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Synthesis and Biological Activities of Novel Pyrazole Oxime Derivatives Containing a 2-Chloro-5-thiazolyl Moiety

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A series of novel pyrazole oxime derivatives containing a 2-chloro-5-thiazolyl moiety were synthesized. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis. The preliminary bioassays showed that all of the title compounds had low acaricidal activity against *Tetranychus cinnabarinus*. However, most of them exhibited excellent insecticidal activity against *Aphis medicagini* at the dosage of 0.5 mg/mL, and some compounds still showed good insecticidal activity against *A. medicagini* even at the dosage of 0.2 mg/mL. Meanwhile, some title compounds displayed fungicidal and plant growth regulatory activities.

KEYWORDS: Pyrazole; oxime; 2-chloro-5-thiazolyl; biological activity; synthesis

INTRODUCTION

Recently, pyrazole oxime derivatives have attracted considerable attention in chemical and medicinal research because of their diverse bioactivities. They are widely used as fungicide, insecticide, acaricide, and antitumor agents (*1*−*5*). Among these compounds, Fenpyroximate (**Figure 1**) was a potent acaricide developed by Nihon Nohyaku Co., Ltd., in Japan in 1991, which showed not only acaricidal but also knockdown activity against agriculturally important phytophagous mites, such as *Polyphagotarsonemus latus* Banks and *Tetranychus urticae* Koch. Fenpyroximate is currently used for the control of mites on various crops (*6, 7*). However, several field populations of *T. urticae* have already developed high levels of Fenpyroximate resistance despite its short-term use, and chemists have begun to study cross-resistance patterns of Fenpyroximate-resistant *T. urticae*, structural modification of Fenpyroximate, and corresponding effects on the biological activities (*8*−*11*).

On the other hand, the thiazole unit plays an important role in many biologically active compounds. Numerous thiazole-based derivatives have been found to exhibit antibiotic, anticancer, fungicidal, insecticidal, and herbicidal activities (*12*−*17*). For example, Thifluzamide and ethaboxam are well-known as agricultural fungicides (*18, 19*). Also, thiamethoxam and clothianidin (**Figure 1**), types of neonicotinoid insecticides, have been increasingly used in the fields of crop protection and animal health because of their low mammalian toxicity and broad insecticidal spectra (*20*−*23*). More recently, Wang and coworkers reported the synthesis of novel 2-cyanoacrylates **B** (**Figure 1**) and replaced the chlorophenyl group of compound **A** (**Figure 1**) with the 2-chloro-5-thiazolyl moiety, resulting in higher herbicidal activity and broader herbicidal spectra (*24*), so we have reason to believe that the 2-chloro-5-thiazolyl group can be used as an important skeleton in exploring novel bioactive molecules.

Motivated by the aforementioned findings, we conceived that replacement of the esterified phenyl group of Fenpyroximate with a 2-chloro-5-thiazolyl moiety and introduction of the CF_3 group to Fenpyroximate might result in new compounds with good biological activities (**Figure 2**). In this paper, we describe the synthesis and biological activities of novel pyrazole oxime derivatives **1** containing a 2-chloro-5-thiazolyl moiety.

MATERIALS AND METHODS

Synthetic Procedures. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AC-P 300 spectrometer (300 MHz, ^{1}H; 75 MHz, ^{13}C) in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instrument Co., Beijing, China) and are uncorrected. Elemental analyses were determined on a Yanaco CHN Corder MT-3 elemental analyzer. All reagents were of analytical reagent grade or were chemically pure. All solvents were dried by standard methods and distilled prior to use. Ethyl 4,4,4-trifluoroacetoacetate (**5**) was prepared by the reaction of ethyl acetate with ethyl trifluoroacetate according to a reported procedure (*25*). 2,3-Dichloro-1-propene (**2**) was purchased from Acros.

Synthesis of 2-Chloro-2-propenyl Isothiocyanate (3). A mixture of 2,3-dichloro-1-propene (20.1 g, 0.18 mol) and sodium thiocyanate (15.4 g, 0.19 mol) in toluene (80 mL) was heated to reflux for 5 h and cooled to room temperature. After the addition of water (50 mL), the reaction mixture was allowed to stand for 30 min, and the organic layer was dried over anhydrous magnesium sulfate. After the solvent had been removed under reduced pressure, the residue was distilled under

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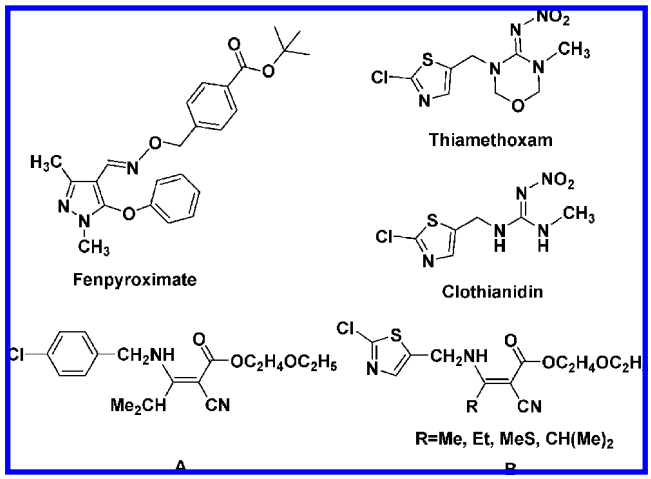


Figure 1. Structures of Fenpyroximate, thiamethoxam, clothianidin, and cyanoacrylates A and B.

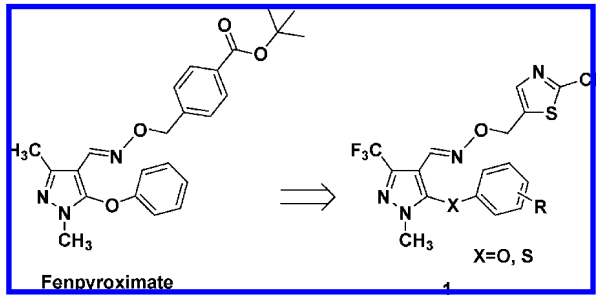
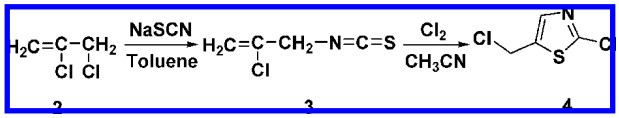
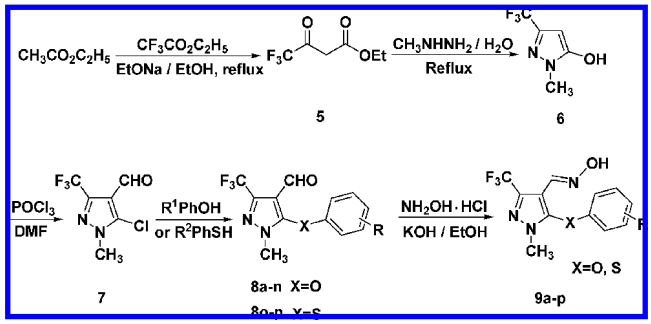


Figure 2. Designed strategy of the target compounds.

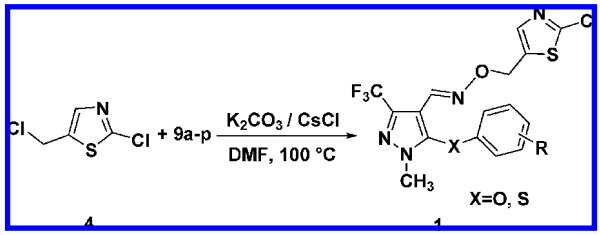
Scheme 1



Scheme 2



Scheme 3



reduced pressure to afford 2-chloro-2-propenyl isothiocyanate (**3**) in 75.2% yield as a brown oil, which was used for the following transformations without further purification.

Synthesis of 2-Chloro-5-chloromethylthiazole (4). To a solution of 2-chloro-2-propenyl isothiocyanate (17.5 g, 0.13 mol) in acetonitrile (45 mL) was introduced chlorine (12.1 g, 0.17 mol) while the temperature was maintained at 10 °C. Then the reaction mixture was stirred at 25 °C for 4 h. After most of the solvent had been evaporated under reduced pressure, the residue was admixed with warm water (20 mL) and extracted with ethyl acetate (3 × 40 mL).The combined organic layer was washed with water (3 × 20 mL) and dried over anhydrous magnesium sulfate. After the removal of the solvent, the residue was further distilled under reduced pressure to give 2-chloro-5-chloromethylthiazole (**4**) in 80.6% yield as a yellow oil: ^{1}H NMR ($CDCl_3$), δ 4.74 (s, 2H, CH_2), 7.36 (s, 1H, C═CH).

Synthesis of 1-Methyl-5-hydroxy-3-(trifluoromethyl)pyrazole (6). Under nitrogen atmosphere, the solution of 40% methylhydrazine (13.8 g, 0.12 mol) was heated to 65 °C, and then ethyl 4,4,4-trifluoroacetoacetate (18.4 g, 0.10 mol) was added dropwise to the above mixture. The reaction mixture was maintained at 65 °C for 3 h, and then it was heated to reflux for another 5 h. The solvent was evaporated under reduced pressure to afford a yellow solid, which was recrystallized from ethanol to afford compound **6** (14.11 g, 85.3%) as a solid: ^{1}H NMR ($CDCl_3$), δ 5.80 (s, 1H, C═CH), 3.79 (s, 3H, N—CH_3).

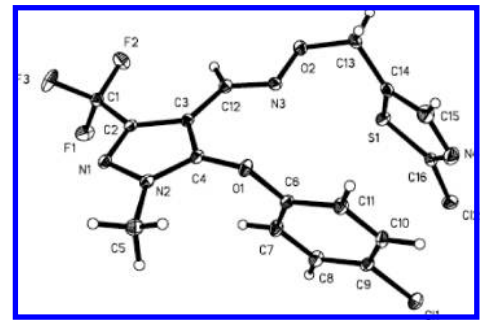


Figure 3. Molecular structure of compound **1g**.

Table 1. Insecticidal Activities of Compounds **1a**—**p** (Mortality, %)[a]

			A. medicagini		*T. cinnabarinus*
compd	X	R	0.5 mg/mL	0.2 mg/mL	0.2 mg/mL
1a	O	2-Me	90.4 ± 2.9	81.3 ± 2.7	9.3 ± 2.0
1b	O	3-Me	93.1 ± 2.1	82.4 ± 2.1	2.3 ± 0.8
1c	O	4-Me	95.3 ± 1.8	85.4 ± 3.9	3.4 ± 1.1
1d	O	4-F	90.2 ± 2.2	75.3 ± 3.5	13.4 ± 1.6
1e	O	2-Cl	59.3 ± 4.7	46.1 ± 4.0	6.2 ± 1.2
1f	O	3-Cl	70.4 ± 3.4	61.2 ± 4.6	7.4 ± 1.4
1g	O	4-Cl	92.3 ± 2.9	84.4 ± 2.6	na[c]
1h	O	4-Br	90.4 ± 3.1	77.4 ± 3.2	4.3 ± 1.3
1i	O	H	41.4 ± 4.2	20.2 ± 3.6	11.2 ± 2.5
1j	O	4-OMe	92.2 ± 2.0	83.4 ± 4.2	13.4 ± 0.6
1k	O	4-t-Bu	89.4 ± 2.6	73.3 ± 3.4	na[c]
1l	O	3,4-Me_2	71.2 ± 4.2	61.4 ± 4.2	6.4 ± 1.3
1m	O	6-Cl-3-Me	83.4 ± 3.3	69.2 ± 3.6	17.4 ± 2.4
1n	O	2,4-Cl_2	97.4 ± 2.3	86.3 ± 2.8	7.2 ± 1.6
1o	S	H	92.2 ± 2.8	83.4 ± 3.6	14.4 ± 1.3
1p	S	4-Cl	91.4 ± 3.1	80.4 ± 3.3	11.3 ± 1.1
A[b]			94.7 ± 2.2	92.1 ± 2.8	nt[d]
B[b]			18.4 ± 2.4	12.4 ± 1.6	99.7 ± 1.5

[a] Each value represents the mean ± SD of three experiments. [b] A and B refer to imidacloprid and fenpyroximate, respectively. [c] Effects can be neglected. [d] Not tested.

Table 2. Toxicities against *Aphis medicagini* of Compounds **1n**, **1p**, Imidacloprid, and Fenpryoximate

compd	regression eq	LC_{50} (CI_{95})[a] (μg/mL)	r^b
1n	$y = 3.18 + 1.34x$	22.9 (16.2—32.3)	0.993
1p	$y = 3.01 + 1.40x$	26.2 (19.2—35.7)	0.996
A[c]	$y = 4.12 + 0.92x$	9.1 (5.4—15.4)	0.991
B[c]	$y = -0.26 + 1.80x$	847.4 (649.8—1105.1)	0.990

[a] LC_{50} and CI_{95} refer to median lethal concentration and 95% confidence interval, respectively. [b] r refers to correlative coefficient. [c] A and B refer to imidacloprid and fenpyroximate,respectively.

Table 3. Fungicidal and Plant Growth Regulatory Activities of Compounds **1a**−**p**

compd	growth inhibition[a] (%, 50 μg/mL)					rhizogenesis[a] (%, 10 μg/mL)
	G. zeae	*A. solani*	*C. rachidicola*	*P. piricola*	*C. cucumerium*	
1a	21.2 ± 1.9	42.6 ± 2.8	10.0 ± 1.8	35.0 ± 3.2	32.6 ± 4.2	−26.8 ± 3.0
1b	33.6 ± 2.0	28.0 ± 2.5	11.8 ± 2.1	45.3 ± 4.5	31.3 ± 3.2	22.7 ± 2.3
1c	23.8 ± 3.8	34.6 ± 3.2	5.9 ± 1.2	21.0 ± 2.1	15.7 ± 2.5	43.6 ± 4.1
1d	29.0 ± 2.2	26.9 ± 2.8	67.2 ± 3.3	24.2 ± 3.2	53.4 ± 4.3	28.6 ± 3.6
1e	24.6 ± 1.3	na[c]	12.6 ± 3.2	23.6 ± 2.5	23.7 ± 2.7	53.9 ± 4.1
1f	26.7 ± 2.3	22.9 ± 2.1	55.3 ± 4.2	21.7 ± 3.5	43.1 ± 4.4	14.2 ± 1.1
1g	36.3 ± 2.7	na	11.8 ± 2.1	32.1 ± 3.8	15.4 ± 2.3	−34.3 ± 3.2
1h	41.6 ± 3.6	12.4 ± 0.9	9.2 ± 1.8	32.9 ± 3.2	17.5 ± 3.2	48.5 ± 4.5
1i	22.4 ± 1.2	65.6 ± 3.5	8.7 ± 1.2	30.3 ± 2.3	21.6 ± 3.6	−12.5 ± 2.1
1j	na	14.6 ± 2.3	22.6 ± 2.6	46.5 ± 3.7	12.3 ± 1.4	30.8 ± 3.4
1k	12.5 ± 0.9	24.8 ± 3.2	na	22.1 ± 2.5	18.1 ± 1.6	72.7 ± 2.0
1l	31.3 ± 1.2	53.2 ± 3.1	32.9 ± 2.1	26.2 ± 3.2	8.9 ± 0.9	−23.8 ± 3.1
1m	na	32.3 ± 2.5	10.1 ± 1.8	29.8 ± 3.6	48.5 ± 3.0	37.9 ± 5.0
1n	24.3 ± 1.5	29.2 ± 3.9	42.5 ± 4.2	na	32.3 ± 3.5	72.3 ± 2.8
1o	40.8 ± 3.2	43.5 ± 3.8	12.7 ± 2.1	29.5 ± 2.5	9.7 ± 1.6	21.8 ± 2.4
1p	32.6 ± 3.6	28.8 ± 2.6	25.8 ± 2.3	42.4 ± 4.2	18.9 ± 0.9	34.7 ± 4.8
B[b]	5.2 ± 1.3	8.3 ± 2.1	12.5 ± 1.4	6.7 ± 0.8	14.5 ± 1.2	10.6 ± 0.7
C[b]	72.6 ± 3.6	66.1 ± 2.7	73.4 ± 2.3	86.7 ± 3.2	81.5 ± 2.6	50.2 ± 3.4

[a] Each value represents the mean ± SD of three experiments. [b] B and C refer to fenpyroximate and triadimefon, respectively. [c] Effects can be neglected.

Synthesis of 5-Chloro-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxaldehyde (7). To a violently stirred cold (−5 °C) solution of DMF (8.80 g, 0.12 mol) was added dropwise phosphorus oxychloride (27.83 g, 0.18 mol). The resulting mixture was stirred at room temperature for 1 h. To the above mixture was added compound **6** (10.02 g, 0.06 mol) in portions, then it was heated to 55 °C for 2 h and stirred at 100 °C for another 5 h. After cooling to room temperature, the mixture was poured into ice−water (200 mL), and the resulting precipitate was collected by filtration; the filtrate was continuously extracted with dichloromethane (4 × 50 mL), and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a brown solid. The solid obtained in two portions was collected together. Recrystallization from ethyl acetate/petroleum ether (60−90 °C) gave compound **7** (10.42 g, 81.7%) as a yellow solid: mp, 41−43 °C; ^{1}H NMR ($CDCl_3$), δ 9.86 (s, 1H, CHO), 3.86 (s, 3H, N−CH_3). Anal. Calcd for $C_6H_4ClF_3N_2O$: C, 33.90; H, 1.90; N, 13.18. Found: C, 33.81; H, 1.96; N, 13.22.

General Synthetic Procedures for Substituted 5-Phenoxy-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxaldehyde (8a−n). To a well-stirred solution of substituted phenol (12 mmol) in DMSO (30 mL) was added powdered potassium hydroxide (15 mmol) in one portion at room temperature. The mixture was warmed to 55−60 °C and stirred for 2 h. To the above mixture was added compound **7** (10 mmol) in portions. Then, the solution was heated to 105 °C and maintained at this temperature for 2 h. The cooled mixture was poured into ice−water (50 mL) and allowed to stand overnight. The precipitate was collected by filtration and washed with water (4 × 30 mL) and hexane (4 × 20 mL). The tan solid was dried under vacuum at 40 °C for 3 h, yielding the corresponding product as a light brown solid.

General Synthetic Procedures for Substituted 5-Phenylthio-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxaldehyde (8o,p). To powdered potassium hydroxide (13 mmol) was added water (10 mL), and the mixture was stirred for 15 min at room temperature; then a solution of substituted benzenethiol (11 mmol) in DMF (30 mL) was added thereto. The resulting solution was heated to 55 °C and stirred for 50 min. Followed by addition of compound **7** (10 mmol), the reaction mixture was stirred at 110 °C for 5 h, cooled, and poured into ice−water (50 mL). The precipitate was filtered to give a brown solid, which was washed with water and petroleum ether. The solid was dried under vacuum at 40 °C for 2 h, affording the corresponding product.

General Synthetic Procedures for Pyrazole Oximes 9a−p. A solution of compound **8** (10 mmol) in ethanol (12 mL) was added dropwise to a mixture of hydroxylamine hydrochloride (15 mmol), potassium hydroxide (20 mmol), and ethanol (12 mL) at 10 °C. The mixture was then heated to reflux for 4 h and cooled to room temperature. The reaction mixture was poured into water (200 mL) and extracted with dichloromethane (4 × 40 mL). The organic layer was washed with saturated brine (3 × 20 mL) and dried over anhydrous sodium sulfate. Dichloromethane was evaporated to afford the corresponding oxime **9**, which was used for the following transformations without further purification.

General Synthetic Procedures for Target Compounds 1a−p. To a stirred solution of intermediate **9** (5 mmol), compound **4** (6 mmol), and powdered potassium carbonate (14 mmol) in anhydrous DMF (25 mL) was added a catalytic amount of cesium chloride at room temperature. The mixture was stirred at 100 °C for 5−6 h. On completion, the mixture was poured into water (150 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic layer was washed with 10% sodium carbonate solution (3 × 20 mL) and then with brine (3 × 20 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography using a mixture of petroleum ether (60−90 °C) and ethyl acetate as an eluent to obtain the target compounds **1a**−**p**.

Data for **1a**: yield, 65.4%; mp, 85−87 °C; ^{1}H NMR ($CDCl_3$), δ 2.40 (s, 3H, Ar−CH_3), 3.76 (s, 3H, N−CH_3), 4.91 (s, 2H, CH_2), 6.46 (d, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.07−7.11 (m, 2H, ArH), 7.24−7.27 (m, 2H, ArH and C=CH), 7.89 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$), δ 16.1 (Ar−CH_3), 35.1 (N−CH_3), 67.7 (OCH_2), 100.3 (4-HetC), 112.9, 122.5 (CF_3), 124.0, 126.1, 126.7, 127.2, 131.8, 136.7 (5-HetC), 139.4, 140.1 (3-HetC), 147.8, 152.8 (CH=N), 154.1. Anal. Calcd for $C_{17}H_{14}ClF_3N_4O_2S$: C, 47.39; H, 3.28; N, 13.00. Found: C, 47.26; H, 3.35; N, 12.82.

Data for **1b**: yield, 75.6%; mp, 60−62 °C; ^{1}H NMR ($CDCl_3$), δ 2.35 (s, 3H, Ar−CH_3), 3.75 (s, 3H, N−CH_3), 4.94 (s, 2H, CH_2), 6.68 (s, 1H, ArH), 6.76 (d, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 6.96−7.23 (m, 2H, ArH), 7.28 (s, 1H, C=CH), 7.92 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$), δ 20.6 (Ar−CH_3), 35.3 (N−CH_3), 67.7 (OCH_2), 100.6 (4-HetC), 112.2, 114.9, 119.0, 124.9 (CF_3), 129.8, 130.5, 133.8, 136.6 (5-HetC), 139.3, 140.3 (3-HetC), 146.3, 152.9 (CH=N), 155.9. Anal. Calcd for $C_{17}H_{14}ClF_3N_4O_2S$: C, 47.39; H, 3.28; N, 13.00. Found: C, 47.21; H, 3.16; N, 13.12.

Data for **1c**: yield, 80.7%; mp, 89−91 °C; ^{1}H NMR ($CDCl_3$), δ 2.35 (s, 3H, Ar−CH_3), 3.74 (s, 3H, N−CH_3), 4.95 (s, 2H, CH_2), 6.77 (d, $^3J_{HH}$ = 8.4 Hz, 2H, ArH), 7.14 (d, $^3J_{HH}$ = 8.4 Hz, 2H, ArH), 7.28 (s, 1H, C=CH), 7.91 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$), δ 20.6 (Ar−CH_3), 35.3 (N−CH_3), 67.7 (OCH_2), 100.6 (4-HetC), 115.0, 118.9, 122.5 (CF_3), 130.5, 133.8, 136.6 (5-HetC), 139.3, 140.3 (3-HetC), 147.7, 152.8 (CH=N), 153.8. Anal. Calcd for $C_{17}H_{14}ClF_3N_4O_2S$: C, 47.39; H, 3.28; N, 13.00. Found: C, 47.28; H, 3.37; N, 12.91.

Data for **1d**: yield, 73.8%; mp, 80−82 °C; ^{1}H NMR ($CDCl_3$), δ 3.77 (s, 3H, N−CH_3), 4.93 (s, 2H, CH_2), 6.83−6.87 (m, 2H, ArH), 7.05 (t, $^3J_{HH}$ = 8.1 Hz, 2H, ArH), 7.30 (s, 1H, C=CH), 7.92 (s, 1H,

CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.7 (OCH_2), 100.6 (4-HetC), 116.4, 116.5, 116.8, 118.9, 122.4 (CF_3), 136.5 (5-HetC), 139.2, 140.3 (3-HetC), 147.3, 151.7, 152.9 (CH═N), 157.4, 160.6. Anal. Calcd for $C_{16}H_{11}ClF_4N_4O_2S$: C, 44.20; H, 2.55; N, 12.89. Found: C, 44.18; H, 2.67; N, 12.72.

Data for **1e***:* yield, 65.4%; mp, 64−66 °C; ^{1}H NMR ($CDCl_3$), δ 3.80 (s, 3H, N—CH_3), 4.93 (s, 2H, CH_2), 6.64 (d, $^3J_{HH}$ = 7.8 Hz, 1H, ArH), 7.13−7.20 (m, 2H, ArH), 7.27 (s, 1H, C═CH), 7.49 (d, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.93 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.8 (OCH_2), 100.6 (4-HetC), 115.1, 118.9, 122.4 (CF_3), 122.9, 125.0, 127.9, 131.8, 136.6 (5-HetC), 139.1, 140.2 (3-HetC), 146.8, 151.2, 152.7 (CH═N); Anal. Calcd for $C_{16}H_{11}Cl_2F_3N_4O_2S$: C, 42.59; H, 2.46; N, 12.42. Found: C, 42.69; H, 2.62; N, 12.31.

Data for **1f***:* yield, 72.5%; mp, 59−61 °C; ^{1}H NMR ($CDCl_3$), δ 3.77 (s, 3H, N—CH_3), 4.92 (s, 2H, CH_2), 6.76 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 2.1 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 7.16 (d, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.25−7.30 (m, 2H, ArH and C═CH), 7.94 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.8 (OCH_2), 100.8 (4-HetC), 113.4, 116.0, 118.8, 122.4 (CF_3), 124.5, 130.8, 135.6, 136.5 (5-HetC), 139.2, 140.2 (3-HetC), 146.6, 152.8 (CH═N), 156.2. Anal. Calcd for $C_{16}H_{11}Cl_2F_3N_4O_2S$: C, 42.59; H, 2.46; N, 12.42. Found: C, 42.46; H, 2.52; N, 12.47.

Data for **1g***:* yield, 76.7%; mp, 90−92 °C; ^{1}H NMR ($CDCl_3$), δ 3.76 (s, 3H, N—CH_3), 4.92 (s, 2H, CH_2), 6.83 (d, $^3J_{HH}$ = 8.7 Hz, 2H, ArH), 7.29 (d, $^3J_{HH}$ = 9.0 Hz, 2H, ArH), 7.33 (s, 1H, C═CH), 7.93 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.8 (OCH_2), 100.7 (4-HetC), 116.6, 118.9, 122.4 (CF_3), 129.4, 130.0, 136.5 (5-HetC), 139.2, 140.4 (3-HetC), 146.9, 152.9 (CH═N), 154.3. Anal. Calcd for $C_{16}H_{11}Cl_2F_3N_4O_2S$: C, 42.59; H, 2.46; N, 12.42. Found: C, 42.45; H, 2.57; N, 12.29.

Data for **1h***:* yield, 75.3%; mp, 101−103 °C; ^{1}H NMR ($CDCl_3$), δ 3.76 (s, 3H, N—CH_3), 4.92 (s, 2H, CH_2), 6.79 (d, $^3J_{HH}$ = 9.0 Hz, 2H, ArH), 7.30 (s, 1H, C═CH), 7.46 (d, $^3J_{HH}$ = 9.0 Hz, 2H, ArH), 7.93 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.7 (OCH_2), 100.7 (4-HetC), 117.0, 118.8, 122.4 (CF_3), 133.0, 136.4 (5-HetC), 138.7, 139.1, 140.4 (3-HetC), 146.8, 152.9 (CH═N), 154.9. Anal. Calcd for $C_{16}H_{11}BrClF_3N_4O_2S$: C, 38.77; H, 2.24; N, 11.30. Found: C, 38.64; H, 2.37; N, 11.22.

Data for **1i***:* yield, 72.6%; mp, 79−81 °C; ^{1}H NMR ($CDCl_3$), δ 3.76 (s, 3H, N—CH_3), 4.91 (s, 2H, CH_2), 6.88 (d, $^3J_{HH}$ = 8.1 Hz, 2H, ArH), 7.17 (t, $^3J_{HH}$ = 7.2 Hz, 1H, ArH), 7.25 (s, 1H, C═CH), 7.36 (t, $^3J_{HH}$ = 7.8 Hz, 2H, ArH), 7.92 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.7 (OCH_2), 100.7 (4-HetC), 115.2, 118.9, 122.5 (CF_3), 124.1, 130.1, 136.6 (5-HetC), 139.3, 140.3 (3-HetC), 147.3, 152.8 (CH═N), 155.8. Anal. Calcd for $C_{16}H_{12}ClF_3N_4O_2S$: C, 46.11; H, 2.90; N, 13.44. Found: C, 46.23; H, 2.82; N, 13.30.

Data for **1j***:* yield, 82.3%; mp, 89−91 °C; ^{1}H NMR ($CDCl_3$), δ 3.75 (s, 3H, N—CH_3), 3.80 (s, 3H, OCH_3), 4.96 (s, 2H, CH_2), 6.81 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ArH), 6.86 (d, $^3J_{HH}$ = 9.6 Hz, 2H, ArH), 7.30 (s, 1H, C═CH), 7.90 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 55.7 (OCH_3), 67.7 (OCH_2), 100.4 (4-HetC), 114.9, 116.2, 118.9, 122.5 (CF_3), 136.6 (5-HetC), 138.4, 138.9, 139.3, 140.3 (3-HetC), 148.0, 149.8, 152.8 (CH═N), 156.1. Anal. Calcd for $C_{17}H_{14}ClF_3N_4O_3S$: C, 45.70; H, 3.16; N, 12.54. Found: C, 45.58; H, 3.27; N, 12.37.

Data for **1k***:* yield, 81.5%; mp, 76−78 °C; ^{1}H NMR ($CDCl_3$), δ 1.31 (s, 9H, C(CH_3)$_3$), 3.75 (s, 3H, N—CH_3), 4.91 (s, 2H, CH_2), 6.81 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ArH), 7.29 (s, 1H, C═CH), 7.35 (d, $^3J_{HH}$ = 7.5 Hz, 2H, ArH), 7.89 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 31.4 (C($\underline{C}H_3$)$_3$), 34.4 ($\underline{C}$(CH_3)$_3$), 35.3 (N—CH_3), 67.6 (OCH_2), 100.5 (4-HetC), 114.7, 118.9, 122.5 (CF_3), 126.8, 136.5 (5-HetC), 139.2, 140.5 (3-HetC), 147.2, 147.9, 152.9 (CH═N), 153.7. Anal. Calcd for $C_{20}H_{20}ClF_3N_4O_2S$: C, 50.79; H, 4.26; N, 11.85. Found: C, 50.62; H, 4.37; N, 11.89.

Data for **1l***:* yield, 71.7%; mp, 63−65 °C; ^{1}H NMR ($CDCl_3$), δ 2.24 (s, 6H, 2 × Ar—CH_3), 3.73 (s, 3H, N—CH_3), 4.97 (s, 2H, CH_2), 6.59 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, ArH), 6.66 (d, $^4J_{HH}$ = 2.4 Hz, 1H, ArH), 7.07 (d, $^3J_{HH}$ = 8.1 Hz, 1H, ArH), 7.27 (s, 1H, C═CH), 7.91 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 19.0 (Ar—CH_3), 20.0 (Ar—CH_3), 35.3 (N—CH_3), 67.7 (OCH_2), 100.7 (4-HetC), 112.2, 116.2, 118.9, 122.5 (CF_3), 130.8, 132.4, 136.7 (5-HetC), 138.7, 139.4, 140.3 (3-HetC), 147.8, 152.9 (CH═N), 154.0. Anal. Calcd for $C_{18}H_{16}ClF_3N_4O_2S$: C, 48.60; H, 3.63; N, 12.59. Found: C, 48.67; H, 3.58; N, 12.41.

Data for **1m***:* yield, 70.8%; mp, 83−84 °C; ^{1}H NMR ($CDCl_3$), δ 2.36 (s, 3H, Ar—CH_3), 3.75 (s, 3H, N—CH_3), 4.95 (s, 2H, CH_2), 6.67 (d, $^3J_{HH}$ = 8.7 Hz, 1H, ArH), 6.76 (s, 1H, ArH), 7.29−7.32 (m, 2H, ArH and C═CH), 7.93 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 20.4 (Ar—CH_3), 35.3 (N—CH_3), 67.7 (OCH_2), 100.8 (4-HetC), 113.9, 117.4, 118.9, 122.4 (CF_3), 129.5, 130.3, 136.5 (5-HetC), 138.2, 139.2, 140.3 (3-HetC), 147.1, 152.9 (CH═N), 154.2. Anal. Calcd for $C_{17}H_{13}Cl_2F_3N_4O_2S$: C, 43.88; H, 2.82; N, 12.04. Found: C, 43.73; H, 2.74; N, 11.95.

Data for **1n***:* yield, 69.2%; mp, 56−58 °C; ^{1}H NMR ($CDCl_3$), δ 3.80 (s, 3H, N—CH_3), 4.94 (s, 2H, CH_2), 6.58 (d, $^3J_{HH}$ = 8.7 Hz, 1H, ArH), 7.16 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.4 Hz, 1H, ArH), 7.32 (s, 1H, C═CH), 7.50 (d, $^4J_{HH}$ = 2.4 Hz, 1H, ArH), 7.93 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 35.3 (N—CH_3), 67.9 (OCH_2), 100.6 (4-HetC), 116.0, 118.8, 122.3 (CF_3), 123.8, 127.9, 129.7, 130.8, 136.4 (5-HetC), 139.1, 140.3 (3-HetC), 146.4, 150.0, 152.9 (CH═N). Anal. Calcd for $C_{16}H_{10}Cl_3F_3N_4O_2S$: C, 39.57; H, 2.08; N, 11.54. Found: C, 39.62; H, 2.23; N, 11.46.

Data for **1o***:* yield, 82.6%; mp, 63−65 °C; ^{1}H NMR ($CDCl_3$), δ 3.89 (s, 3H, N—CH_3), 5.17 (s, 2H, CH_2), 7.04 (d, $^3J_{HH}$ = 7.2 Hz, 2H, ArH), 7.24−7.30 (m, 3H, ArH), 7.45 (s, 1H, C═CH), 8.15 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 37.8 (N—CH_3), 67.9 (OCH_2), 117.3 (4-HetC), 118.9, 122.5 (CF_3), 127.3, 127.5, 129.8, 133.1, 133.8, 136.5 (5-HetC), 140.6 (3-HetC), 140.7, 153.0 (CH═N). Anal. Calcd for $C_{16}H_{12}ClF_3N_4OS_2$: C, 44.39; H, 2.79; N, 12.94. Found: C, 44.32; H, 2.82; N, 12.81.

Data for **1p***:* yield, 75.2%; mp, 59−61 °C; ^{1}H NMR ($CDCl_3$), δ 3.90 (s, 3H, N—CH_3), 5.17 (s, 2H, CH_2), 6.98 (d, $^3J_{HH}$ = 8.1 Hz, 2H, ArH), 7.27 (d, $^3J_{HH}$ = 7.8 Hz, 2H, ArH), 7.46 (s, 1H, C═CH), 8.13 (s, 1H, CH═N); ^{13}C NMR ($CDCl_3$), δ 37.9 (N—CH_3), 67.9 (OCH_2), 117.5 (4-HetC), 118.9, 122.5 (CF_3), 128.9, 129.9, 131.6, 133.0, 133.5, 136.4 (5-HetC), 140.3 (3-HetC), 140.8, 153.1 (CH═N). Anal. Calcd for $C_{16}H_{11}Cl_2F_3N_4OS_2$: C, 41.12; H, 2.37; N, 11.99. Found: C, 41.05; H, 2.42; N, 12.06.

X-ray Diffraction. The crystal structure of compound **1g** was determined, and X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). θ_{max} = 25.02°, 3218 independent reflections were obtained. All calculations were refined anisotropically. All hydrogen atoms were located from a difference Fourier map, placed at calculated positions, and included in the refinements in the riding mode with isotropic thermal parameters.

Bioassay of Insecticidal Activities. The two insect species, carmine spider mites (*Tetranychus cinnabarinus*) and alfalfa aphids (*Aphis medicagini*), were provided by the Biological Assay Center, Nankai University, China. The insecticidal activities of compounds **1a**−**p** against *T. cinnabarinus* and *A. medicagini* were tested according to a reported procedure (*26*). These insects were placed in a room maintained at 26 °C and 60% relative humidity with a 14 h photoperiod. Stock solutions of each test sample was prepared in acetone at a concentration of 0.5 mg/mL 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 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 or size of live larvae in the treated bottles relative to that in the untreated controls after 48 h. Controls were performed under the same conditions. Each test was performed in triplicate. The data were subjected to probit analysis.

Bioassay of Fungicidal Activities. Inhibition effects of the title compounds **1a**−**p** on phytopathogenic fungi were studied according to a reported method (*27*). The five fungi used in the fungicidal bioassay, *Gibberella zeae*, *Alternaria solani*, *Physalospora piricola*, *Cercosporaa rachidicola*, and *Cladosporium cucumerium*, were obtained from the Biological Assay Center, Nankai University, China. The solution of each compound was prepared at a concentration of 500 μg/mL. Then the above solution (1 mL) was injected into glass Petri dishes, followed by the addition of agar culture medium (9 mL), and then formed some

plates of samples (50 μg/mL). An inoculum (4 mm diameter) was diverted from the fringes of active mycelium, and then put in the center of the above plates and incubated at 23 °C. The diameter of the mycelium was measured after 3 days, and a mixture of sterile water and culture medium was used as the blank control. Each experiment for one compound was triplicated. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibition rate (percent), C is the control settlement diameter, and T is the treatment group fungi settlement diameter.

Bioassay of Plant Growth Regulatory Activities. The plant growth regulatory activities of compounds **1a**−**p** were evaluated by means of cucumber cotyledon test according to a reported procedure (*28*). The cucumber seeds (JINKE, No. 4) were supplied by the Biological Assay Center, Nankai University, China. These seeds were incubated at 24 °C in a dark room for 3 days, and 10 pieces of cotyledons of the same size were selected. The test samples were dissolved in DMF at a concentration of 10 μg/mL. A sample solution (0.3 mL) was sprayed over a filter paper (6 cm diameter), and solvent was volatilized to dryness on air. The filter paper thus prepared was placed into an incubation vessel (6 cm diameter) and soaked with distilled water (3 mL). Finally, 10 pieces of cotyledons were added. These cotyledons were incubated at 24 °C in a dark room for 3 days. The rhizogenesis numbers of every 10 pieces of hypocotyls were measured. Each treatment was performed three times. In contrast, the distilled water was used as a control.

Statistical Analysis. The results were expressed as means ± standard deviation (SD) of three parallel experiments. Data were analyzed by Student's t test. The LC_{50} (median lethal concentration) was analyzed using probit analysis performed with the statistical software SAS.

RESULTS AND DISCUSSION

Synthesis. Intermediate 2-chloro-5-chloromethylthiazole (**4**) was synthesized from 2,3-dichloro-1-propene (**2**) as shown in **Scheme 1**. Compound **2** reacted with sodium thiocyanate to give 2-chloro-2-propenyl isothiocyanate (**3**) in good yield. Further reaction with chlorine afforded 2-chloro-5-chloromethylthiazole (**4**) in satisfactory yield (*29, 30*).

5-Chloro-1-methyl-3-(trifluoromethyl)-4-pyrazolecarboxaldehyde (**7**) was prepared from ethyl 4,4,4-trifluoroacetoacetate (**5**) as shown in **Scheme 2**. Compound **5** was easily condensed with 40% methylhydrazine to obtain 1-methyl-5-hydroxy-3-(trifluoromethyl)pyrazole (**6**) in 85.3% yield. Compound **6** was then subjected to the Vilsmeier−Haack chloroformylation using DMF and appropriate amounts of $POCl_3$ to afford the corresponding 5-chloro-4-formylpyrazole (**7**) in 81.7% yield, whereas the reported yield was 40% (*31*). Further introduction of nucleophiles (substituted phenols or benzenethiols) into compound **7** by nucleophilic aromatic substitution provided 5-substituted pyrazoles (**8**) in good yields (*32, 33*). We speculated that the facile introduction of nucleophiles into 5-chloropyrazole (**7**) was activated by the electron-withdrawing formyl substituent in the 4-position and the CF_3 group in the 3-position.

The treatment of 4-formylpyrazoles (**8**) with hydroxylamine hydrochloride using potassium hydroxide as alkali gave pyrazole oximes (**9**) without any problem (**Scheme 2**).

The reaction of intermediates **9** with **4** proceeded smoothly by the addition of a catalytic amount of cesium chloride and afforded the target compounds **1a**−**p** in satisfactory yields (**Scheme 3**). The structures of compounds **1a**−**p** were confirmed by ^{1}H NMR, ^{13}C NMR, and elemental analysis. In addition, the (*E*)-configuration of typical compound **1g** was established by X-ray single-crystal structure analysis. It can be seen from the single-crystal structure of compound **1g** that the substituted pyrazole ring and alkyloxy group are of the opposite sides of the C═N double bond (**Figure 3**). The torsion angle of C(3)—C(12)—N(3)—O(2) is 177.91(14)° (see the Supporting Information), which indicates that the C═N double bond is in the (*E*)-configuration.

Insecticidal Activities. The insecticidal activity results of the compounds **1a**−**p** against *T. cinnabarinus* and *A. medicagini* are shown in **Table 1**. Fenpyroximate and imidacloprid were used as controls. All of the title compounds showed lower activities against *T. cinnabarinus* at the dosage of 0.2 mg/mL, as compared with Fenpyroximate. Encouragingly, most of the designed compounds displayed excellent insecticidal activity against *A. medicagini* at the dosage of 0.5 mg/mL. For example, the mortalities of compounds **1a**, **1b**, **1c**, **1d**, **1g**, **1h**, **1j**, **1n**, **1o**, and **1p** were 90.4, 93.1, 95.3, 90.2, 92.3, 90.4, 92.2, 97.4, 92.2, and 91.4%, respectively, which were comparable to that of the control imidacloprid. Moreover, some of them still exhibited good insecticidal activity against *A. medicagini* when the concentration was reduced to 0.2 mg/mL, compounds **1a**, **1b**, **1c**, **1g**, **1j**, **1n**, **1o**, and **1p** having a >80% inhibition rate. From the data presented in **Table 1**, we found that among the chlorinated derivatives, the 4-substituted analogue **1g** showed a higher insecticidal activity than did the corresponding 2- and 3-substituted analogues (**1e** and **1f**); for example, compounds **1e**, **1f**, and **1g** exhibited 59.3, 70.4, and 92.3% insecticidal activity against *A. medicagini* at the dosage of 0.5 mg/mL, respectively. At the same time, the compounds containing a phenylthio moiety displayed insecticidal activity comparable to that of corresponding phenoxy analogues. In addition, **Table 2** showed the results of further toxicity assay about the typical candidates **1n**, **lp**, the parent compound Fenpyroximate, and the positive control imidacloprid against *A. medicagini*. The data listed in **Table 2** indicate that compounds **1n** and **1p** had much more potency against *A. medicagini* than Fenpyroximate, but had slightly less potency than the control imidacloprid, and the LC_{50} values of compounds **1n** and **1p**, Fenpyroximate, and imidacloprid were 22.9, 26.2, 847.4, and 9.1 μg/mL, respectively. All of the above results imply that structural modification of Fenpyroximate with a 2-chloro-5-thiazolyl moiety and a CF_3 group could afford some new compounds possessing potent insecticidal activity. Further studies on structural optimization and structure−activity relationships of these pyrazole oxime derivatives are in progress.

Fungicidal Activities. The five used fungi included *G. zeae*, *A. solani*, *P. piricola*, *C. rachidicola*, and *C. cucumerium*. The results of preliminary bioassays were compared with that of a commercial fungicide Triadimefon. As indicated in **Table 3**, some compounds exhibited potential fungicidal activities. For example, compounds **1i**, and **1l** showed 65.6 and 53.2% fungicidal activity against *A. solani*, respectively, and the inhibitory effect of **1i** on *A. solani* was comparable to that of the control Triadimefon (66.1%). Compounds **1d** and **1f** displayed 67.2 and 55.3% fungicidal activity against *C. rachidicola*, respectively. In addition, compounds **1d**, and **1m** exhibited 53.4 and 48.5% inhibitory activity against *C. cucumerium*, respectively.

Plant Growth Regulatory Activities. The plant growth regulatory activities of the title compounds **1a**−**p** were screened by cucumber cotyledon test at a concentration of 10 μg/mL. As shown in **Table 3**, some compounds, such as **1c**, **1e**, **1h**, **1k**, and **1n**, exhibited potential promoting activity, with values of 43.6, 53.9, 48.5, 72.7, and 72.3%, respectively. Interestingly, some compounds displayed certain inhibitory activity. For example, **1a** and **1g** showed 26.8 and 34.3% inhibition, respectively.

Supporting Information Available: Tables of crystal data and structure refinement, equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, and torsion angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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