

Synthesis, Crystal Structure, and Insecticidal Activity of Novel *N*-Alkyloxyoxalyl Derivatives of 2-Arylpyrrole

YU ZHAO,[†] CHUNHUI MAO,^{‡,†} YONGQIANG LI,[†] PENGXIANG ZHANG,[†]
ZHIQIANG HUANG,[†] FUCHUN BI,[†] RUNQIU HUANG,[†] AND QINGMIN WANG^{*,†}

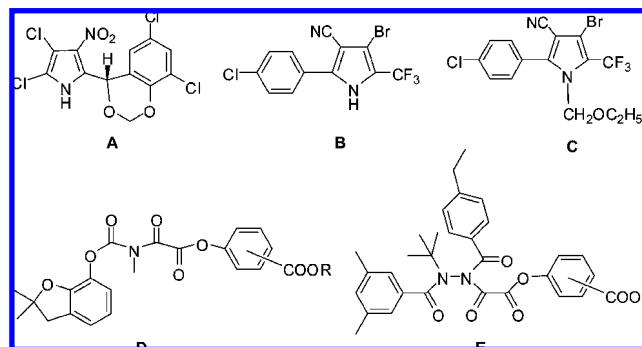
State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China, and Hunan Branch of National Pesticide R&D South Center, Hunan Research Institute of Chemical Industry, Changsha 410007, Hunan Province, People's Republic of China

Two series of novel *N*-alkyloxyoxalyl derivatives of 2-arylpyrrole were synthesized, and their structures were characterized by ¹H NMR spectroscopy, elemental analysis, and single-crystal X-ray diffraction analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal activities, and their insecticidal activities against oriental armyworm, mosquito, and spider mite are comparable to those of the commercialized Chlorfenapyr.

KEYWORDS: Arylpyrrole; Chlorfenapyr; *N*-alkyloxyoxalyl derivatives; insecticidal activity; oriental armyworm; spider mite; mosquito

INTRODUCTION

In 1987, scientists from the American Cyanamid Co. isolated and identified dioxapyrrolomycin (**A**) 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 the SS Pharmaceutical Co. in Japan as an antibiotic (2, 3). However, an oral LD₅₀ to mice of dioxapyrrolomycin was 14 mg kg⁻¹, which did not make dioxapyrrolomycin a candidate for development, but its structure was simple enough to warrant consideration as a takeoff for synthetic modification. Then American Cyanamid found that the compound **B** exhibited excellent activity against tobacco budworm, two-spotted spider mite, and potato leafhopper. However, 2-arylpyrrole **B** was found to have high levels of phytotoxicity. To circumvent this problem, American Cyanamid further prepared its derivative **C** by introduction of an ethoxymethyl group into the compound **B** by substituting the hydrogen on the nitrogen atom and found that the compound **C** retained the high insecticidal activity of the parent pyrrole **B** with none of the undesirable phytotoxic properties (4). Compound **C** was the first to be commercialized as an insecticide–miticide under the trade name Chlorfenapyr and the IUPAC name 4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-(trifluoromethyl)pyrrole-3-carbonitrile (5, 6). It is a pro-insecticide activated by the oxidative in vivo removal of its *N*-ethoxymethyl group (7). Its resistance has been detected (8–11).



The activity spectrum of a pesticide is often determined by the physical properties of the 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). It was reported that *N*-oxalyl derivatives of carbofuran containing a carboxylic acid or ester substituent (**D**) displayed an insecticidal activity comparable or superior to that of carbofuran. In our previous work, the synthesis and insecticidal evaluation of novel *N*-oxalyl derivatives of tebufenozide (**E**) was reported, and the results of bioassay showed that they exhibit excellent larvicidal activity (13).

Encouraged by these findings, we developed an idea that the introduction of an oxalyl substituent into 2-arylpyrrole **B** by substituting the hydrogen on the nitrogen atom could improve biological properties and decrease resistance. There-

* Author to whom correspondence should be addressed [telephone +86-(0)22-23499842; fax +86-(0)22-23499842; e-mail wang98h@263.net].

[†] Nankai University.

[‡] Hunan Research Institute of Chemical Industry.

Table 1. Melting Points, Yields, and Elemental Analyses of Compounds **Vla**–**Vlo**

| compd | R ₁ | mp (°C) | yield (%) | elemental analysis (%), calcd (found) | | |
|------------|----------------------|-----------|-----------|---------------------------------------|-------------|-------------|
| | | | | C | H | N |
| Vla | methyl | 98–99 | 37.3 | 41.27 (41.49) | 1.95 (2.08) | 6.02 (5.91) |
| Vlb | ethyl | 101–103 | 36.4 | 42.57 (42.37) | 2.31 (2.18) | 5.84 (5.74) |
| Vlc | <i>n</i> -propyl | 63–64 | 58.0 | 43.79 (43.88) | 2.65 (2.61) | 5.67 (5.51) |
| Vld | <i>i</i> -propyl | 64–65 | 58.1 | 43.79 (44.00) | 2.65 (2.45) | 5.67 (5.65) |
| Vle | <i>n</i> -butyl | 72–74 | 36.4 | 44.95 (44.90) | 2.98 (3.07) | 5.52 (5.40) |
| Vlf | <i>i</i> -butyl | 108–109 | 19.7 | 44.95 (44.79) | 2.98 (2.94) | 5.52 (5.68) |
| Vlg | <i>s</i> -butyl | 79–80 | 35.2 | 44.95 (45.09) | 2.98 (3.03) | 5.52 (5.41) |
| Vlh | <i>t</i> -butyl | 110–111 | 61.1 | 44.95 (44.72) | 2.98 (2.90) | 5.52 (5.97) |
| Vli | cyclopentylmethyl | 100–102 | 64.7 | 47.26 (47.25) | 3.21 (3.30) | 5.25 (5.20) |
| Vlj | cyclohexyl | oil | 29.1 | 47.26 (47.28) | 3.21 (3.29) | 5.25 (4.99) |
| Vlk | propenyl | 258–260 | 61.4 | 43.97 (43.75) | 2.26 (2.45) | 5.70 (5.51) |
| Vll | 2-fluoroethyl | 84–86 | 69.4 | 41.03 (40.94) | 2.03 (2.17) | 5.63 (5.42) |
| Vlm | 2,2,2-trifluoroethyl | 200 (dec) | 47.1 | 38.26 (38.21) | 1.51 (1.77) | 5.25 (5.27) |
| Vln | 2-methoxyethyl | 106–108 | 51.1 | 42.42 (42.30) | 2.57 (2.41) | 5.50 (5.41) |
| Vlo | 2-ethoxyethyl | 220 (dec) | 41.3 | 43.58 (43.31) | 2.89 (2.72) | 5.35 (5.45) |

Table 2. ¹H NMR of Compounds **Vla**–**Vlo**

| compd | ¹ H NMR (CDCl ₃) δ (ppm) |
|------------|---|
| Vla | 3.95 (s, 3H); 5.94 (s, 2H); 7.51 (dd, 4H, ³ J _{HH} = 8.1 Hz) |
| Vlb | 1.40 (t, 3H, ³ J _{HH} = 6.9 Hz); 4.40 (q, 2H, ³ J _{HH} = 6.9 Hz); 5.93 (s, 2H); 7.51 (dd, 4H, ³ J _{HH} = 8.4 Hz) |
| Vlc | 0.99 (t, 3H, ³ J _{HH} = 7.4 Hz); 1.73–1.82 (m, 2H); 4.28 (t, 2H, ³ J _{HH} = 6.7 Hz); 5.92 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.4 Hz) |
| Vld | 1.37 (d, 6H, ³ J _{HH} = 6.3 Hz); 5.13–5.23 (m, 1H); 5.91 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.4 Hz) |
| Vle | 0.97 (t, 3H, ³ J _{HH} = 7.5 Hz); 1.39–1.48 (m, 2H); 1.69–1.79 (m, 2H); 4.33 (q, 2H, ³ J _{HH} = 7.5 Hz); 5.93 (s, 2H); 7.51 (dd, 4H, ³ J _{HH} = 8.4 Hz) |
| Vlf | 0.99 (d, 6H, ³ J _{HH} = 6.7 Hz); 2.02–2.09 (m, 1H); 4.11 (d, 2H, ³ J _{HH} = 6.7 Hz); 5.93 (s, 2H); 7.49 (d, 2H, ³ J _{HH} = 8.5 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.5 Hz) |
| Vlg | 0.94 (t, 3H, ³ J _{HH} = 7.4 Hz); 1.34 (d, 3H, ³ J _{HH} = 6.3 Hz); 1.64–1.76 (m, 2H); 4.98–5.07 (m, 1H); 5.92 (s, 2H); 7.49 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.51 (d, 2H, ³ J _{HH} = 8.4 Hz) |
| Vlh | 1.57 (s, 9H); 5.90 (s, 2H); 7.51 (dd, 4H, ³ J _{HH} = 8.4 Hz) |
| Vli | 1.24–1.27 (m, 2H); 1.55–1.62 (m, 4H); 1.77–1.80 (m, 2H); 2.25–2.34 (m, 1H); 4.21 (d, 2H, ³ J _{HH} = 7.2 Hz); 5.92 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.5 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.5 Hz) |
| Vlj | 1.24–1.42 (m, 3H); 1.53–1.59 (m, 3H); 1.75–1.79 (m, 2H); 1.90–1.94 (m, 2H); 4.86–4.95 (m, 1H); 5.91 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.5 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.5 Hz) |
| Vlk | 4.77–4.81 (m, 2H); 5.32–5.45 (m, 2H); 5.93–6.03 (m, 1H); 5.96 (s, 2H); 7.41 (d, 2H, ³ J _{HH} = 8.5 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.5 Hz) |
| Vll | 4.65 (dt, 2H, ³ J _{HH} = 4.2 Hz, ² J _{HF} = 80.1 Hz); 4.62 (q, 3H, ³ J _{HH} = ³ J _{HF} = 2.6 Hz); 5.95 (s, 2H); 7.46 (d, 2H, ³ J _{HH} = 8.6 Hz); 7.56 (d, 2H, ³ J _{HH} = 8.6 Hz) |
| Vlm | 4.67 (q, 2H, ³ J _{HH} = 8.0 Hz); 5.97 (s, 2H); 7.44 (d, 2H, ³ J _{HH} = 8.6 Hz); 7.56 (d, 2H, ³ J _{HH} = 8.6 Hz) |
| Vln | 3.41 (s, 3H); 3.69 (t, 2H, ³ J _{HH} = 4.56 Hz); 4.46 (t, 2H, ³ J _{HH} = 4.67 Hz); 5.93 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.4 Hz) |
| Vlo | 1.21 (t, 3H, ³ J _{HH} = 6.9 Hz); 3.54 (q, 2H, ³ J _{HH} = 6.97 Hz); 3.72 (t, 2H, ³ J _{HH} = 3.8 Hz); 4.45 (t, 2H, ³ J _{HH} = 3.8 Hz); 5.92 (s, 2H); 7.45 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.4 Hz) |

fore, in a search for new arylpyrrole insecticides with improved profiles, we designed and synthesized two series of novel *N*-alkyloxyoxalyl derivatives of 2-arylpyrrole as shown in **Schemes 4** and **6**.

MATERIALS AND METHODS

Instruments. ¹H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in CDCl₃ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. 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. 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 (14–18). *N*-(Hydroxymethyl)acetamide acetate (**I**) was obtained according to the reported procedure (19). *tert*-Butyl potassium oxalate (**Vh**) was synthesized according to the published procedure (20).

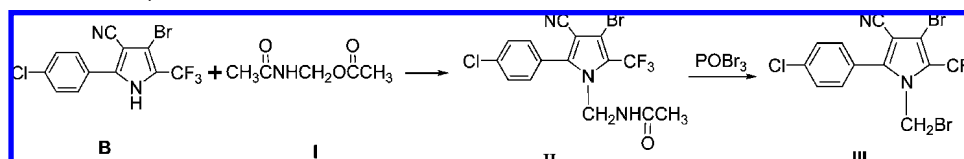
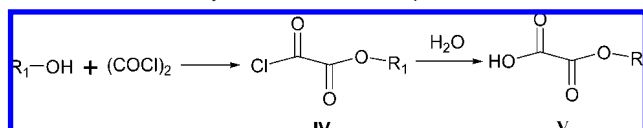
Synthetic Procedure for 4-Bromo-1-(bromomethyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (III). A slurry of 4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**B**) (17.47 g, 0.05 mol) and tetrahydrofuran (60 mL) was cooled to 10 °C and treated portionwise over 20 min with sodium hydride (2.2 g, 60% in oil, 0.055 mol). After 15 min of stirring, 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 cooled to room temperature, diluted with water

Table 3. Melting Points, Yields, and Elemental Analyses of Compounds IXa–IXl

| compd | R ₂ | mp(°C) | yield (%) | elemental analysis (%), calcd (found) | | |
|-------|------------------------|---------|-----------|---------------------------------------|-------------|-------------|
| | | | | C | H | N |
| IXa | <i>n</i> -propyl | 74–75 | 67.6 | 43.88 (43.62) | 2.86 (2.82) | 8.53 (8.36) |
| IXb | <i>i</i> -propyl | 127–129 | 68.1 | 43.88 (43.95) | 2.86 (2.98) | 8.53 (8.40) |
| IXc | <i>n</i> -butyl | 107–109 | 60.1 | 45.04 (45.05) | 3.18 (3.18) | 8.29 (8.14) |
| IXd | <i>s</i> -butyl | 113–115 | 57.0 | 45.04 (45.27) | 3.18 (3.11) | 8.29 (7.92) |
| IXe | <i>t</i> -butyl | 70–72 | 60.9 | 45.04 (45.03) | 3.18 (3.28) | 8.29 (8.32) |
| IXf | propenyl | 106–108 | 63.1 | 44.06 (13.94) | 2.41 (2.40) | 8.56 (8.45) |
| IXg | cyclohexyl | 162–164 | 50.0 | 47.34 (47.21) | 3.41 (3.47) | 7.89 (7.86) |
| IXh | phenyl | 97–99 | 67.5 | 47.89 (47.80) | 2.30 (2.46) | 7.98 (7.76) |
| IXi | <i>o</i> -methylphenyl | 166–168 | 43.8 | 48.87 (48.62) | 2.61 (2.48) | 7.77 (7.80) |
| IXj | <i>p</i> -methylphenyl | 149–151 | 45.8 | 48.87 (48.98) | 2.61 (2.68) | 7.77 (7.64) |
| IXk | <i>o</i> -chlorophenyl | 136–138 | 57.1 | 44.95 (44.73) | 1.98 (2.04) | 7.49 (7.59) |
| IXl | <i>p</i> -chlorophenyl | 153–155 | 48.4 | 44.95 (44.72) | 1.98 (1.99) | 7.49 (7.53) |

Table 4. ¹H NMR of Compounds IXa–IXl

| compd | ¹ H NMR (CDCl ₃ , δ) |
|-------|---|
| IXa | 0.97 (t, 3H, ³ J _{HH} = 7.4 Hz); 1.55–1.65 (m, 2H); 3.24–3.36 (m, 2H); 5.91 (s, 2H); 7.10 (br, 1H); 7.48 (d, 2H, ³ J _{HH} = 8.7 Hz); 7.54 (d, 2H, ³ J _{HH} = 8.7 Hz) |
| IXb | 1.24 (d, 6H, ³ J _{HH} = 6.6 Hz); 4.06–4.16 (m, 1H); 5.91 (s, 2H); 6.72–6.80 (br, 1H); 7.49 (d, 2H, ³ J _{HH} = 8.7 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.7 Hz) |
| IXc | 0.94 (t, 3H, ³ J _{HH} = 7.4 Hz); 1.34–1.39 (m, 2H); 1.52–1.57 (m, 2H); 3.32–3.37 (m, 2H); 5.90 (s, 2H); 6.95 (br, 1H); 7.48 (d, 2H, ³ J _{HH} = 8.6 Hz); 7.53 (d, 2H, ³ J _{HH} = 8.6 Hz) |
| IXd | 0.93 (t, 3H, ³ J _{HH} = 7.5 Hz); 1.21 (d, 3H, ³ J _{HH} = 6.6 Hz); 1.50–1.57 (m, 2H); 3.88–3.97 (m, 1H); 5.92 (s, 2H); 6.73 (br, 1H); 7.49 (d, 2H, ³ J _{HH} = 8.7 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.7 Hz) |
| IXe | 1.41 (s, 9H); 5.90 (s, 2H); 6.81 (br, 1H); 7.49 (d, 2H, ³ J _{HH} = 8.7 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.7 Hz) |
| IXf | 3.96–4.00 (m, 2H); 5.23–5.30 (m, 2H); 5.78–5.96 (m, 1H); 5.92 (s, 2H); 7.02 (br, 1H); 7.48 (d, 2H, ³ J _{HH} = 8.5 Hz); 7.55 (d, 2H, ³ J _{HH} = 8.5 Hz) |
| IXg | 1.21–1.66 (m, 6H); 1.72–1.77 (m, 2H); 1.92–1.97 (m, 2H); 3.73–3.82 (m, 1H); 5.90 (s, 2H); 6.82 (br, 1H); 7.48 (d, 2H, ³ J _{HH} = 8.4 Hz); 7.53 (d, 2H, ³ J _{HH} = 8.4 Hz) |
| IXh | 5.99 (s, 2H); 7.40–7.64 (m, 9H); 8.67 (s, 1H) |
| IXi | 2.33 (s, 3H); 5.99 (s, 2H); 7.16–8.02 (m, 8H); 8.65 (s, 1H) |
| IXj | 2.35 (s, 3H); 5.97 (s, 2H); 7.14–8.01 (m, 8H); 8.77 (s, 1H) |
| IXk | 6.00 (s, 2H); 7.14–8.42 (m, 8H); 9.33 (s, 1H) |
| IXl | 5.98 (s, 2H); 7.35–8.76 (m, 8H); 8.68 (s, 1H) |

Scheme 1. Synthetic Route of Compound III**Scheme 2.** General Synthetic Route of Compound V

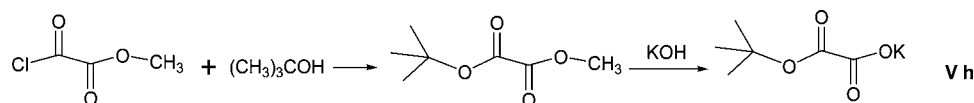
(30 mL), and extracted with ethyl acetate (3 × 60 mL). The organic extract was washed with water (2 × 40 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a solid. The solid was purified by column chromatography on a silica gel using a mixture of petroleum ether (60–90 °C) 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 C₁₅H₁₀BrClF₃N₃O: 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 reflux temperature for 30 min and then diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic extract were washed successively with water (20 mL) and brine (20 mL), dried over anhydrous magnesium

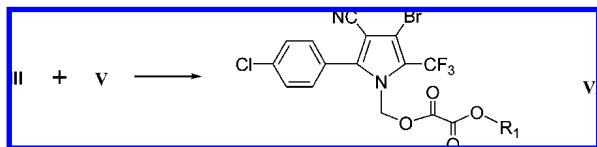
sulfate, and concentrated in vacuo to obtain a solid. Recrystallization from a mixture of ethyl acetate and heptane gave the desired compound III as a white solid (1.02 g, 80%); mp 136–138 °C; ¹H NMR δ 5.61 (s, 2H), 7.49 (d, 2H, ³J_{HH} = 8.7 Hz), 7.54 (d, 2H, ³J_{HH} = 8.7 Hz). Anal. calcd. (%) for C₁₃H₆Br₂ClF₃N₂: C, 35.29; H, 1.37; N, 6.33. Found (%): C, 35.32; H, 1.54; N, 6.57.

General Synthetic Procedure for Alkyloxyoxalic Acid (V). The appropriate alcohol (100 mmol) was added dropwise over 20 min to an excess of oxalyl chloride (200 mmol) at 0 °C. When the addition was complete, the mixture was allowed to warm to room temperature. Excess oxalyl chloride was removed by vacuum distillation. Further distillation afforded alkyloxyoxalyl chloride (IV). Then water (15 mL) was added dropwise over 10 min to alkyloxyoxalyl chloride at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ethyl ether (30 mL). The organic layer was washed successively with brine (20 mL) and water (20 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated to give alkyloxy oxalic acid (V) as colorless oil, which was directly used for the next step without further purification.

Scheme 3. Synthetic Route of Compound Vh



Scheme 4. General Synthetic Route of the Title Compound VI

Synthetic Procedure for *tert*-Butylpotassium Oxalate (Vh).

Methyl oxalyl chloride (5.0 g, 40.80 mmol) was added dropwise to a mixture of anhydrous pyridine (5.06 g, 64.05 mmol), *tert*-butyl alcohol (4.74 g, 64.05 mmol) and anhydrous ether (80 mL). The mixture was stirred at room temperature for 1.5 h. Then the mixture was washed successively with water (60 mL), saturated aqueous sodium hydrogen carbonate solution (100 mL), and water (60 mL) and then dried over anhydrous sodium sulfate. The solvent was evaporated to give *tert*-butyl methyl oxalate as a colorless oil: ^1H NMR (CDCl_3) δ 1.56 (s, 9H), 3.87 (s, 3H).

Methyl *tert*-butyl oxalate (3.22 g, 20.10 mmol) was dissolved in a mixture of acetonitrile (10 mL) and water (10 mL), followed by the addition of potassium hydroxide (1.37 g, 82%, 20.1 mmol). The mixture was stirred at room temperature for 2 h. The solvent was evaporated to give *tert*-butyl potassium oxalate (Vh) (3.18 g) as a white solid, which was directly used for the next step without further purification.

General Synthetic Procedure for the Title Compounds VIa–VIo.

Alkyloxyoxalic acid (V) (4.50 mmol) was added to a stirred suspension of sodium hydroxide (0.18 g, 4.50 mmol) in dimethylformamide (10 mL) at room temperature. After 1 h of stirring, the solution of compound III (0.40 g, 0.90 mmol) in dimethylformamide (3 mL) was added dropwise. After 6 h of stirring 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 aqueous saturated sodium hydrogen carbonate solution (20 mL) and water (3×20 mL) and brine (20 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by recrystallization from a mixture of ethyl acetate and petroleum ether (60–90 °C) to afford the title compounds VIa–VIo. The melting points, yields, and elemental analyses of compounds VIa–VIo are listed in Table 1. The ^1H NMR data are listed in Table 2.

General Synthetic Procedure for Alkylaminooxalic Acid (VIII).

A solution of ethyl oxalyl chloride (6.82 g, 0.05 mol) in dry toluene (20 mL) was added to a mixture of appropriate amine (0.03 mol), toluene (45 mL), and aqueous potassium carbonate (30 mL, 1 mol L^{-1}) at 0–10 °C over 20 min. The layers were separated, and then aqueous sodium hydroxide solution (36 mL, 1 mol L^{-1}) was added to the organic layer, and the mixture was heated to 40–45 °C for 30 min to hydrolyze ester VII. The organic layer was discarded. Ethyl acetate was added to the aqueous phase. The mixture was cooled to 10 °C, acidified with

aqueous sulfuric acid (5 mol L^{-1}), and then saturated with sodium chloride. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated to give alkylaminooxalic acid (VIII), which was directly used for the next step without further purification.

General Synthetic Procedure for the Title Compounds IXa–IXI.

Alkylaminooxalic acid (VIII) (4.50 mmol) was added to a stirred suspension of sodium hydroxide (0.18 g, 4.50 mmol) in dimethylformamide (10 mL) at room temperature. After 1 h of stirring, the solution of compound III (0.40 g, 0.90 mmol) in dimethylformamide (3 mL) was added dropwise. After 6 h of stirring 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 water (3×20 mL) and brine (20 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by recrystallization from a mixture of ethyl acetate and petroleum ether (60–90 °C) to afford the title compounds IXa–IXI. The melting points, yields, and elemental analyses of compounds IXa–IXI are listed in Table 3. The ^1H NMR data are listed in Table 4.

X-ray Diffraction. The crystal structure of compound VIIi was determined, and X-ray intensity data were recorded on a Bruker SMART 1000 CCD diffraction meter using graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å). In the range of $1.64^\circ \leq \theta \leq 27.87^\circ$, 5386 independent reflections were obtained. All calculations were refined anisotropically. All hydrogen atoms were located from a difference Fourier map and were placed at calculated positions and were included in the refinements in the riding mode with isotropic thermal parameters.

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 are based on a percentage scale of 0–100, where 0 equals no activity and 100 equals total kill. Error of the experiments was 5%. For comparative purpose, Chlorfenapyr was tested under the same conditions. The insecticidal activity is summarized in Table 6.

Insecticidal Activity against Oriental Armyworm (*Mythimna separata*). The insecticidal activities of the title compounds VIa–VIo, and IXa–IXI and Chlorfenapyr were evaluated using the reported procedure (22, 23). The insecticidal activity against oriental armyworm was tested by foliar application; individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times.

Insecticidal Activity against Mosquito (*Culex pipiens pallens*). The toxicities of the title compounds VIa–VIo and IXa–IXI and Chlorfenapyr against mosquito were evaluated according to the reported procedure (24–26). One milliliter of different concentrated dilutions of each compound was added to 99 mL of water to get different concentrations of tested solutions. Then 20 fourth-instar mosquito larvae were put into 10 mL of the test solution and raised for 2 days; the result was expressed by death percentage.

Insecticidal Activity against Spider Mite (*Tetranychus cinnabarinus* Boisduval). The insecticidal activities of the title compounds VIa–VIo and IXa–IXI 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 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 plants

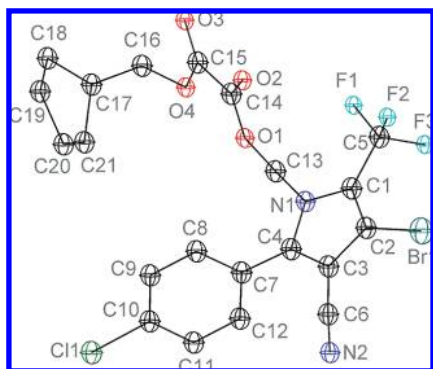


Figure 1. Molecular structure of compound VIIi.

Scheme 5. General Synthetic Route of Compound VIII

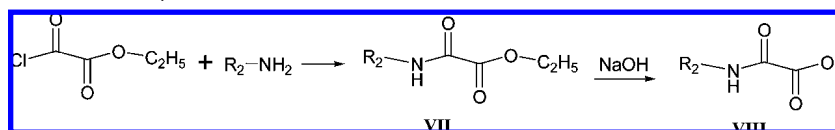
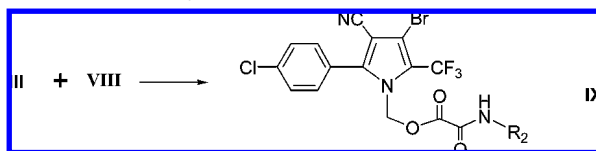


Table 5. Selected Bond Lengths and Torsion Angles of Compound VII

| selected bond | length (Å) | selected bond | length (Å) | selected torsion angle | torsion angle (deg) |
|---------------------------|------------|---------------|------------|------------------------|---------------------|
| C(1)–C(2) | 1.364(5) | N(1)–C(4) | 1.382(4) | C(4)–N(1)–C(1)–C(2) | 1.3(4) |
| C(2)–C(3) | 1.421(5) | N(1)–C(1) | 1.403(4) | C(13)–N(1)–C(1)–C(2) | 179.2(3) |
| C(3)–C(4) | 1.381(5) | Br(1)–C(2) | 1.854(4) | C(4)–N(1)–C(1)–C(5) | –177.4(3) |
| C(1)–C(5) | 1.546(5) | Cl(1)–C(10) | 1.745(4) | C(13)–N(1)–C(1)–C(5) | 0.5(5) |
| C(3)–C(6) | 1.425(5) | F(1)–C(5) | 1.291(4) | N(1)–C(1)–C(2)–C(3) | –0.2(4) |
| C(4)–C(7) | 1.474(4) | F(2)–C(5) | 1.327(4) | C(5)–C(1)–C(2)–C(3) | 178.4(3) |
| C(7)–C(8) | 1.385(4) | F(3)–C(5) | 1.329(4) | N(1)–C(1)–C(2)–Br(1) | –175.6(2) |
| C(8)–C(9) | 1.385(5) | O(1)–C(14) | 1.339(4) | C(5)–C(1)–C(2)–Br(1) | 3.0(5) |
| C(9)–C(10) | 1.383(5) | O(1)–C(13) | 1.441(4) | C(1)–C(2)–C(3)–C(4) | –0.9(4) |
| C(10)–C(11) | 1.372(5) | O(2)–C(14) | 1.198(4) | Br(1)–C(2)–C(3)–C(4) | 174.7(2) |
| C(11)–C(12) | 1.383(5) | O(3)–C(15) | 1.198(4) | C(1)–C(2)–C(3)–C(6) | –179.4(3) |
| C(7)–C(12) | 1.400(4) | N(1)–C(13) | 1.441(4) | Br(1)–C(2)–C(3)–C(6) | –3.9(5) |
| O(4)–C(15) | 1.321(4) | N(2)–C(6) | 1.147(4) | C(2)–C(3)–C(4)–N(1) | 1.7(4) |
| O(4)–C(16 ^{''}) | 1.468(10) | O(4)–C(16) | 1.480(7) | C(6)–C(3)–C(4)–N(1) | –179.8(3) |
| O(4)–C(16') | 1.469(8) | | | C(2)–C(3)–C(4)–C(7) | –172.9(3) |

Scheme 6. General Synthetic Route of the Title Compound IX



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 number of live and dead adults was counted.

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 the 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**.

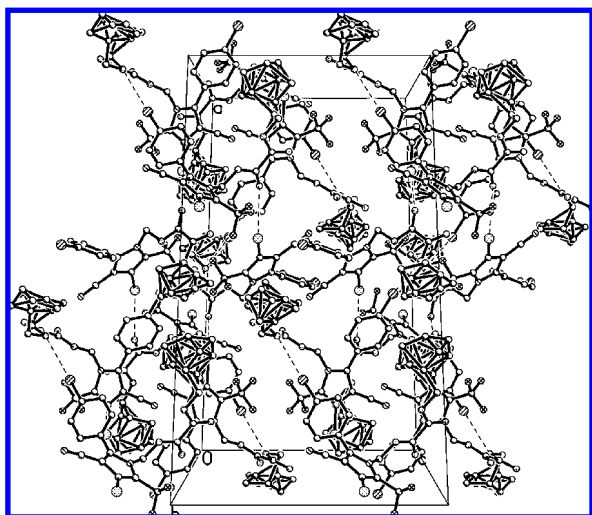


Figure 2. Packing diagram of compound VII.

Alkyloxyloxalic acid (**V**) was synthesized from alcohol and oxalyl chloride as shown in **Scheme 2**. However, *tert*-butoxyloxalic acid cannot be achieved using this method because the boiling points of *tert*-butoxyoxalyl chloride and oxalyl chloride are so close that it is impossible to purify *tert*-butoxyoxalyl chloride by distillation. Hence, intermediate **Vh** was synthesized according to the literature described in **Scheme 3** (20).

The title compounds **VIa–VIo** were synthesized from intermediates **III** and **V** as shown in **Scheme 4**. The key intermediate **III** was reacted with alkyloxyloxalic acid (**V**) in dimethylformamide using sodium hydroxide as alkali to yield *N*-oxalyl derivatives of 2-arylpyrrole **VIa–VIo**. The title compounds **VIa–VIo** could be purified by recrystallization from a mixture of ethyl acetate and petroleum ether. The melting points, yields, and elemental analyses of compounds **VIa–VIo** are listed in **Table 1**. The ¹H NMR data are listed in **Table 2**.

Alkylaminooxalic acid (**VIII**) was synthesized as shown in **Scheme 5**. Ethyl oxalyl chloride was reacted with appropriate amine in the presence of potassium carbonate to obtain ester **VII**, and subsequent hydrolysis using sodium hydroxide gave intermediate **VIII**.

The title compounds **IXa–IXl** were synthesized from intermediates **III** and **VIII** as shown in **Scheme 6**. The key intermediate **III** was reacted with alkylaminooxalic acid (**VIII**) in dimethylformamide using sodium hydroxide as alkali to yield *N*-oxalyl derivatives of 2-arylpyrrole **IXa–IXl**. The title compounds **IXa–IXl** could be purified by recrystallization from a mixture of ethyl acetate and petroleum ether. The melting points, yields, and elemental analyses of compounds **IXa–IXl** are listed in **Table 3**. The ¹H NMR data are listed in **Table 4**.

Crystal Structure Analysis. Compound **VII** was recrystallized from ethyl acetate/petroleum ether to give colorless crystal suitable for X-ray single-crystal diffraction with the following crystallographic parameters: *a* = 28.617(4) Å, *b* = 28.617(4) Å, *c* = 14.3516(18) Å, α = 90°, β = 90°, γ = 120°, μ = 1.990 mm^{−1}, *V* = 10178(2) Å³, *Z* = 18, *D_x* = 1.567 mg m^{−3}, *F*(000) = 4824, *T* = 113(2) K, 1.64° ≤ θ ≤ 27.87°, and the final *R* factor, *R*₁ = 0.0506, ω*R*₂ = 0.1294.

It could be seen from the X-ray single-crystal analysis that the molecule consists of one benzene ring, one pyrrole ring,

Table 6. Insecticidal Activities of Compounds **Vla–Vlo** and **IXa–IXl** against Oriental Armyworm, Mosquito, and Spider Mite

| compd | toxicities against oriental armyworm at | | | toxicities against mosquito at | | | toxicities against spider mite at | | |
|--------------|---|------------------------|-----------------------|--------------------------------|--------------------------|--------------------------|-----------------------------------|-------------------------|------------------------|
| | 20 mg kg ⁻¹ | 10 mg kg ⁻¹ | 5 mg kg ⁻¹ | 0.50 mg kg ⁻¹ | 0.25 mg kg ⁻¹ | 0.10 mg kg ⁻¹ | 200 mg kg ⁻¹ | 100 mg kg ⁻¹ | 50 mg kg ⁻¹ |
| Vla | 100 | 15 | | | | | | | |
| Vlb | 100 | 80 | | | | | | | |
| Vlc | 100 | 100 | 0 | 100 | 100 | 10 | 100 | | |
| Vld | 100 | 70 | | 100 | 100 | 20 | 100 | | |
| Vle | 100 | 100 | | | | | | | |
| Vlf | 100 | 100 | 0 | 100 | 90 | 10 | 100 | | |
| Vlg | 100 | 100 | 0 | 100 | 90 | 10 | 100 | | |
| Vlh | 100 | 10 | | | | | | | |
| Vli | 100 | 30 | | 100 | 100 | 20 | 100 | 90 | 84 |
| Vlj | 100 | 20 | | 100 | 90 | 20 | | | |
| Vlk | 100 | 30 | | 100 | 100 | 80 | | | |
| Vll | 100 | 10 | | 100 | 100 | 100 | 100 | 92 | 83 |
| Vlm | 70 | 10 | | 100 | 30 | 0 | 100 | 95 | 92 |
| Vln | 100 | 20 | | 100 | 90 | 20 | 100 | 95 | 94 |
| Vlo | 100 | 20 | | 100 | 100 | 80 | | | |
| IXa | 100 | 25 | | 100 | 100 | 80 | | | |
| IXb | 100 | 20 | | 100 | 80 | 30 | 100 | 95 | 87 |
| IXc | 100 | 0 | | 100 | 90 | 20 | 48 | 0 | |
| IXd | 100 | 30 | | | | | | | |
| IXe | 100 | 20 | | 100 | 30 | 10 | | | |
| IXf | 100 | 15 | | | | | 96 | 93 | 89 |
| IXg | 100 | 20 | | 100 | 90 | 20 | 76 | 46 | |
| IXh | 100 | 0 | | 100 | 30 | 0 | 99 | 92 | 86 |
| IXi | 100 | 10 | | 100 | 100 | 100 | | | |
| IXj | 100 | 10 | | 100 | 100 | 40 | 96 | 90 | 79 |
| IXk | 100 | 30 | | | | | 71 | 51 | |
| IXl | 100 | 20 | | 100 | 10 | 0 | 100 | 92 | 84 |
| Chlorfenapyr | 100 | 100 | 0 | 100 | 100 | 100 | 100 | 97 | 93 |

and one cyclopentane ring. The benzene ring and the pyrrole ring are connected through the C4 atom of the benzene ring and the C7 atom of the pyrrole ring. The dihedral angle between the plane of the benzene ring and the plane of the pyrrole ring is about 66°. In addition, the cyclopentane ring exhibits a disordered state (**Figure 1**). Selected bond lengths are listed in **Table 5**. The bond lengths of C(1)–C(2) and C(3)–C(4) are 1.364(5) and 1.381(5) Å, respectively, which are longer than normal C=C (1.34 Å). The bond length of C(2)–C(3) [1.421(5) Å] is shorter than normal C–C (1.54 Å). The bond lengths of C(4)–N(1) [1.382(4) Å] and C(1)–N(1) [1.403(4) Å] are shorter than the normal C–N single bond (1.49 Å). The bond lengths of C(14)–O(2) [1.198(4) Å] and C(15)–O(3) [1.198(4) Å] are shorter than normal C=O (1.34 Å), and the bond lengths of C(14)–O(1) [1.339(4) Å] and C(15)–O(4) [1.321(4) Å] are shorter than normal single C–O (1.44 Å). The packing structure of this compound is shown in **Figure 2**.

Bioassay. **Table 6** shows the insecticidal activities of the title compounds **Vla–Vlo** and **IXa–IXl** and that of contrast compound Chlorfenapyr against oriental armyworm, mosquito, and spider mite.

Insecticidal Activities against Oriental Armyworm (*M. separata* Walker). The results of insecticidal activities given in **Table 6** indicate that most of the title compounds **Vla–Vlo** exhibit excellent activity against oriental armyworm, which are good compared to the commercialized Chlorfenapyr. For instance, the insecticidal activities of the title compounds **Vlc**, **Vle**, **Vlf**, and **Vlg** were equal to that of Chlorfenapyr. Among R₁ of the title compounds **Vla–Vlo**, a saturated short-chain alkyl group is most prominent in increasing activity. From **Table 6**, we can also find that the title compounds **IXa–IXl** exhibit lower insecticidal activities against oriental armyworm than the title compounds **Vla–Vlo**.

Insecticidal Activities against Mosquito (*C. pipiens pallens*). The insecticidal activities of the title compounds **Vla–Vlo** and **IXa–IXl** against mosquito were evaluated. The results indicate

that some of the title compounds **Vla–Vlo** and **IXa–IXl** exhibited excellent activities against mosquito. For example, the insecticidal activities of compounds **Vll** and **IXi** against mosquito at 0.10 mg kg⁻¹ were 100%, which is parallel to that of the commercialized Chlorfenapyr.

Insecticidal Activities against Spider Mite (*T. cinnabarinus* Boisduval). The result of insecticidal activities given in **Table 6** show that most of the title compounds **Vla–Vlo** and **IXa–IXl** exhibit excellent activities against spider mite. For example, the insecticidal activities of the title compounds **Vlm** and **Vln** were equal to that of the commercialized Chlorfenapyr at 50 mg kg⁻¹.

In summary, two series of novel *N*-alkyloxyoxalyl derivatives of 2-arylpyrrole were synthesized from 4-bromo-1-(bromomethyl)-2-(4-chlorophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile, and their structures were characterized by ¹H NMR spectroscopy, elemental analysis, and single-crystal X-ray diffraction analysis. The insecticidal activities of the new compounds were evaluated. The results of bioassays indicated that some of these title compounds exhibited excellent insecticidal activities, and their insecticidal activities against oriental armyworm, mosquito, and spider mite are comparable to that of the commercial insecticide Chlorfenapyr.

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. In *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., Ed.; American Chemical Society: Washington, DC, 1984; pp 87–101.
- (13) Mao, C.; Wang, Q.; Huang, R.; Bi, F.; Chen, L.; Liu, Y.; Shang, J. Synthesis and insecticidal evaluation of novel *N*-oxalyl derivatives of tebufenozide. *J. Agric. Food Chem.* **2004**, 52, 6737–6741.
- (14) Kameswaran, V.; Barton, J. M. Process for the manufacture of pesticidal 1-(alkoxymethyl)-pyrrole compounds. U.S. Patent 5151536, 1992.
- (15) Kameswaran, V.; Princeton, J. N. Method for the preparation of 2-aryl-5-(trifluoromethyl)pyrrole compounds. U.S. Patent 5256796, 1993.
- (16) Kameswaran, V.; Princeton, J. N. Ammonium oxazole and amino oxazolium intermediates, methods for the preparation thereof and the use thereof in the manufacture of insecticidal arylpyrroles. U.S. Patent 5925773, 1999.
- (17) Kameswaran, V.; Princeton, J. N. Oxazole amines as intermediate in the manufacture of insecticidal arylpyrroles. U.S. Patent 5631379, 1997.
- (18) Kameswaran, V.; Princeton, J. N. Perfluoroalkanoyl aminotrioles. U.S. Patent 5426225, 1995.
- (19) Kameswaran, V. *N*-Alkanoylaminomethyl and *N*-aroylaminomethyl pyrrole insecticidal and acaricidal agents. U.S. Patent 5130328, 1991.
- (20) Cox, R. J.; Wang, P. S. H. Synthesis and *in vitro* enzyme activity of aza, oxa and thia derivatives of bacterial cell wall biosynthesis intermediates. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2022–2034.
- (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*-sulphenyl-*N'*-*tert*-butyl-*N,N'*-diacylhydrazines. 1. *N*-Alkoxysulfenyl 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. *Zhongguomeijieshengwuxue jikanzhizhi Zazhi* **2005**, 16 (6), 413–416.
- (25) Raymond, M.; Marquine, M. Evolution of insecticide resistance in *Culex pipiens* populations: 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*-Aminoalkylcarboxyloxypyrrole insecticidal, acaricidal and molluscicidal agents. U.S. Patent 5286743, 1992.
- (28) Kuhn, D. G.; Kameswaran, V. Insecticidal, Acaricidal and Molluscicidal 1-(Substituted)thioalkylpyrroles. U.S. Patent 5302383, 1993.

Received for review April 27, 2008. Revised manuscript received June 11, 2008. Accepted June 12, 2008. This work was supported by the National Key Project for Basic Research (2003CB114400) and the National Natural Science Foundation of China (20672064).

JF801311H