Synthesis and Biological Activities of 3-1-(3-(2-Chloro-3,3,3-trifluoro- prop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-Substituted Phenyl thiourea

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Summary: Some thiourea compounds containing pyrethroids are synthesized. Their structures were confirmed by ^{1}H-NMR, MS and elemental analysis. The bioassay results indicated that they showed moderate insecticidal and fungicidal activity.

Keywords: Pyrethroid, Synthesis, Insecticidal activity, Fungicidal activity.

Introduction

Cyclopropane derivatives, as a kind of highly bioactive compounds, have been studied broadly for many years [1-8]. In 1940s, cyclopropane compounds, especially pyrethroids were marketed as low toxic insecticides. From then on, a large variety of pyrethroids derivatives have been synthesized and lots of them, such as Deltamethrin, Cypermethrin, Bifenthrin, Fenvalerate, Tefluthrin and so on, are commercially available [9, 10]. So it is a research hotspot in agriculture, many biologically active and structurally stable cyclopropane compounds had been synthesized [11-15].

Thiourea is widely used in medicinal chemistry and agricultural chemistry, because of their excellent biological activities [16-19] or the useful synthetic intermediate [20, 21]. Thiourea and its derivatives, especially acyl-thiourea compounds, exhibit broad biological activities, such as herbicidal, fungicidal and insecticidal activities and so on. They had variety bioactivities; perhaps due to thiourea contain amide group and thioamide group [22, 33]. In line with our continuous efforts to synthesize bioactive lead compounds for crop protection, the title compounds were designed some thiourea compounds and their biological activity tested. The preliminary biological test showed that the synthesized compound has moderate activity.

Results and Discussion

Chemistry

The synthetic routes of title compounds were illustrated as outlined in Scheme-1. The starting material lambda cyhalthrin acid 1 was treated with $SOCl_2$ as chlorination reagent to generate acid chloride 2. The excess thionyl chloride was removed by reduced pressure distillation. For the next step the acyl chloride was used without additional purification. After solubilization in dry acetonitrile, acid chloride was treated with a solution of potassium rhodanate in acetonitrile to afford acyl isothiocyanate. The resulting acyl isothiocyanate was not isolated from the mixture and was converted into the corresponding thioureas by adding various substituted anilines and refluxing for an hour in dry acetonitrile.

The chemical structures of the title compounds were confirmed by ^{1}H-NMR, mass, and elemental analysis. The ^{1}H-NMR, mass spectra, and elemental analysis data of the compounds are in agreement with the proposed structures. In the ^{1}H-NMR spectra, the N-H protons of the thiourea derivatives were observed as singlets at 8.88-9.62 ppm and 11.66-12.68 ppm, respectively. All other aromatic protons were observed in the expected regions.

Bioassay

Fungicidal activity

The *in vivo* fungicidal results of all of the compounds against *Rhizoctonia solani*, *Pseudoperonospora cubensis*, *Sphaerotheca fuliginea* and *Botrytis cinerea* were listed in Table-1. As shown in Table **1**, all these compounds did not display obvious fungicidal activities against *Rhizoctonia solani*, *Pseudoperonospora cubensis*, *Sphaerotheca fuliginea*. Among them, Compounds **5c**, **5h** and **5j** have fair to moderate fungicidal activity (41%~68%) against *Botrytis cinerea* at the concentration of 200 $\mu g \cdot mL^{-1}$.

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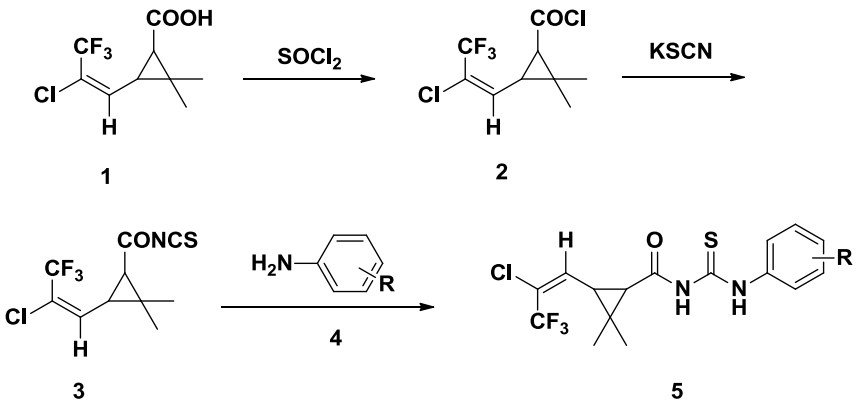

5a, R=H; 5b, R=4-CH_3; 5c, R=3-CH_3; 5d, R=4-Cl; 5e, R=3-Cl; 5f, R=4-NO_2; 5g, R=4-OMe
5h, R=3-F; 5i, R=2-CF_3; 5j, R=3,4-Cl_2; 5k, R=2,4-F_2; 5l, R=2,4,6-Cl_3

Scheme-1: The synthetic route of title compounds.

Table-1: The fungicidal activities of 5 (Inhibition/%).

Compd.	*Sphaerotheca fuliginea*	*Pseudoperonospora cubensis*	*Botrytis cinerea*	*Rhizoctonia solani*
5a	**0**	**0**	**20.7**	**0**
5b	**0**	**0**	**22.0**	**0**
5c	**0**	**0**	**41.9**	**0**
5d	**0**	**0**	**13.4**	**0**
5e	**13.7**	**9.1**	**16.7**	**3.6**
5f	**0**	**0**	**26.1**	**0**
5g	**6.3**	**8.8**	**13.5**	**14.6**
5h	**3.4**	**0**	**68.5**	**24.3**
5i	**0**	**0**	**27.8**	**0**
5j	**5.7**	**13.8**	**67.3**	**33.4**
5k	**0**	**0**	**4.9**	**0**
5l	**0**	**0**	**5.7**	**0**

Insecticidal activity

The insecticidal activity of compounds **5** against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus* and *Aphis medicagini* was summarized in Table-2. In general, all the title compounds exhibited no insecticidal activity against *Aphis medicagini*. Also, title compounds showed low insecticidal activities against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus.* Surprisingly, only compounds **5j** displayed moderate insecticidal activity against *Mythimna separate*.

Table-2:The insecticidal activities of 5 (Mortality/%).

Compd.	*Nilaparvata legen*	*Mythimna separate*	*Tetranychus cinnabarnus*	*Aphis medicagini*
5a	**13.8**	**26.7**	**29.8**	**0**
5b	**10.3**	**0**	**8.8**	**0**
5c	**8.3**	**0**	**7.3**	**0**
5d	**18.5**	**8.8**	**13.6**	**0**
5e	**16.1**	**8.3**	**16.3**	**0**
5f	**0**	**2.6**	**0**	**0**
5g	**6.3**	**9.7**	**6.1**	**0**
5h	**26.4**	**6.4**	**0**	**0**
5i	**0**	**10.8**	**5.8**	**0**
5j	**24.3**	**36.3**	**31.0**	**0**
5k	**11.8**	**11.3**	**8.9**	**0**
5l	**14.9**	**12.7**	**2.8**	**0**

Experimental

Materials and Methods

Melting points were determined by an X-4 apparatus and uncorrected. ^{1}H-NMR spectra were measured on a Bruker Avance 400 DMX instrument using TMS as an internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on a HP 5989B mass detector instrument. Elemental analyses were performed on a Carlo erba EA1110 elemental analyzer. All the reagents are of analytical grade or freshly prepared before use.

Synthesis

Lambda cyhalthrin acid was synthesized in our laboratory according to literature. Thionyl chloride (100 mL) was added into lambda cyhalthrin acid (2.75g, 10mmol) and the mixture was refluxed for 8 h. Next, the excessive thionyl chloride was distilled off under reduced pressure. The desired acid chloride was not purification. KNCS (1.46 g, 15 mmol), acid chloride, CH_3CN (20 mL) were charged into a dry round-bottomed flask equipped with a magnetic stirrer bar and stirred at reflux temperature for 1 h. Subsequently remove the precipitate KCl using pumping filtration and the filtrate can be directly used without purification. Add substituted aniline (8.8 mmol) to the filtrate followed by reflux for 3~4 h at 80 ºC. TLC was employed to trace the process. Stop the reaction and cool the resultant mixture under room temperature. Finally pumping filtration gives yellow powder washed with petroleum. Then the products were recrystallized from DMF-EtOH-H_2O. Finally, the acyl thiourea was obtained as a solid.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-phenyl thiourea (5a). Yellow crystal; yield， 89.4%; mp, 211-214℃; ^{1}H-NMR ($CDCl_3$) δ: 1.34(s, 6H, CH_3), 1.92(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.32(t, J=8.0 Hz, 1H, cyclopropane H), 6.96 (d, *J*=8.8 Hz, 1H, C=CH), 7.26-7.40(m, 3H, Ph), 7.62-7.64(m, 2H, Ph), 9.51(s, 1H, NH), 12.28(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 377(M^+, 33), 341(3), 225(10), 192(100), 141(19), 119(52), 77(20); Anal. Calcd for $C_{16}H_{16}N_2OSClF_3$(%): C 51.00, H 4.28, N 7.43, found: C 51.12, H 4.25, N 7.48.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(4-methyl-phenyl) thiourea (5b). White crystal; yield, 56.9%; mp, 188-191℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.86(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.32(t, *J*=8.8 Hz, 1H, cyclopropane H), 2.37(s, 3H, CH_3), 6.96 (d, *J*=9.2 Hz, 1H, C=CH), 7.19-7.21(m, 2H, Ph), 7.48-7.50(m, 2H, Ph), 9.20(s, 1H, NH), 12.12(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 391 (M^+, 37), 355(2), 206(100), 141(13), 133(53), 91(19), 63(3); Anal. Calcd for $C_{17}H_{18}N_2OSClF_3$(%): C 52.24, H 4.64, N 7.17, found: C 52.32, H 4.60, N 7.21.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(3-methylphenyl) thiourea(5c). White crystal; yield, 53.7%; mp, 192-195℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.85(d, *J*=8.4 Hz, 1H, cyclopropane H), 2.33(t, *J*=8.8 Hz, 1H, cyclopropane H), 2.38(s, 3H, CH_3), 6.96 (d, *J*=9.6 Hz, 1H, C=CH), 7.07-7.09(m, 1H, Ph), 7.26-7.30(m, 1H, Ph), 7.26-7.30(m, 1H, Ph), 7.41-7.47(m, 1H, Ph), 9.14(s, 1H, NH), 12.19(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 391 (M^+, 29), 355(3), 206(100), 141(36), 133(57), 91(12), 63(6); Anal. Calcd for $C_{17}H_{18}N_2OSClF_3$(%): C 52.24, H 4.64, N 7.17, found: C 52.38, H 4.60, N 7.21.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(4-chlorophenyl) thiourea(5d). White crystal; yield, 74.6%; mp, 187-190℃; ^{1}H-NMR ($CDCl_3$) δ: 1.36(s, 6H, CH_3), 1.82(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.33(t, *J*=9.6 Hz, 1H, cyclopropane H), 6.93 (d, *J*=8.0 Hz, 1H, C=CH), 7.35-7.37(m, 2H, Ph), 7.60-7.63(m, 2H, Ph), 9.03(s, 1H, NH), 12.22(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 411 ($[M-1]^+$, 33), 377(3), 226(100), 187(6), 170(7), 153(33), 141(19), 83(14), 63(4); Anal. Calcd for $C_{16}H_{15}N_2OSCl_2F_3$(%): C 46.73, H 3.68, N 6.81, found: C 46.61, H 3.72, N 6.83.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-eny)-2,2-dimethylcyclopropanecarbonyl)-3-(3-chlorophenyl) thiourea(5e). White crystal; yield, 59.3%; mp, 194-197℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.63(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.35(t, *J*=8.4 Hz, 1H, cyclopropane H), 6.94 (d, *J*=9.2 Hz, 1H, C=CH), 7.20-7.43(m, 2H, Ph), 7.51-7.53(m, 1H, Ph), 7.78-7.83(m, 1H, Ph), 9.42(s, 1H, NH), 12.30(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 412 ($[M-1]^+$, 34), 377(2), 226(100), 187(38), 170(12), 153(33), 141(29), 83(14), 63(4); Anal. Calcd for $C_{16}H_{15}N_2OSCl_2F_3$(%): C 46.73, H 3.68, N 6.81, found: C 46.64, H 3.75, N 6.77.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(4-nitrophenyl) thiourea(5f). Yellow crystal; yield, 86.5%; mp, 189-192℃; ^{1}H-NMR ($CDCl_3$) δ: 1.37(s, 6H, CH_3), 1.83(d, *J*=8.4 Hz, 1H, cyclopropane H), 2.38(t, *J*=8.4 Hz, 1H, cyclopropane H), 6.92 (d, *J*=8.8 Hz, 1H, C=CH), 7.99-8.01(m, 2H, Ph), 8.26-8.28(m, 2H, Ph), 9.00(s, 1H, NH), 12.68(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 422 (M^+, 46), 237(100), 225(31), 164(18), 141(24), 108(5), 83(16), 63(5); Anal. Calcd for $C_{16}H_{15}N_3O_3SClF_3$(%): C 45.56, H 3.58, N 9.96, found: C 45.43, H 3.62, N 10.01.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(4-methoxyphenyl) thiourea (5g). White crystal; yield, 57.2%; mp, 177-180℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.88(d, *J*=8.4 Hz, 1H, cyclopropane H), 2.31(t, *J*=8.8 Hz, 1H, cyclopropane H), 3.82(s, 3H, CH_3), 6.91 (d, *J*=8.8 Hz, 1H, C=CH), 6.94-6.97(m, 1H, Ph), 7.48-7.51(m, 1H, Ph), 7.26-7.30(m, 1H, Ph), 7.41-7.47(m, 1H, Ph), 9.14(s, 1H, NH), 12.19(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 406 (M^+, 41), 370(3), 226(100), 180(46), 129(15), 77(8); Anal. Calcd for $C_{17}H_{18}N_2O_2SClF_3$(%): C 50.19, H 4.46, N 6.89, found: C 50.01, H 4.53, N 6.86.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(2-fluorophenyl) thiourea(5h). Yellow crystal; yield, 50.1%; mp, 181-184℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.90(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.56(t, *J*=8.0 Hz, 1H, cyclopropane H), 6.95 (d, *J*=8.0 Hz, 1H, C=CH), 7.35-7.41(m, 3H, Ph), 7.71-7.73(m, 1H, Ph), 9.00(s, 1H, NH), 12.35(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 395(M^+, 43), 359(2), 226(100), 169(21), 154(19), 110(7), 91(47), 77(11); Anal. Calcd for $C_{16}H_{15}N_2OSClF_4$(%): C 48.67, H 3.83, N 7.10, found: C 48.83, H 3.81, N 7.13.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-

2,2-dimethylcyclopropanecarbonyl)-3-(3-trifluoromethylphenyl) thiourea(5i). Yellow crystal; yield, 66.4%; mp, 170-173℃; ^{1}H-NMR ($CDCl_3$) δ: 1.37(s, 6H, CH_3), 1.83(d, *J*=8.4 Hz, 1H, cyclopropane H), 2.36(t, *J*=8.8 Hz, 1H, cyclopropane H), 6.94 (d, *J*=8.0 Hz, 1H, C=CH), 7.52-7.53(m, 2H, Ph), 7.88(s, 1H, Ph), 7.99(s, 1H, Ph), 9.06(s, 1H, NH), 12.36(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 445 (M^+, 33), 409(2), 260(100), 225(15), 187(45), 141(22), 83(17), 63(3); Anal. Calcd for $C_{17}H_{15}N_2OSClF_6$(%): C 45.90, H 3.40, N 6.30, found: C 46.03, H 3.45, N 6.24.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl-3-(3,4-dichorophenyl) thiourea(5j). White crystal; yield, 94.1%; mp, 154-157℃; ^{1}H-NMR ($CDCl_3$) δ: 1.36(s, 6H, CH_3), 1.78(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.36(t, *J*=8.8 Hz, 1H, cyclopropane H), 6.92 (d, *J*=9.6 Hz, 1H, C=CH), 7.44-7.54(m, 2H, Ph), 7.91-7.92(m, 1H, Ph), 8.88(s, 1H, NH), 12.26(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 446(M^+, 32), 410(4), 226(100), 220(36), 188(14), 161(57), 90(9), 77(6); Anal. Calcd for $C_{16}H_{14}N_2OSCl_3F_3$(%): C 43.12, H 3.17, N 6.29 found: C 43.29, H 3.20, N 6.24.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-(2,4-difluorophenyl) thiourea(5k) Yellow crystal; yield, 91.3%; mp, 165-168℃; ^{1}H-NMR ($CDCl_3$) δ: 1.36(s, 6H, CH_3), 1.83(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.35(t, *J*=8.8 Hz, 1H, cyclopropane H), 6.92 (d, *J*=8.0 Hz, 1H, C=CH), 6.93-6.96(m, 2H, Ph), 8.04-8.09(m, 1H, Ph), 9.15(s, 1H, NH), 12.07(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 413 (M^+, 27), 377(3), 228(100), 172(12), 155(48), 141(28), 83(17), 63(5); Anal. Calcd for $C_{16}H_{14}N_2OSClF_5$(%): C 46.55, H 3.42, N 6.79 found: C 46.71, H 3.40, N 6.72.

1-(3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl-3-(2,4,6-trichlorophenyl) thiourea(5l). White crystal; yield, 64.9%; mp, 177-179℃; ^{1}H-NMR ($CDCl_3$) δ: 1.35(s, 6H, CH_3), 1.92(d, *J*=8.0 Hz, 1H, cyclopropane H), 2.34(t, *J*=8.8 Hz, 1H, cyclopropane H), 6.94 (d, *J*=9.2 Hz, 1H, C=CH), 7.43(s, 2H, Ph), 9.62(s, 1H, NH), 11.66(s, 1H, NH); EI-MS *m/z* (relative intensity/%): 480(M^+, 38), 445(2), 255(17), 226(100), 219(28), 184(53), 148(14), 89(9), 77(15); Anal. Calcd for $C_{16}H_{13}N_2OSCl_4F_3$ (%): C 40.02, H 2.73, N 5.83 found: C 40.16, H 2.75, N 5.80.

Biological Activities

Bioassay of Fungicidal Activities

The method for testing the primary biological activities was performed in an isolated culture. Under a sterile condition, 1 mL DMSO of title compound was added to the culture plates, followed by the addition of 9 mL of culture medium. The final mass concentration of the title compound was 50 μg/mL. The blank assay was performed with 1 mL of sterile water. Circle mycelium with a diameter of 4 mm was cut using a drill. The culture plates were cultivated at (24±1)℃. The extended diameters of the circle mycelium were measured after 72 h. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

Relative inhibition rate (%)=[(CK-PT)/CK]×100%

where CK is the extended diameter of the circle mycelium during the blank assay; and PT, is the extended diameter of the circle mycelium during testing.

Bioassay of Insecticidal Activities

Insecticidal activities against *Nilaparvata legen, Mythimna separate, Tetranychus cinnabarnus* and *Aphis medicagini* were performed in the greenhouse. The bioassay was operated at 25 ± 1 ℃ according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected according to Abbott's formula. Percent mortality was evaluated. Error of the experiments was 5%. For comparative purpose, compound **5** were tested as control under the same conditions.

The insecticidal activities of compounds **5** were evaluated according FAO procedure. The insecticidal activity against oriental armyworm was tested by foliar application, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. Then every 10 fourth-instar oriental armyworm larvae were put into each dish. Percent mortalities were evaluated 2 days after treatment. Each treatment was replicated for three times.

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