DOI:10.1021/jf1001793

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

Design, Synthesis and Insecticidal Activity of Novel Phenylpyrazoles Containing a 2,2,2-Trichloro-1-alkoxyethyl Moiety

Qiqi Zhao, Yongqiang Li, Lixia Xiong, and Qingmin Wang*

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

A series of novel phenylpyrazoles containing a 2,2,2-trichloro-1-alkoxyethyl moiety were designed and synthesized via the key intermediate 5-trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (**5**). The addition reaction of the imine **5** was closely related with the nature of the alcohol. The target compounds were confirmed by ^{1}H NMR and elemental analysis. The results of bioassays indicated that the target compounds possessed excellent activities against a broad spectrum of insects such as bean aphid (*Aphis craccivora*), mosquito (*Culex pipiens pallens*) and diamondback moth (*Plutella xylostella*). Especially, the foliar contact activity against bean aphid of compound **7h** at 2.5 mg kg^{-1} was 89%, the larvacidal activity against mosquito of compound **6c** at 2.5 μg kg^{-1} was 100%, the activity against diamondback moth of compound **7a** at 5 mg kg^{-1} was 87%, and all of these activities were much higher than the contrast ethiprole. The results of insecticidal activities showed that the two pairs of enantiomers **7d-1** and **7d-2** gave activities without distinctive difference, and it was the similar situation for **7e-1** and **7e-2**. Interestingly, the target compounds exhibited high selectivity between diamondback moth and oriental armyworm, both of which are of the order *Lepidoptera*. The 2,2,2-trichloro-1-alkoxyethyl moiety was essential for high insecticidal activities.

KEYWORDS: Phenylpyrazole; GABA receptor; 2,2,2-trichloro-1-alkoxyethyl; insecticidal activity; broad spectrum

INTRODUCTION

Synthetic 1-phenylpyrazoles such as fipronil (**A**) and ethiprole (**B**) (**Figure 1**) belong to an important kind of insecticide, and the toxicity of 1-phenylpyrazoles to insects and mammals is attributable to their action at the GABA receptor as noncompetitive blockers of the GABA-gated chloride channel (*1*−*4*). **A** was once one of the most important insecticides for control of soil insects on corn (*5*) and fleas on cats and dogs (*6*). Ethiprole **B** is a new 1-phenylpyrazole insecticide effective against a broad spectrum of chewing and sucking insects with pronounced plant systemic activity (*7*) as well as stored grain insect pests (*8*).

Besides fipronil and ethiprole, vaniliprole (**C**) (*9*), acetoprole (**D**) (*10*), pyrafluprole (**E**) (*11*) and pyriprole (**F**) (*12*) (**Figure 2**) are among the 1-phenylpyrazole insecticides. In common, there are an electron-withdrawing group (cyano or acetyl), a sulfenyl (or sulfinyl) group, and an amino (or substituted amino) on the 3-position, 4-position and 5-position of the pyrazole ring, respectively. It is noticed that vaniliprole, pyrafluprole and pyriprole could be prepared by reaction of the corresponding 5-amino compound with the proper aromatic aldehyde, and a subsequent reduction of the resulting imine intermediate is needed for pyrafluprole and pyriprole (*11*, *12*).

*To whom correspondence should be addressed. Tel: +86-(0)22-23499842. Fax: +86-(0)22-23499842. E-mail: wang98h@263.net, wangqm@nankai.edu.cn.

A trivial change in structure of a pesticide would lead to great changes in properties and activities. According to refs *13*, *14*, a 2,2,2-trichloro-1-methoxyethyl group had been introduced to organophosphorus pesticide (**G**) (**Figure 3**) so as to change the toxicological properties and enhance the selectivity.

Herein a series of novel phenylpyrazoles containing a 2,2,2-trichloro-1-alkoxyethyl moiety (**H**) (**Figure 3**) were designed and synthesized, and their insecticidal activities against bean aphid (*Aphis craccivora*), mosquito (*Culex pipiens pallens*), diamondback moth (*Plutella xylostella*) and oriental armyworm (*Mythimna separata*) were tested and discussed.

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized.

General Synthesis. All anhydrous solvents as well as sulfur chloride were dried and purified by standard techniques just before use. Chloral was prepared from chloral hydrate by dehydration with concentrated sulfuric acid (*15*). The synthetic route is given in **Scheme 1**.

Synthesis of 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazole (2). Concentrated sulfuric acid (2.8 mL) was added

 Published on Web 03/29/2010

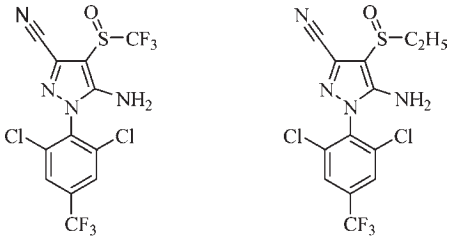

Figure 1. Chemical structures of fipronil (**A**) and ethiprole (**B**).

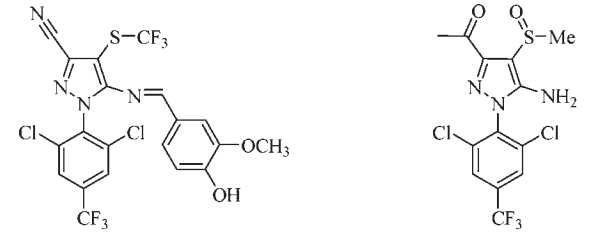

Figure 2. Chemical structures of vaniliprole (**C**), acetoprole (**D**), pyrafluprole (**E**) and pyriprole (**F**).

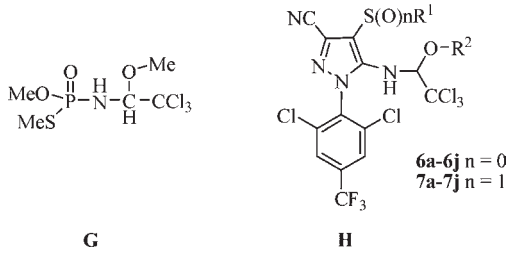

Figure 3. Chemical structures of compound **G** and the title compounds **H**.

dropwise to sodium nitrite (0.76 g, 11 mmol) placed in a round-bottom flask with mechanical stirring, and the reaction mixture was stirred for 15 min before acetic acid (2.5 mL) was added. After the mixture had cooled to room temperature, 2,6-dichloro-4-trifluoromethylaniline (**1**, 2.12 g, 9.2 mmol) dissolved in acetic acid (10 mL) was slowly added. The mixture was then heated at 55−60 °C for 40 min and poured into a solution of ethyl 2,3-dicyanopropionate (1.4 g, 9.2 mmol) in acetic acid (6 mL) and water (10 mL) at 5 °C. After the mixture was stirred for 2 h at room temperature, water and dichloromethane were added and the aqueous layer was extracted twice with dichloromethane. The combined organic layer was vigorously stirred with ammonium hydroxide (30%, 80 mL) overnight at room temperature. The separated organic layer was then washed with water (2 × 30 mL) and 1 M hydrochloric acid (25 mL), dried over sodium sulfate, filtered, and concentrated. The crude oil was crystallized from dichloromethane and petroleum ether (60−90 °C) to give **2** as a slight yellow solid (2.12 g, 72%). Mp: 142−143 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 2H, Ph), 6.05 (s, 1H, pyrazole), 3.81 (s, 2H, NH_2).

Synthesis of Bis(5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazol-4-yl) Disulfide (3). To a cooled (−15 °C) solution of **2** (18.6 g, 60 mmol) in dichloromethane (150 mL) was added dropwise a solution of sulfur chloride (4.19 g, 31 mmol) in dichloromethane (20 mL). Then the mixture was stirred overnight at room temperature, and the yellow slurry was filtered and the cake was washed with dichloromethane to afford disulfide **3** as a yellow solid (20.1 g, 95%). Mp > 300 °C. ^{1}H NMR (DMSO-d_6): δ 7.97 (s, 4H, Ph), 6.68 (s, 4H, NH_2).

General Synthesis of 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (4). To a solution of disulfide **3** (5.64 g, 8 mmol) in dimethylformamide (130 mL) was added alkyl halide (18 mmol), and then potassium hydrogen phosphate (4.53 g, 26 mmol) in water (60 mL) was added, followed by addition of sodium dithionite (4.48 g, 26 mmol) in portions. The mixture was stirred for 4 h at room temperature, and then water (200 mL) and ethyl acetate (100 mL) were added. After separation, the water phase was again extracted by ethyl acetate (2 × 80 mL). The combined organic phase was washed with water (2×100 mL) and brine (2×100 mL) successively, dried over sodium sulfate, and concentrated to give **4** as a white solid. The alkylating reagents were iodomethane and ethyl bromide for **4a** and **4b**, respectively.

Data for 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-methylsulfenylpyrazole (4a). Yield: 92%. Mp 173−175 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 2H, Ph), 4.14 (s, 2H, NH_2), 2.34 (s, 3H, CH_3).

Data for 5-Amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethylsulfenylpyrazole (4b). Yield: 89%. Mp 152−154 °C. ^{1}H NMR ($CDCl_3$): δ 7.79 (s, 2H, Ph), 4.14 (s, 2H, NH_2), 2.17 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3).

General Synthesis of 5-Trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (5). A mixture of **4** (11 mmol) and chloral (35 g, 240 mmol) was refluxed in the presence of molecular sieves (4 Å, 1 g) for 36 h, and then most of the chloral was removed by distillation. The residue was purified by column chromatography on a silica gel using petroleum ether (60−90 °C) and dichloromethane as the eluent to afford **5** as a slight yellow solid.

Data for 5-Trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-methylsulfenylpyrazole (5a). Yield: 44%. Mp: 113−115 °C. ^{1}H NMR ($CDCl_3$): δ 8.82 (s, 1H, CH=N), 7.74 (s, 2H, Ph), 2.58 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_6Cl_5F_3N_4S$ (%): C, 33.86; H, 1.22; N, 11.28. Found: C, 33.99; H, 1.21; N, 11.12.

Data for 5-Trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-ethylsulfenylpyrazole (5b). Yield: 53%. Mp: 112−114 °C. ^{1}H NMR ($CDCl_3$): δ 9.00 (s, 1H, CH=N), 7.75 (s, 2H, Ph), 2.95 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2), 1.28 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3). Anal. Calcd for $C_{15}H_8Cl_5F_3N_4S$ (%): C, 35.29; H, 1.58; N, 10.97. Found: C, 35.21; H, 1.59; N, 10.97.

General Synthesis of 5-(2,2,2-Trichloro-1-alkoxylethylamino)-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (6). The solution of imine **5** (2 mmol) in an alcohol (10 mL) was heated at a certain temperature for several hours, and monitored by TLC. After the imine **5** disappeared, the alcohol was removed in vacuo. The residue was purified by column chromatography on a silica gel using petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the target compound **6** as a white solid. The physical properties and elemental analysis of compounds **6a**−**6j** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

General Synthesis of 5-(2,2,2-Trichloro-1-alkoxylethylamino)-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfinylpyrazole (7). To a solution of **6** (1 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (1 mL), and then the reaction mixture was cooled to 10 °C. Hydrogen peroxide (0.23 mL of 30%, w/w, 2 mmol) was added dropwise at 12−15 °C, and the mixture was kept at this temperature for 3 h. Then sodium bisulfite (1.04 g, 10 mmol) was added in portions, and the mixture was stirred for 1 h at room temperature. Water (15 mL) was then added, and the aqueous phase was extracted with dichloromethane (2 × 15 mL). The combined organic layer was washed with water (15 mL) and brine (15 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography on a silica gel using petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the sulfinyl compound **7** as a white solid. The physical properties and elemental analysis of compounds **7a**−**7j** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a

Scheme 1. General Synthetic Route for Compounds **6a**−**6j** and **7a**−**7j**

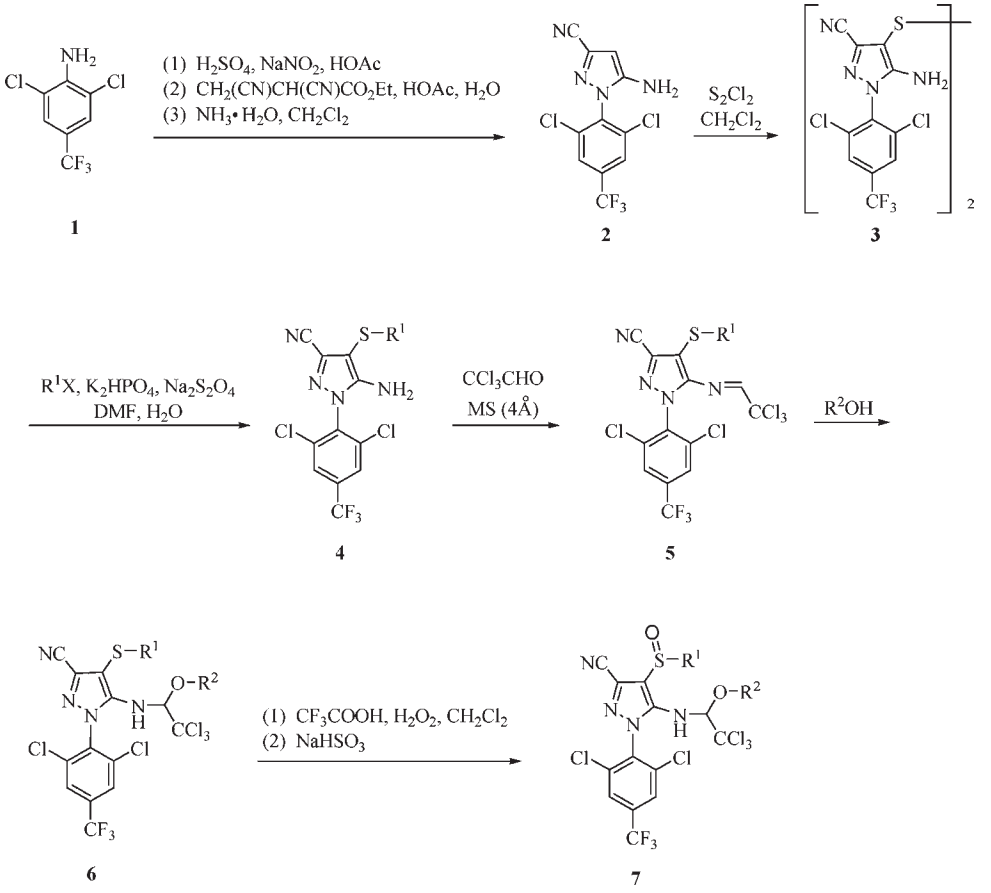

Table 1. Physical Properties and Elemental Analyses of Compounds **6a**−**6j** and **7a**−**7j**

					elemental anal. (%) (calcd)		
compd	R^1	R^2	mp (°C)	yield (%)	C	H	N
6a	Me	Me	91−92	99	34.19 (34.09)	2.05 (1.91)	10.61 (10.60)
6b	Me	Et	127−128	99	35.44 (35.42)	2.19 (2.23)	10.43 (10.33)
6c	Me	*n*-Pr	147−149	96	36.51 (36.68)	2.59 (2.54)	10.00 (10.07)
6d	Me	FCH_2CH_2	129−131	40	34.09 (34.28)	2.10 (1.98)	9.79 (9.99)
6e	Me	$ClCH_2CH_2$	142−144	54	33.38 (33.30)	1.92 (1.92)	9.72 (9.71)
6f	Et	Me	123−124	99	35.41 (35.42)	2.39 (2.23)	10.39 (10.33)
6g	Et	Et	137−139	99	36.71 (36.68)	2.59 (2.54)	10.08 (10.07)
6h	Et	*n*-Pr	119−121	99	37.67 (37.88)	2.95 (2.83)	9.76 (9.82)
6i	Et	FCH_2CH_2	147−149	42	35.40 (35.53)	2.32 (2.28)	9.95 (9.75)
6j	Et	$ClCH_2CH_2$	123−125	59	34.09 (34.54)	2.29 (2.22)	9.55 (9.48)
7a	Me	Me	110−112	87	33.28 (33.08)	2.00 (1.85)	10.37 (10.29)
7b	Me	Et	98−100	83	34.57 (34.40)	2.24 (2.17)	10.09 (10.03)
7c	Me	*n*-Pr	158−160	79	35.45 (35.66)	2.41 (2.46)	9.79 (9.78)
7d-1	Me	FCH_2CH_2	150−152	82[a]	33.12 (33.33)	2.05 (1.92)	9.67 (9.72)
7d-2	Me	FCH_2CH_2	141−143		33.18 (33.33)	2.15 (1.92)	9.75 (9.72)
7e-1	Me	$ClCH_2CH_2$	151−153	67[b]	32.56 (32.40)	1.98 (1.87)	9.26 (9.45)
7e-2	Me	$ClCH_2CH_2$	133−135		32.49 (32.40)	1.95 (1.87)	9.30 (9.45)
7f	Et	Me	147−149	89	34.32 (34.40)	2.28 (2.17)	10.07 (10.03)
7g	Et	Et	133−134	97	35.90 (35.66)	2.65 (2.46)	9.54 (9.78)
7h	Et	*n*-Pr	49−51	73	36.81 (36.85)	2.78 (2.75)	9.80 (9.55)
7i	Et	FCH_2CH_2	67−69	64	33.93 (34.57)	2.68 (2.22)	9.42 (9.49)
7j	Et	$ClCH_2CH_2$	52−54	72	33.53 (33.63)	2.23 (2.16)	9.10 (9.23)

[a] The overall yield of **7d-1** and **7d-2**. Compounds **7d-1** and **7d-2** were two pairs of enantiomers, and the ratio of **7d-1** to **7d-2** was about 1:1.3. [b] The overall yield of **7e-1** and **7e-2**. Compounds **7e-1** and **7e-2** were two pairs of enantiomers, and the ratio of **7e-1** to **7e-2** was about 1:1.5.

dead/alive basis and mortality rates were corrected using Abbott's formula (*16*). Evaluations are based on a percentage scale of 0−100 in which 0 = no activity and 100 = total kill.

Foliar Contact Activity against Bean Aphid (*Aphis craccivora*). The foliar contact activities of compounds **6a**−**6j**, **7a**−**7j** and ethiprole against bean aphid were tested according to a reported procedure (*17*−*19*). Stock solutions of each test sample was prepared in dimethylformamide at a concentration of 200 mg L^{-1} and then diluted to the required concentration with water containing TW-20. Tender shoots of soybean with 60 insects of each species were dipped in the diluted

Table 2. ^{1}H NMR of Compounds **6a**−**6j** and **7a**−**7j**

compd	δ (ppm)
6a	7.80 (s, 2H, Ph), 5.69 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.45 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.53 (s, 3H, OCH_3), 2.45 (s, 3H, SCH_3)
6b	7.81 (s, 1H, Ph), 7.80 (s, 1H, Ph), 5.78 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.44 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.87−3.63 (m, 2H, OCH_2), 2.45 (s, 3H, SCH_3), 1.23 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)
6c	7.80 (s, 2H, Ph), 5.75 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.45 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.74−3.63 (m, 1H, OCH_2), 3.57−3.47 (m, 1H, OCH_2), 2.44 (s, 3H, SCH_3), 1.65−1.55 (m, 2H, $OCH_2CH_2CH_3$), 0.91 (t, 3H, $^3J_{HH}$ = 7.6 Hz, $OCH_2CH_2CH_3$)
6d	7.80 (s, 2H, Ph), 5.92 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.61 (t, $^3J_{HH}$ = 3.6 Hz, 1H, FCH_2), 4.57−4.44 (m, 3H, FCH_2 and NH), 4.08−3.85 (m, 2H, OCH_2), 2.45 (s, 3H, SCH_3)
6e	7.81 (s, 2H, Ph), 5.92 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.51 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 4.04−3.89 (m, 2H, OCH_2), 3.62 (t, $^3J_{HH}$ = 5.6 Hz, 2H, $ClCH_2$), 2.46 (s, 3H, SCH_3)
6f	7.81 (s, 2H, Ph), 5.58 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.49 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.52 (s, 3H, OCH_3), 2.93−2.79 (m, 2H, CH_2), 1.34 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3)
6g	7.81 (s, 1H, Ph), 7.80 (s, 1H, Ph), 5.64 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.48 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.84−3.75 (m, 1H, OCH_2), 3.73−3.64 (m, 1H, OCH_2), 2.93−2.77 (m, 2H, SCH_2), 1.33 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3), 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)
6h	7.81 (s, 1H, Ph), 7.80 (s, 1H, Ph), 5.60 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.51 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.71−3.64 (m, 1H, OCH_2), 3.54−3.47 (m, 1H, OCH_2), 2.90−2.79 (m, 2H, SCH_2), 1.62−1.54 (m, 2H, $OCH_2CH_2CH_3$), 1.33 (t, $^3J_{HH}$ = 7.6 Hz, 3H, SCH_2CH_3), 0.90 (t, 3H, $^3J_{HH}$ = 7.6 Hz, $OCH_2CH_2CH_3$)
6i	7.83 (s, 1H, Ph), 7.82 (s, 1H, Ph), 5.81 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.61 (t, $^3J_{HH}$ = 4.0 Hz, $^2J_{HF}$ = 47.6 Hz, 1H, FCH_2), 4.56 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 4.49 (t, $^3J_{HH}$ = 4.0 Hz, $^2J_{HF}$ = 47.6 Hz, 1H, FCH_2), 4.07−3.87 (m, 2H, OCH_2), 2.95−2.80 (m, 2H, SCH_2), 1.34 (t, 3H, $^3J_{HH}$ = 7.6 Hz, SCH_2CH_3)
6j	7.82 (s, 1H, Ph), 7.81 (s, 1H, Ph), 5.80 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.54 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 4.03−3.88 (m, 2H, OCH_2), 3.61 (t, $^3J_{HH}$ = 6.0 Hz, $ClCH_2$), 2.93−2.80 (m, 2H, SCH_2), 1.34 (t, $^3J_{HH}$ = 7.2 Hz, SCH_2CH_3)
7a	7.85 (s, 1H, Ph), 7.82 (s, 1H, Ph), 6.31 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.59 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.33 (s, 3H, OCH_3), 3.14 (s, 3H, SCH_3)
7b	7.84 (s, 1H, Ph), 7.81 (s, 1H, Ph), 6.17 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.71 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.77−3.64 (m, 1H, O CH_2), 3.40−3.29 (m, 2H, OCH_2), 3.15 (s, 3H, SCH_3), 1.12 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)
7c	7.85 (s, 1H, Ph), 7.81 (s, 1H, Ph), 6.24 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 4.71 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.62−3.52 (m, 1H, OCH_2), 3.19−3.08 (m, 4H, OCH_2 and SCH_3), 1.53−1.44 (m, 2H, $OCH_2CH_2CH_3$), 0.86 (t, 3H, $^3J_{HH}$ = 7.6 Hz, $OCH_2CH_2CH_3$)
7d-1	7.84 (s, 1H, Ph), 7.81 (s, 1H, Ph), 5.89 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 5.06 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 4.62−4.51 (m, 1H, FCH_2), 4.50−4.38 (m, 1H, FCH_2), 4.03−3.96 (m, 1H, OCH_2), 3.95−3.87 (m, 1H, OCH_2), 3.16 (s, 3H, SCH_3)
7d-2	7.84 (s, 1H, Ph), 7.81 (s, 1H, Ph), 6.30 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.84 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 4.60−4.32 (m, 2H, FCH_2), 3.95−3.63 (m, 2H, OCH_2), 3.15 (s, 3H, SCH_3)
7e-1	7.85 (s, 1H, Ph), 7.82 (s, 1H, Ph), 5.91 (d, $^3J_{HH}$ = 10.8 Hz, 1H, CH), 5.10 (d, $^3J_{HH}$ = 10.8 Hz, 1H, NH), 3.90 (t, $^3J_{HH}$ = 6.0 Hz, 2H, OCH_2), 3.57 (t, 2H, $^3J_{HH}$ = 6.0 Hz, $ClCH_2$), 3.17 (s, 3H, SCH_3)
7e-2	7.82 (s, 2H, Ph), 6.30 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.84 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 4.60−4.32 (m, 2H, FCH_2), 3.95−3.63 (m, 2H, OCH_2), 3.15 (s, 3H, SCH_3)
7f	The product was isolated as a mixture of two pairs of enantiomers in a ratio of 1.1:1. For major enantiomers: 7.83 (s, 2H, Ph), 6.58 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.55 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.37 (s, 3H, OCH_3), 3.36−3.24 (m, 2H, CH_2), 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3). For minor enantiomers: 7.83 (s, 2H, Ph), 6.15 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.73 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.43 (s, 3H, OCH_3), 3.36−3.24 (m, 2H, SCH_2), 1.40 (t, 3H, $^3J_{HH}$ = 7.2 Hz, SCH_2CH_3)
7g	The product was isolated as a mixture of two pairs of enantiomers in a ratio of 1.8:1. For major enantiomers: 7.83 (s, 2H, Ph), 6.42 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.65 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.78−3.66 (m, 1H, OCH_2), 3.45−3.23 (m, 3H, OCH_2 and SCH_2), 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3), 1.14 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3). For minor enantiomers: 7.83 (s, 2H, Ph), 6.11 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.79 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.78−3.66 (m, 1H, OCH_2), 3.61−3.53 (m, 1H, OCH_2), 3.45−3.23 (m, 2H, SCH_2), 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3), 1.14 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)
7h	The product was isolated as a mixture of two pairs of enantiomers in a ratio of 1.1:1. For major enantiomers: 7.83 (s, 2H, Ph), 6.47 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.60 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.65−3.53 (m, 1H, OCH_2), 3.40−3.24 (m, 2H, SCH_2), 3.24−3.23 (m, 1H, OCH_2), 1.55−1.46 (m, 2H, $OCH_2CH_2CH_3$), 1.40 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3), 0.87 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $OCH_2CH_2CH_3$). For minor enantiomers: 7.82 (s, 2H, Ph), 6.22 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.74 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.65−3.53 (m, 1H, OCH_2), 3.40−3.24 (m, 3H, SCH_2 and OCH_2), 1.55−1.46 (m, 2H, $OCH_2CH_2CH_3$), 1.39 (t, $^3J_{HH}$ = 7.2 Hz, 3H, SCH_2CH_3), 0.86 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $OCH_2CH_2CH_3$)
7i	The product was isolated as a mixture of two pairs of enantiomers in a ratio of 1.1:1. For major enantiomers: 7.83 (s, 2H, Ph), 6.56 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.79 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 4.61−4.36 (m, 2H, FCH_2), 4.00−3.70 (m, 2H, OCH_2), 3.42−3.24 (m, 2H, SCH_2), 1.41 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3). For minor enantiomers: 7.84 (s, 2H, Ph), 6.14 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 5.05 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 4.61−4.36 (m, 2H, FCH_2), 4.00−3.70 (m, 2H, OCH_2), 3.42−3.24 (m, 2H, SCH_2), 1.41 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)
7j	The product was isolated as a mixture of two pairs of enantiomers in a ratio of 1.2:1. For major enantiomers: 7.86 (s, 2H, Ph), 6.61 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 4.75 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.95−3.86 (m, 1H, OCH_2), 3.71−3.65 (m, 1H, OCH_2), 3.59−3.54 (m, 2H, $ClCH_2$), 3.39−3.25 (m, 2H, SCH_2),1.42 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3). For minor enantiomers: 7.84 (s, 2H, Ph), 6.14 (d, $^3J_{HH}$ = 11.2 Hz, 1H, CH), 5.08 (d, $^3J_{HH}$ = 11.2 Hz, 1H, NH), 3.95−3.86 (m, 1H, OCH_2), 3.82−3.77 (m, 1H, OCH_2), 3.59−3.54 (m, 2H, $ClCH_2$), 3.39−3.25 (m, 2H, SCH_2), 1.41 (t, $^3J_{HH}$ = 7.2 Hz, 3H, OCH_2CH_3)

solutions of the chemicals for 5 s, then the superfluous liquor was removed, and they were kept in the conditioned room for normal cultivation. The mortality was evaluated by the number of live larvae in the treated bottles relative to that in the untreated controls after 24 h. Controls were performed under the same conditions. Each test was performed in triplicate.

Toxicity against Mosquito (*Culex pipiens pallens*). The toxicities of the target compounds **6a**−**6j** and **7a**−**7j** against mosquito were evaluated according to the reported procedure (*18*, *20*). One milliliter of different concentrated dilutions of each compound was added to 99 mL of water to obtain different concentrations of tested solution. Then 20 fourth-instar mosquito larvae were put into the solution. Percentage mortalities were evaluated 1 day after treatment. For comparative purposes, ethiprole was tested under the same conditions, and each test was performs three times.

Stomach Toxicity against Diamondback Moth (*Plutella xylostella*). The stomach toxicities of the target compounds **6a**−**6j**, **7a**−**7j** and the contrast ethiprole against diamondback moth were tested by the leaf-dip method using the reported procedure (*21*, *22*). A stock solution of each test sample was prepared in dimethylformamide at a concentration of 200 mg L^{-1} and then diluted to the required concentration with water containing TW-20. Leaf disks (6 cm × 2 cm) were cut from fresh cabbage

leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf disks were placed individually into glass tubes. Each dried treated leaf disk was infested with seven third-instar diamondback moth larvae. Percentage mortalities were evaluated 3 days after treatment. Leaves treated with water and dimethylformamide were provided as controls. Each treatment was performed three times.

Stomach Toxicity against Oriental Armyworm (*Mythimna separata*). The stomach toxicities of the target compounds **6a**−**6j**, **7a**−**7j** and the contrast ethiprole against oriental armyworm were evaluated by foliar application using the reported procedure (*23*, *24*). For the foliar armyworm tests, 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. The dishes were infested with 10 fourth-instar Oriental armyworm larvae. Percentage mortalities were evaluated 3 days after treatment. Each treatment was performed three times.

RESULTS AND DISCUSSION

Synthesis. The target compounds **6a**−**6j** and **7a**−**7j** were prepared from 2,6-dichloro-4-trifluoromethylaniline (**1**) as shown in **Scheme 1**. Compound **1** was converted to 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazole (**2**) according to the reported method with a little modification (*4*), and further treatment with sulfur chloride provided bis(5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)pyrazol-4-yl) disulfide (**3**). The cleavage of disulfide **3** by alkylation assisted with an alkali and a reducing reagent afforded the sulfenyl compound **4** in high yield (*25*). Then the key intermediate 5-trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (**5**) was synthesized by reaction of **4** with chloral in the presence of molecular sieves (4 Å). The imine **5** was reacted with the proper alcohol to afford 5-(2,2,2-trichloro-1-alkoxylethylamino)-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (**6**), which was converted to the sulfinyl compound **7** by hydrogen peroxide and trifluoroacetic acid.

The addition reaction of imine **5** was closely related with the nature of the alcohol. When the alcohol was methanol or ethanol, the reaction was completed under reflux in 2 h, while propanol needed 5 h, and all of them gave high yields. As for 2-fluoroethanol or 2-chloroethanol, the reaction was carried out at about 80 °C for more than 10 h with relatively low yield, while a higher temperature or reflux could decompose the imine **5** markedly. In addition, other nucleophilic reagent such as 2-propanol, 2,2,2-trifluoethanol, 1-propanethiol and acetic acid were also tried but failed to give addition products under similar conditions.

It was noticed that compound **7** has two chiral centers each on the sulfur and carbon atoms, and there were two pairs of enantiomers theoretically. It was very interesting that only one pair was obtained for **7a**−**7c**, while both of the two pairs were generated and separated for **7d** (noted as **7d-1** and **7d-2**, **Figure 4**) and **7e** (noted as **7e-1** and **7e-2**). But as for **7f**−**7j**, only a mixture of two pairs of enantiomers was obtained because of the high similarity of R_f. But the corresponding ^{1}H NMR spectra, especially the C*H* and N*H* of **7f**−**7j**, were different for the two pairs, and could also explain their ratio (**Table 2**).

Bioassays. *Foliar Contact Activity against Bean Aphid* (*Aphis craccivora*). **Table 3** showed the foliar contact activities of the target compounds **6a**−**6j**, **7a**−**7j** and the contrast ethiprole against bean aphid. The results indicate that the target compounds have excellent foliar contact activities against bean aphid, and some of them exhibited much higher activities than ethiprole. For example, the activities of **6a**, **7a**, **7b**, **7c**, **7d-1**, **7d-2**, **7e-1**, **7e-2**, **7f**, **7g**, **7h** and **7i** were 89%, 100%, 85%, 100%, 100%, 100%, 96%, 100%, 87%, 100%, 100% and 100% at 10 mg kg^{-1}, respectively, whereas ethiprole caused only 31% mortality at the same concentration. In particular, the activities of **7a**, **7c**, **7g** and 7h were 88%, 91%, 81% and 100% at 5 mg kg^{-1}, respectively, while ethiprole caused no detectable mortality at this concentration. It was especially mentioned that the activity of **7h** was still 89% at 2.5 mg kg^{-1}. It was observed that the *n*-Pr group of R^2 played a negative role in **6** but a positive role in **7**, and most of the sulfinyl compounds **7a**−**7j** were more potent than the corresponding sulfenyl compounds **6a**−**6j**. The LC_{50} values in **Table 4** showed that the foliar contact activities of **7a**, **7c** and **7h** were 4.2-, 4.3-, and 7.9-fold as high as that of ethiprole, respectively. Moreover, the activities of compounds **7d-1** and **7e-1** were very

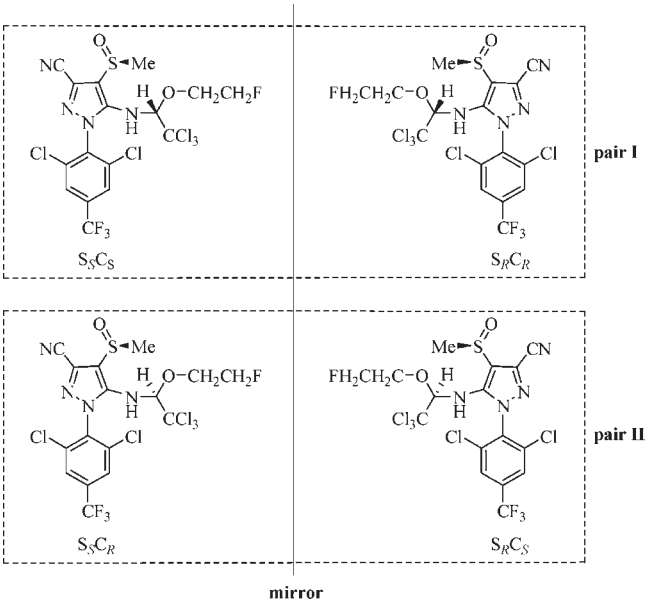

Figure 4. Stereoisomers of **7d**. The mixture of enantioners S_SC_S and S_RC_R was noted as pair I, and the mixture of S_SC_R and S_RC_S was noted as pair II. Then **7d-1** was one of the two pairs, and **7d-2** was the other pair. It was a similar situation for **7e-1** and **7e-2**.

Table 3. Foliar Contact Activities against Bean Aphid of Compounds **6a**−**6j**, **7a**−**7j** and Ethiprole

			larvicidal activity (%) at concn (mg kg^{-1})						
compd	R^1	R^2	200	100	50	25	10	5	2.5
6a	Me	Me	100	100	100	94	89	43	0
6b	Me	Et	100	100	56	43	0	0	
6c	Me	*n*-Pr	100	100	90	43	21	0	0
6d	Me	FCH_2CH_2	100	100	100	74	62	28	0
6e	Me	$ClCH_2CH_2$	100	100	100	98	73	69	62
6f	Et	Me	93	90	80	62	0		
6g	Et	Et	90	86	75	35	0		
6h	Et	*n*-Pr	95	90	85	53	0		
6i	Et	FCH_2CH_2	100	100	100	29	11	0	
6j	Et	$ClCH_2CH_2$	100	100	100	100	51	0	
7a	Me	Me	100	100	100	100	100	88	0
7b	Me	Et	100	100	100	100	85	63	0
7c	Me	*n*-Pr	100	100	100	100	100	91	0
7d-1	Me	FCH_2CH_2	100	100	100	100	100	72	43
7d-2	Me	FCH_2CH_2	100	100	100	100	100	70	46
7e-1	Me	$ClCH_2CH_2$	100	100	100	100	96	61	0
7e-2	Me	$ClCH_2CH_2$	100	100	100	100	100	68	0
7f	Et	Me	100	100	100	96	87	76	0
7g	Et	Et	100	100	100	100	100	81	0
7h	Et	*n*-Pr	100	100	100	100	100	100	89
7i	Et	FCH_2CH_2	100	100	100	100	100	73	43
7j	Et	$ClCH_2CH_2$	100	100	100	100	48	0	
ethiprole			100	100	100	100	31	0	

Table 4. LC_{50} Values of Compounds **7a**, **7c**, **7h** and Ethiprole of Foliar Contact Toxicities against Bean Aphid

compd	$y = a + bx$	LC_{50}[a] (mg kg^{-1})	toxic ratio
7a	$y = -2.3051 + 5.0099x$	2.8848	4.2
7c	$y = -2.1989 + 4.9845x$	2.7616	4.3
7h	$y = -0.7833 + 4.5433x$	1.4873	7.9
ethiprole	$y = -7.9808 + 7.4646x$	11.7263	1

[a] LC_{50} is the median lethal concentration.

Table 5. Larvacidal Activities against Mosquito of Compounds **6a**−**6j**, **7a**−**7j** and Ethiprole

			larvicidal activity (%) at concn (μg kg^{-1})					
compd	R^1	R^2	100	50	25	10	5	2.5
6a	Me	Me	100	100	100	100	100	70
6b	Me	Et	100	100	100	100	100	80
6c	Me	*n*-Pr	100	100	100	100	100	100
6d	Me	FCH_2CH_2	100	100	100	40		
6e	Me	$ClCH_2CH_2$	100	100	100	100	20	
6f	Et	Me	100	100	100	100	100	30
6g	Et	Et	100	100	100	100	0	
6h	Et	*n*-Pr	100	100	100	100	50	
6i	Et	FCH_2CH_2	100	100	100	100	0	
6j	Et	$ClCH_2CH_2$	100	100	100	100	100	60
7a	Me	Me	100	50				
7b	Me	Et	100	100	30			
7c	Me	*n*-Pr	100	100	50			
7d-1	Me	FCH_2CH_2	20					
7d-2	Me	FCH_2CH_2	50					
7e-1	Me	$ClCH_2CH_2$	100	40				
7e-2	Me	$ClCH_2CH_2$	50					
7f	Et	Me	100	100	0			
7g	Et	Et	100	100	40			
7h	Et	*n*-Pr	100	100	0			
7i	Et	FCH_2CH_2	100	20				
7j	Et	$ClCH_2CH_2$	100	0				
ethiprole			100	100	50			

close to those of their corresponding isomers **7d-2** and **7e-2**. Compounds **7f**−**7j** were different from ethiprole at the 5-position of the pyrazole ring, but most of them exhibited higher activities than ethiprole. Thus, the R^1 group, sulfinyl group and 2,2,2-trichloro-1-alkoxyethyl group were important for the activity against bean aphid.

Toxicity against Mosquito (*Culex pipiens pallens*). **Table 5** showed the larvacidal activities of the target compounds **6a**−**6j**, **7a**−**7j** and the contrast ethiprole against mosquito. Generally, the sulfenyl compounds **6a**−**6j** were more potent than the sulfinyl compounds **7a**−**7j**. The activities of **6a**, **6b**, **6c**, **6f** and **6j** were 100% at 5 μg kg^{-1}, while the activities of the compounds **7a**−**7j** as well as ethiprole were not higher than 50% at 25 μg kg^{-1}. Moreover, the substituents of the target compounds were also important for the activities against mosquito. For instance, the difference between the structures of compounds **6c** and **6d** was only the replacement of an *n*-propyl group by a 2-fluoroethyl group, but the activity of **6c** was 100% at 2.5 μg kg^{-1}, whereas the activity of **6d** was only 40% at 10 μg kg^{-1}.

Stomach Toxicity against Diamondback Moth (*Plutella xylostella*). **Table 6** showed the larvacidal activities of the target compounds **6a**−**6j**, **7a**−**7j** and the contrast ethiprole against diamondback moth. Overall, the activities of the target compounds were higher when the R^1 group was fixed as methyl than as ethyl. The results indicated that some of the target compounds exhibited excellent activities, much higher than ethiprole. For example, the activities of **6a**, **6d**, **6e**, **7a** and **7b** were at least 85% at 10 mg kg^{-1}, and the activities of **6d**, **6e** and **7a** were still higher

Table 6. Larvacidal Activities against Diamondback Moth of Compounds **6a**−**6j**, **7a**−**7j** and Ethiprole

			larvicidal activity (%) at concn (mg kg^{-1})						
compd	R^1	R^2	200	100	50	25	10	5	2.5
6a	Me	Me	100	100	100	100	86	76	25
6b	Me	Et	100	100	100	84	68	43	0
6c	Me	*n*-Pr	100	100	36	17	0		
6d	Me	FCH_2CH_2	100	100	100	100	89	81	34
6e	Me	$ClCH_2CH_2$	100	100	100	100	100	87	62
6f	Et	Me	100	100	94	34	0		
6g	Et	Et	100	100	96	44	18		
6h	Et	*n*-Pr	100	100	89	58	17		
6i	Et	FCH_2CH_2	100	100	100	100	29	0	
6j	Et	$ClCH_2CH_2$	100	100	88	43	27	0	
7a	Me	Me	100	100	100	100	91	88	34
7b	Me	Et	100	100	100	100	85	63	0
7c	Me	*n*-Pr	100	100	100	100	71	30	0
7d-1	Me	FCH_2CH_2	100	100	100	92	77	56	0
7d-2	Me	FCH_2CH_2	100	100	100	89	76	54	0
7e-1	Me	$ClCH_2CH_2$	100	100	100	100	81	60	0
7e-2	Me	$ClCH_2CH_2$	100	100	100	100	79	56	0
7f	Et	Me	100	100	86	31	0		
7g	Et	Et	100	100	100	100	72	29	0
7h	Et	*n*-Pr	100	100	100	87	44	27	0
7i	Et	FCH_2CH_2	100	100	91	46	30	0	
7j	Et	$ClCH_2CH_2$	100	100	100	46	32	0	
ethiprole			100	100	100	69	23	0	

than 80% at 5 mg kg^{-1}, while the activity of ethiprole was less than 70% at 25 mg kg^{-1}. Moreover, a small change in structure of the target compounds could lead to a remarkable change of activity. The activity of **6c** was only 36% at 50 mg kg^{-1}, whereas the activity of **6e** was 87% at 5 mg kg^{-1}. The activity of **7a** was 88% at 5 mg kg^{-1}, much higher than the activity of **7f**, which was 86% at 50 mg kg^{-1}. Both of the structural changes from **6c** to **6e** and from **7a** to **7f** only involved replacement of one substituent at the pyrazole ring, so the 2,2,2-trichloro-1-alkoxyethyl moiety as well as the R^1 group was quite critical for the activity against diamondback moth.

Stomach Toxicity against Oriental Armyworm (*Mythimna separata*). Most of the target compounds and ethiprole showed no detectable activity, for example, the activities against oriental armyworm of **6i**, **7c** and ethiprole were 20%, 40% and 0 at 200 mg kg^{-1}, respectively. These data formed a sharp contrast to the activities against diamondback moth, which was also of the order *Lepidoptera*. The results indicated that the action passway or metabolism of the target compounds probably varied for different pest species.

In summary, a series of novel phenylpyrazole containing a 2,2,2-trichloro-1-alkoxyethyl moeity were designed and synthesized via the key intermediate 5-trichloroethylideneimino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-alkylsulfenylpyrazole (**5**). The addition reaction of the imine **5** was attempted and discussed, and it was closely related with the nature of the nucleophilic reagent. The results of bioassays indicated that the target compounds possessed excellent activities against a broad spectrum of insects such as bean aphid, mosquito and diamondback moth, even much higher than the contrast ethiprole. In particular, the foliar contact activity against bean aphid of compound **7h** at 2.5 mg kg^{-1} was 89%, the larvacidal activity against mosquito of compound **6c** at 2.5 μg kg^{-1} was 100%, the larvacidal activity against diamondback moth of compound **7a** at 5 mg kg^{-1} was 87%, and all of these activities were much higher than the contrast ethiprole. The bioactivity against bean aphid and diamondback moth also showed that the two pairs of enantiomers **7d-1** and **7d-2** gave activities without distinctive

difference, and it was a similar situation for **7e-1** and **7e-2** against bean aphid and diamondback moth. Moreover, the target compounds exhibited high selectivity between diamondback moth and oriental armyworm, both of which are of the order *Lepidoptera*. The results of insecticidal activities also suggested that the structural requirement varied for different insect species, for instance, compound **6c** exhibited high activity against mosquito but relatively low activity against bean aphid and diamondback moth. The 2,2,2-trichloro-1-alkoxyethyl moiety was essential for high insecticidal activities.

LITERATURE CITED

(1) Cole, L. M.; Nicholson, R. A.; Casida, J. E. Action of phenylpyrazole insecticides at the GABA-gated chloride channel. *Pestic. Biochem. Physiol.* **1993**, *46*, 47–54.

(2) Casida, J. E. Insecticide action at the GABA-gated chloride channel: recognition, progress, and prospects. *Arch. Insect Biochem. Physiol.* **1993**, *22*, 13–23.

(3) Gant, D. B.; Chalmers, A. E.; Wolff, M. A.; Hoffman, H. B.; Bushey, D. F. Fipronil: action at the GABA receptor. *Rev. Toxicol.* **1998**, *2*, 147–156.

(4) Caboni, P.; Sammelson, R. E.; Casida, J. E. Phenylpyrazole insecticide photochemistry, metabolism, and GABAergic action: Ethiprole compared with fipronil. *J. Agric. Food Chem.* **2003**, *51*, 7055–7061.

(5) Colliot, F.; Kukorowski, K. A.; Hawkins, D. W.; Roberts, D. A. Fipronil: a new soil and foliar broad spectrum insecticide. *Brighton Crop Protection Conference-Pests and Diseases*; British Crop Protection Council: Farnham, U.K., 1992; Vol. 1, pp 29−34.

(6) Dryden, M. W.; Denenberg, T. M.; Bunch, S. Control of fleas on naturally infested dogs and cats and in private residences with topical spot applications of fipronil or imidacloprid. *Vet. Parasitol.* **2000**, *93*, 69–75.

(7) Wu, T.-T. Pesticidal 5-amino-4-ethylsulfinyl-1-arylpyrazoles. US 5,814,652, 1998.

(8) Arthur, F. H. Efficacy of ethiprole applied alone and in combination with conventional insecticides for protection of stored wheat and stored corn. *J. Econ. Entomol.* **2002**, *95*, 1314–1318.

(9) Huang, J.; Ayad, H. M.; Timmons, Philip R. Preparation of 1-aryl-5-(arylalkylideneimino)- pyrazoles as pesticides. EP 511845, 1992.

(10) Phillips, J.; Pilato, M.; Wu, T. Preparation of arylpyrazoles as pesticides. WO 9828277, 1998.

(11) Okui, S.; Kyomura, N.; Fukuchi, T.; Tanaka, K.; Katsurada, M.; Okano, K.; Sumitani, N.; Miyauchi, A.; Yabe, A. Preparation of 4-amino-1-phenyl-3-cyanopyrazole derivatives and process for producing the same, and pesticides containing the same as the active ingredient. WO 2001000614, 2001.

(12) Okui, S.; Kyomura, N.; Fukuchi, T.; Okano, K.; He, L.; Miyauchi, A. Preparation process of pyrazole derivatives in pest controllers containing the same as the active ingredient. WO 2002010153, 2002.

(13) Liu, W. P.; Zhou, S. S.; Zhang, D. T.; Li, S. Q. Preparation of phosphoramide organophosphorus compound. CN 101139360, 2008.

(14) Zhou, S. S.; Wang, L. M.; Li, L.; Liu, W. P. Stereoisomeric separation and bioassay of a new organophosphorus compound, *O*,*S*-dimethyl-*N*-(2,2,2-trichloro-1-methoxyethyl)phosphoramidothioate: some implications for chiral switch. *J. Agric. Food Chem.* **2009**, *57*, 6920–6926.

(15) Xu, H.; Song, Y. Q.; Zhai, J.; Zhan, Z. Q. Conditions of synthesis of rosone using benzene-anhydrous trichloroacetaldehyde method. *Gansu Gongye Daxue Xuebao* **2000**, *26* (3), 113−116 (Chinese).

(16) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.

(17) Luo, Y. P.; Yang, G. F. Discovery of a new insecticide lead by optimizing a target-diverse scaffold: tetrazolinone derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 1716–1724.

(18) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C. Insecticidal benzoyl phenylurea-S-carbamate: a new propesticide with two effects of both benzoylphenylureas and carbamates. *J. Agric. Food Chem.* **2007**, *55*, 2659–2663.

(19) Dai, H.; Li, Y. Q.; Du, D.; Qin, X.; Zhang, X.; Yu, H. B.; Fang, J. X. Synthesis and biological activities of novel pyrazole oxime derivatives containing a 2-chloro-5-thiazolyl moiety. *J. Agric. Food Chem.* **2008**, *56*, 10805–10810.

(20) Raymond, M.; Marquine, M. Evolution of insecticide resistance in *Culex pipiens* polulations: the Corsican paradox. *J. Evol. Biol.* **1994**, *7*, 315–337.

(21) Sun, R. F.; Zhang, Y. L.; Chen, L.; Li, Y. Q.; Li, Q. S.; Song, H. B.; Huang, R. Q.; Bi, F. C.; Wang, Q. M. Design, Synthesis and Insecticidal Activities of New N-Benzoyl-N′-phenyl-N′-sulfenylureas. *J. Agric. Food Chem.* **2009**, *57*, 3661–3668.

(22) Sayyed, A. H.; Ferre, J.; Wright, D. J. Mode of inheritance and stability of resistance to Bacillus thuringiensis var kurstaki in a diamondback moth (*Plutella xylostella*) population from Malaysia. *Pest Manage. Sci.* **2000**, *56*, 743–748.

(23) Mao, C. H.; Wang, Q. H.; Huang, R. Q.; Bi, F. C.; Chen, L.; Liu, Y. X.; Shang, J. Synthesis and insecticidal evaluation of novel *N*-oxalyl derivatives of tebufenozide. *J. Agric. Food Chem.* **2004**, *52*, 6737–6741.

(24) Zhao, Q. Q.; Shang, J.; Liu, Y. X.; Wang, K. Y.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. Synthesis and Insecticidal Activities of Novel *N*-Sulfenyl-*N*′-tert-butyl-*N*,*N*′-diacylhydrazines. 1. *N*-Alkoxysulfenate Derivatives. *J. Agric. Food Chem.* **2007**, *55*, 9614–9619.

(25) Tang, R. T.; Zhong, P.; Lin, Q. L. A convenient conversion of pyrazolyl disulfide to sulfides by sodium dithionite and synthesis of sulfoxides. *J. Fluorine Chem.* **2006**, *127*, 948–953.

Received for review January 16, 2010. Revised manuscript received March 13, 2010. Accepted March 19, 2010. We gratefully acknowledge the support of this work by the National Key Project for Basic Research (2010CB126106).