and 417 ul of triethylamine (3 mmol) added.

15 After cooling the solution to 0° degress, a freshly prepared solution of 168mg 3-furfuryl acid chloride (1.5 mmol) was added in dropwise fashion under stirring. After addition the icebath was removed and the resulting suspension stirred ambient temperature for another 2 hrs before 1 ml of conc aq. ammonia was added. After 12 hrs the reaction mixture was concentrated to dryness (N₂-stream) and consequently worked-up by liquid-liquid
20 extraction with EtOAc/ 1N HCl. The resulting crude material was used without further purification in the next step.

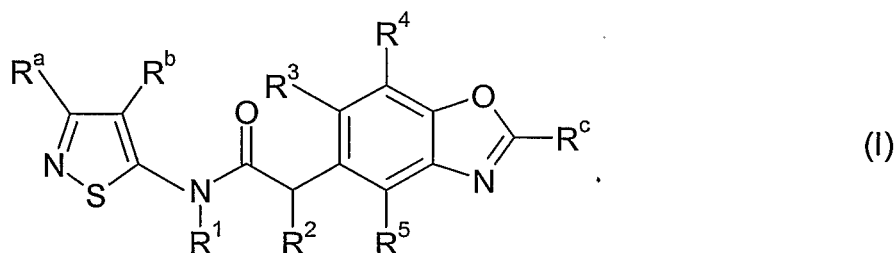
Step 2:

25 The crude material was dissolved in 6 ml trichloroethylene, 40 mg (0.2 mmol) p-TsOH added and the resulting suspension heated under stirring to 150 deg overnight. After removal of the solvent the remaing crude material was dissolved in 2ml DMF and the required product separated via RP-HPLC.

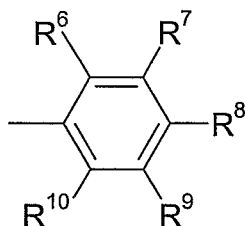
- 10 -

CLAIMS

1. A process for the preparation of compounds of formula (I)



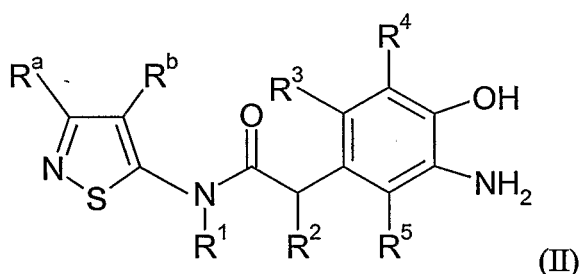
- 5 wherein R^a is C₁₋₃ alkyl; R^b is halogen; R^c is C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, furfuryl or is a group



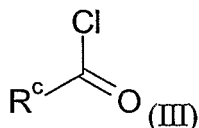
- 10 R¹ is hydrogen, C₁₋₂ alkyl, (C₁₋₆)alkoxymethyl or propargyl; R² is hydrogen, methyl or fluoro; R³, R⁴ and R⁵ are, independently, hydrogen, halogen, C₁₋₂ alkyl, C₁₋₂ alkoxy or C₁₋₂ haloalkyl; R⁶ and R¹⁰ are, independently, hydrogen, halogen, C₁₋₃ alkyl, C₁₋₂ haloalkyl, C₁₋₂ alkoxy, nitro, cyano, C₁₋₂ haloalkoxy, C₁₋₈ alkylthio, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyl, amino, C₁₋₃ alkylamino or di(C₁₋₃)alkylamino; R⁷, R⁸ and R⁹ are, independently, hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy(C₁₋₆)alkoxy, C₂₋₆ alkynyloxy, C₃₋₆ cycloalkyl, nitro, cyano, C₁₋₆ haloalkoxy, C₂₋₆ haloalkenyloxy, S(O)_pR¹¹, OSO₂R¹², NR¹³SO₂R¹⁴, NR¹⁵R¹⁶, NR¹⁷COR¹⁸, COR¹⁹, SiR²⁰R²¹R²², SCN, optionally substituted aryl or optionally substituted heteroaryl or optionally substituted heterocyclyl;
- 15

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R^{11} , R^{12} and R^{14} are, independently, C_{1-6} alkyl, C_{1-6} haloalkyl or optionally substituted aryl; R^{13} and R^{17} are, independently, hydrogen or C_{1-2} alkyl; R^{15} and R^{16} are, independently, hydrogen or C_{1-3} alkyl; or R^{15} and R^{16} together with the N atom to which they are attached form a five or six-membered optionally substituted heterocyclic ring which may contain a further heteroatom selected from O and S; R^{18} and R^{19} are, independently, hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted aryl, optionally substituted heteroaryl or $NR^{23}R^{24}$; R^{20} , R^{21} and R^{22} are, independently, C_{1-4} alkyl or aryl; R^{23} and R^{24} are, independently, hydrogen or C_{1-3} alkyl; or R^{23} and R^{24} together with the N atom to which they are attached form a five or six-membered optionally substituted heterocyclic ring which may contain a further heteroatom selected from O and S; and p is 0, 1 or 2 the process comprising reacting a formula of compound II



where R^a , R^b , R^1 , R^2 , R^3 , R^4 and R^5 are as defined in relation to formula (I) with a compound of formula III



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where R^c is as defined in relation to formula (I) followed by treatment with a base and cyclising the resulting adduct.

2. A process as claimed in claim 1 where R⁶ and R¹⁰ are, independently, hydrogen,
5 halogen, C₁₋₃ alkyl, C₁₋₂ haloalkyl, C₁₋₂ alkoxy, nitro, cyano, C₁₋₂ haloalkoxy, C₁₋₂ alkylthio, amino, C₁₋₃ alkylamino or di(C₁₋₃)alkylamino, provided that at least one of R⁶ and R¹⁰ is not hydrogen; and R⁷, R⁸ and R⁹ are, independently, hydrogen, halogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, nitro, cyano, C₁₋₆ haloalkoxy,
10 S(O)_pR¹¹, OSO₂R¹², NR¹³SO₂R¹⁴, NR¹⁵R¹⁶, NR¹⁷COR¹⁸, COR¹⁹, SiR²⁰R²¹R²², SCN, optionally substituted aryl or optionally substituted heteroaryl.
3. A process as claimed in claim 1 wherein R^c is C₁₋₆ alkyl or C₁₋₆ haloalkyl.
- 15 4. A process as claimed in any preceding claim where R¹ is hydrogen, C₁₋₂ alkyl or (C₁₋₆) alkoxymethyl.
5. A process as claimed in any of the preceding claims where R² is hydrogen or fluoro.
- 20 6. A process as claimed in any of the preceding claims where R³, R⁴ and R⁵ are each, independently, hydrogen or halogen.