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Synthesis, Insecticidal, and Acaricidal Activities of Novel 2-Aryl-pyrrole Derivatives Containing Ester Groups

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A series of novel 2-aryl-pyrrole derivatives containing ester groups were synthesized, and their structures were characterized by ^{1}H NMR spectroscopy and elemental analysis. The insecticidal activities against oriental armyworm, mosquito, diamondback moth, green rice leafhopper, and bean aphids and acaricidal activities against spider mite of these new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal and acaricidal activities. The insecticidal activities against oriental armyworm of compounds **IVa**, **IVd**, **IVe**, **IVf**, **IVg**, **IVi**, **IVk**, and **IVp** were equal to commercialized Chlorfenapyr, and the insecticidal activities of most of compounds **IVb**, **IVc**, **IVd**, **IVf**, **IVg**, **IVj**, **IVk**, **IVl**, **IVs**, **IVt**, **IVu**, **IVw**, **IVx**, **IVz**, and Chlorfenapyr against mosquito at 0.10 mg kg^{-1} were 100%, and the acaricidal activities of compounds **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVi**, and **IVk** were equal or superior to Chlorfenapyr. Especially, the results indicated that the acaricidal activity of [4-bromo-2-(4-chlorophenyl)-3-cyano-5-(trifluoromethyl)pyrrol-1-yl]methyl 3-methylbutanoate (**IVg**) against spider mite was 2.65-fold as high as that of Chlorfenapyr from the value of LC_{50}.

KEYWORDS: Aryl-pyrrole; Chlorfenapyr; ester group; insecticidal activity; acaricidal activity; oriental armyworm; mosquito; diamondback moth; green rice leafhopper; bean aphids; spider mite

INTRODUCTION

In 1987, the American Cyanamid Company isolated and identified dioxapyrrolomycin (**A**, **Figure 1**) from a *Streptomyces* strain and found that dioxapyrrolomycin exhibited moderate broad spectrum insecticidal and miticidal activities (*1*). At about the same time, this pyrrole **A** was also reported by Meiji Seika Kaisha and SS Pharmaceutical Company in Japan as an antibiotic (*2, 3*). However, an oral LD_{50} of 14 mg kg^{1-} to mice showed it to be highly toxic. Then, the American Cyanamid Company found that compound **B** (**Figure 1**) exhibited excellent activities against tobacco budworm and two-spotted spider mite and potato leafhopper. However, they once again found that compound **B** had severe phytotoxicity. To circumvent this problem, the American Cyanamid Company further prepared its derivative **C** by introduction of an ethoxymethyl group into compound **B** by substituting the hydrogen on the nitrogen atom and found that compound **C** retained the high insecticidal activity of the parent pyrrole **B** with none of the undesirable phytotoxic properties (*4*). The compound **C** (**Figure 1**) was the first to be commercialized as an insecticide−miticide under the trade name Chlorfenapyr (*5, 6*). It is a pro-insecticide activated by the oxidative in vivo removal of its *N*-ethoxymethyl group (*7*). Recently, its resistance has already been detected (*8*−*11*).

The activity spectrum of a pesticide is often determined by physical properties of compound, and it is possible to develop a compound of new style by attaching an appropriate functional group to a present insecticide. Moreover, the physical properties of an insecticidal compound may be manipulated to obtain products with other selected types of activity by proper selection of the derivative moiety (*12*). For example, it was reported that *N*-ester derivatives of diacylhydrazine (**D**, **Figure 1**) displayed an insecticidal activity comparable or superior to that of the parent compound (*13*). In our previous work, it was found that benzoylphenylureas derivatives containing an ester group (**E**, **Figure 1**) exhibited excellent larvicidal activity (*14*).

Encouraged by these reports, we developed an idea that the introduction of an ester group into 2-aryl-pyrrole **B** by substituting the hydrogen on the nitrogen atom could improve biological properties and decrease resistance. Therefore, in a search for new aryl-pyrrole insecticides with improved profiles, we designed and synthesized a series of novel 2-aryl-pyrrole derivatives containing ester groups as shown in **Schemes 2** and **3**.

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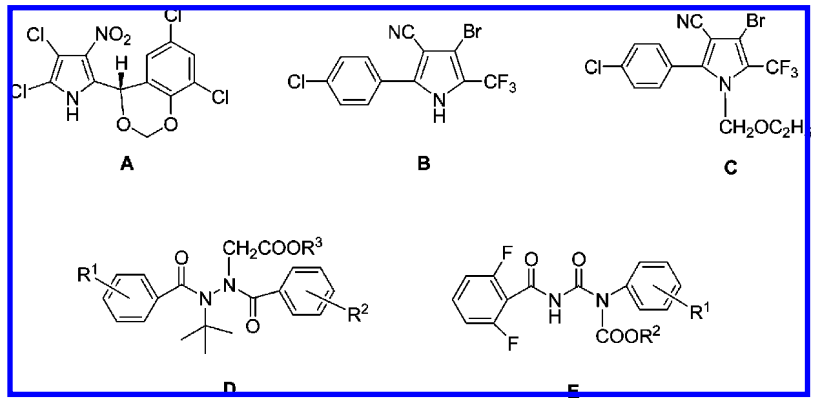
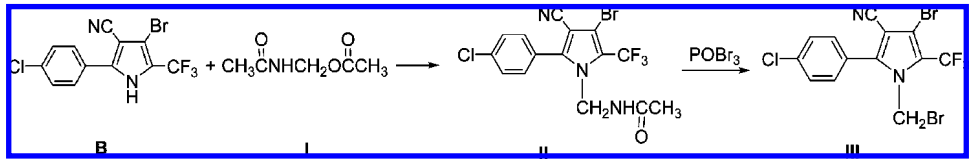
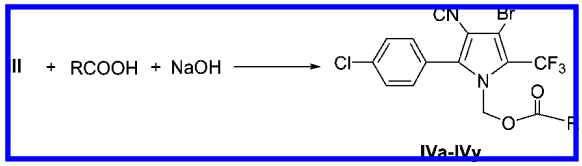


Figure 1. Chemical structures of compounds **A**−**E**.

Scheme 1. Synthetic Route of Compound **III**



Scheme 2. General Synthetic Route of the Title Compounds **IVa**−**IVy**



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 $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were 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 were uncorrected. Yields were not optimized. The reagents were all analytically or chemically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. 4-Bromo-2-(4-chlorophenyl)-5- (trifluoromethyl)pyrrole-3-carbonitrile (**B**) was prepared according to the literature (*15*−*19*). *N*-(Hydroxymethyl)acetamide acetate (**I**) was obtained according to the reported procedure (*20*).

Synthetic Procedure for 4-Bromo-1-(bromomethyl)-2-(4-chlorophenyl)-5- (trifluoromethyl)pyrrole-3-carbonitrile (III). A slurry of 4-bromo-2-(4-chlorophenyl)-5- (trifluoromethyl)pyrrole-3-carbonitrile (**B**) (17.47 g, 0.05 mol) and tetrahydrofuran (60 mL) was cooled to 10 °C and treated portionwise over 20 min with sodium hydride (2.2 g, 60% in oil, 0.055 mol). After it was stirred for 15 min, this solution was added dropwise to a 50 °C solution of *N*-(hydroxymethyl)acetamide acetate (**I**) (9.65 g, 0.074 mol) in tetrahydrofuran (40 mL). The reaction mixture was refluxed for 4 h and cooled to room temperature, diluted with water (30 mL), and extracted with ethyl acetate (3 × 60 mL). The organic extract was washed with water (2 × 40 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a solid. The solid was purified by column chromatography on a silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford compound **II** as a white crystal (8.00 g, 36%); mp 149−151 °C. Anal. calcd (%) for $C_{15}H_{10}BrClF_3N_3O$: C, 42.83; H, 2.40; N, 9.99. Found (%): C, 42.86; H, 2.41; N, 9.82.

A mixture of compound **II** (1.22 g, 2.90 mmol) and phosphoryl tribromide (2.35 g, 8.2 mmol) was heated at refluxed temperature for 30 min, then diluted with water, and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed successively with water (20 mL) and brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to obtain a solid. Recrystallization from a mixture of ethyl acetate and heptane gave the desired compound **III** as a white solid (1.02 g, 80%); mp 136−138 °C. ^{1}H NMR: δ 5.61 (s, 2H); 7.49 (d, 2H, $^3J_{HH}$ = 8.7 Hz), 7.54 (d, 2H,$^3J_{HH}$ = 8.7 Hz). Anal. calcd (%) for $C_{13}H_6Br_2ClF_3N_2$: C, 35.29; H, 1.37; N, 6.33. Found (%): C, 35.32; H, 1.54; N, 6.57.

General Synthetic Procedure for the Title Compounds IVa−**IVy.** The appropriate acid (4.50 mmol) was added to a stirred suspension of sodium hydroxide (0.18 g, 4.50 mmol) in dimethylformamide (10 mL) at 0 °C. After it was stirred for 1 h, the solution of compound **III** (4.50 mmol) in dimethylformamide (3 mL) was added dropwise. After it was stirred for 6 h at room temperature, the reaction mixture was poured into ice water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate solution (20 mL), water (3 × 20 mL), and brine (20 mL) and then dried over anhydrous sodium sulfate. After the solvent was removed, the residue was purified by recrystallization from a mixture of ethyl acetate and petroleum ether (60−90 °C) to afford the title compounds **IVa**−**IVy**.

Synthetic Procedure for the Title Compound IVz. Potassium hydroxide (5.6 g, 0.1 mol) in alcohol (100 mL) was added to a stirred solution of diethyl carbonate (17.7 g, 0.15 mol) in alcohol (100 mL). After it was stirred for 2 h, the product was precipitated and filtered to give potassium ethyl carbonate (10.8 g, 84.3%) as a white solid, which was directly used for the next step without further purification.

Potassium ethyl carbonate (0.58 g, 4.50 mmol) was dissolved in dimethylformamide (10 mL) at room temperature. Then, a solution of compound **III** (4.50 mmol) in dimethylformamide (3 mL) was added dropwise. After it was stirred for 6 h at room temperature, the reaction

Scheme 3. General Synthetic Route of the Title Compound **IVz**

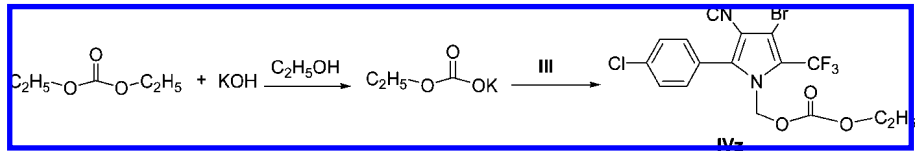


Table 1. Melting Points, Yields, and Elemental Analyses of the Compounds **IVa**−**IVz**

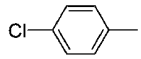
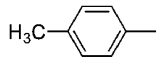
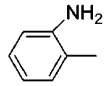
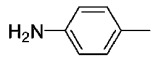
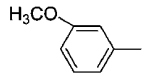
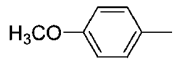
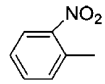
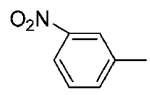
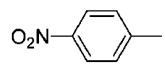
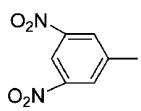
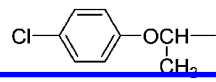
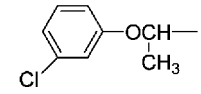
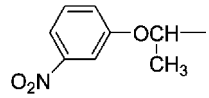
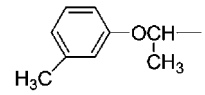
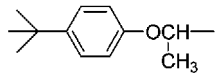
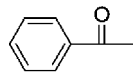
Compd.	R	mp (°C)	Yield (%)	Elemental Analysis (%) calcd. (found)		
				C	H	N
IV a	H	139−140	71.1	41.26(41.26)	1.73(1.70)	6.97(6.80)
IV b	CH_3	121−122	63.0	42.73(42.52)	2.15(2.25)	6.64(6.44)
IV c	C_2H_5	71−72	58.5	44.11(44.59)	2.55(2.50)	6.43(6.79)
IV d	n-Pr	55−56	45.0	45.41(45.22)	2.91(2.89)	6.23(6.42)
IV e	i-Pr	64−66	20.1	45.41(45.40)	2.91(2.73)	6.23 (6.38)
IV f	n-Bu	60−62	46.63	46.63(46.42)	3.26(3.26)	6.04 (6.26)
IV g	i-Bu	79−80	43.9	46.63(46.68)	3.26(3.27)	6.04 (6.08)
IV h		103−105	66.7	49.67(49.67)	2.29(2.27)	5.79(5.89)
IV i		136−137	66.5	46.36(46.24)	1.95(2.01)	5.41(5.41)
IV j		110−112	89.1	46.36(46.49)	1.95(2.04)	5.41(5.43)
IV k		129−131	65.9	50.68(51.07)	2.63 (2.68)	5.63(5.64)
IV l		134−136	53.3	48.17(48.15)	2.43(2.62)	8.43(8.41)
IV m		150−151	62.5	48.17(48.21)	2.43(2.27)	8.43(8.40)
IV n		83−85	41.3	49.10(48.92)	2.55(2.69)	5.45(5.54)
IV o		119−121	45.6	49.10(49.35)	2.55(2.53)	5.45(5.65)
IV p		164−165	71.5	45.44(45.49)	1.91(2.03)	7.95(7.91)
IV q		143−145	84.2	45.44(45.48)	1.91(1.90)	7.95(7.93)
IV r		162−164	63.1	45.44(45.45)	1.91(1.88)	7.95(7.83)
IV s		82−84	66.7	41.87(41.84)	1.58(1.78)	9.77(9.89)
IV t		86−88	82.0	47.00(46.87)	2.51(2.68)	4.98(4.76)

Table 1. Continued

Compd.	R	mp (°C)	Yield (%)	Elemental Analysis (%) calcd. (found)		
				C	H	N
IV u		111−113	66.0	47.00(46.95)	2.51(2.65)	4.98(4.71)
IV v		126−128	82.3	46.14(46.31)	2.46(2.47)	7.34(7.54)
IV w		104−106	82.1	50.99(50.81)	3.16(3.22)	5.17(5.20)
IV x		158−159	81.9	53.49(53.33)	3.97(3.95)	4.80(4.83)
IV y		172−174	25.0	49.29(49.18)	2.17(2.17)	5.47(5.41)
IV z	C_9H_8O	59−61	70.9	42.55(42.69)	2.46(2.57)	6.20(6.10)

mixture was poured into ice water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate solution (20 mL), water (3 × 20 mL), and brine (20 mL) and then dried over anhydrous sodium sulfate. After the solvent was removed, the residue was purified by recrystallization from a mixture of ethyl acetate and petroleum ether (60−90 °C) to afford the title compound **IVz**.

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 dead/alive basis, and mortality rates were corrected using Abbott's formula (*21*). Evaluations were based on a percentage scale of 0−100, where 0 equals no activity and 100 equals total kill. The error of the experiments was 5%. For comparative purpose, Chlorfenapyr was tested under the same conditions.

Insecticidal Activity against Oriental Armyworm (Mythimna separata). The insecticidal activities against oriental armyworm of the title compounds **IVa**−**IVz** and Chlorfenapyr were evaluated by foliar application using the reported procedure (*22, 23*). 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 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times. The insecticidal activities against oriental armyworm of the title compounds **IVa**−**IVz** and Chlorfenapyr are summarized in **Table 3**.

Insecticidal Activity against Mosquito (Culex pipiens pallens). The toxicities of the title compounds **IVa**−**IVz** and Chlorfenapyr against mosquito were evaluated by the reported procedure (*24*−*26*). One milliliter of different concentrated dilution of each compound was added to 99 mL of water to get different concentrations of tested solutions. Then, 20 four-instar mosquito larva were put into 10 mL of the test solution and raised for 2 days, and the results were expressed by death percentage. The results of the insecticidal activity of the title compounds **IVa**−**IVz** and Chlorfenapyr are shown in **Table 3**

Acaricidal Activity against Spider Mite (Tetranychus cinnabarinus Boisduval). The acaricidal activities against spider mite of the title compounds **IVa**−**IVz** and Chlorfenapyr were evaluated using the reported procedure (*27, 28*). Sieva bean plants (*Phaseolus vulgaris* L.) with primary leaves expanded to 10 cm were selected and cut back to one plant per pot. A small piece was cut from a leaf taken from the main colony and placed on each leaf of the test plants. This was done about 2 h before treatment to allow the mites to move over to the test plant and to lay eggs. The size of the piece was varied to obtain about 60−100 mites per leaf. At the time of the treatment, the piece of leaf used to transfer the mites was removed and discarded. The mite-infested plant were dipped in the test formulation for 3 s with agitation and set in the hood to dry. Plants were kept for 2 days before the numbers of live and dead adults were counted. The acaricidal activities against spider mite of the title compounds **IVa**−**IVz** and Chlorfenapyr are summarized in **Table 3**.

Acaricidal Activity against Two Spot Spider Mite (T. cinnabarinus Boisduval). The acaricidal activities of the title compound **IVg** and Chlorfenapyr against two spot spider mites were evaluated using the slide immersion method recommended by FAO (*29*). Thirty female adult spider mites were fixed dorsally to a strip of double-sided tape attached to the slide by using a small brush. The slide was immersed and shaken for 10 s in the diluted solution of the test compound. After the excessive solution was removed, the treated slides with the mites were kept at 25 ± 2 °C in a Petri dish with moist filter paper. The number of the dead mites was recorded 24 h after treatment. Each treatment was replicated thrice, and each replicate involved 30 adult mites. Chlorfenapyr was used as a standard. The data for the mortality−regression lines of the compounds were subjected to probit analysis by Finney's method. The results of the median lethal concentrations (LC_{50}) of the title compound **IVg** and Chlorfenapyr against two spot spider mites are shown in **Table 4**.

Insecticidal Activity against Diamondback Moth (Plutella xylostella L.). The insecticidal activities of the title compound **IVg** and Chlorfenapyr against diamondback moth were evaluated using the leaf disk assay (*29*). The Leaf disks (1.8 cm diameter) were cut from fresh cabbage leaves and then dipped into the test solution for 15 s. After air drying, the treated leaf disks were placed in a Petri dish (9 cm diameter) lined with a filter paper, and then, the second-instar diamondback moth larvae were transferred to the Petri dish. Three replicates (10 larvae per replicate) were carried out. Chlorfenapyr was used as a standard. The data for the mortality−regression lines of the compounds were subjected to probit analysis by Finney's method. The

Table 2. ^{1}H NMR of the Compounds **IVa**−**IVz**

compd	^{1}H NMR ($CDCl_3$) δ (ppm)
IVa	5.89 (s, 2H); 7.43 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.55 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 8.01 (s, 1H)
IVb	2.10 (s, 3H); 5.79 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.54 (d, 2H, $^3J_{HH}$ = 8.6 Hz)
IVc	1.41 (t, 3H, $^3J_{HH}$ = 7.5 Hz); 2.37 (q, 2H, $^3J_{HH}$ = 7.5 Hz); 5.79 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.6 Hz)
IVd	0.94 (t, 3H, $^3J_{HH}$ = 7.4 Hz); 1.59−1.69 (m, 2H); 2.32 (t, 2H, $^3J_{HH}$ = 7.4 Hz); 5.79 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.6 Hz)
IVe	1.17 (d, 6H, $^3J_{HH}$ = 7.0 Hz); 2.54−2.63 (m, 1H); 5.76 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.3 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.3 Hz)
IVf	0.92 (t, 3H, $^3J_{HH}$ = 7.3 Hz); 1.28−1.35 (m, 2H); 1.56−1.63 (m, 2H); 2.34 (t, 2H, $^3J_{HH}$ = 7.4 Hz); 5.78 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.4 Hz)
IVg	0.95 (d, 6H, $^3J_{HH}$ = 6.6 Hz); 2.00−2..12 (m, 1H); 2.22 (d, 2H, $^3J_{HH}$ = 7.2 Hz); 5.78 (s, 2H); 7.41 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.4 Hz)
IVh	6.04 (s, 2H); 7.43−8.00 (m, 9H)
IVi	6.03 (s, 2H); 7.45 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.52 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.42 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.92 (d, 2H, $^3J_{HH}$ = 8.6 Hz)
IVj	6.04 (s, 2H); 7.46 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.53 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.33−7.80 (m, 4H)
IVk	6.01 (s, 2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.51 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.26 (d, 2H, $^3J_{HH}$ = 8.0 Hz); 7.87 (d, 2H, $^3J_{HH}$ = 8.0 Hz)
IVl	5.69 (br, 2H); 5.99 (s, 2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.51 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 6.63−7.55 (m, 4H)
IVm	4.19 (br, 2H); 5.97 (s, 2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.51 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 6.63 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.79 (d, 2H, $^3J_{HH}$ = 8.5 Hz)
IVn	3.85 (s, 3H); 6.02 (s, 2H); 7.43 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.52 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.15−7.59 (m,4H)
IVo	3.88 (s, 3H); 6.00 (s, 2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.51 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 6.94 (d, 2H, $^3J_{HH}$ = 8.9 Hz); 7.94 (d, 2H, $^3J_{HH}$ = 8.9 Hz)
IVp	6.05 (s, 2H); 7.43 (d,2H, $^3J_{HH}$ = 8.3 Hz); 7.59 (d, 2H, $^3J_{HH}$ = 8.3 Hz); 7.64−8.05 (m, 4H)
IVq	6.10 (s, 2H); 7.44(d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.54 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.71−8.81 (m, 4H)
IVr	6.09 (s, 2H); 7.43 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.54 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 8.16 (d, 2H, $^3J_{HH}$ = 8.9 Hz); 8.32 (d, 2H, $^3J_{HH}$ = 8.9 Hz)
IVs	6.17 (s, 2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.57 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 9.08−9.29 (m, 3H)
IVt	1.62 (d, 3H, $^3J_{HH}$ = 6.8 Hz); 4.75 (q, 1H, $^3J_{HH}$ = 6.7 Hz); 5.78 (q, 2H, $^2J_{HH}$ = 11.4 Hz); 6.76 (d, 2H, $^3J_{HH}$ = 8.8 Hz); 7.34 (d, 2H, $^3J_{HH}$ = 8.8 Hz); 7.21 (d, 2H, $^3J_{HH}$ = 8.0 Hz); 7.27 (d, 2H, $^3J_{HH}$ = 8.0 Hz)
IVu	1.63 (d,3H, $^3J_{HH}$ = 6.8 Hz); 4.77 (q,1H, $^3J_{HH}$ = 6.8 Hz); 5.80 (q,2H, $^2J_{HH}$ = 11.4 Hz); 6.71−7.06 (m,4H); 7.24 (d, 2H, $^3J_{HH}$ = 8.4 Hz); 7.37 (d, 2H, $^3J_{HH}$ = 8.4 Hz)
IVv	1.67 (d, 3H, $^3J_{HH}$ = 6.8 Hz); 4.88 (q, 1H, $^3J_{HH}$ = 6.8 Hz); 5.85 (q, 2H, $^2J_{HH}$ = 11.4 Hz); 7.17−7.93 (m, 4H); 7.32 (d, 2H, $^3J_{HH}$ = 8.5 Hz); 7.44 (d, 2H, $^3J_{HH}$ = 8.5 Hz)
IVw	1.62 (d, 3H, $^3J_{HH}$ = 6.8 Hz); 2.33 (s, 3H); 4.79 (q, 1H, $^3J_{HH}$ =6.8 Hz); 5.76 (q, 2H, $^2J_{HH}$ = 11.4 Hz); 6.61−7.19 (m, 4H); 7.20 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.27 (d, 2H, $^3J_{HH}$ = 8.6 Hz)
IVx	1.34 (s, 9H); 1.63 (d, 3H, $^3J_{HH}$ = 6.8 Hz); 4.78 (q, 1H, $^3J_{HH}$ = 6.8 Hz); 5.76 (q, 2H, $^2J_{HH}$ = 11.4 Hz); 7.00−7.30 (m, 8H)
IVy	6.04 (s, 2H); 7.43 (d, 2H, $^3J_{HH}$ = 8.3 Hz); 7.59 (d, 2H, $^3J_{HH}$ = 8.3 Hz); 7.47−7.98 (m, 5H)
IVz	1.32 (t, 3H, $^3J_{HH}$ = 7.1 Hz); 4.23 (q, 1H, $^3J_{HH}$ = 7.1 Hz); 5.81 (s,2H); 7.44 (d, 2H, $^3J_{HH}$ = 8.6 Hz); 7.54 (d, 2H, $^3J_{HH}$ = 8.6 Hz)

results of the median lethal concentrations (LC_{50}) of the title compound **IVg** and Chlorfenapyr against diamondback moth larvae are shown in **Table 5**.

Insecticidal Activity against Green Rice Leafhopper (Nephotettix cincticeps Uhler). The insecticidal activities of the title compound **IVg** and Chlorfenapyr against green rice leafhoppers were evaluated using the seedling-dipping method (*29*). Fifteen rice seedlings with two leaves and a bud were dipped in the test solution of the compounds for 15 s, dried in air, and placed into a test tube (diameter 2.5 cm × height 30 cm). Fifteen third-instar green rice leafhoppers were introduced into each test tube. The test tubes were capped with the white gauze and maintained at a constant condition. Mortality was calculated 48 h after treatment. At least five concentrations, a blank control, and a standard Chlorfenapyr were included in each bioassay, and triplicates were done. The data for the mortality−regression lines of the compounds were subjected to probit analysis by Finney's method. The results of the median lethal concentrations (LC_{50}) of the title compound **IVg** and Chlorfenapyr against green rice leafhoppers are shown in **Table 6**.

Insecticidal Activity against Bean Aphids (Aphis fabae Scopoli). The insecticidal activities of the title compound **IVg** and Chlorfenapyr against bean aphids were evaluated (*29*). Bean aphids were dipped according to a slightly modified FAO dip test. The tender shoots of soybean with 40−60 healthy apterous adult aphids were dipped in the diluted solutions of the compounds for 5 s, and the superfluous fluid was removed and placed in the conditioned room. Mortality was calculated 48 h after treatment. Each treatment was performed three times. Chlorfenapyr was used as a standard. The data for the mortality−regression lines of the compounds were subjected to probit analysis by Finney's method. The results of the median lethal concentrations (LC_{50}) of the title compound **IVg** and Chlorfenapyr against bean aphids are listed in **Table 7**.

RESULTS AND DISCUSSION

Synthesis. 4-Bromo-1-(bromomethyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**III**) was synthesized as shown in **Scheme 1**. 4-Bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**B**) was prepared according to the literature (*14*−*18*). *N*-(Hydroxymethyl)acetamide acetate (**I**) was obtained according to reported procedure (*19*). The intermediate **B** was reacted with compound **I** in the presence of sodium hydride to give compound **II**, and subsequent treatment using phosphoryl tribromide as a bromination reagent provided the key intermediate **III**.

The title compounds **IVa**−**IVy** were synthesized from intermediate **III** and appropriate acid as shown in **Scheme 2**. The key intermediate **III** was reacted with appropriate acid in dimethylformamide using sodium hydroxide as alkali to yield 2-aryl-pyrrole derivatives containing ester groups **IVa**−**IVy**. The title compound **IVz** was synthesized from intermediate **III** and potassium ethyl carbonate as shown in **Scheme 3**.

The title compounds **IVa**−**IVz** could be purified by recrystallization from a mixture of ethyl acetate and petroleum ether. The melting points, yields, and elemental analyses of compounds **IVa**−**IVz** are listed in **Table 1**. The ^{1}H NMR data are listed in **Table 2**.

Structure−**Activity Relationship (SAR). Table 3** shows the insecticidal activities against oriental armyworm and mosquito and acaricidal activities against spider mite of the title compounds **IVa**−**IVz** and contrast compound Chlorfenapyr.

Insecticidal Activities against Oriental Armyworm (M. separata Walker). The results of insecticidal activities given in **Table 3** indicate that some of the title compounds **IVa**−**IVz** exhibit excellent activity against oriental armyworm, which are good as compared to the commercialized Chlorfenapyr. For instance, the insecticidal activities of compounds **IVa**, **IVd**, **IVe**, **IVf**, **IVg**, **IVi**, **IVk**, and **IVp** were equal to Chlorfenapyr. Among the *R* values of the title compounds **IVa**−**IVz**, saturated short alkyl groups are most prominent in increasing activity. From **Table 3**, we also found that aromatic-substituted compounds exhibit lower insecticidal activities against oriental armyworm than saturated short alkyl-substituted compounds.

Insecticidal Activities against Mosquito (C. pipiens pallens). The insecticidal activities of the title compounds **IVa**−**IVz**

Table 3. Insecticidal and Acaricidal Activities of Compounds **IVa**−**IVz** against Oriental Armyworm, Mosquito, and Spider Mite

	toxicities against oriental armyworm at concn (mg kg^{-1})			toxicities against mosquito at concn (mg kg^{-1})			toxicities against spider mite at concn (mg kg^{-1})		
compd	20	10	5	0.50	0.25	0.10	200	100	50
IVa	100	100	0	100	100	50	100	89	82
IVb	100	90	0	100	100	100	0		
IVc	100	90	0	100	100	100	100	92	88
IVd	100	100	0	100	100	100	100	100	100
IVe	100	100	0				100	100	100
IVf	100	100	0	100	100	100	100	100	100
IVg	100	100	0	100	100	100	100	100	100
IVh	100	60	0	100	20	10	100	100	100
IVi	100	100	10	100	20	10	100	100	100
IVj	100	35	0	100	100	100	99	95	93
IVk	100	100	0	100	100	100	100	100	100
IVl	10	0	0	100	100	100	0		
IVm	40	0	0	100	10	10	0		
IVn	100	90	0	100	65	50	100	65	50
IVo	100	90	0	70	30	20	0		
IVp	100	100	20	100	20	10	0		
IVq	100	0	0	80	40	30	98	94	90
IVr	100	50	0	100	60	20	95	93	92
IVs	100	0	0	100	100	100	0		
IVt	100	80	0	100	100	100	98	95	94
IVu	100	45	0	100	100	100	98	93	93
IVv	100	85	0	100	100	90	0		
IVw	100	40	0	100	100	100	100	98	96
IVx	80	30	0	100	100	100	100	96	94
IVy	100	60	0				100	88	79
IVz	100	90	0	100	100	100	100	89	84
chlorfenapyr	100	100	0	100	100	100	100	97	93

Table 4. Acaricidal Activities of **IVg** and Chlorfenapyr against Two Spot Spider Mite

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
IVg	$y = 5.9227 + 2.5257x$	0.43	2.65
Chlorfenapyr	$y = 4.8332 + 3.0078x$	1.14	1.00

Table 5. Insecticidal Activities of **IVg** and Chlorfenapyr against Diamondback Moth

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
IVg	$y = 3.8885 + 4.0690x$	1.88	0.97
Chlorfenapyr	$y = 4.1005 + 3.8385x$	1.82	1.00

Table 6. Insecticidal Activities of **IVg** and Chlorfenapyr against Green Rice Leafhopper

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
IVg	$y = -0.9351 + 3.8704x$	34.12	0.79
Chlorfenapyr	$y = 0.9679 + 2.8227x$	26.82	1.00

Table 7. Insecticidal Activities of **IVg** and Chlorfenapyr against Bean Aphids

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
IVg	$y = 3.4188 + 1.2639x$	17.83	0.69
Chlorfenapyr	$y = 4.1005 + 3.8385x$	12.23	1.00

against mosquito were evaluated. The results indicate that most of the title compounds **IVa**−**IVz** exhibited excellent activities against mosquito. For example, the insecticidal activities of compounds **IVb**−**IVd**, **IVf**, **IVg**, **IVj**−**IVl**, **IVs-IVu**, **IVw**, **IVx**, and **IVz** against mosquito at 0.10 mg kg^{-1} are 100%, which is parallel to that of the commercialized Chlorfenapyr.

Acaricidal Activities against Spider Mite (T. cinnabarinus Boisduval). The result of acaricidal activities given in **Table 3** shows that most of the title compounds **IVa**−**IVz** exhibit excellent activities against spider mite. For example, the acaricidal activities of compounds **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVi**, and **IVk** were equal or superior to the commercialized Chlorfenapyr at 50 mg kg^{-1}. In particular, **IVg** was sent for advanced testing of the acaricidal activities against two spot spider mite and the insecticidal activities against diamondback moth, green rice leafhopper, and bean aphids.

Acaricidal Activity against Two Spot Spider Mite (T. cinnabarinus Boisduval). The results of the median lethal concentrations (LC_{50}) and the toxicity regression equations of compound **IVg** and Chlorfenapyr are shown in **Table 4**. The results indicate that the acaricidal activity of **IVg** against two spot spider mite was 2.65-fold as high as that of Chlorfenapyr from the value of LC_{50}.

Insecticidal Activity against Diamondback Moth (P. xylostella L.). The results of the median lethal concentrations (LC_{50}) and the toxicity regression equations of compound **IVg** and Chlorfenapyr are shown in **Table 5**. The title compound **IVg** almost exhibited equal activity as that of the commercialized Chlorfenapyr.

Insecticidal Activity against Green Rice Leafhopper (N. cincticeps Uhler). The results of the median lethal concentrations (LC_{50}) and the toxicity regression equations of compound **IVg** and Chlorfenapyr are shown in **Table 6**. The title compound **IVg** showed a little lower insecticidal activity against green rice leafhopper than the commercialized Chlorfenapyr.

Insecticidal Activity against Bean Aphids (Aphis craccivora). The results of the median lethal concentrations (LC_{50}) and the toxicity regression equations of compound **IVg** and Chlorfenapyr are shown in **Table 7**. The title compound **IVg** exhibited lower insecticidal activities against bean aphids than the commercialized Chlorfenapyr.

In summary, a series of novel 2-aryl-pyrrole derivatives containing ester groups were synthesized from 4-bromo-1-(bromomethyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-

3-carbonitrile, and their structures were characterized by ^{1}H NMR spectroscopy and elemental analysis. The insecticidal activities against oriental armyworm, mosquito, diamondback moth, green rice leafhopper, and bean aphids and acaricidal activity against spider mite of the title compounds **IVa**−**IVz** and contrast compound Chlorfenapyr were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal and acaricidal activities. The insecticidal activities against oriental armyworm of compounds **IVa**, **IVd**, **IVe**, **IVf**, **IVg**, **IVi**, **IVk**, and **IVp** were equal to Chlorfenapyr, and the insecticidal activities of most of compounds **IVb**, **IVc**, **IVd**, **IVf**, **IVg**, **IVj**, **IVk**, **IVl**, **IVs**, **IVt**, **IVu**, **IVw**, **IVx**, and **IVz** against mosquito at 0.10 mg kg^{-1} are 100%, which is parallel to that of Chlorfenapyr, and the acaricidal activities of compounds **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, **IVi**, and **IVk** are equal or superior to Chlorfenapyr. In particular, the acaricidal activity of (4-bromo-2-(4-chlorophenyl)-3-cyano-5-(trifluoromethyl)pyrrol-1-yl)methyl 3-methylbutanoate (**IVg**) against spider mite was 2.65-fold as high as that of Chlorfenapyr from the value of LC_{50}.

LITERATURE CITED

(1) Cater, G. T.; Nietsche, J. N.; Goodman, J. J.; Torrey, M. J.; Dunne, T. S.; Borders, D. B.; Testa, R. T. LL-F42248α, a novel chlorinated pyrrole antibiotic. *J. Antibiot.* **1987**, *40*, 233–234.

(2) Nakamura, H.; Shiomi, K.; Iinuma, H.; Naganawa, H.; Obata, T.; Takeuchi, T.; Umezawa, H. Isolation and characterization of a new antibiotic, dioxapyrrolomycin, related to pyrrolomycins. *J. Antibiot.* **1987**, *40*, 899–903.

(3) Yano, K.; Oono, J.; Mogi, K.; Asaoka, T.; Nakashima, T. Pyrroxamycin, a new antibiotic taxonomy, fermentation, isolation, structure determination and biological properties. *J. Antibiot.* **1987**, *40*, 961–969.

(4) Addor, R. W.; Babcock, T. J.; Black, B. C.; Brown, D. G.; Diehl, R. E.; Furch, J. A.; Kameswaran, V.; Kamhi, V. M. Insecticidal pyrroles: Discovery and overview. Baker, D., Ed.; *Synthesis and Chemistry of Agrochemicals III*; ACS Symposium Series 504; American Chemical Society: Washington, DC, 1992; pp 283−297.

(5) Treacy, M. F.; Miller, T. P.; Gard, I. E.; Lovell, J. B.; Wright, D. P., Jr. Characterization of insecticidal properties of AC303,630 against tobacco budworm, *Heliothis virescens* (Fabricius), larvae. *Proc. Beltwide Cotton Conf.* **1991**, *2*, 738–740.

(6) Miller, T. P.; Treacy, M. F.; Gard, I. E.; Lovell, J. B.; Wright, D. P., Jr.; Addor, R. W.; Kamhi, V. M. AC303630, summary of 1988−1989 field trial results. *Brighton Crop Prot. Conf.—Pests Dis.* **1990**, *1*, 41–45.

(7) Treacy, M.; Miller, T.; Black, B.; Gard, I.; Hunt, D.; Hollingworth, R. M. Uncoupling activity and pesticide properties of pyrroles. Colloquium on the design of mitochondrial electron transport inhibitors as agrochemicals. *Biochem. Soc. Trans.* **1994**, *22*, 244–247.

(8) Herron, G. A.; Rophail, J. First detection of chlorfenapyr (Secure) resistance in two-spotted spider mite (Acari: Tetranychidae) from nectarines in an Australian orchard. *Exp. Appl. Acarol.* **2003**, *31*, 131–134.

(9) Herron, G. A.; Rophail, J.; Wilson, L. J. Chlorfenapyr resistance in two-spotted spider mite (Acari: Tetranychidae) from Australian cotton. *Exp. Appl. Acarol.* **2004**, *34*, 315–321.

(10) Zhao, F.; Wang, M.; Li, J. H. Resistance of *Plutella xylostella* to nine insecticides in several field populations in China. *Chin. Bull. Entomol.* **2006**, *43* (5), 640–643.

(11) Jiang, X. Y.; Wang, K. Y.; Yi, M. Q. Study on resistance of*Plutella xylostella* (L.) in different areas to insecticides. *Chin. J. Pestic. Sci.* **2000**, *12* (4), 44–48.

(12) Fukuto, T. R. Propesticides. In *Pesticides Synthesis through Rational Approaches*; Magee, P. S., Eds.; American Chemical Society: Washington, DC, 1984; pp 87−101.

(13) Cao, S.; Qian, X.; Song, G. *N*′-*tert*-Butyl-*N*′-aroyl-*N*-(alkoxycarbonylmethyl)-*N*-aroylhydrazines, a novel nonsteroidal ecdysone agonist: Syntheses, insecticidal activity, conformational, and crystal structure analysis. *Can. J. Chem.* **2001**, *79*, 272–278.

(14) Chen, L.; Wang, Q. M.; Huang, R. Q.; Mao, C. H.; Shang, J.; Bi, F. C. Synthesis and insecticidal evaluation of propesticides of benzoylphenylureas. *J. Agric. Food Chem.* **2005**, *53*, 38–41.

(15) Kameswaran, V.; Barton, J. M. Process for the manufacture of pesticidal 1-(alkoxymethyl)- pyrrole compounds. U.S. Patent 5,151,536, 1992.

(16) Kameswaran, V.; Princton, J. N. Method for the preparation of 2-aryl-5-(triflroromethyl)pyrrole compounds. U.S. Patent 5,256,796, 1993.

(17) Kameswaran, V.; Princton, J. N. Ammonium oxazole and amino oxazolium intermediates, methods for the prepartion thereof and the use thereof in the manufacture of insecticidal arylpyrroles. U.S. Patent 5,925,773, 1999.

(18) Kameswaran, V.; Princton, J. N. Oxazole amines as intermediate in the manufacture of insecticidal arylpyrroles. U.S. Patent 5,631,379, 1997.

(19) Kameswaran, V.; Princton, J. N. Perfluoroalkanoyl aminonttriles. U.S. 5,426,225, 1995.

(20) Kameswaran, V. N-Alkanoylaminomethyl and N-aroylaminomethyl pyrrole insecticidal and acaricidal agents. U.S. Patent 5,130,328, 1991.

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

(22) 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.

(23) 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.

(24) Cui, F.; Tan, Y.; Su, A. F.; Fu, J. C.; Zhu, Q.; Qiao, C. L. Insecticide resistance and overproduced esterases in populations *Culex pipiens* complex of China. *Zhongguo Meijie Shengwuxue Ji Kongzhi Zazhi* **2005**, *16* (6), 413–416.

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

(26) 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.

(27) Kuhn, D. G.; Donovan, S. F.; Furch, J. A. N-Aminoalkylcarbonyloxylpyrrole insecticidal, acaricidal and molluscicidal agents. U.S. Patent 5,286,743, 1992.

(28) Kuhn, D. G.; Kameswaran, V. Insecticidal, acaricidal and molluscicidal 1-(substituted)thioalkylpyrroles. U.S. Patent 5,302,383, 1993.

(29) Wang, Y. J.; Ou, X. M.; Pei, H.; Lin, X. M.; Yu, K. Toxicities of novel insecticide chlorfenpyr against several insects in lab. *Agrochem. Res. Appl.* **2006**, *10*, 20–23.

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