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Synthesis and Insecticidal Activities of Novel *N*-Sulfenyl-*N′*-*tert*-butyl-*N,N′*-diacylhydrazines. 3. *N*-(Alkyldithio), *N*-(Aminothio), and *N,N*-Dithio Derivatives

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A series of novel *N*-(alkyldithio) and *N*-aminothio derivatives of *N′*-*tert*-butyl-*N,N′*-diacylhydrazines were designed and synthesized as insect growth regulators via the key intermediates *N*-chlorosulfenyl-*N′*-*tert*-butyl-*N,N′*-diacylhydrazines. A series of novel *N,N*-dithio derivatives were also designed and synthesized with *N′*-*tert*-butyl-*N,N′*-diacylhydrazines and sulfur chloride in the presence of sodium hydride. Compared to the parent compounds, these derivatives displayed better solubility and improved hydrophobicities. The insecticidal activities of the target compounds were evaluated. The results of bioassays showed that the target compounds possessed comparable activities against oriental armyworm with the corresponding parent compounds. In particular, *N*-(morpholinosulfenyl)-*N′*-*tert*-butyl-*N*-4-ethylbenzoyl-*N′*-3,5-dimethylbenzoylhydrazide (**IIIk**) has higher toxicities against oriental armyworm and diamondback moth than the parent compound, **RH-5992**.

KEYWORDS: ***N*-Sulfenate; derivative; *N*-(alkyldithio)diacylhydrazine; *N*-(aminothio)diacylhydrazine; *N,N*-dithiodiacylhydrazine; RH-5992; insecticidal activity; insect growth regulator**

INTRODUCTION

N-*tert*-Butyl-*N,N′*-diacylhydrazines are a class of chemically and mechanistically novel insect growth regulators that have been found to act as nonsteroidal ecdysone agonists inducing, especially in *Lepidoptera*, precocious molting, leading to death (*1*−*3*). Because of their unique action, simple structure, low toxicity to vertebrates, and high insecticidal selectivity, diacylhydrazines have attracted considerable attention in recent years (*4*−*7*). Among these active compounds, *N*-*tert*-butyl-*N,N′*-dibenzoylhydrazine (**RH-5849**, **Figure 1**) was the first to be thoroughly investigated with regard to insecticidal effects and functional modes (*1*−*3*), and tebufenozide (**RH-5992**, **Figure 1**) was the first to be commercialized as a leptidopteran-specific insecticide (*8, 9*). Halofenozide (**RH-0345**, **Figure 1**) was found to exhibit high activity against Coleopteran larvae and ova (*10*), whereas methoxyfenozide (**RH-2485**, **Figure 1**) exhibited higher activity against Lepidoptera and a wider insecticidal spectrum than tebufenozide (*11, 12*). Both methoxyfenozide and halofenozide were characterized with significant root systemic activity. It has been reported that *N′*-benzoheterocyclecarbonyl-*N*-*tert*-butyl-3,5-dimethylbenzohydrazide analogues showed high insecticidal activities, of which **ANS-118** and **JS-118** (**Figure 1**) represent successful examples (*13, 14*).

However, the preceding diacylhydrazines have low solubility in water and limited solubility in common organic solvents. Moreover, they have poor hydrophobicity and cuticular penetration. These disadvantages impede their field application (*12, 15*). The activity spectrum of a pesticide is often determined by the physical properties of the compound, and it is possible to develop a new insecticide with improved biological properties by attaching an appropriate functional group to an insecticide (*15*−*19*). For example, Qian synthesized a series of *N′*-*tert*-butyl-*N′*-aroyl-*N*-(alkoxycarbonylmethyl)-*N*-aroylhydrazines (**A**, **Figure 1**) and evaluated their insecticidal activities against armyworm (*4*). Mulvihill synthesized a diverse series of novel insecticidally active propionyloxy(*p*-tolyl)methyl methoxyfenozide-*N*-carboxylate (**B**, **Figure 1**) as well as 2-oxo-3-phenyl-1-(propionyloxy)-propyl halofenozide-*N*-carboxylate (**C**, **Figure 1**) (*20, 21*). Our group reported a series of novel *N′*-*tert*-butyl-*N′*-3,5-dimethylbenzoyl-*N*-aryloxyoxalyl-*N*-4-ethylbenzoyl hydrazines (**D**, **Figure 1**) containing a carboxylic acid or ester substituent on the aryl and their larvicidal activities (*15*).

In our previous work, *N*-methoxysulfenyl-*N′*-*tert*-butyl-*N*-4-ethylbenzoyl-*N′*-3,5-dimethylbenzoylhydrazide (**E**, **Figure 1**)

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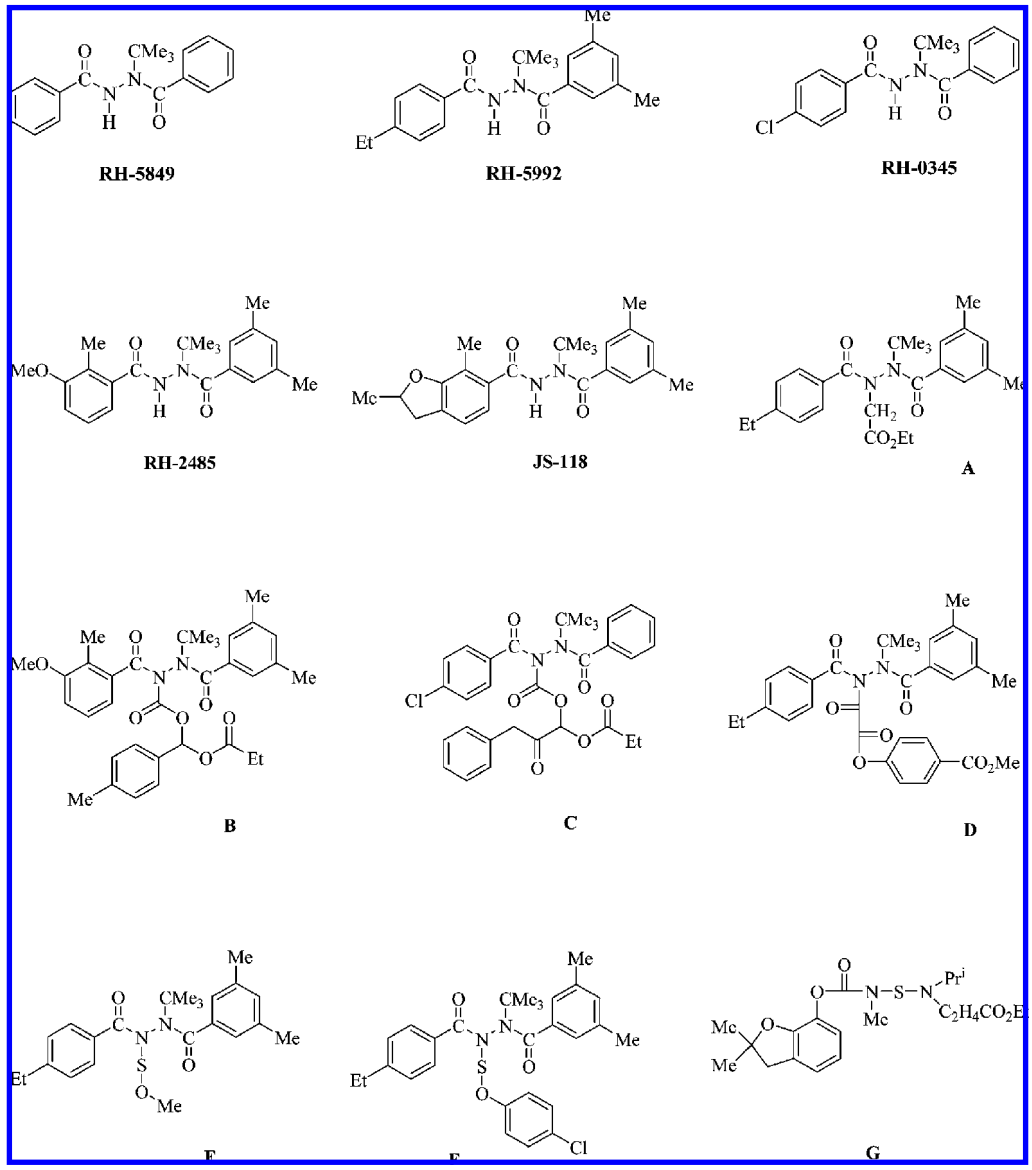

Figure 1. Chemical structures of compounds **RH-5849**, **RH-5992**, **RH-0345**, **RH-2485**, **JS-118**, and **A**−**G**.

and *N*-(4-chlorophenoxy)sulfenyl-*N*′-*tert*-butyl-*N*-4-ethylbenzoyl-*N*′-3,5-dimethylbenzoylhydrazide (**F**, **Figure 1**), the *N*-sulfenate derivatives of **RH-5992**, showed higher stomach toxicities against oriental armyworm and contact activities against Asian corn borer, tobacco cutworm, and cotton bollworm than the parent compound, **RH-5992** (*18, 19*).

It has been reported that the introduction of an *N*-(alkyldithio) or*N*-aminothio substituent or an *N*,*N*-dithio linker into carbamate insecticides maintained their high level of pesticidal activity while greatly reducing their mammalian toxicity, for example, commercialized benfuracarb (**G**, **Figure 1**) (*17, 22*−*24*). Hence, we proposed that the introduction of these derivative groups into *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines by substituting the hydrogen on the *N*′ atom could improve hydrophobicity and biological properties. Herein, we report the synthesis and insecticidal activities of a series of novel *N*-(alkyldithio), *N*-aminothio, and *N*,*N*-dithio derivatives of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**III**) as shown in **Figures 2**, **3**, and **4**, respectively.

MATERIALS AND METHODS

Instruments. The target compounds were synthesized under a nitrogen atmosphere. ^{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) 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.

General Synthesis. All anhydrous solvents were dried and purified by standard techniques just before use. *N*′-*tert*-Butyl-*N*,*N*′-diacylhydrazines (**I**) were synthesized according to the literature method (*3*). Sulfur dichloride was prepared by the reaction of sulfur chloride with chlorine (*25*). Sulfur chloride was distilled just before use. Pyridine was distilled over sodium hydroxide pellets and kept dry by storage over the same reagent.

General Synthetic Procedure for II. To a magnetically stirred and cooled (−20 °C) solution of sulfur dichloride (0.83 g, 8 mmol) in dichloromethane (15 mL) was added dropwise a solution of pyridine (0.63 g, 8 mmol) in dichloromethane (5 mL). After the addition was complete, the reaction mixture was stirred below −15 °C for 15 min. Then, a solution of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**I**) (7 mmol) in dichloromethane (5 mL) was added, and the resulting mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo to afford a viscous residue, and then toluene (20 mL) was added. The

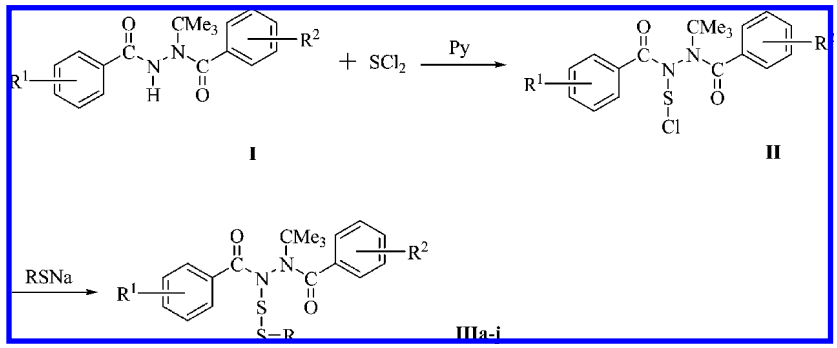

Figure 2. General synthetic route for compounds **IIIa-j**.

Table 1. Physical Properties and Elemental Analyses of Compounds **IIIa−y**

						elemental analysis (%, calcd)		
compd	R	R^1	R^2	mp (°C)	yield (%)	C	H	N
IIIa	*n*-Pr	4-Et	3,5-Me_2	79−81	27.9	65.42 (65.46)	7.30 (7.47)	6.27 (6.11)
IIIb	*n*-Bu	4-Et	3,5-Me_2	81−83	43.9	65.92 (66.06)	7.75 (7.68)	6.04 (5.93)
IIIc	*n*-Pr	H	H	oil	30.9	62.45 (62.65)	6.50 (6.51)	6.92 (6.96)
IIId	*n*-Bu	H	H	oil	32.2	63.68 (63.43)	6.84 (6.77)	6.89 (6.72)
IIIe	*n*-Pr	*a*	3,5-Me_2	141−143	47.7	64.68 (64.76)	7.01 (7.25)	5.85 (5.59)
IIIf	*n*-Bu	*a*	3,5-Me_2	44−46	26.1	65.03 (65.33)	7.31 (7.44)	5.44 (5.44)
IIIg	*n*-Pr	3-OMe, 2-Me	3,5-Me_2	102−104	49.0	62.98 (63.26)	7.39 (7.22)	5.89 (5.90)
IIIh	*n*-Bu	3-OMe, 2-Me	3,5-Me_2	94−95	58.9	63.71 (63.90)	7.47 (7.42)	5.72 (5.73)
IIIi	*n*-Pr	Cl	H	oil	58.3	57.49 (57.71)	5.94 (5.77)	6.37 (6.41)
IIIj	*n*-Bu	Cl	H	oil	61.6	58.42 (58.58)	5.92 (6.03)	6.23 (6.21)
IIIk		morpholino	132−134	65.9	66.21 (66.49)	7.46 (7.51)	8.78 (8.95)	
IIIl		piperidinyl	127−129	42.8	69.38 (69.34)	7.89 (7.97)	9.09 (8.99)	
IIIm		H	*p*-Cl-Ph	162−164	55.6	65.71 (65.93)	6.20 (6.32)	8.38 (8.24)
IIIn		Et	Et	44−46	58.8	68.24 (68.53)	8.08 (8.18)	9.52 (9.22)
IIIo		*n*-Bu	*n*-Bu	95−96	49.0	70.56 (70.41)	8.69 (8.86)	8.43 (8.21)
IIIp		Me	Ph	140−141	55.6	71.09 (71.13)	7.25 (7.20)	8.49 (8.58)
IIIq		$PhCH_2$	$C_2H_4CO_2Et$	86−88	62.7	69.24 (69.24)	7.30 (7.35)	7.11 (7.12)
IIIr		H	*p*-Me-Ph	159−161	45.9	70.92 (71.13)	7.10 (7.20)	8.75 (8.58)
IIIs		H	H	148−150	80.6	66.02 (66.03)	6.24 (5.85)	8.68 (8.56)
IIIt		4-Et	3,5-Me_2	128−130	86.6	68.82(68.90)	7.36 (7.10)	7.20 (7.30)
IIIu		4-Cl	H	143−145	85.6	59.65 (59.75)	5.12 (5.01)	7.68 (7.74)
IIIv		4-Cl	3-Me	130−132	90.5	60.70 (60.71)	5.38 (5.36)	7.42 (7.45)
IIIw		H	3,5-Me_2	147−149	84.0	67.52 (67.58)	6.67 (6.52)	7.95 (7.88)
IIIx		H	3-Me	133−135	90.5	65.29 (66.84)	6.33 (6.20)	8.60 (8.20)
IIIy		4-Cl	3,5-Me_2	150−152	89.7	60.84 (61.61)	5.91(5.69)	7.05 (7.18)

[a] R^1 is identical with the corresponding substituents of the parent compound (**JS-118**).

mixture was stirred at −10 °C for 15 min and then filtered to remove the pyridinium chloride. The filtrate was directly used for the next step without further purification.

General Synthetic Procedure for the Target Compounds IIIa−j. To a stirred suspension of sodium hydride (2.5 mmol) in dry xylene (20 mL) was added thiol (2.2 mmol) in portions at room temperature. The reaction mixture was warmed to about 70 °C, and stirring was continued for 2 h and then cooled to −10 °C. A filtrate of *N*-chlorosulfenyl diacylhydrazine (**II**) (2 mmol) was added dropwise, and then the resulting mixture was stirred at room temperature for 4 h and filtered; the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the target compounds **IIIa−j**.

General Synthetic Procedure for the Target Compounds IIIk−r. To a cooled (−5 °C) solution of *N*-chlorosulfenyl diacylhydrazine (**II**) (3 mmol) in toluene (10 mL) was added a mixture of amine (3 mmol) and triethylamine (3 mmol) in toluene (3 mL) dropwise, and then the resulting mixture was stirred at room temperature for 30 min and filtered; the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the target compounds **IIIk−r**.

General Synthetic Procedure for the Target Compounds IIIs−y. To a solution of diacylhydrazine (**I**) (6 mmol) in THF (25 mL) was added sodium hydride (7 mmol) in portions. The resulting mixture was stirred until no gas was released, and then a solution of sulfur chloride (3 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature overnight and then filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate as the eluent to afford the target compounds **IIIs−y**.

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 (*26*). Evaluations were based on a percentage scale of 0−100 in which 0 = no activity and 100 = total kill.

Larvicidal Activity against Oriental Armyworm (*Mythimna separata*). The larvicidal activities of the target compounds **IIIa−y** and the parent compounds **I** against oriental armyworm were evaluated by foliar application using the reported procedure (*18, 27, 28*). For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed three times. For comparative purposes, the parent compounds, **RH-5849**, **RH-5992**, **JS-118**, **RH-2485**, and **RH-0345**, were tested under the same conditions.

Larvicidal Activity against Diamondback Moth (*Plutella xylostella*). The larvicidal activities of the target compound **IIIk** and the

Table 2. ^{1}H NMR of Compounds **IIIa**−**y**

compd	δ
IIIa	7.16−6.85 (m, 7H, Ph), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, PhC**H**$_2$CH$_3$), 2.39−2.02 (m, 8H, Ph(C**H**$_3$)$_2$ and C**H**$_2$CH$_2$CH$_3$), 1.70 (s, 9H, C(CH$_3$)$_3$), 1.30−1.06 (m, 5H, PhCH$_2$C**H**$_3$ and CH$_2$C**H**$_2$CH$_3$), 0.68 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$C**H**$_3$)
IIIb	7.17−6.83 (m, 7H, Ph), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, PhC**H**$_2$CH$_3$), 2.33−2.05 (m, 8H, Ph(C**H**$_3$)$_2$ and C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.70 (s, 9H, C(CH$_3$)$_3$), 1.31−0.93 (m, 7H, PhCH$_2$C**H**$_3$ and CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.74 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IIIc	7.50 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 7.45−7.34 (m, 4H, Ph), 7.26 (t, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 6.90 (t, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 2.23−2.14 (m, 1H, C**H**$_2$CH$_2$CH$_3$), 2.13−2.04 (m, 1H, C**H**$_2$CH$_2$CH$_3$), 1.71 (s, 9H, C(CH$_3$)$_3$), 1.22−1.10 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 0.68 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$C**H**$_3$)
IIId	7.50 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 7.45−7.32 (m, 4H, Ph), 7.26 (t, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 6.90 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 2.27−2.15 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.15−2.03 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.71 (s, 9H, C(CH$_3$)$_3$), 1.18−0.98 (m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.73 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IIIe	7.13 (s, 2H, Ph), 7.03 (s, 1H, Ph), 6.80 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ph), 6.07−5.52 (m, 1H, Ph), 4.96−4.80 (m, 1H, PhOC**H**(CH$_3$)CH$_2$), 3.32−3.18 (m, 1H, PhC**H**$_2$), 2.82−2.68 (m, 1H, PhC**H**$_2$), 2.31−1.84 (m, 11H, Ph(C**H**$_3$)$_2$, PhC**H**$_3$ and C**H**$_2$CH$_2$CH$_3$), 1.71 (s, 9H, C(CH$_3$)$_3$), 1.43 (d, $^3J_{HH}$ = 6.3 Hz, 3H, PhOCH(C**H**$_3$)CH$_2$), 1.28−1.12 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 0.77−0.68 (m, 3H, CH$_2$CH$_2$C**H**$_3$)
IIIf	7.21−6.74 (m, 4H, Ph), 6.32−5.28 (m, 1H, Ph), 4.95−4.81 (m, 1H, PhOC**H**(CH$_3$)CH$_2$), 3.33−3.18 (m, 1H, PhC**H**$_2$), 2.83−2.68 (m, 1H, PhC**H**$_2$), 2.36−1.89 (m, 11H, Ph(C**H**$_3$)$_2$, PhC**H**$_3$ and C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.70 (s, 9H, C(CH$_3$)$_3$), 1.43 (d, $^3J_{HH}$ = 6.0 Hz, 3H, PhOCH(C**H**$_3$)CH$_2$), 1.23−1.04 (m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.81−0.72 (m, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IIIg	7.16−6.72 (m, 6H, Ph), 3.78 (s, 3H, OCH$_3$), 2.33−2.02 (m, 11H, Ph(C**H**$_3$)$_2$, PhC**H**$_3$ and C**H**$_2$CH$_2$CH$_3$), 1.70 (s, 9H, C(CH$_3$)$_3$), 1.25−1.02 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 0.68 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$C**H**$_3$)
IIIh	7.17−6.69 (m, 6H, Ph), 3.78 (s, 3H, OCH$_3$), 2.32−2.03 (m, 11H, 11H, Ph(C**H**$_3$)$_2$, PhC**H**$_3$ and C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.71 (s, 9H, C(CH$_3$)$_3$), 1.18−0.97 (m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.74 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IIIi	7.50−7.32 (m, 5H, Ph), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 6.83 ((d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 2.33−2.23 (m, 1H, C**H**$_2$CH$_2$CH$_3$), 2.23−2.13 (m, 1H, C**H**$_2$CH$_2$CH$_3$), 1.69 (s, 9H, C(CH$_3$)$_3$), 1.31−1.17 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 0.74 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH$_2$CH$_2$C**H**$_3$)
IIIj	7.50−7.32 (m, 5H, Ph), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 6.83 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ph), 2.36−2.27 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 2.25−2.15 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_3$), 1.69 (s, 9H, C(CH$_3$)$_3$), 1.28−1.01 (m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.78 (t, $^3J_{HH}$ = 6.8 Hz, 3H, CH$_2$CH$_2$CH$_2$C**H**$_3$)
IIIk	7.17−7.03 (m, 5H, Ph), 6.95−6.83 (m, 2H, Ph), 3.63−3.50 (m, 2H, CH$_2$OCH$_2$), 3.37−3.17 (m, 2H, CH$_2$OCH$_2$), 3.16−3.02 (m, 1H, CH$_2$NCH$_2$), 2.99−2.85 (m, 1H, CH$_2$NCH$_2$), 2.81−2.68 (m, 1H, CH$_2$NCH$_2$), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, PhC**H**$_2$CH$_3$), 2.48−2.34 (m, 1H, CH$_2$NCH$_2$), 2.30 (s, 6H, Ph(C**H**$_3$)$_2$), 1.67 (s, 9H, C(CH$_3$)$_3$), 1.20 (t, J = 7.6 Hz, 3H, PhCH$_2$C**H**$_3$)
IIIl	7.17 (s, 2H, Ph), 7.11 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ph), 7.04 (s, 1H, Ph), 6.96−6.85 (m, 2H, Ph), 2.98−2.83 (m, 2H, piperidinyl), 2.74−2.48 (m, 4H, piperidinyl and PhC**H**$_2$CH$_3$), 2.30 (s, 6H, Ph(C**H**$_3$)$_2$), 1.67 (s, 9H, C(CH$_3$)$_3$), 1.45−1.35 (m, 2H, piperidinyl), 1.31−1.15 (m, 5H, piperidinyl and PhCH$_2$C**H**$_3$), 1.20−0.96 (m, 2H, piperidinyl)
IIIm	7.12 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ph), 7.06−6.84 (m, 7H, Ph), 6.41−6.27 (m, 2H, Ph), 5.50 (s, 1H, NH), 2.69 (q, $^3J_{HH}$ = 7.5 Hz, 2H, PhC**H**$_2$CH$_3$), 2.21 (s, 6H, PH(C**H**$_3$)$_2$), 1.63 (s, 9H, C(CH$_3$)$_3$), 1.27 (t, $^3J_{HH}$ = 7.5 Hz, 3H, PhCH$_2$C**H**$_3$)
IIIn	7.14 (s, 2H, Ph), 7.08 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 7.02 (s, 1H, Ph), 6.96−6.86 (m, 2H, Ph), 2.97−2.85 (m, 1H, N(C**H**$_2$CH$_3$)$_2$), 2.75−2.57 (m, 5H, N(C**H**$_2$CH$_3$)$_2$ and PhC**H**$_2$CH$_3$), 2.29 (s, 6H, Ph(C**H**$_3$)$_2$), 1.66 (s, 9H, C(CH$_3$)$_3$), 1.18 (t, $^3J_{HH}$ = 7.6 Hz, 3H, PhCH$_2$C**H**$_3$), 0.74 (t, $^3J_{HH}$ = 6.4 Hz, 3H, N(CH$_2$C**H**$_3$)$_2$), 0.68 (t, $^3J_{HH}$ = 7.6 Hz, 3H, N(CH$_2$C**H**$_3$)$_2$)
IIIo	7.15 (s, 2H, Ph), 7.09 (d, $^3J_{HH}$ = 7.6 Hz, 2H, Ph), 7.02 (s, 1H, Ph), 6.99−6.89 (m, 2H, Ph), 2.91−2.79 (m, 1H, NC**H**$_2$CH$_2$CH$_2$CH$_3$), 2.66−2.39 (m, 5H, N(C**H**$_2$CH$_2$CH$_2$CH$_3$)$_2$ and PhC**H**$_2$CH$_3$), 2.29 (s, 6H, Ph(C**H**$_3$)$_2$), 1.67 (s, 9H, C(CH$_3$)$_3$), 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, PhCH$_2$C**H**$_3$), 1.12−0.89 (m, 8H, N(CH$_2$C**H**$_2$C**H**$_2$CH$_3$)$_2$), 0.79−0.67 (m, 6H, N(CH$_2$CH$_2$CH$_2$C**H**$_3$)$_2$)
IIIp	7.23−6.83 (m, 11H, Ph), 6.68 (s, 1H, Ph), 2.91−2.52 (m, 5H, NCH$_3$ and PhC**H**$_2$CH$_3$), 2.27(s, 3H, Ph(C**H**$_3$)$_2$), 2.18 (s, 3H, Ph(C**H**$_3$)$_2$), 1.74 (s, 4H, C(CH$_3$)$_3$), 1.39 (s, 5H, C(CH$_3$)$_3$), 1.26 (q, $^3J_{HH}$ = 7.5 Hz, 3H, PhCH$_2$C**H**$_3$)
IIIq	7.33 (s, 1H, Ph), 7.25−6.86 (m, 11H, Ph), 4.33−4.18 (m, 1H, NC**H**$_2$Ph), 4.06−3.81 (m, 3H, NC**H**$_2$Ph and NCH$_2$CH$_2$CO$_2$C**H**$_2$CH$_3$), 3.74−3.61 (m, 1H, NC**H**$_2$CH$_2$CO$_2$CH$_2$CH$_3$), 3.17−3.03 (m, 1H, NC**H**$_2$CH$_2$CO$_2$CH$_2$CH$_3$), 2.87−2.73 (m, 1H, NCH$_2$C**H**$_2$CO$_2$CH$_2$CH$_3$), 2.65−2.51 (m, 2H, PhC**H**$_2$CH$_3$), 2.49−2.39 (m, 1H, NCH$_2$C**H**$_2$CO$_2$CH$_2$CH$_3$), 2.37 (s, 3H, Ph(C**H**$_3$)$_2$), 2.33 (s, 3H, Ph(C**H**$_3$)$_2$), 1.70 (d, $^3J_{HH}$ = 8.8 Hz, 9H, C(CH$_3$)$_3$), 1.22−1.05 (m, 6H, NCH$_2$CH$_2$CO$_2$CH$_2$C**H**$_3$ and PhCH$_2$C**H**$_3$)
IIIr	7.11 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99−6.80 (m, 7H, Ph), 6.43 (d, $_3J_{HH}$ = 8.1 Hz, 2H, Ph), 5.46 (s, 1H, NH), 2.68 (q, $^3J_{HH}$ = 7.5 Hz, 2H, PhC**H**$_2$CH$_3$), 2.24 (s, 3H, PhC**H**$_3$), 2.18 (s, 6H, Ph(C**H**$_3$)$_2$), 1.64 (s, 9H, C(CH$_3$)$_3$), 1.26 (t, $^3J_{HH}$ = 7.5 Hz, 3H, PhCH$_2$C**H**$_3$)
IIIs	7.37−7.24 (m, 20H, Ph), 1.70 (s, 9H, C(CH$_3$)$_3$), 1.56 (s, 9H, C(CH$_3$)$_3$)
IIIt	7.32−7.49 (m, 18H, Ph), 6.64−7.17 (m,14H, Ph), 2.62 (m, 4H, PhC**H**$_2$CH$_3$), 2.27 (s, 6H, Ph(C**H**$_3$)$_2$), 2.20 (s, 6H, Ph(C**H**$_3$)$_2$), 1.69 (s, 9H, C(CH$_3$)$_3$), 1.56 (s, 9H, C(CH$_3$)$_3$), 0.84 (t, 6H, PhCH$_2$C**H**$_3$)
IIIu	7.49−7.32 (m, 18H, Ph), 1.68 (s, 18H, C(CH$_3$)$_3$)
IIIv	7.82−6.39 (m, 16H, Ph), 2.21 (s, 6H, Ph(C**H**$_3$)$_2$), 1.69 (s, 9H, C(CH$_3$)$_3$), 1.46 (s, 9H, C(CH$_3$)$_3$)
IIIw	6.51−7.57 (m, 16H, Ph). 2.20 (s, 12H, Ph(C**H**$_3$)$_2$), 1.77 (s, 9H, C(CH$_3$)$_3$), 1.55 (s, 9H, C(CH$_3$)$_3$)
IIIx	7.71−6.47 (m, 18H, Ph), 2.23 (s, 6H, Ph(C**H**$_3$)$_2$), 1.79 (s, 9H, C(CH$_3$)$_3$), 1.57 (s, 9H, C(CH$_3$)$_3$)
IIIy	7.48−6.44 (m, 14H, Ph), 2.20(s, 12H, Ph(C**H**$_3$)$_2$), 1.80 (s, 9H, C(CH$_3$)$_3$), 1.74 (s, 9H, C(CH$_3$)$_3$)

corresponding parent compound **RH-5992** against diamondback moth were tested by leaf-dip method using the reported procedure (*29*). Leaf disks (1.8 cm diameter) were cut from fresh cabbage leaves and then were 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 piece of filter paper, and then 10 second-instar diamondback moth larvae were transferred to the Petri dish. Percentage mortalities were evaluated 6 days after treatment, and three replicates were carried out. The data for the mortality−regression lines of the compounds were subjected to probit analysis by Finney's method, and the median lethal concentrations (LC_{50}) of the compounds against diamontback moth larvae were calculated.

RESULTS AND DISCUSSION

Synthesis. *N*-(Alkyldithio)diacylhydrazine (**IIIa**−**j**) and *N*-(aminothio)diacylhydrazine (**IIIk**−**r**) were synthesized as shown in **Figures 2** and **3**, respectively. *N*-Chlorosulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**II**) were prepared by the reaction of sulfur dichloride with *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**I**) in the presence of pyridine according to our previous work (*18, 19*). The key intermediates **II** without further purification were reacted with sodium alkyl mercaptide or with amine to give the target compounds **IIIa**−**r**. *N*,*N*-Dithiodiacylhydrazine (**IIIs**−**y**) were synthesized with *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines and sulfur chloride in the presence of sodium hydride according to **Figure 4**.

We found that the target compounds **III** have better solubility than the parent compounds **I** in organic solvents such as methylene dichloride, chloroform, toluene, xylene, petroleum ether, which should make them easier to apply in the field. Moreover, compared to the parent compounds **I**, the hydropho-

Table 3. Larvicidal Activities against Oriental Armyworm of Compounds **IIIa**−**r** and Parent Compounds

	larvicidal activity (%) at						
compd	200 mg kg^{-1}	100 mg kg^{-1}	50 mg kg^{-1}	25 mg kg^{-1}	10 mg kg^{-1}	5 mg kg^{-1}	2.5 mg kg^{-1}
IIIa					100	100	100
IIIb					100	100	90
IIIc			100	90	0		
IIId			100	90	0		
IIIe				100	100	100	100
IIIf				100	100	100	80
IIIg				100	100	100	100
IIIh				100	100	100	100
IIIi				100	80	20	0
IIIj				100	90	30	0
IIIk						100	75
IIIl						100	80
IIIm				100	90	80	0
IIIn						100	85
IIIo						100	85
IIIp						100	80
IIIq							100
IIIr							100
RH-5849			100	70	0		
RH-5992					100	95	55
RH-0345	100					70	10
JS-118						100	90
RH-2485						100	100

Table 4. Larvicidal Activities against Oriental Armyworm of Compounds **IIIs**−**y** and Parent Compounds[a]

	larvicidal activity (%) at concentration mg kg^{-1})						
compd	200 mg kg^{-1}	100 mg kg^{-1}	50 mg kg^{-1}	40 mg kg^{-1}	30 mg kg^{-1}	20 mg kg^{-1}	10 mg kg^{-1}
IIIs	95	85	60				5
IIIt	100	100	100	100	100	95	10
IIIu		100	100	100	85	75	10
IIIv	100	100	100				0
IIIw	100	70	10				0
IIIx	100	50	10				0
IIIy	100	90	60				0
Is			95				0
It	100	100	100	100	100	100	75
Iu		100	100	100	95	85	0
Iv	100	100	90				0
Iw	100	100	80				10
Ix	100	50	30				0
Iy	100	100	100	100		50	30

[a] **Is**−**y** were the corresponding parent compounds of target compounds **IIIs**−**y**. The larvacidal activities against oriental armyworm in **Table 4** and that in **Table 3** were tested during different periods, so the data of the same parent compounds were of some derivation.

Table 5. Larvicidal Activities against Diamondback Moth of Compounds **IIIk** and **RH-5992**

compd	$y = a + bx$	LC_{50} (mg/L)	toxic ratio
IIIk	$y = 2.0358 + 1.9102x$	35.63	1.6
RH-5992	$y = -0.9391 + 3.3847x$	56.85	1

bicities of the target compounds **III** were obviously improved. The physical properties and elemental analyses of the target compounds **IIIa**−**y** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Bioassay. *Larvicidal Activity against Oriental Armyworm (M. separata).* **Table 3** shows the larvicidal activities of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines and their *N*-(alkyldithio) and *N*-aminothio derivatives **IIIa**−**r** against oriental armyworm. The

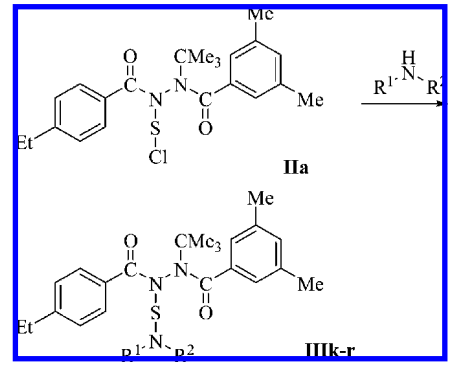

Figure 3. General synthetic route for compounds **IIIk**−**r**.

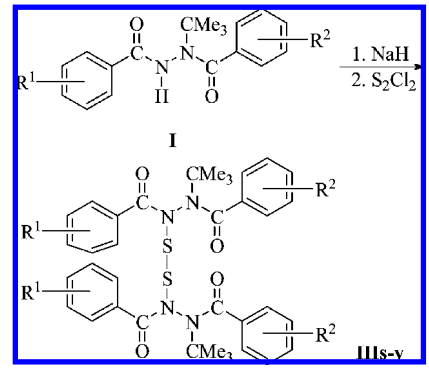

Figure 4. General synthetic route for compounds **IIIs**−**y**.

results indicate that the target compounds **IIIa**−**r** have excellent larvicidal activities against oriental armyworm, and some of the target compounds **III** exhibit higher larvicidal activities than the corresponding parent compounds. For example, the larvicidal activities of **IIIc** and **IIId** were 90% at 25 mg kg^{-1}, whereas the corresponding parent compound, **RH-5849**, caused 70% mortality at this concentration; the larvicidal activities of **IIIe**, **IIIf**, **IIIg**, and **IIIh** were almost the same as that of their parent compounds, **JS-118** and **RH-2485**; the larvicidal activities of **IIIa**, **IIIb**, **IIIk**, **IIIl**, **IIIn**, **IIIo**, **IIIp**, **IIIq**, and **IIIr** at 2.5 mg kg^{-1} were 100, 90, 75, 80, 85, 85, 80, 100, and 100%, respectively, as compared with 55% mortality of the corresponding parent compound, **RH-5992**, at the same concentration. In particular, **IIIi** was sent for advanced testing against diamondback moth.

Table 4 shows the larvicidal activities of the target compounds **IIIs**−**y** and their parent compounds against oriental armyworm. Although some of the target compounds were somewhat lower than the parent compound, the larvicidal activities of **IIIu**, **IIIv**, and **IIIx** were comparable with those of the corresponding parent compounds. Interestingly, the larvicidal activity of **IIIu** was 75% at 20 mg kg^{-1}, whereas the larvicidal activity of **Iu** was 85% at the same concentration; the activities of **IIIv** and **Iv** at 50 mg kg^{-1} were 100 and 90%, respectively; also, the activities of both **IIIx** and **Ix** were 50% at 100 mg kg^{-1}.

Larvicidal Activity against Diamondback Moth (P. xylostella). **Table 5** shows the larvicidal activity of **IIIk** and the corresponding parent compound, **RH-5992**, against diamondback moth. The results indicate that the larvicidal activity of **IIIk** against diamondback moth was 1.6-fold higher than that of **RH-5992** from the value of LC_{50}.

The results of the larvicidal activities of the target compounds **III** against oriental armyworm and diamondback moth implied that the introduction of the derivative substituents was essential

for the larvicidal activity, and the changes in physical properties might account for the improvement of larvicidal activities.

In summary, a series of novel *N*-(alkyldithio) and *N*-aminothio derivatives of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines were designed and synthesized as insect growth regulators via the key intermediate *N*-chlorosulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines. A series of novel *N*,*N*-dithio derivatives were also prepared with *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines and sulfur chloride in the presence of sodium hydride. Compared to *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines, these *N*-(alkyldithio), *N*-aminothio, and *N*,*N*-dithio derivatives exhibited better solubility and improved hydrophobicities. The results of bioassays showed that some of the target compounds possessed higher larvicidal activities than the corresponding parent compounds. In particular, *N*-(morpholinosulfenyl)-*N*′-*tert*-butyl-*N*-4-ethylbenzoyl-*N*′-3,5-dimethylbenzoylhydrazide (**IIIk**) has higher larvicidal activities against both oriental armyworm and diamondback moth than the corresponding parent compound, **RH-5992**.

LITERATURE CITED

(1) Wing, K. D. RH5849, a nonsteroidal ecdysone agonist: effects on a *Drosophila* cell line. *Science (Washington, DC)* **1988**, *241*, 467–469.

(2) Wing, K. D.; Slawecki, R. A.; Carlson, G. R. RH5849, a nonsteroidal ecdysone agonist effects on *Lepidoptera*. *Science (Washington, DC)* **1988**, *241*, 470–472.

(3) Hsu, A. C.-T. 1,2-Diacyl-1-alkylhydrazines, a new class of insect growth regulators. In *Synthesis and Chemistry of Agrochemicals II*; Baker, B. R.; Fenyes, J. G.; Moberg, W. K., Eds.; ACS Sympoisum Series 443; American Chemical Society: Washington, DC,1991; pp 478−490.

(4) Qian, X. H. Molecular modeling study on the structure−activity relationship of substituted dibenzoyl-1-*tert*-butylhydrazines and their structural similarity to 20-hydroxyecdysone. *J. Agric. Food Chem.* **1996**, *44*, 1538–1542.

(5) Cao, S.; Qian, X. H.; Song, G. H. *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.

(6) Zhao, P. L.; Li, J.; Yang, G. F. Synthesis and insecticidal activity of chromanone and chromone analogues of diacylhydrazines. *Bioorg. Med. Chem.* **2007**, *15*, 1888–1895.

(7) Sawada, Y.; Yanai, T.; Nakagawa, H.; Tsukamoto, Y.; Yokoi, S.; Yanagi, M.; Toya, T.; Sugizaki, H.; Kato, Y.; Shirakura, H.; Watanabe, T.; Yajima, Y.; Kodama, S.; Masui, A. Synthesis and insecticidal activity of benzoheterocyclic analogues of *N*′-benzoyl-*N*-(*tert*-butyl)benzohydrazide: Part 1. Design of benzoheterocyclic analogues. *Pest Manage. Sci.* **2003**, *59*, 25–35.

(8) Dhadialla, T. S.; Jansson, R. K. Non-steroidal ecdysone agonists: new tools for IPM and insect resistance management. *Pestic. Sci.* **1999**, *55*, 357–359.

(9) Heller, J. J.; Mattioda, H.; Klein, E.; Sagenmuller, A. Field evalution of RH-5992 on lepidopterous pests in Europe. *Brighton Crop Prot. Conf. Pests Dis.* **1992**, *1*, 59–66.

(10) Cowles, R. S.; Villani, M. G. Susceptibility of Japanese beetle, Oriental beetle, and European chafer (Coleoptera: Scarabaeidae) to halofenozide, an insect growth regulator. *J. Econ. Entomol.* **1996**, *89*, 1356–1365.

(11) Le, D. P.; Thirugnanam, M.; Lidert, Z.; Carlson, G. R.; Ryan, J. B. RH-2485: a new selective insecticide for caterpillar control. *Brighton Crop Prot. Conf. Pests Dis.* **1996**, 481–486.

(12) Carlson, G. R.; Dhadialla, T. S.; Hunter, R.; Jansson, R. K.; Jany, C. S.; Lidert, Z.; Slawecki, R. A. The chemical and biological properties of methoxyfenozide, a new insecticidal ecdysteroid agonist. *Pest Manage. Sci.* **2001**, *57*, 115–119.

(13) Yanagi, M.; Watanabe, T.; Masui, A. ANS-118: a novel insecticide. *Brighton Crop Prot. Conf. Pests Dis.* **2000**, *2*, 27–32.

(14) Zhang, X. N.; Li, Y. F.; Zhu, L. M.; Liu, L. Y.; Sha, X. Y.; Xu, H.; Ma, H. J.; Wang, F. Y.; Ni, Y. P.; Guo, L. P. Preparation of diacylhydrazines insecticides and their intermediates. CN 1313276, 2001.

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

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

(17) Umetsu, N.; Nishioka, T.; Fukuto, T. R. Formation of alkoxysulfenyl derivatives of carbofuran by acid-catalyzed alcoholysis of carbosulfan. *J. Agric. Food Chem.* **1984**, *32*, 765–768.

(18) 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.

(19) Zhao, Q. Q.; Shang, J.; Huang, Z. Q.; 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. 2. *N*-Substituted phenoxysulfenate derivatives. *J. Agric. Food Chem.* **2008**, *56*, 5254–5259.

(20) Mulvihill, M. J.; Nguyen, D. V.; MacDougall, B.; Martinez-Teipel, B.; Joseph, R.; Gallagher, J.; Weaver, D.; Gusev, A.; Chung, K.; Mathis, W. Benzaldehyde-derived chloroformates and their application towards the synthesis of methoxyfenozide-*N*-[(acyloxy)-benzyloxy]carbonyl derivatives. *Tetrahedron Lett.* **2001**, *42*, 7751–7754.

(21) Mulvihill, M. J.; Gallagher, J.; MacDougall, B. S.; Weaver, D. G.; Nguyen, D. V.; Chung, K.; Mathis, W. Synthesis and application of novel glyoxylate-derived chloroformates. *Synthesis* **2002**, 365–370.

(22) Brown, M. S. Dithio-substituted carbamates. U.S. 3914259, 1975.

(23) Black, L.; Fukuto, T. R. Insecticidal benzofuranyl (aminosulfenyl)carbamates. DE2433680, 1975.

(24) Goto, T.; Takao, H.; Yasudomi, N.; Osaki, N.; Murata, T. Carbamate derivatives and insecticidal, miticidal or nematocidal compositions containing these derivatives. BE 892302, 1982.

(25) He, Z. R. Sulfur dichloride. *Inorganic Preparation Chemistry Handbook*; Fuel Chemical Industry Press: Beijing, China, 1972; p224 (in Chinese).

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

(27) Hsu, A. C.; Murphy, R. A.; Aller, H. E.; Hamp, D. W.; Weinstein, B. Insecticidal *N*′-substituted-*N*,*N*′-disubstitutedhydrazines. U.S. 5117057, 1992.

(28) 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.

(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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