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Synthesis and Insecticidal Evaluation of Novel N-Oxalyl Derivatives of Diacylhydrazines Containing Methylcarbamate Moieties

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ABSTRACT: *A series of new N-oxalyl derivatives of diacylhydrazines containing methylcarbamate moieties were synthesized by the reaction of N-oxalyl chloride of N-methylcarbmates with N-tert-butyl-N,N′-diacylhydrazines in the presence of sodium hydride. The reaction of oxalyl chloride with N-tert-butyl-N, N′-diacylhydrazines to yield 1,3,4-oxadiazole and 4-tert-butyl-2-substituted-phenyl-4H-1,3,4-oxadiazine-5,6-dione was found, and the reaction was studied in some detail. The title compounds were evaluated for molting hormone mimicking activity. The results of bioassay showed that the title compounds exhibit moderate larvicidal activities, and toxicity assays indicated that these compounds can induce a premature, abnormal, and lethal larval molt.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:472–475, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20135

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INTRODUCTION

Recently, synthetic *N-tert*-butyl-*N*,*N*′-diacylhydrazines have been found to work as nonsteroidal ecdysone agonists inducing, especially in *Lepidoptera*, precocious molting, leading to death [1–5]. *N-tert*-Butyl-*N*′-(4-ethylbenzoyl)-*N*-3,5-dimethylbenzoyl-hydrazide (tebufenozide; RH-5992), with its new and selective mode of action, has been the first to be commercialized as an agricultural insecticide to control caterpillar pests by Rohm and Hass [6]. At present, another three new structural analogues: methoxyfenozide (RH-2485), halofenozide (RH-0345), and chromafenozide (ANS-118) have already been successfully launched [7,8]. In our previous work [9,10], synthesis and insecticidal evaluation of a series of novel *N*-sulfenylated derivatives of diacylhydrazines have been reported, and the results of bioassay showed that they exhibit excellent larvicidal activity, inducing a premature, abnormal and lethal molting.

It has been reported that *N*-oxalyl derivatives of *N*-methylcarbamates retain the good insecticidal activity of the parent methylcarbamates, and compared to the parent insecticides, the derivatives displayed significantly reduced toxicity to the white mouse at the same time [11]. Encouraged by these reports, we developed an idea that introduction of *N*-methylcarbamates into *N-tert*-butyl-*N*,*N*′-diacylhydrazines through oxalyl group may retain

insecticidal activities of the two parent insecticides, while the toxicity of the parent methylcarbamates to mammals would be reduced at the same time. Therefore, in a search for insect growth regulators with improved profiles, we designed and synthesized a series of the title compounds.

RESULTS AND DISCUSSION

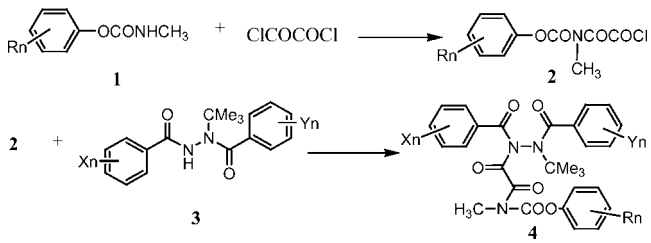
Synthesis of the Products

We synthesized a series of new *N*-oxalyl derivatives of diacylhydrazines containing methylcarbamate moieties **4** as shown in Scheme 1.

Phenyl *N*-methylcarbmates **1** were treated with oxalyl chloride in the 1,2-dichloroethane under reflux to give *N*-oxalyl chloride of *N*-methylcarbmates **2**, and subsequent reaction with *N-tert*-butyl-*N*,*N*′-diacylhydrazines **3** and sodium hydride in the tetrahydrofuran provided the title compounds **4**.

In order to obtain the title compounds **4** containing various substituted-phenyl *N*-methylcarbamates, we attempted to react *N-tert*-butyl-*N*′-(4-ethylbenzoyl)-*N*-3,5-dimethylbenzoylhydrazide **5** with oxalyl chloride to yield *N*-oxalyl chloride of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines **6**, further reaction with substituted-phenyl *N*-methyl carbamate **1** yielded the title compounds **4**. But according to the above method, the target compound **6** has not been obtained. Interestingly, we found that the reaction was processed under room temperature using pyridine as acid acceptor to yield 2-(3,5-dimethyl)-phenyl-5-(4-ethyl)-phenyl-1,3,4- oxadiazole **7**. While compound **5** was treated with oxalyl chloride in the 1,2-dichloroethane under reflux, the reaction yielded 2-(3,5-dimethyl)-phenyl-5-(4-ethyl)-phenyl-1,3,4-oxadiazole **7** and 4-*tert*-butyl-2-(4-ethylphenyl)-4*H*-1,3,4-oxadiazine-5,6-dione **8**. The compound **8** was treated with anhydrous alcohol under reflux to yield ethyl 2-(*N*′-*tert*-butyl-4-ethylbenzoylamido)-2-oxoactate **9** shown as Scheme 2.

It has been reported that the *N*,*N*′-diacylhydrazines are reacted with phosphorus oxychloride [12,13], or thionyl chloride [14] to yield 2,5-disubstituted-1,3,4-oxadiazoles. However, the reactions of *N*-substituted-*N*,*N*′-diacylhydrazines with oxalyl chloride have not been reported, and the compound 4-*tert*-butyl-2-(4-ethyl phenyl)-4*H*-1,3,4-oxadiazine-5,6-dione **8** and the compound ethyl 2-(*N*′-*tert*-butyl-4-ethylbenzoylamido)-2-oxoactate **9** are obtained for the first time.



SCHEME 1

The Structures of Products

All the synthesized compounds were colorless solids, and their structures were confirmed by ^{1}H NMR, EI-MS or APCI-MS, and elemental analysis. The data are summarized in Table 1–3.

BIOLOGICAL ACTIVITY

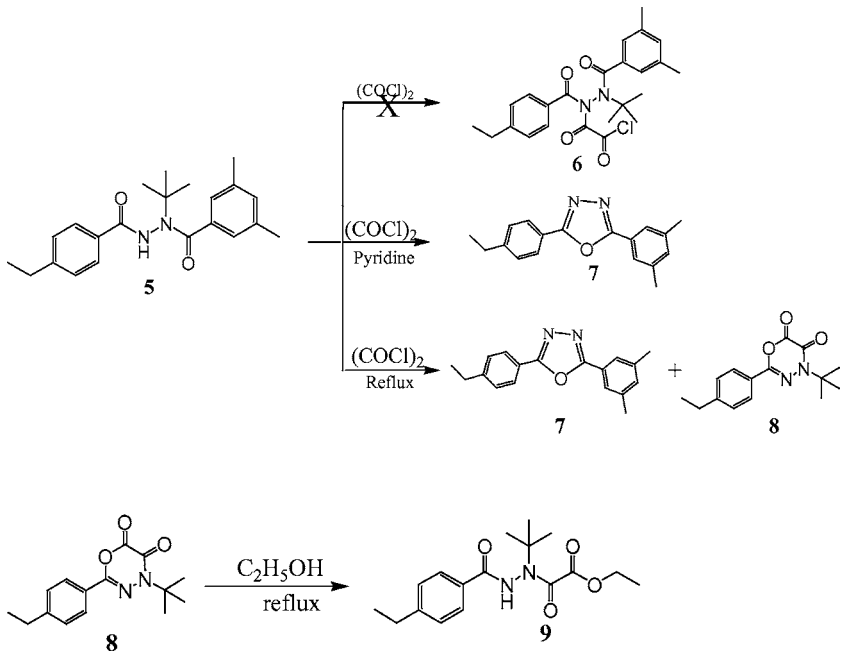
The larvicidal activities of the novel *N*-oxalyl derivatives of diacylhydrazines containing methylcarbamate moieties **(4a–4d)**, the compound **7–9**, and the parent compounds RH-5992, RH-5849 (*N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine) were evaluated using a previously reported procedure [9,10]. The larvicidal activity was tested against Oriental armyworm [*Mythimna (= Pseudaletia) separata* (Walker)] by foliar application. 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 ten 4th-instar armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Evaluations are based on a percentage scale of 0–100 in which 0 = no activity and 100 = total kill. For comparative purposes, the parent compounds RH-5992 and RH-5849 were tested under the same conditions.

The results indicated that at a dose of 500 mg/kg, the larvicidal activities of compound **4a**, **4b, 4c, 4d,** RH-5992, and RH-5849 are 75.0%, 40%, 95.5%, 90%, 100%, and 100% respectively, whereas the compound **7–9** have no larvicidal activities.

The results of bioassy showed that the title compounds **4a–4d** exhibit larvicidal activities, and toxicity assays indicated that they, like the parent compounds, diacylhydrazines, can induce a premature, abnormal, and lethal larval molt.

EXPERIMENTAL

Proton NMR spectra were obtained at 200 MHz with a Bruker AC-P 200 spectrometer, using tetramethylsilane (TMS) as internal standard and deuterochloroform as solvent. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental



SCHEME 2

analyzer. LC-MS was recorded with an Agilent 1100 series LC/MSD using APCI method. GC-MS was recorded with a HP 6890/5973 GC/MS using EI method. Melting points were taken on a Thomas–Hoover melting point apparatus, and the values are uncorrected.

Synthesis of Intermediates

Technical grade substituted-phenyl *N*-methylcarbamates **1** obtained from Hunan Haili Chemical and Technical Corporation, China, were used as starting materials after purification by recrystallization from appropriate solvents (benzene, toluene, dichloromethane).

Substituted-phenyl *N*-methyl(chloroglyoxyloyl)-carbamate **2** was prepared by reaction of oxalyl chloride with substituted-phenyl *N*-methylcarbamate in 1,2-dichloroethane under reflux according to the reported procedures [11]. *N-tert*-butyl-*N*,*N*′-diacylhydrazine **3** was synthesized according to the reported procedure [15].

Synthesis of the Products **4***: General Procedure*

To a stirred solution of *N-tert*-butyl-*N*,*N*′-diacylhydrazine **3** (3.0 mmol) in anhydrous THF (30 mL) at room temperature was added portion wise sodium hydride (0.15 g, 50% purity, 3.05 mmol).The mixture was stirred at room temperature for 0.5 h and cooled to 0°C. Then the solution of substituted-phenyl *N*-methyl (chloroglyoxyloyl)carbamate **2** (3.05 mmol) in 5 mL anhydrous THF was added dropwise. After the addition, the reaction mixture was stirred for 4 h at room temperature. Then the solid was filtered off and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on a silica gel using 6:1 petroleum ether (60–90°C)/ethyl

TABLE 1 Physical Constants of the Synthesized Compounds

No	*Xn*	*Yn*	*Rn*	*mp (°C)*	*Yield (%)*	*MS*
4a	4-Et	3,5-di-Me	3-Me	102–105	42.8	572 $[M+H]^+$
4b	4-Et	3,5-di-Me	2-i-Pr	117–118	40.5	–
4c	H	H	2-i-Pr	147–148	47.4	–
4d	H	H	3-Me	Unshaped	49.2	–
7	–	–	–	121–122	60.8	278 (m/e)
8	–	–	–	127–128	45.3	274 (m/e)
9	–	–	–	164–165	92.7	319 $[M-H]^-$

TABLE 2 Elemental Analysis of Synthesized Compounds

	Elemental Analysis Found (Calcd, %)		
Compd.	*C*	*H*	*N*
4a	69.15 (69.33)	6.45 (6.52)	7.45 (7.35)
4b	69.96 (70.10)	6.75 (6.89)	7.13 (7.01)
4c	68.38 (68.49)	6.17 (6.12)	7.81 (7.73)
4d	67.52 (67.56)	5.75 (5.67)	8.19 (8.15)
7	77.60 (77.67)	6.60 (6.52)	10.0 (10.06)
8	65.30 (65.68)	6.78 (6.61)	10.23 (10.21)
9	63.83 (63.73)	7.74 (7.55)	9.05 (8.74)

TABLE 3 ^{1}H NMR Data of Synthesized Compounds

No	*^{1}H NMR δ (ppm)*
4a	1.17–1.27 (m, 3H, CH_3); 1.55 (s, 9H, $C(CH_3)_3$); 1.97–2.28 (m, 6H, Ph-$(CH_3)_2$); 2.39 (s, 3H, Ph-CH_3); 2.62–3.13 (m, 5H, Ph-CH_2, N-CH_3); 6.90–7.29 (m, 11H, Ph)
4b	1.24–2.97 (m, 30H, CH_3, CH_2, CH); 6.85–7.39 (m, 11H, Ph)
4c	1.21 (d, 6H, $C(CH_3)_2$); 1.36–1.78 (m, 9H, $C(CH_3)_3$); 2.87–3.47 (m, 4H, N-CH_3, Ph-C**H**); 7.05–7.48 (m, 14H, Ph)
4d	1.41–1.74 (m, 9H, $C(CH_3)_3$); 2.40 (s, 3H, Ph-CH_3); 2.87 (s, 3H, N-CH_3); 6.92–7.48 (m, 14H)
7	1.28 (t, 3H, $PhCH_2C\mathbf{H}_3$); 2.40 (s, 6H, Ph$(CH_3)_2$); 2.73 (q, 2H, $PhC\mathbf{H}_2CH_3$); 7.16–8.07 (m, 7H, Ph)
8	1.24 (t, 3H, $PhCH_2C\mathbf{H}_3$); 1.63 (s, 9H, $C(CH_3)_3$); 2.69 (q, 2H, $PhC\mathbf{H}_2CH_3$); 7.26, 7.80 (dd, 4H, $J = 8.2$ Hz, Ph)
9	1.11 (t, 3H, $OCH_2C\mathbf{H}_3$); 1.22 (t, 3H, $PhCH_2C\mathbf{H}_3$); 1.50 (s, 9H, $C(CH_3)_3$); 2.67 (q, 2H, $PhC\mathbf{H}_2CH_3$); 4.11 (q, 2H, $OC\mathbf{H}_2CH_3$); 7.25, 7.66 (dd, 4H, $J = 7.6$ Hz, Ph); 8.70 (s, 1H, NH)

acetate as the eluent. Finally, the colorless crystalline **4** was obtained.

Synthesis of the Compound **7**

To a stirred solution of *N-tert*-butyl-*N′*-(4-ethylbenzoyl)-*N*-3,5-dimethylbenzoylhydrazide **5** (3.52 g, 0.01 mol) in 1,2-dichloroethane (50 mL) was added oxalyl chloride (1.91 g, 0.015 mol), then added dropwise pyridine (1.19 g, 0.015 mol) in a ice bath. After the mixture was stirred at room temperature for 6 h, the solid was filtered off and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on a silica gel using 8:1 petroleum ether (60–90°C)/ethyl acetate as the eluent. Finally, the colorless crystalline **7** (1.69 g, yield 60.8%) was obtained.

Synthesis of the Compound **8**

Oxalyl chloride (1.91 g, 0.015 mol) was added to a solution of *N-tert*-butyl-*N′*-(4-ethylbenzoyl)-*N*-3,5-dimethylbenzoyl-hydrazide **5** (3.52 g, 0.01 mol) in 1,2-dichloroethane (50 mL). After refluxed for 8 h, the mixture was concentrated under vacuum. The residue was purified by column chromatography on a silica gel using 8:1 petroleum ether (60–90°C)/ethyl acetate as the eluent. Finally, the colorless crystalline **8** (1.24 g, yield 45.3%) and **7** (0.89 g, yield 32.0%) were obtained.

Synthesis of the Compound **9**

Compound **8** (1.5 g, 5.5 mmol) was dissolved in ethanol (10 mL), the mixture was refluxed for 2 h, then concentrated under vacuum. The residue was recrystallized from petroleum ether (60–90°C)/ethyl acetate (5:1) to provide the colorless crystalline **9** (1.63 g, yield 92.7%).

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