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ARTICLE

Synthesis and Insecticidal Activity of *N-tert*-Butyl-*N*, *N*′-diacylhydrazines Containing 1,2,3-Thiadiazoles

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N-tert-Butyl-*N,N*′-diacylhydrazines are nonsteroidal ecdysone agonists used as environmental benign pest regulators. In this paper, two series of new *N-tert*-butyl-*N,N*′-diacylhydrazine derivatives containing 1,2,3-thiadiazole were designed and synthesized. All structures of the synthesized compounds were confirmed by proton nuclear magnetic resonance (^{1}H NMR), infrared spectroscopy (IR), and high-resolution mass spectrometry (HRMS). Bioasssay results indicated that most of the synthesized compounds possessed good insecticidal activities against *Plutella xylostella* L. and *Culex pipiens pallens* as compared with the positive control, tebufenozide. The results of this study indicated that 1,2,3-thiadiazoles, as an important active substructure, could improve or maintain the activity of the dicylhydrazines and favor novel pesticide development.

KEYWORDS: 4-Methyl-1,2,3-thiadiazole; diacylhydrazine; insect growth regulator

INTRODUCTION

Diacylhydrazines have been identified as one of the most important insect regulators since the discovery of the *N-tert*-butyl-*N,N*′-diacylhydrazines in the mid-1980s by Rohm and Haas Co. (*1*, *2*). They mimic the action of 20-hydroxyecdysone (*3*) and therefore affect the ecdysone receptor, leading to lethal premature molting. Currently, diacylhydrazines have attracted considerable attention because of their unique action with high insecticidal selectivity, simple structure, and lower toxicity to vertebrates (*3*−*6*). Among nonsteroidal ecdysone agonists, *N-tert*-buyl-*N,N*′-dibenzoylhydrazine (**RH-5849**) was the first thoroughly investigated as an insecticide (*1*, *2*, *7*). However, *N-tert*-butyl-*N*′-(4-ethylbenzoyl)-3,5-dimethylbenzoylhydrazine (tebufenozide) was first commercialized (*8*). At present, analogues of tebufenozide such as methoxyfenozide (**RH-2485**), halofenozide (**RH-0345**), and chromafenozide (**ANS-118**) have already been brought into the agrochemical market (*9*, *10*). In addition, **JS-118**, a furan derivative containing *N-tert*-butyl-*N,N*′-diacylhydrazine, has already been registered in China as an insecticide (*11*). The corresponding structures mentioned above are presented in **Figure 1**.

Heterocyclic compounds as the main sources of lead molecules play an important role in agrochemicals. In the 1960s, Merck & Co. Int. discovered and developed thiabendazole as a fungicide. Afterward, many thiazoles including a number of widely used fungicides (e.g., tricyclazole, probenazole, trifluzamide) and plant elicitors (e.g., acibenzolar-*S*-methyl, BTH) have been introduced into the pesticide market (*12*, *13*). 1,2,3-Thiadiazoles as an important class of sulfur-containing compounds with various interesting properties are becoming a rapidly growing and independent branch of the chemistry of thiazoles (*14*, *15*). They have shown many biological activities such as anti-HIV (*16*, *17*), insecticidal (*18*), fungicidal (*14*, *19*−*22*), and antiviral activities (*23*, *24*), systemic acquired resistance (*14*, *25*), and herbicidal activity (*26*). More significantly, the structure of 1,2,3-thiadiazoles

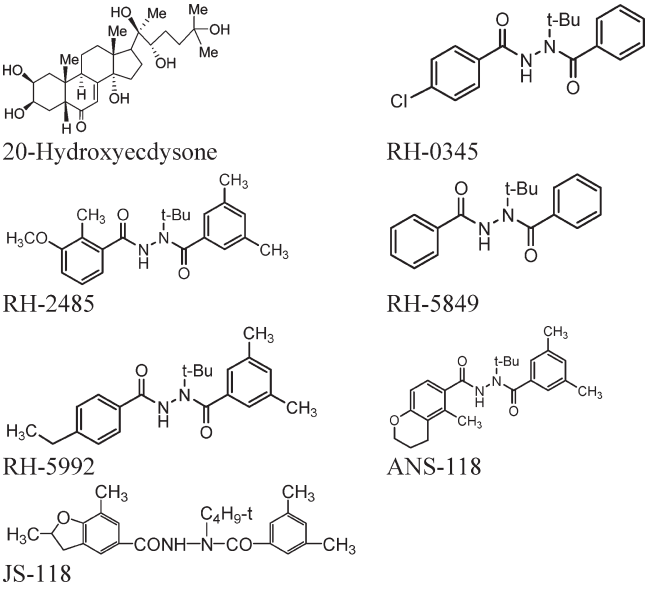

Figure 1. Structures of commercialized diacylhydrazines and their lead, 20-hydroxyecdysone.

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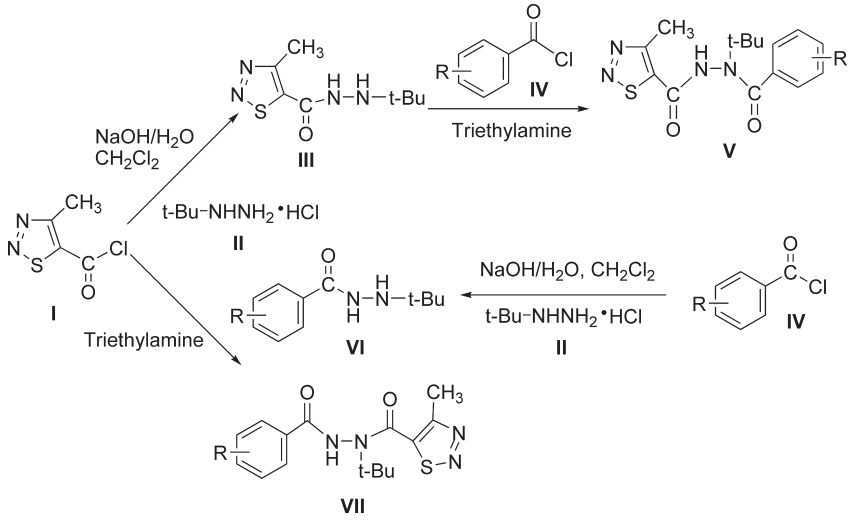
Scheme 1. Molecular Structures and Synthesis of the Target Compounds **V**



can be easily decomposed into lower molecular weight compounds by releasing N_2; the decomposed low molecular weight compounds lost their activities, and this favors the use of its derivates as environmentally benign pesticides with low toxicity and suitable duration of efficiency to the target biology and half-life in the agroecosystem (*14*). However, studies on the synthesis and biological activity of 1,2,3-thiadazole are seldomly reported, and very limited products are commercialized currently. In our previous studies, some new 1,2,3-thiadizole compounds with fungicidal activity, antiviral activity, and systemic acquired resistance were reported (*27*−*29*). Encouraged by these results, we continued to investigate the insecticidal activity of 1,2,3-thiadiazole-containing *N-tert*-butyl-*N*,*N*′-diacylhydrazines, which were synthesized according to the routine described in **Scheme 1**.

MATERIALS AND METHODS

Equipment and Materials. Melting points of all compounds were determined on an X-4 binocular microscope (Gongyi Tech. Instrument Co., Henan, China), and the thermometer was not corrected. Proton NMR spectra were obtained using a Bruker AVANCE-400 MHz spectrometer, and chemical shift values (δ) were reported in parts per million with deuterochloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as the internal standard. High-resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS Varian 7.0T FTICR-MS instrument. IR was recorded on a Bruker Vector 22 FTIR spectrometer using a KBr pellet press. All solvents and reagents were of analytical reagent grade. Column chromatography purification was carried out using silica gel.

General Synthetic Procedure for Compound III. 4-Methyl-1,2,3-thiadiazole-5-carbonyl chloride (**I**) was synthesized from 4-methyl-1,2,3-thiadiazole-5-carboxylic acid according to the method given in ref *27*. To a solution of *tert*-butylhydrazine hydrochloride (**II**, 50.0 g, 0.4 mol) in dichloromethane (280 mL) was dropwise added a solution of sodium hydroxide (25 g, 96%, 0.6 mol) in water (20 mL) in batches below 10 °C. After 15 min of stirring, 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (**I**, 0.2 mol) was dropwise added in batches below 10 °C. After 0.5 h of stirring in an ice−water bath, the mixture was permitted to stand for another 1 h at room temperature. Then, the organic layer was washed successively with water (3 × 15 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulfate. After filtration, the solvent was removed under vacuum to give the white solid (**III**) (34.6 g) with a yield of 80.1%, which was not optimized (**Scheme 1**).

General Synthetic Procedure for Target Compounds V (1−15). A solution of substituted benzoyl chloride (**IV**, 5.2 mmol) in dichloromethane (10 mL) was added dropwise to a stirred mixture of *N-tert*-butyl-*N*′-(4-methyl-1,2,3-thiadiazole)-5-formylhydrazine (**III**, 5.2 mmol), triethylamine (0.56 g, 5.5 mmol), and dichloromethane (10 mL) in an ice bath. After the reaction had been stirred at room temperature for 10 h, dichloromethane (20 mL) was added. The reaction mixture was washed successively with water (3 × 20 mL) and brine (20 mL). The organic layer was then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated. The residue was then purified by recrystallization in ethyl acetate or column chromatography on silica gel using ethyl acetate and petroleum ether (60−90 °C) with 1:2 to 1:4 v/v as an eluent to obtain compounds **V**, and yields were also not optimized (**Scheme 1**). The yields, physical properties, and ^{1}H NMR, HRMS, and IR data of the target compounds **V** were as follows.

Data for ***V-1****:* white needle crystal; yield, 32%; mp, 194−196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.57 (s, 9H, $C(CH_3)_3$), 2.32 (s, 3H, $-CH_3$), 2.50 (s, 3H, thiadiazolyl-CH_3), 7.08−7.24 (m, 4H, Ph-H), 7.94 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1384; IR (KBr pellet press, ν, cm^{-1}), 3177 (NH, st), 2980, 1699 (C═O, st), 1627, 1456, 1376, 1317, 1276, 1201, 1150, 1018, 765.

Data for ***V-2****:* white needle crystal; yield, 43%; mp, 195−196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.54 (s, 9H, $C(CH_3)_3$), 2.28 (s, 3H, $-CH_3$), 2.50 (s, 3H, thiadiazolyl-CH_3), 7.09−7.15 (m, 4H, Ph-H), 8.52 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1372; IR (KBr pellet press, ν, cm^{-1}), 3185 (NH, st), 2982, 1691 (C═O, st), 1633, 1526, 1422, 1395, 1031, 980.

Data for ***V-3****:* white solid; yield, 44%; mp, 208−210 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.57 (s, 9H, $C(CH_3)_3$), 2.33 (s, 3H, $-CH_3$), 2.57 (s, 3H, thiadiazolyl-CH_3), 7.12 (d, 2H, J = 8.0 Hz, Ph-H), 7.32 (d, 2H, J = 8.0 Hz, Ph-H), 7.77 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1382; IR (KBr pellet press, ν, cm^{-1}), 3198 (NH, st), 2974, 2929, 2360, 2341, 1698 (C═O, st), 1620, 1569, 1507, 1361, 1278, 1235, 1198, 1030, 874, 755.

Data for ***V-4****:* white needle crystal; yield, 44%; mp, 228−230 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.59 (s, 3H, thiadiazolyl-CH_3), 3.91 (s, 3H, $-OCH_3$), 6.87 (d, 1H, J = 8.4 Hz, Ph-H), 6.98 (t, 1H, J = 7.2 Hz, Ph-H), 7.31 (t, 1H, J = 7.6 Hz, Ph-H), 7.39 (d, 1H, J = 7.2 Hz, Ph-H), 8.27 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 371.1148, found, 371.1154; IR (KBr pellet press, ν, cm^{-1}), 3176 (NH, st), 2981, 1697 (C═O, st), 1636, 1560, 1537, 1490, 1462, 1319, 1268, 1020, 768.

Data for ***V-5****:* white needle crystal; yield, 45%; mp, 166−167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.56 (s, 9H, $C(CH_3)_3$), 2.56 (s, 3H, thiadiazolyl-CH_3), 3.77 (s, 3H, $-OCH_3$), 6.88−6.92 (m, 3H, Ph-H), 7.20 (t, 1H, J = 8.0 Hz, Ph-H), 8.08 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 371.1148, found, 371.1149; IR (KBr pellet press, ν, cm^{-1}), 3177 (NH, st), 2981, 2360, 2341, 1690 (C═O, st), 1630, 1580, 1529, 1376, 1316, 1204, 1051, 886, 767, 696.

Data for ***V-6****:* white needle crystal; yield, 46%; mp, 176−177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.55 (s, 9H, $C(CH_3)_3$), 2.58 (s, 3H, thiadiazolyl-CH_3), 3.79 (s, 3H, $-OCH_3$), 6.79 (d, 2H, J = 8.8 Hz, Ph-H), 7.36 (d, 2H, J = 8.8 Hz, Ph-H), 8.09 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 371.1148, found, 371.1153; IR (KBr pellet press, ν, cm^{-1}), 3186 (NH, st), 2979, 2604, 2498, 1686 (C═O, st), 1629, 1479, 1383, 1366, 1256, 1173, 1036, 850.

*Data for **V-7**:* white solid; yield, 53%; mp, 207−208 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.59 (s, 3H, thiadiazolyl-CH_3), 7.22−7.39(m, 4H, Ph-H), 8.03 (s, 1H, NH); HRMS (*m*/*z*) $(M - H)^-$, 351.0688, found, 351.0685; IR (KBr pellet press, ν, cm^{-1}), 3166 (NH, st), 2982, 2359, 2341, 1701 (C═O, st), 1633, 1591, 1568, 1450, 1265, 768.

*Data for **V-8**:* white needle crystal; yield, 46%; mp, 202−204 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.57 (s, 9H, $C(CH_3)_3$), 2.61 (s, 3H, thiadiazolyl-CH_3), 7.27−7.38 (m, 4H, Ph-H), 7.95(s, 1H, NH); HRMS (*m*/*z*) $(M - H)^-$, 351.0688, found, 351.0682; IR (KBr pellet press, ν, cm^{-1}), 3188 (NH, st), 2981, 1689 (C═O, st), 1635, 1524, 1451, 1419, 1396, 1231, 1015, 632.

*Data for **V-9**:* light yellow crystal; yield, 57%; mp, 194−197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.56 (s, 9H, $C(CH_3)_3$), 2.59 (s, 3H, thiadiazolyl-CH_3), 7.35 (d, 2H, *J* = 8.4 Hz, Ph-H), 7.52 (d, 2H, *J* = 8.4 Hz, Ph-H), 8.00 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 353.0833, found, 353.0833; IR (KBr pellet press, ν, cm^{-1}), 3193 (NH, st), 2981, 2932, 1685 (C═O, st), 1635, 1522, 1313, 1232, 1201, 1139, 825, 713.

*Data for **V-10**:* white needle crystal; yield, 23%; mp, 173−175 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.56 (s, 9H, $C(CH_3)_3$), 2.54 (s, 3H, thiadiazolyl-CH_3), 7.46−7.66 (m, 4H, Ph-H), 7.68 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 409.0917, found, 409.0912; IR (KBr pellet press, ν, cm^{-1}), 3210 (NH, st), 2984, 1704 (C═O, st), 1643, 1530, 1385, 1316, 1266, 1182, 1124, 902, 772.

*Data for **V-11**:* white needle crystal; yield, 10%; mp, 165−168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.71 (s, 9H, $C(CH_3)_3$), 2.60 (s, 3H, thiadiazolyl-CH_3), 7.49−7.76 (m, 4H, Ph-H), 8.38 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 409.0917, found, 409.0914; IR (KBr pellet press, ν, cm^{-1}), 3315 (NH, st), 2937, 1629 (C═O, st), 1624, 1548, 1427, 1331, 1049, 893, 819, 568.

*Data for **V-12**:* white solid; yield, 33%; mp, 186−189 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.57 (s, 9H, $C(CH_3)_3$), 2.51 (s, 3H, thiadiazolyl-CH_3), 7.49 (d, 1H, *J* = 8.0 Hz, Ph-H), 7.57 (d, 1H, *J* = 8.4 Hz, Ph-H), 8.12 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 409.0917, found, 409.0916; IR (KBr pellet press, ν, cm^{-1}), 3191 (NH, st), 2985, 1687 (C═O, st), 1640, 1526, 1408, 1327, 1276, 1171, 1133, 1017, 873, 758.

*Data for **V-13**:* white solid; yield, 20%; mp, 119−123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.20 (s, 9H, $C(CH_3)_3$), 2.99 (s, 3H, thiadiazolyl-CH_3), 3.81 (s, 1H, NH), 7.52−7.83 (m, 4H, Ph-H); HRMS (*m*/*z*) $(M + H)^+$, 364.1074, found, 364.1071; IR (KBr pellet press, ν, cm^{-1}), 3182 (NH, st), 2977, 2934, 1705 (C═O, st), 1677, 1653, 1574, 1532, 1476, 1381,1316, 1030, 864, 735.

*Data for **V-14**:* white needle crystal; yield, 45%; mp, 202−205 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.61 (s, 9H, $C(CH_3)_3$), 2.63 (s, 3H, thiadiazolyl-CH_3), 7.54−8.25(m, 4H, Ph-H), 8.04 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 364.1074, found, 364.1074; IR (KBr pellet press, ν, cm^{-1}), 3190 (NH, st), 2987, 1689 (C═O, st), 1636, 1616, 1533, 1397, 1374, 1351, 1227, 630.

*Data for **V-15**:* white needle crystal; yield, 18%; mp, 99−101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.41 (s, 9H, $C(CH_3)_3$), 1.55 (s, 3H, thiadiazolyl-CH_3), 5.29 (s, 1H, NH), 8.20 (d, 2H, *J* = 8.4 Hz, Ph-H), 8.28 (d, 2H, *J* = 8.4 Hz, Ph-H); HRMS (*m*/*z*) $(M - H)^-$, 362.0929, found, 362.0931; IR (KBr pellet press, ν, cm^{-1}), 3406 (NH, st), 2987, 2927, 1715 (C═O, st), 1608, 1525, 1279, 1099, 875, 840, 718.

General Synthetic Procedure for Compounds VI (1−15). To a solution of *tert*-butylhydrazine hydrochloride (**II**, 1.2 g, 10 mmol) in dichloromethane (20 mL) was dropwise added a solution (water, 5 mL) of sodium hydroxide (0.7 g, 96%, 15 mmol) in batches below 10 °C. After 15 min of stirring, substituted benzoyl chloride (**IV**, 5 mmol) was dropwise added in batches below 10 °C. After stirring in an ice−water bath for 0.5 h, the mixture was permitted to stand for another 1 h at room temperature. Then, the organic layer was washed successively with water (3 × 10 mL) and brine (10 mL). The mixture was then dried over anhydrous sodium sulfate. After filtration, the solvent was removed under vacuum to give the compounds **VI**; the yields were not optimized (**Scheme 1**).

General Synthetic Procedure for the Target Compounds VII (1−15). A solution of 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (**I**, 5.2 mmol) in dichloromethane (10 mL) was added dropwise to a mixture of *N*-*tert*-butyl-*N*′-benzoyl formyl hydrazine (**VI**, 5.2 mmol), triethylamine (0.56 g, 5.5 mmol), and dichloromethane (10 mL) in an ice bath. After 10 h of stirring at room temperature, the reaction mixture with an addition of dichloromethane (20 mL) was washed successively with water (3 × 20 mL) and brine (20 mL). The organic layer was then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated. The residue was then purified by recrystallization in ethyl acetate or by column chromatography on silica gel using ethyl acetate and petroleum ether (60−90 °C) with 1:2 to 1:4 v/v as an eluent to obtain the compounds **VII**, and the yields were not optimized (**Scheme 1**). The yields, physical properties, and ^{1}H NMR, HRMS, and IR data of the target compounds **VII** were as follows.

*Data for **VII-1**:* white needle crystal; yield, 13%; mp, 145−147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.21 (s, 9H, $C(CH_3)_3$), 2.41 (s, 3H, $-CH_3$), 2.85 (s, 3H, thiadiazolyl-CH_3), 5.74 (s, 1H, NH), 7.24−7.43 (m, 4H, Ph-H); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1375; IR (KBr pellet press, ν, cm^{-1}), 3314 (NH, st), 3028, 2972, 1686 (C═O, st), 1531, 1485, 1439, 1371, 1236, 1127, 1015, 932.

*Data for **VII-2**:* white needle crystal; yield, 30%; mp, 142−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.35 (s, 3H, $-CH_3$), 2.79 (s, 3H, thiadiazolyl-CH_3), 7.29−7.41 (m, 4H, Ph-H), 8.26 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1373; IR (KBr pellet press, ν, cm^{-1}), 3345 (NH, st), 3007, 2930, 1667 (C═O, st), 1607, 1586, 1506, 1484, 1393, 1378, 1361, 1298, 1218, 1186, 647.

*Data for **VII-3**:* white solid; yield, 6%; mp, 143−144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.18 (s, 9H, $C(CH_3)_3$), 2.46 (s, 3H, $-CH_3$), 2.92 (s, 3H, thiadiazolyl-CH_3), 5.75 (s, 1H, NH), 7.32 (d, 2H, *J* = 8.0 Hz, Ph-H), 7.79 (d, 2H, *J* = 8.0 Hz, Ph-H); HRMS (*m*/*z*) $(M + H)^+$, 333.1380, found, 333.1380; IR (KBr pellet press, ν, cm^{-1}), 3348 (NH, st), 3024, 2928, 2866, 1699 (C═O, st), 1606, 1559, 1506, 1456, 1393, 1288, 1019, 934.

*Data for **VII-4**:* white solid; yield, 35%; mp, 141−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.86 (s, 3H, thiadiazolyl-CH_3), 4.014 (s, 3H, $-OCH_3$), 7.00−8.02 (m, 4H, Ph-H), 9.52 (s, 1H, NH); HRMS (*m*/*z*) $(M + Na)^+$, 371.1148, found, 371.1142; IR (KBr pellet press, ν, cm^{-1}), 3412 (NH, st), 2982, 1680 (C═O, st), 1600, 1506, 1483, 1436, 1386, 1248, 1168, 1116, 1021, 743.

*Data for **VII-5**:* white needle crystal; yield, 23%; mp, 151−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.81 (s, 3H, thiadiazolyl-CH_3), 3.81 (s, 3H, $-OCH_3$), 7.06−7.33 (m, 4H, Ph-H), 8.13 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 337.1129, found, 337.1131; IR (KBr pellet press, ν, cm^{-1}), 3364 (NH, st), 2931, 2851, 1657 (C═O, st), 1624, 1528, 1425, 1351, 1099, 898, 839, 800, 561.

*Data for **VII-6**:* white needle crystal; yield, 30%; mp, 135−137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.81 (s, 3H, thiadiazolyl-CH_3), 3.85 (s, 3H, $-OCH_3$), 6.90 (d, 2H, *J* = 8.4 Hz, Ph-H), 7.59 (d, 2H, *J* = 8.0 Hz, Ph-H), 8.20 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 349.1329, found, 349.1327; IR (KBr pellet press, ν, cm^{-1}), 3218 (NH, st), 2970, 2934, 1688 (C═O, st), 1660, 1608, 1521, 1488, 1396, 1376, 1362, 1264, 1211, 1182, 1012, 936, 750.

*Data for **VII-7**:* white solid; yield, 20%; mp, 165−169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.62 (s, 9H, $C(CH_3)_3$), 2.80 (s, 3H, thiadiazolyl-CH_3), 7.11−7.40 (m, 4H, Ph-H), 8.15 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 353.0833, found, 353.0834; IR (KBr pellet press, ν, cm^{-1}), 3193 (NH, st), 2984, 1701 (C═O, st), 1628, 1558, 1519, 1455, 1367, 1208, 617.

*Data for **VII-8**:* white needle crystal; yield, 40%; mp, 138−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.79 (s, 3H, thiadiazolyl-CH_3), 7.33−7.59 (m, 4H, Ph-H), 8.33 (s, 1H, NH); HRMS (*m*/*z*) $(M - H)^-$, 351.0688, found, 351.0685; IR (KBr pellet press, ν, cm^{-1}), 3346 (NH, st), 2981, 1683 (C═O, st), 1632, 1519, 1471, 1397, 1368, 1264, 1234, 1032, 651.

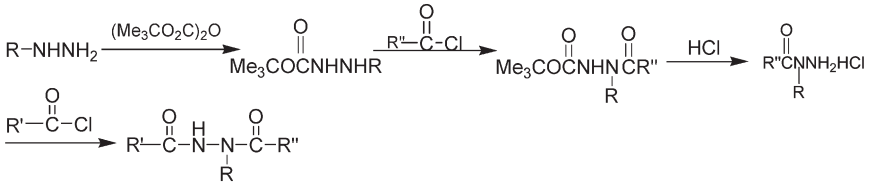
*Data for **VII-9**:* white solid; yield, 55%; m.p.: 137−139 °C; ^{1}HNMR ($CDCl_3$, 400 MHz): δ1.58(s, 9H, $C(CH_3)_3$), 2.76(s, 3H, thiadiazolyl-CH_3), 7.38(d, 2H, *J* = 8.4 Hz, Ph-H), 7.55(d, 1H, *J* = 8.4 Hz, Ph-H), 8.60(s, 1H, NH); HRMS (*m*/*z*): $(M+H)^+$: 353.0833, found:353.0833; IR (KBr pellet press, ν, cm^{-1}): 3714(NH, st), 2976, 1699(C═O, st), 1660, 1593, 1361, 1284, 1267, 1190, 1092, 1009, 946, 874.

*Data for **VII-10**:* white solid; yield, 20%; mp, 198−199 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.60 (s, 9H, $C(CH_3)_3$), 2.98 (s, 3H, thiadiazolyl-CH_3), 5.80 (d, 1H, *J* = 7.6 Hz, NH), 7.46−7.75 (m, 4H, Ph-H); HRMS (*m*/*z*) $(M + H)^+$, 387.1097, found, 387.1097; IR (KBr pellet press, ν, cm^{-1}), 3233 (NH, st), 2990, 1699 (C═O, st), 1648, 1371, 1316, 1270, 1130, 1054, 905, 771, 662.

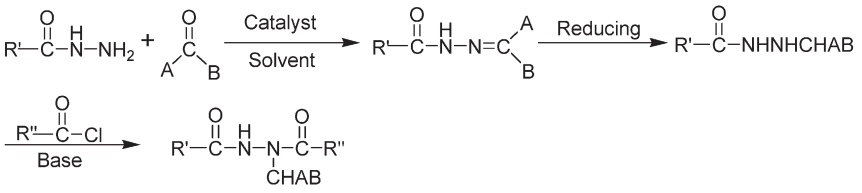
*Data for **VII-11**:* white solid; yield, 28%; mp, 200−203 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 1.59 (s, 9H, $C(CH_3)_3$), 2.78 (s, 3H, thiadiazolyl-CH_3), 7.56 (t, 1H, *J* = 8.0 Hz, Ph-H), 7.78 (q, 2H, *J* = 7.6 Hz, Ph-H), 7.89

Scheme 2. Regular Synthesis Methods for the Diacylhydrazines

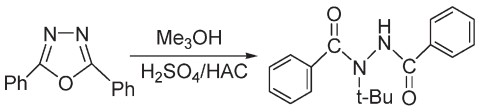
The first method :



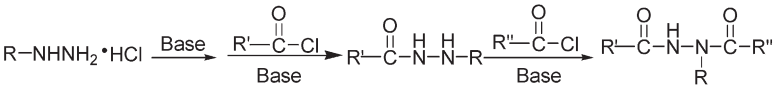
The second method :



The third method :



The forth method :



(R, R′, R″, A, B represent various alkyl or phenyl substitutients)

(s, 1H, Ph-H), 8.55 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 387.1097, found, 387.1097; IR (KBr pellet press, *ν*, cm^{-1}), 3230 (NH, st), 2981, 1674 (C═O, st), 1522, 1488, 1357, 1336, 1271, 1175, 1130, 1071, 913, 759, 700, 665, 420.

Data for ***VII-12****:* white needle crystal; yield, 46%; mp, 149−151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* 1.59 (s, 9H, $C(CH_3)_3$), 2.78 (s, 3H, thiadiazolyl-CH_3), 7.69 (m, 4H, Ph-H), 8.49 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 387.1097, found, 387.1091; IR (KBr pellet press, *ν*, cm^{-1}), 3235 (NH, st), 2971, 2935, 1704 (C═O, st), 1658, 1486, 1334, 1268, 1212, 1129, 1012, 898, 852, 763, 671.

Data for ***VII-13****:* white needle crystal; yield, 25%; mp, 193−195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* 1.65 (s, 9H, $C(CH_3)_3$), 2.74 (s, 6H, thiadiazolyl-CH_3), 6.39 (d, 1H, *J* = 7.6 Hz, Ph-H), 7.51−7.60 (m, 2H, Ph-H), 8.02 (d, 1H, *J* = 8.0 Hz, Ph-H), 8.23 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 364.1074, found, 364.1074; IR (KBr pellet press, *ν*, cm^{-1}), 3321 (NH, st), 3072, 2982, 1699 (C═O, st), 1655, 1533, 1506, 1351, 1298, 1264, 932, 847, 733.

Data for ***VII-14****:* white solid; yield, 54%; mp, 167−176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* 1.61 (s, 9H, $C(CH_3)_3$), 2.78 (s, 3H, thiadiazolyl-CH_3), 7.64−8.46 (m, 4H, Ph-H), 9.05 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 364.1074, found, 364.1066; IR (KBr pellet press, *ν*, cm^{-1}), 3317 (NH, st), 2984, 1689 (C═O, st), 1639, 1533, 1398, 1286, 1001, 907, 837.

Data for ***VII-15****:* white solid; yield, 20%; mp, 152−155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz), *δ* 1.59 (s, 9H, $C(CH_3)_3$), 2.77 (s, 3H, thiadiazolyl-CH_3), 7.77 (d, 2H, *J* = 8.8 Hz, Ph-H), 8.24 (d, 1H, *J* = 8.8 Hz, Ph-H), 8.78 (s, 1H, NH); HRMS (*m*/*z*) $(M + H)^+$, 364.1074, found, 364.1069; IR (KBr pellet press, *ν*, cm^{-1}), 3209 (NH, st), 3193, 3007, 2975, 1705 (C═O, st), 1659, 1522, 1483, 1359, 1321, 1298, 1212, 1106, 1009, 942, 812.

Crystal Structure Determination for Compound VII-2. The crystal of compound **VII-2** was cultured from the mixture of dichloromethane and petroleum (crystal data are given in the Supporting Information). X-ray intensity data were recorded on a Bruker SMART 1000CCD diffraction meter using graphite monochromated Mo Kα radiation (*λ* = 0.71073 Å). A total of 11153 reflections were measured, of which 2956 were unique (R_{int} = 0.0737) in the range of 2.56° ≤ *θ* ≤ 25.02°(*h*, −13 to 13; *k*, −11 to 10; *l*, −18 to 14), and 2073 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F^2. The structure was solved by direct methods with the SHELXS-97 program. All of the non-H atoms were refined anisotropically by full-matrix least-squares to give the final R = 0.0547 and wR = 0.1246 ($w = 1/[\sigma^2((F_o^2) + (0.0684P)^2 + 0.0000P]$, where $P = (F_o^2 + 2F_c^2)/3$ with $(\Delta/\sigma)_{max}$ = 1.000 and S = 1.052 by using the SHELXL program. The hydrogen atoms were located from a difference Fourier map and refined isotropically.

Evaluation of Insecticidal Activity. The insecticidal activity of the target compounds **V** and **VII** was conducted according to the standard operation practice (SOP) as described in ref *27* and the following procedures.

Insecticide Activity of the Target Compounds against Plutella xylostella L. The larvicidal activities of the target compounds **V** and **VII** and the positive control tebufenozide against *P. xylostella* L. were tested by leaf film feeding method, which was operated as follows: fresh cabbage leaves were dipped into the 200 μg/mL test water solution, which was prepared with 5% of acetone to help the compounds dissolve, for 10 s. After air-drying to evaporate off the acetone and water, the treated leaves were cut into small pieces and placed in Petri dishes of 9 cm diameter. Ten individuals of second-instar larvae of *P. xylostella* L. were then transferred into 10 cm diameter Petri dishes. The Petri dishes were finally fastened with rubber bands and placed in the standard culturation room for 96 or 120 h at 25 °C and 80% humidity. The percentage of mortalities was evaluated according to the corresponding CK, which uses water to dispose only. The insects that had no reaction when touched by a brush pen were regared as dead. Each treatment was repeated three times. The data for the mortality regression lines of the active compounds were subjected to probit analysis by POLO for the median lethal concentration (LC_{50}) determination.

Insecticide Activity of the Target Compounds against Larval Culex pipiens pallens. The larvicidal activities of the target compounds **V** and **VII** against *C. pipiens pallens* were evaluated by the following procedures. Each compound of 2 mg was weighed into a panicilin bottle; 10 mL of acetone was added to dissolve the compound to prepare 200 μg/mL of mother solution. The working solution of 2 μg/mL was prepared by diluting 1 mL of mother solution with 89 mL of water and 10 mL of feeding solution into a 100 mL beaker. Ten individuals of fourth-instar larvae of *C. pipiens pallens* were transferred into the beaker. Thereafter, the beakers with mosquito larvae were put into the standard conditioned rooms for further cultivation with temperature of 25 °C and humidity of 80%. After 24 or 96 h of cultivation, the mortalities of the larvae were calculated by the corresponding CK, which was prepared by 1 mL of acetone for substituting 1 mL of mother solution; the observation was conducted until all of the larvae metamorphosized into pupation or died. Tebufenozide was chosen as a positive control.

RESULTS AND DISCUSSION

Synthetic Chemistry of the Title Compounds. As nonsteroidal ecdysone agonists, the *N-tert*-butyl-*N*,*N*′-diacylhydrazine motif has attracted extensive attention. Four widely applied methods for the synthesis of *N-tert*-butyl-*N*,*N*′-diacylhydrazine were reported. The first method is acylation of protected alkyl hydrazine. This method can be used for synthesizing the asymmetric diacylhydrazine with a high purity by using *tert*-butyloxycarbonyl (Boc) or carbobenzyloxy (Cbz) as protection of the alkyl hydrazine. However, when the benzene ring possesses the substitution of halogen or nitro, Cbz protection is unsuitable (*7*, *30*). The second method is the reduction of *N*-carbonyl hydrazones, with the catalysis of acetic acid, trifluoroacetic acid, and oxalic acid for aldehyde condensation. The reducing agent commonly used is sodium cyanoborohydride or sodium borohydride (*30*). The third method is 1,3,4-oxadiazole ring-opening; however, harsh reaction conditions such as strong acid catalyst (e.g., sulfuric acid) are usually required (*31*). The last method is alkyl hydrazine acylation, which is also used herein, and this convenient synthesis method is the most commonly used and accepted method in the laboratory or even in industry (*7*, *30*) (**Scheme 2**).

All of the title compounds were synthesized according to **Scheme 1**. The intermediate (i.e., 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride, **I**) was synthesized according to the method given in ref *27*. The reaction conditions were not optimized. Because of the moisture in the solvents, yields of some target compounds were low. All structures of the target compounds were confirmed by ^{1}H NMR, IR, and HRMS determination. For further validation of these kinds of compounds, compound **VII-2** was cultured and determined by X-ray single-crystal diffraction in this study (**Figure 2**). Bond lengths and angles within the heterocyclic system agreed well with the standard values for compound **VII-2**. This compound is nonplanar with a dihedral angle of 65.48° between the two rings.

Insecticidal Activity of the Target Compounds V and VII. The results of insecticidal screening are given in **Table 1**. Data in **Table 1** show that most of the title compounds exhibited good insecticidal activities against *P. xylostella* L. and *C. pipiens pallens* when compared with the positive control. For insecticidal activity against *P. xylostella* L., compounds **V-5**, **V-7**, and **V-11** exhibited 37, 79, and 46% insecticidal activity at 200 μg/mL, respectively. Compound **V-13** exhibited 45% insecticidal activity at 400 μg/mL. Compounds **VII-1**, **VII-3**, **VII-11**, **VII-14**, and **VII-15** displayed 68, 37, 32, 34, and 33% insecticidal activity at 200 μg/mL, respectively. Compound **VII-9** exhibited 43% insecticidal activity at 400 μg/mL. These data indicate that compounds **V-7** and **VII-1** possessed a higher insecticidal activity as compared with the positive control, tebufenozide, at the same concentration. Compounds **V-5**, **V-11**, **VII-3**, **VII-11**, **VII-14**, and **VII-15** showed the same insecticidal activity as compared with tebufenozide at the same concentration. Although compound **V-7** possessed a higher insecticidal activity than tebufenozide at only one concentration, later precision toxicological study results of compounds **V-7** and tebufenozide indicated that the insecticidal activity of compound **V-7** was at the same level as that of tebufenozide with very close LC_{50} values of 28 and 26 μg/mL, respectively (**Table 2**). It is noteworthy that methoxyfenozide (**RH-2485**) was 3−5-fold more potent than tebufenozide against the susceptible Egyptian cotton leaf worm *Spodoptera littoralis* and 7−14-fold more potent against its field strain (*32*); to avoid skipping any potential active new compounds synthesized, here we chose the moderately active compound tebufenozide as positive control.

The compounds **V-9**, **VII-1**, **VII-11**, and tebufenozide showed 100% insecticidal activity against *C. pipiens pallens* at 1 μg/mL (**Table 1**),

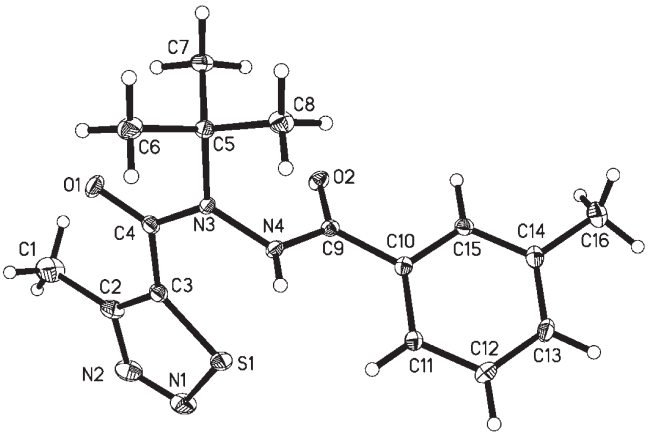


Figure 2. X-ray structure of the title compound **VII-2**.

Table 1. Insecticidal Activities of Target Compounds **V** and **VII**

		mortality (%)				mortality (%)	
compd	R	PXL[a]	CPP[b]	compd	R	PXL[a]	CPP[b]
V-1	*o*-CH_3	8	20	**VII-1**	*o*-CH_3	68	100
V-2	*m*-CH_3	0	20	**VII-2**	*m*-CH_3	12	20
V-3	*p*-CH_3	15	10	**VII-3**	*p*-CH_3	37	0
V-4	*o*-OCH_3	30[c]	10	**VII-4**	*o*-OCH_3	29	10
V-5	*m*-OCH_3	37	20	**VII-5**	*m*-OCH_3	10[c]	10
V-6	*p*-OCH_3	25	10	**VII-6**	*p*-OCH_3	28[c]	10
V-7	*o*-Cl	79	10	**VII-7**	*o*-Cl	24	20
V-8	*m*-Cl	0	30	**VII-8**	*m*-Cl	25	0
V-9	*p*-Cl	25	100	**VII-9**	*p*-Cl	43[c]	20
V-10	*o*-CF_3	15	10	**VII-10**	*o*-CF_3	ND	ND
V-11	*m*-CF_3	46	40	**VII-11**	*m*-CF_3	32	100
V-12	*p*-CF_3	5	30	**VII-12**	*p*-CF_3	13	40
V-13	*o*-NO_2	45[c]	10	**VII-13**	*o*-NO_2	16	20
V-14	*m*-NO_2	23[c]	30	**VII-14**	*m*-NO_2	34	10
V-15	*p*-NO_2	5	10	**VII-15**	*p*-NO_2	33	30
tebufenozide	_	40	100				

[a] PXL, *Plutella xylostella* L., 96 h, 200 μg/mL. [b] CPP, *Culex pipiens pallens*, 2 μg/mL. [c] Results of 400 μg/mL.

Table 2. Determination of LC_{50} of **V-7** against *Plutella xylostella* L.

compd	96 h LC_{50} value (μg/mL)	slope ± SD	χ-square
V-7	28 (7−67)[a]	0.483 ± 0.164	0.071
tebufenozide	26 (1−64)[a]	0.774 ± 0.190	4.089

[a] 95% confidence limits are expressed in parentheses.

Table 3. Death Rate of Compounds Active against *Culex pipiens pallens*

compd	concn (μg/mL)	death rate (%)	compd	concn (μg/mL)	death rate (%)
V-9	2	100	**VII-11**	2	100
	1	100		1	100
	0.5	10		0.5	0
VII-1	2	100	tebufenozide	2	100
	1	100		1	100
	0.5	30		0.5	60

and so did the tebufenozide. When the concentration was decreased to 0.5 μg/mL, the insecticidal activity of the compounds **V-9**, **VII-1**, **VII-11** and tebufenozide decreased dramatically, ranging from 10 to 60% (**Table 3**).

As mentioned above, one series of the target compounds with the benzoyl ring near the *tert*-butyl and another series with the 5-methyl-1,2,3-thiadiazole near the *tert*-butyl are shown in **Scheme 1**. According to the results, the structure−activity relationship via parallel activity contrasting between the two series of compounds against *P. xylostella* L. at the same concentration (200 μg/mL) can be evaluated. Most of the contrasting results between the two series had almost equal insecticidal activities as a whole. However, compounds **VII** showed a better insecticidal avtivity. Moreover, in compounds **V** when the R group was substituted with chloride, the newly synthesized compounds had comparable good insecticidal activities. In compounds **VII**, when the R group was substituted with strong electron-withdrawing groups in the benzene ring such as trifluoro and nitro groups, the insecticidal activities were usually kept or improved. These results suggested that introducing a 4-methyl-1,2,3-thiadiazole moiety into the biological active molecules had a positive effect on keeping the insecticidal activity as compared with positive control. Promisingly, 1,2,3-thiadiazole-containing *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines had good insecticidal activity, and it is an important active substructure for novel pesticide development.

ABBREVIATIONS USED

Boc, *tert*-butyloxycarbonyl; Cbz, carbobenzyloxy; $CDCl_3$, deuterochloroform; CPP, *Culex pipiens pallens*; ^{1}H NMR, hydrogen nuclear magnetic resonance; HRMS, high-resolution mass spectrometry; IR, infrared; PXL, *Plutella xylostella* Linnaeu; SOP, standard operation practice; TMS, tetramethylsilane.

Supporting Information Available: Crystal data of the compound **VII-2**: r91027b. This material is available free of charge via the Internet at http://pubs.acs.org.

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