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(54) Title: PROCESSES FOR THE PREPARATION OF PESTICIDAL COMPOUNDS

(57) Abstract: This application relates to efficient and economical synthetic chemical processes for the preparation of pesticidal thioether and pesticidal sulfoxides efficiently and in high yield from commercially available starting materials. Further, the present application relates to certain novel compounds necessary for their synthesis. Specifically a process is provided for the production of N-acyl thioethers comprising acylation of an aminopyrazole precursor with 3-chloropropionyl chloride followed by thioalkylation of the product.



## PROCESSES FOR THE PREPARATION OF PESTICIDAL COMPOUNDS

## CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims the benefit of the following U.S. Provisional Applications:  
5 Serial No. 62/043,040, filed August 28, 2014; and Serial No. 61/892,127, filed October 17, 2013, the entire disclosure of these applications are hereby expressly incorporated by reference into this Application.

## TECHNICAL FIELD

10 This application relates to efficient and economical synthetic chemical processes for the preparation of pesticidal thioether and pesticidal sulfoxides. Further, the present application relates to certain novel compounds necessary for their synthesis. It would be advantageous to produce pesticidal thioether and pesticidal sulfoxides efficiently and in high yield from commercially available starting materials.

## DETAILED DESCRIPTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

As used herein, the term "alkyl" denotes branched or unbranched hydrocarbon chains.

20 As used herein, the term "alkynyl" denotes branched or unbranched hydrocarbon chains having at least one  $C\equiv C$ .

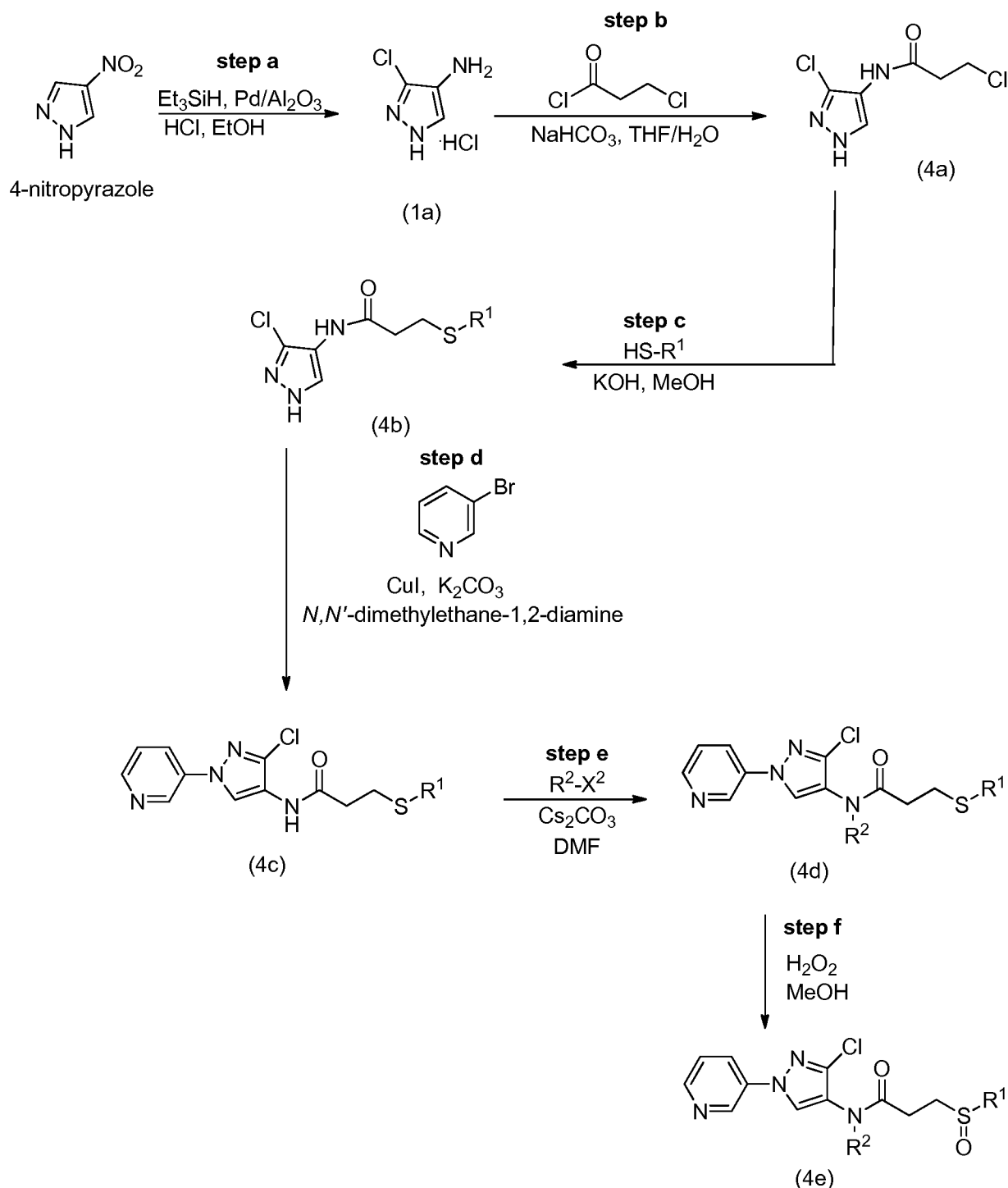
Unless otherwise indicated, the term "cycloalkyl" as employed herein alone is a saturated cyclic hydrocarbon group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term "thio" as used herein as part of another group refers to a sulfur atom serving as  
25 a linker between two groups.

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine.

The compounds and process of the present application are described in detail below in scheme 1.

Scheme 1



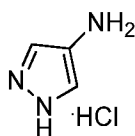
In step a of Scheme 1, 4-nitropyrrole is halogenated and reduced to yield 3-chloro-1*H*-pyrazol-4-amine hydrochloride (1a). The halogenation occurs at the 3-carbon through the use of concentrated (37 weight percent) hydrochloric acid (HCl). The reduction occurs with triethylsilane (Et<sub>3</sub>SiH) and palladium on alumina (Pd/Al<sub>2</sub>O<sub>3</sub>, preferably about 1 to 10 weight percent palladium on alumina, more preferably about 5 weight percent). This reaction may be conducted at a temperature from about 0 °C to about 40 °C, preferably about 10 °C to about 20 °C. This reaction may be conducted in a polar protic solvent, such as methanol (MeOH) or

ethanol (EtOH), preferably ethanol. It was surprisingly discovered, that by utilizing about 1 equivalents to about 4 equivalents, preferably, about 2.5 equivalents to about 3.5 equivalents of triethylsilane in this step, while conducting the reaction between about 10 °C and about 20 °C, gives about a 10:1 molar ratio of the desired halogenated product 3-chloro-1*H*-pyrazol-4-amine hydrochloride (1a)



(1a)

versus the undesired product

1*H*-pyrazol-4-amine hydrochloride

In step b of Scheme 1, 3-chloro-1*H*-pyrazol-4-amine hydrochloride (1a) is reacted with between about 1 equivalent and about 2 equivalents of 3-chloropropionyl chloride in the presence of a base, preferably, metal carbonates, metal hydroxides, metal phosphates, more preferably sodium bicarbonate (NaHCO<sub>3</sub>) to yield 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a). The reaction may be conducted in a mixture of tetrahydrofuran (THF), and water. It was surprisingly discovered that a chloro substituent must be present at the 3-position for this reaction to proceed to completion and to also avoid over acylation. Described herein is a comparative example without a halogen at the 3-position that yielded the double acylated product (see “CE-1”). Further, comparative example with a bromo group at the 3-position afforded the product in a surprisingly low yield compared to the yield with the chloro group (see “CE-2”).

In step c of Scheme 1, 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a) undergoes nucleophilic substitution by a thiol (HS-R<sup>1</sup>), in the presence of an inorganic base, preferably, metal carbonates, metal hydroxides, metal phosphates, metal hydrides, more preferably, potassium hydroxide, conducted in the presence of a polar solvent, preferably methanol, wherein R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-haloalkyl and C<sub>1</sub>-C<sub>4</sub>-alkyl-C<sub>3</sub>-C<sub>6</sub>-halocycloalkyl, preferably, R<sup>1</sup> is selected from CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub> or CH<sub>2</sub>(2,2-difluorocyclopropyl) to yield thioether (4b).

In step d of Scheme 1, thioether (4b) is reacted with a halopyridine, preferably, 3-bromopyridine in the presence of a copper salt, (such as copper(I) chloride (CuCl), copper(II) chloride (CuCl<sub>2</sub>) or copper(I) iodide (CuI)), a base such as potassium phosphate (K<sub>3</sub>PO<sub>4</sub>), or

potassium carbonate ( $K_2CO_3$ ), preferably potassium carbonate, and *N,N'*-dimethylethane-1,2-diamine to yield amide (4c). This synthetic method is simpler and reduces the costs of starting materials over known heteroarylation methods. The process may be conducted in a polar solvent, such as, acetonitrile (MeCN), dioxane, or *N,N*-dimethylformamide at a temperature  
5 between about 50 °C and about 110 °C, preferably between about 70 °C and about 90 °C. It is preferred that the reaction mixture is stirred with heating for between 2 hours and 24 hours.

In step e of Scheme 1, pesticidal thioether (4c) is alkylated preferably with a  $R^2-X^2$  to yield pesticidal thioether (4d), wherein  $X^2$  is a leaving group. The leaving group may be selected from halo, mesylate, or tosylate.  $R^2$  is selected from  $C_1$ - $C_4$ -alkyl,  $C_2$ - $C_4$ -alkynyl,  
10 preferably, methyl, ethyl, and propargyl.  $R^2-X^2$  may be selected from methyl iodide, ethyl bromide, ethyl iodide, propargyl chloride, propargyl bromide, ethyl mesylate, propargyl mesylate, ethyl tosylate, and propargyl tosylate. The alkylation is conducted in the presence of an inorganic base, preferably, metal carbonates, metal hydroxides, metal phosphates, metal hydrides, more preferably, cesium carbonate ( $Cs_2CO_3$ ), conducted in the presence of a polar  
15 solvent, preferably *N,N*-dimethylformamide (DMF) at temperatures from about 0 °C to about 50 °C.

Alternatively, in step e of Scheme 1, the alkylation of pesticidal thioether (3b) may be conducted in the presence of a base such as sodium hydride (NaH), in the presence of a polar aprotic solvent, such as *N,N*-dimethylformamide, tetrahydrofuran, hexamethylphosphoramide  
20 (HMPA), dimethylsulfoxide (DMSO), *N*-methyl-2-pyrrolidinone (NMP), and sulfolane, at temperatures from about 0 °C to about 50 °C. It has been unexpectedly discovered that the use of sulfolane as solvent promotes the alkylation reaction over the competitive retro-Michael-type elimination of the  $C_1$ - $C_4$ -alkyl-S- $R^1$  unit (see "CE-3"). It has been discovered that the catalytic use of an additive, such as potassium iodide (KI) or tetrabutylammonium iodide (TBAI)  
25 decreases the time necessary for the reaction to occur to about 24 hours.

In step f of Scheme 1, thioether (4d) is oxidized with hydrogen peroxide ( $H_2O_2$ ) in methanol to yield the desired pesticidal sulfoxide (4e).

## EXAMPLES

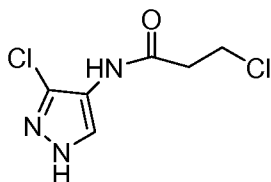
30 The following examples are presented to better illustrate the processes of the present application.

Example 1 3-chloro-1*H*-pyrazol-4-amine hydrochloride (1a):



A 1000-mL, multi-neck cylindrical jacketed reactor, fitted with a mechanical stirrer, temperature probe and nitrogen (N<sub>2</sub>) inlet, was charged with 4-nitropyrazole (50.0 g, 429 mmol) and palladium on alumina (5 wt%, 2.5 g). Ethanol (150 mL) was added, followed by a slow addition of concentrated hydrochloric acid (37 wt%, 180 mL). The reaction was cooled to 15 °C, and triethylsilane (171 mL, 1072 mmol) was added slowly *via* addition funnel over 1 hour, while maintaining the internal temperature at 15 °C. The reaction was stirred at 15 °C for 72 hours, after which the reaction mixture was filtered through a Celite® pad and the pad was rinsed with warm ethanol (40 °C, 2 × 100 mL). The combined filtrates were separated and the aqueous layer (bottom layer) was concentrated to ~100 mL. Acetonitrile (200 mL) was added and the resulting suspension was concentrated to ~100 mL. Acetonitrile (200 mL) was added and the resulting suspension was concentrated to ~100 mL. Acetonitrile (200 mL) was added and the resulting suspension was stirred at 20 °C for 1 hour and filtered. The filter cake was rinsed with acetonitrile (2 × 100 mL) and dried under vacuum at 20 °C to afford a white solid (~10:1 mixture of 1a and 1*H*-pyrazole-4-amine, 65.5 g, 99%): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.52 (bs, 3 H), 8.03 (s, 1 H) EIMS *m/z* 117 ([M]<sup>+</sup>).

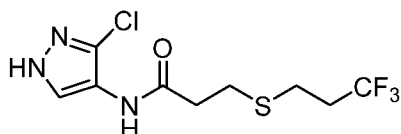
Example 2 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl) propanamide (4a):



A 250-mL 3-neck flask was charged with 3-chloro-1*H*-pyrazol-4-amine·hydrochloride (10.0 g, 64.9 mmol), tetrahydrofuran (50 mL), and water (50 mL). The resulting suspension was cooled to 5 °C and sodium bicarbonate (17.6 g, 210 mmol) was added, followed by dropwise addition of 3-chloropropanoyl chloride (7.33 g, 57.7 mmol) at <5 °C. The reaction was stirred at <10 °C for 1 hour, at which point thin layer chromatography (TLC) [Eluent: 1:1 ethyl acetate (EtOAc)/hexane] analysis indicated the starting material was consumed and the desired product was formed. It was diluted with water (50 mL) and ethyl acetate (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were concentrated to dryness to afford a pale brown solid, which was purified by flash column chromatography using ethyl acetate as eluent. The pure fractions were concentrated to afford a white solid (9.20 g, 77%): mp: 138–140 °C; <sup>1</sup>H NMR (400 MHz,

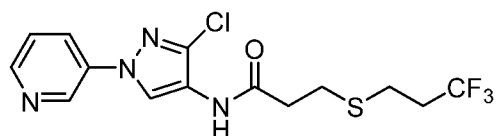
DMSO-*d*<sub>6</sub>)  $\delta$  12.91 (s, 1 H), 9.68 (s, 1 H), 8.03 (d, *J* = 1.7 Hz, 1 H), 3.85 (t, *J* = 6.3 Hz, 2 H), 2.85 (t, *J* = 6.3 Hz, 2 H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  167.52, 130.05, 123.59, 116.48, 40.75, 37.91; EIMS *m/z* 207 ([M]<sup>+</sup>).

- 5 Example 3 *N*-(3-chloro-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (Compound 3.4):



- A 100 mL, 3-neck round bottom flask was charged with 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (1.00 g, 4.81 mmol) and methanol (10 mL), potassium hydroxide (KOH, 0.324 g, 5.77 mmol) was added, followed by 3,3,3-trifluoropropane-1-thiol (0.751 g, 5.77 mmol). The mixture was heated at 50 °C for 4 hours, at which point thin layer chromatography analysis [Eluent: ethyl acetate] indicated that the reaction was complete to give exclusively a new product. It was cooled to 20 °C and diluted with water (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (20 mL). The organic layers were combined and dried over sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness to afford a light yellow oil, which was purified by flash column chromatography using 40% ethyl acetate/hexanes as eluent to afford a white solid after concentration (1.02 g, 70%): mp 83–85 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.90 (s, 1H), 9.59 (s, 1 H), 8.02 (s, 1 H), 2.82 (t, *J* = 7.2 Hz, 2 H), 2.76–2.69 (m, 2 H), 2.66 (t, *J* = 7.1 Hz, 2 H), 2.62–2.48 (m, 2 H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  168.97, 129.95, 126.60 (q, *J* = 277.4 Hz), 123.42, 116.60, 35.23, 33.45 (q, *J* = 27.3 Hz), 26.85, 23.03 (q, *J* = 3.4 Hz); EIMS *m/z* 301 ([M]<sup>+</sup>).

- 25 Example 4 *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (Compound 4.4):



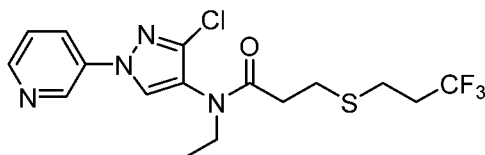
- A 100 mL, 3-neck round bottom flask was charged with copper(I) iodide (0.343 g, 1.80 mmol), acetonitrile (50 mL), *N,N'*-dimethylethane-1,2-diamine (0.318 g, 3.61 mmol), *N*-(3-chloro-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (2.72 g, 9.02 mmol), potassium carbonate (2.49 g, 18.0) and 3-bromopyridine (1.71 g, 10.8 mmol). The mixture was purged with nitrogen three times and heated to 80 °C for 4 hours, at which point thin layer

chromatography analysis [Eluent: ethyl acetate] indicated that only a trace of starting material remained. The mixture was filtered through a Celite® pad and the pad was rinsed with acetonitrile (20 mL). The filtrates were concentrated to dryness and the residue was purified by flash column chromatography using 0–100% ethyl acetate/hexanes as eluent. The fractions

5 containing pure product were concentrated to dryness and further dried under vacuum to afford a white solid (1.82 g, 53%): mp 99–102 °C; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.92 (s, 1 H), 9.05 (d, *J* = 2.7 Hz, 1 H), 8.86 (s, 1H), 8.54 (dd, *J* = 4.5, 1.4 Hz, 1 H), 8.21 (ddd, *J* = 8.4, 2.7, 1.4 Hz, 1 H), 7.54 (dd, *J* = 8.4, 4.7 Hz, 1 H), 2.86 (t, *J* = 7.3 Hz, 2 H), 2.74 (td, *J* = 6.5, 5.6, 4.2 Hz, 4 H), 2.59 (ddd, *J* = 11.7, 9.7, 7.4 Hz, 2 H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 169.32,

10 147.49, 139.44, 135.47, 133.40, 126.60 (q, *J* = 296 Hz), 125.49, 124.23, 122.30, 120.00, 35.18, 33.42 (q, *J* = 27.2 Hz), 26.77, 23.05 (q, *J* = 3.3 Hz); EIMS *m/z* 378 ([M]<sup>+</sup>).

Example 5 *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-*N*-ethyl-3-((3,3,3-trifluoropropyl)thio)propanamide (Compound 5.4):



15 A 100 mL, 3-neck round bottom flask, equipped with mechanical stirrer, temperature probe and nitrogen inlet was charged with cesium carbonate (654 mg, 2.01 mmol), *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (380 mg, 1.00 mmol) and *N,N*-dimethylformamide, (5 mL). Iodoethane (0.089 mL, 1.10 mmol) was added

20 dropwise. The reaction was stirred at 40 °C for 2 hours, at which point thin layer chromatography analysis [(Eluent: ethyl acetate)] indicated that only a trace of starting material remained. The reaction mixture was cooled to 20 °C and water (20 mL) was added. It was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were concentrated to dryness at <40 °C. The residue was purified by flash column chromatography using 0–100%

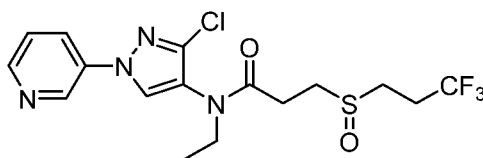
25 ethyl acetate/hexane as eluent. The fractions containing pure product were concentrated to dryness to afford a colorless oil (270 mg, 66%): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.11 (d, *J* = 2.7 Hz, 1 H), 8.97 (s, 1 H), 8.60 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.24 (ddd, *J* = 8.4, 2.8, 1.4 Hz, 1 H), 7.60 (ddd, *J* = 8.4, 4.7, 0.8 Hz, 1 H), 3.62 (q, *J* = 7.1 Hz, 2 H), 2.75 (t, *J* = 7.0 Hz, 2 H), 2.66–2.57 (m, 2 H), 2.57–2.44 (m, 2 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 1.08 (t, *J* = 7.1 Hz, 3 H);

30 EIMS *m/z* 406 ([M]<sup>+</sup>).



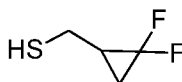
Alternate synthetic route to *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-*N*-ethyl-3-((3,3,3-trifluoropropyl)thio)propanamide (Compound 5.4): To 3-neck round bottomed flask (50 mL) was added sodium hydride (60% in oil, 0.130 g, 3.28 mmol) and sulfolane (16 mL). The gray suspension was stirred for 5 minutes then *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (1.20 g, 3.16 mmol) dissolved in sulfolane (25 mL) was slowly added dropwise over 5 minutes. The mixture became a light gray suspension after 3 minutes and was allowed to stir for 5 minutes after which time ethyl bromide (0.800 mL, 10.7 mmol) and potassium iodide (0.120 g, 0.720 mmol) were added sequentially. The cloudy suspension was then allowed to stir at room temperature. The reaction was quenched after 6 hours by being poured drop-wise into cooled ammonium formate/acetonitrile solution (30 mL). The resulting orange colored solution was stirred and tetrahydrofuran (40 mL) was added. The mixture was assayed, using octanophenone as a standard, and found to contain (1.09 g, 85%) of the desired product with a selectivity versus the retro-Michael-like decomposition product of 97:3.

Example 6 *N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-*N*-ethyl-3-((3,3,3-trifluoropropyl)sulfoxo)propanamide (Compound 6.4):



*N*-(3-chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-*N*-ethyl-3-((3,3,3-trifluoropropyl)thio)propanamide (57.4 g, 141 mmol) was stirred in methanol (180 mL). To the resulting solution was added hydrogen peroxide (43.2 mL, 423 mmol) dropwise using a syringe. The solution was stirred at room temperature for 6 hours, at which point LCMS analysis indicated that the starting material was consumed. The mixture was poured into dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>, 360 mL) and washed with aqueous sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>). The organic layer was dried over sodium sulfate and concentrated to provide thick yellow oil. The crude product was purified by flash column chromatography using 0 – 10% methanol/ethyl acetate as eluent and the pure fractions were combined and concentrated to afford the desired product as an oil (42.6 g, 68%): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.09 (dd, *J* = 2.8, 0.7 Hz, 1 H), 8.98 (s, 1 H), 8.60 (dd, *J* = 4.7, 1.4 Hz, 1 H), 8.24 (ddd, *J* = 8.4, 2.7, 1.4 Hz, 1 H), 7.60 (ddd, *J* = 8.4, 4.7, 0.8 Hz, 1 H), 3.61 (q, *J* = 7.4, 7.0 Hz, 2 H), 3.20 – 2.97 (m, 2 H), 2.95 – 2.78 (m, 2 H), 2.76 – 2.57 (m, 2 H), 2.58 – 2.45 (m, 2 H), 1.09 (t, *J* = 7.1 Hz, 3 H); ESIMS *m/z* 423 ([*M*+*H*]<sup>+</sup>).

Example PE-1 Prophetic preparation of (2,2-difluorocyclopropyl)methanethiol:



To a solution of 2-(bromomethyl)-1,1-difluorocyclopropane (about 1 equivalent) in a solvent, such as methanol (at a concentration ranging from about 0.01 M to about 1 M), at temperatures between about 0 °C and about 40 °C may be added thioacetic acid (about 1 equivalent to about 2 equivalents), and a base, such as potassium carbonate (about 1 equivalent to 2 equivalents). An additional amount of a base, such as potassium carbonate (about 1 equivalent to 2 equivalents) may be added after a time ranging from about 30 minutes to 2 hours to the mixture to remove the acyl group. The reaction may be stirred until it is determined to be complete. The product may then be obtained using standard organic chemistry techniques for workup and purification.

Alternative prophetic preparation of (2,2-difluorocyclopropyl)methanethiol: To a solution of 2-(bromomethyl)-1,1-difluorocyclopropane (about 1 equivalent) in a solvent, such as methanol (at a concentration ranging from about 0.01 M to about 1 M), at temperatures between about 0 °C and about 40 °C may be added thioacetic acid (about 1 equivalent to about 2 equivalents), and a base, such as potassium carbonate (about 1 equivalent to 2 equivalents). The intermediate thioester product may then be obtained using standard organic chemistry techniques for workup and purification. To the thioester (about 1 equivalent) in a solvent, such as methanol (at a concentration ranging from about 0.01 M to about 1 M), at temperatures between about 0 °C and about 40 °C may be added a base, such as potassium carbonate (about 1 equivalent to 2 equivalents). The reaction may be stirred until it is determined to be complete. The product may then be obtained using standard organic chemistry techniques for workup and purification.

## BIOLOGICAL EXAMPLES

Example A Bioassays on Green Peach Aphid (“GPA”) (*Myzus persicae*) (MYZUPE.

GPA is the most significant aphid pest of peach trees, causing decreased growth, shriveling of leaves, and the death of various tissues. It is also hazardous because it acts as a vector for the transport of plant viruses, such as potato virus Y and potato leafroll virus to members of the nightshade /potato family *Solanaceae*, and various mosaic viruses to many other food crops. GPA attacks such plants as broccoli, burdock, cabbage, carrot, cauliflower, daikon, eggplant, green beans, lettuce, macadamia, papaya, peppers, sweet potatoes, tomatoes,

watercress and zucchini among other plants. GPA also attacks many ornamental crops such as carnations, chrysanthemum, flowering white cabbage, poinsettia and roses. GPA has developed resistance to many pesticides.

Several molecules disclosed herein were tested against GPA using procedures described below.

Cabbage seedling grown in 3-in pots, with 2-3 small (3-5 cm) true leaves, were used as test substrate. The seedlings were infested with 20-5- GPA (wingless adult and nymph stages) one day prior to chemical application. Four posts with individual seedlings were used for each treatment. Test compounds (2 mg) were dissolved in 2 mL of acetone/methanol (1:1) solvent, forming stock solutions of 1000 ppm test compound. The stock solutions were diluted 5X with 0.025% Tween 20 in water to obtain the solution at 200 ppm test compound. A hand-held aspirator-type sprayer was used for spraying a solution to both sides of the cabbage leaves until runoff. Reference plants (solvent check) were sprayed with the diluent only containing 20% by volume acetone/methanol (1:1) solvent. Treated plants were held in a holding room for three days at approximately 25 °C and ambient relative humidity (RH) prior to grading. Evaluation was conducted by counting the number of live aphids per plant under a microscope . Percent Control was measured by using Abbott's correction formula (W.S. Abbott, "A Method of Computing the Effectiveness of an Insecticide" J. Econ. Entomol 18 (1925), pp.265-267) as follows.

$$\text{Corrected \% Control} = 100 * (X - Y) / X$$

where

**X** = No. of live aphids on solvent check plants and

**Y** = No. of live aphids on treated plants

The results are indicated in the table entitled "**Table 1: GPA (MYZUPE) and sweetpotato whitefly-crawler (BEMITA) Rating Table**".

Example B Bioassays on Sweetpotato Whitefly Crawler (*Bemisia tabaci*) (BEMITA.)

The sweetpotato whitefly, *Bemisia tabaci* (Gennadius), has been recorded in the United States since the late 1800s. In 1986 in Florida, *Bemisia tabaci* became an extreme economic pest. Whiteflies usually feed on the lower surface of their host plant leaves. From the egg hatches a minute crawler stage that moves about the leaf until it inserts its microscopic, threadlike mouthparts to feed by sucking sap from the phloem. Adults and nymphs excrete honeydew (largely plant sugars from feeding on phloem), a sticky, viscous liquid in which dark sooty molds grow. Heavy infestations of adults and their progeny can cause seedling death, or reduction in vigor and yield of older plants, due simply to sap removal. The honeydew can stick

cotton lint together, making it more difficult to gin and therefore reducing its value. Sooty mold grows on honeydew-covered substrates, obscuring the leaf and reducing photosynthesis, and reducing fruit quality grade. It transmitted plant-pathogenic viruses that had never affected cultivated crops and induced plant physiological disorders, such as tomato irregular ripening and squash silverleaf disorder. Whiteflies are resistant to many formerly effective insecticides.

Cotton plants grown in 3-inch pots, with 1 small (3-5 cm) true leaf, were used at test substrate. The plants were placed in a room with whitely adults. Adults were allowed to deposit eggs for 2-3 days. After a 2-3 day egg-laying period, plants were taken from the adult whitefly room. Adults were blown off leaves using a hand-held Devilbliss sprayer (23 psi). Plants with egg infestation (100-300 eggs per plant) were placed in a holding room for 5-6 days at 82°F and 50% RH for egg hatch and crawler stage to develop. Four cotton plants were used for each treatment. Compounds (2 mg) were dissolved in 1 mL of acetone solvent, forming stock solutions of 2000 ppm. The stock solutions were diluted 10X with 0.025% Tween 20 in water to obtain a test solution at 200 ppm. A hand-held Devilbliss sprayer was used for spraying a solution to both sides of cotton leaf until runoff. Reference plants (solvent check) were sprayed with the diluent only. Treated plants were held in a holding room for 8-9 days at approximately 82°F and 50% RH prior to grading. Evaluation was conducted by counting the number of live nymphs per plant under a microscope. Insecticidal activity was measured by using Abbott's correction formula (see above) and presented in Table 1.

Table 1: GPA (MYZUPE) and sweetpotato whitefly-crawler (BEMITA) Rating Table

Example Compound	BEMITA	MYZUPE
1a	B	B
4a	B	D
Compound 3.4	B	B
Compound 4.4	B	A
Compound 5.4	A	A
Compound 6.4	A	A

**% Control of Mortality**

**Rating**

80-100

A

More than 0 - Less than 80

B

Not Tested

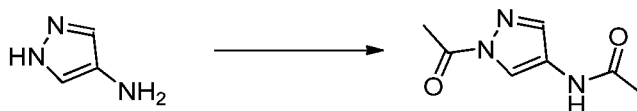
C

No activity noticed in this bioassay

D

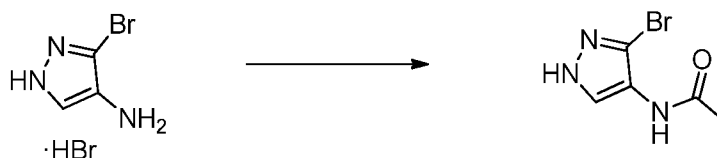
## COMPARATIVE EXAMPLES

Example CE-1 *N*-(1-acetyl-1*H*-pyrazol-4-yl)acetamide:



A 250-mL 3-neck flask was charged with 1*H*-pyrazol-4-amine (5 g, 60.2 mmol) and dichloromethane (50 mL). The resulting suspension was cooled to 5 °C and triethylamine (TEA, 9.13 g, 90.0 mmol) was added, followed by acetic anhydride (Ac<sub>2</sub>O, 7.37 g, 72.2 mmol) at <20 °C. The reaction was stirred at room temperature for 18 h, at which point thin layer chromatography [Eluent: ethyl acetate] analysis indicated that the reaction was incomplete. Additional triethylamine (4.57 g, 45.0 mmol) and acetic anhydride (3.70 g, 36.0 mmol) were added and the reaction was heated at 30 °C for an additional 3 hours to give a dark solution, at which point thin layer chromatography analysis indicated that only a trace of starting material remained. The reaction mixture was purified by flash column chromatography using ethyl acetate as eluent. The fractions containing pure product were combined and concentrated to dryness to afford an off-white solid. The solid was dried under vacuum at room temperature for 18 hours (5.55 g, 55%): <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.30 (s, 1 H), 8.39 (d, *J* = 0.7 Hz, 1 H), 7.83 (d, *J* = 0.7 Hz, 1 H), 2.60 (s, 3 H), 2.03 (s, 3 H); EIMS *m/z* 167 ([M]<sup>+</sup>).

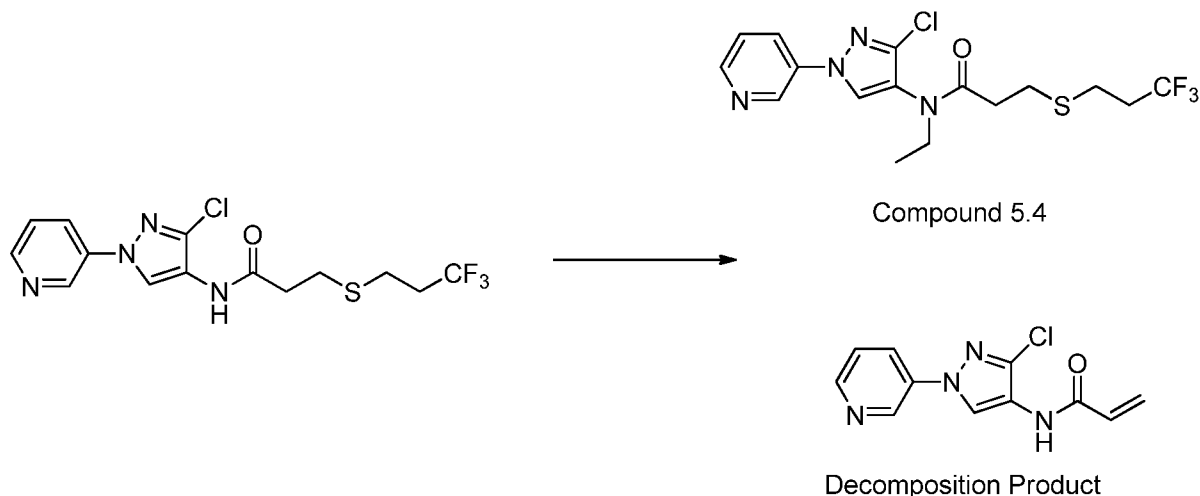
Example CE-2 *N*-(3-Bromo-1*H*-pyrazol-4-yl)acetamide:



A 250 mL 3-neck round bottom flask was charged with 1*H*-pyraz-4-amine•hydrobromide (4.00 g, 24.7 mmol) and water (23 mL). To the mixture, sodium bicarbonate (8.30 g, 99.0 mmol) was added slowly over 10 minutes, followed by tetrahydrofuran (23 mL). The mixture was cooled to 5 °C and acetic anhydride (2.60 g, 25.4 mmol) was added over 30 minutes while maintaining the internal temperature at <10 °C. The reaction mixture was stirred at ~5 °C for 20 minutes, at which point <sup>1</sup>H NMR and UPLC analyses indicated that the starting material was consumed and the desired product as well as bis-acetylated byproduct were formed. The reaction was extracted with ethyl acetate and the organic layers were dried over magnesium sulfate (MgSO<sub>4</sub>) and concentrated. The crude mixture was triturated with methyl *tert*-butylether (MTBE) to remove the bisacetylated product

to afford ~1.24 g of a white solid.  $^1\text{H}$  NMR analysis showed it was 1:1.1 desired to undesired bisacetylated product. The solid was purified by flash column chromatography using 50–100% ethyl acetate/hexanes as eluent to afford the desired product as a white solid (380 mg, 7.5%) and the bisacetylated product as a white solid (~800 mg):  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.01 (s, 1 H), 9.36 (s, 1 H), 7.92 (s, 1 H), 2.03 (s, 3 H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  167.94, 123.93, 119.19, 119.11, 22.63; ESIMS  $m/z$  204 ( $[\text{M}+\text{H}]^+$ ).

Example CE-3 Alkylation versus retro-Michael-like decomposition:



A suspension of sodium hydride (60% in oil, 1.03 equivalent) and solvent (1 vol) was stirred for 5 minutes. *N*-(3-Chloro-1-(pyridin-3-yl)-1*H*-pyrazol-4-yl)-3-((3,3,3-trifluoropropyl)thio)propanamide (1 equivalent) dissolved in solvent (2 vol) was slowly added dropwise over 5 minutes. Ethyl bromide (3.3 equivalents) and additive (0.22 equivalents) were added sequentially. The suspension was then allowed to stir at room temperature until consumption of starting material was observed. The selectivity of Compound 6.3 over the decomposition product was determined by HPLC (See Table 2).

Table 2

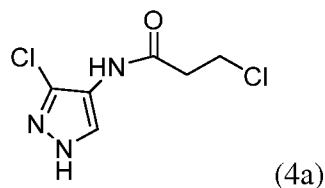
Entry	Additive	Solvent	Time (hours)	Compound 6.3:Decomposition Product
1	tetrabutylammonium iodide	<i>N,N</i> -dimethylformamide	24	81:19
2	potassium iodide	<i>N,N</i> -dimethylformamide	72	94:6
3	potassium iodide	<i>N</i> -methylpyrrolidinone	20	92:8

It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto.

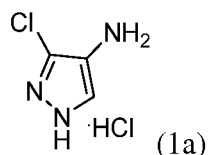
- 5 Certain modifications and variations in any given material, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow.

WHAT IS CLAIMED IS:

1. A process for the preparation of 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a) useful in the preparation of pesticidal thioethers (4b), (4c), (4d) and pesticidal sulfoxides (4e),

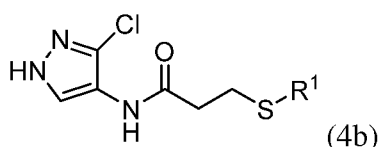


which comprises acylating 3-chloro-1*H*-pyrazol-4-amine hydrochloride

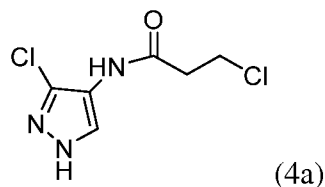


with 3-chloropropionyl chloride in the presence of a base.

2. A process according to claim 1, wherein the base is sodium bicarbonate.
3. A process according to claim 1, wherein the reaction is carried out in a mixture of tetrahydrofuran and water.
4. A process for the preparation of thioethers (4b) useful in the preparation of pesticidal thioethers (4c), (4d) and pesticidal sulfoxides (4e),



wherein R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> haloalkyl and C<sub>1</sub>-C<sub>4</sub> alkyl-C<sub>3</sub>-C<sub>6</sub> halocycloalkyl, said process which comprises reacting 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a)



with HS-R<sup>1</sup> in the presence of a base.

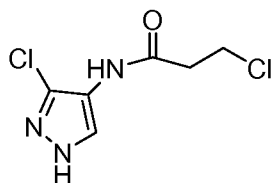
5. A process according to claim 4, wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> haloalkyl.



6. A process according to claim 5, wherein R<sup>1</sup> is CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>.
7. A process according to claim 4, wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl-C<sub>3</sub>-C<sub>6</sub> halocycloalkyl.
8. A process according to claim 7, wherein R<sup>1</sup> is CH<sub>2</sub>(2,2-difluorocyclopropyl).
9. A process according to claim 4, wherein the base is potassium hydroxide.

10. A compound having the following structure

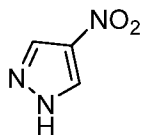
3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a)



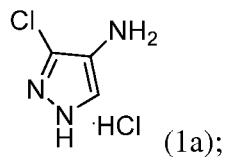
11. A process of applying the compound according to claim 10 to a locus to control insects.

12. A process comprising:

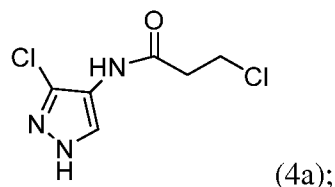
- (a) halogenating and reducing 4-nitropyrazole



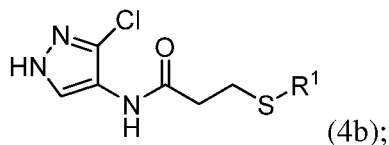
with concentrated hydrochloric acid at a temperature between about 10 °C and about 20 °C with between about 1 equivalent and about 4 equivalents of triethylsilane and about 1 to 10 weight percent palladium on alumina to yield 3-chloro-1*H*-pyrazol-4-amine hydrochloride (1a)



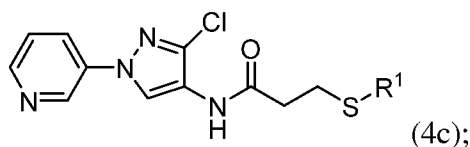
- (b) acylating 1(a) with 3-chloropropionyl chloride in the presence of a base to yield 3-chloro-*N*-(3-chloro-1*H*-pyrazol-4-yl)propanamide (4a)



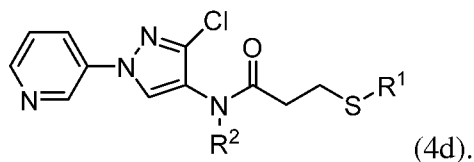
(c) reacting (4a) with HS-R<sup>1</sup> in the presence of a base wherein R<sup>1</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> haloalkyl and C<sub>1</sub>-C<sub>4</sub> alkyl-C<sub>3</sub>-C<sub>6</sub> halocycloalkyl to yield pesticidal thioethers (4b),



(d) heteroarylation of (4b) with a halopyridine in the presence of a copper salt, an amine, and a base, to yield thioether (4c)



(e) alkylating a thioether (4c) with R<sup>2</sup>-X<sup>2</sup> in the presence of a base wherein R<sup>2</sup> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub>-alkyl and C<sub>2</sub>-C<sub>4</sub>-alkynyl, and wherein X<sup>2</sup> is a leaving group, to yield thioether (4d)



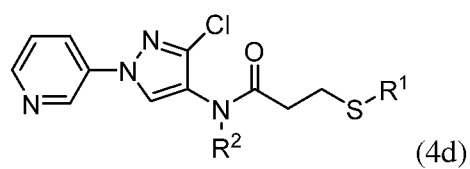
13. A process according to claim 12 wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> haloalkyl.

14. A process according to claim 12 wherein R<sup>1</sup> is CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>.

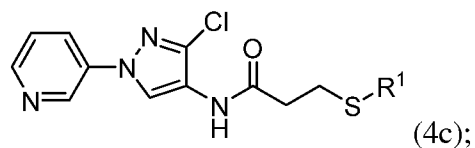
15. A process according to claim 12 wherein R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl-C<sub>3</sub>-C<sub>6</sub> halocycloalkyl.

16. A process according to claim 12 wherein R<sup>1</sup> is CH<sub>2</sub>(2,2-difluorocyclopropyl).

17. A process according to claim 12, wherein thioether (4d)



is prepared by alkylating thioether (4c) with  $R^2-X^2$



wherein  $R^2$  is selected from the group consisting of  $C_1$ - $C_4$ -alkyl and  $C_2$ - $C_4$ -alkynyl, wherein  $X^2$  is a leaving group, in the presence of a base, in the presence of a polar aprotic solvent, and in the presence of an additive.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/61012

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A01N 43/56; 47/40; 25/00; C07D 231/40 (2014.01) CPC - A01N 43/56; A01N 47/40; A01N 25/00; C07D 231/40 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC(8): A01N 43/56; 47/40; 25/00; C07D 231/40 (2014.01) CPC: A01N 43/56; A01N 47/40; A01N 25/00; C07D 231/40 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 504/209; 261; 282; 548/372.5; 364.1; 546/275.4 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Scholar, PubWEST pesticide/insecticide, pyrazole, carboxamide, 3-chloropropionyl chloride, alkanethiol, thioether, sulfoxide, 4-nitropyrazole, aminopyrazole, bromopyridine, iodopyribine		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/0109566 A1 (NIYAZ et al.) 02 May 2013 (02.05.2013) para [0250]-[0252], [0254], [0426]-[0427], [0442]-[0443], [0454], [0456], [0553]-[0555]	1-17
Y	US 2006/0135778 A1 (SCHNATTERER et al.) 22 June 2006 (22.06.2006) para [0001], [0193], [0196]	1-17
Y	US 2010/0286169 A1 (GUILLES et al.) 11 November 2010 (11.11.2010) para [0231], [0233], pg 12, Table	4-9, 12-17
Y	US 2006/0287365 A1 (BILLEN et al.) 21 December 2006 (21.12.2006) para [0002], [0446], [0466]-[0467]	7-8 and 15-16
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 November 2014 (23.11.2014)		Date of mailing of the international search report <b>15 DEC 2014</b>
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774