SHORT PAPER

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Synthesis and biological activity of novel *N*-sulfenylated derivatives of diacylhydrazines†

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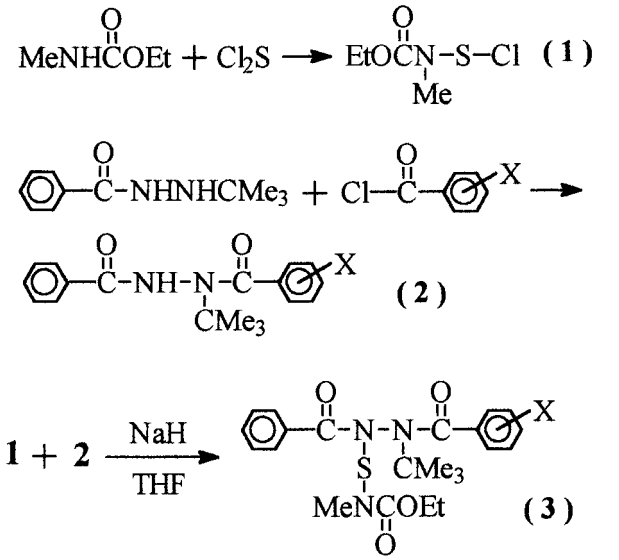
A series of new *N*-sulfenylated derivatives of diacylhydrazines were synthesised and evaluated for moulting hormone mimicking activity, and the results of bioassay showed that the title compounds exhibit excellent larvicidal activities, and toxicity assays indicated that the title compounds can induce a premature, abnormal and lethal larval moult.

Keywords: N-sulfenylated derivatives, diacylhydrazines, carbamate, larvicidal activity

Recently, a new class of insect growth regulators, the *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines, have been found to mimic the action of 20-hydroxyecdysone to activate the ecdysone receptor, leading to lethal premature moulting.[1] Among nonsteroidal ecdysone agonists, *N*-*tert*-butyl-*N*′-(4-ethylbenzoyl)-3,5-dimethylbenzoylhydrazine has been the first to be commercialised as a lepidopteran-specific insecticide, with a low toxicity profile towards mammals, birds and fishes, as well as towards non-target arthropods such as insect pollinators, predators, and parasitoids.[2]

It has been reported that biscarbamoyl sulfide derivatives of methylcarbamate insecticides retained the good insecticidal activity of the parent methylcarbamate but were substantially less toxic to the white mouse.[3] Encouraged by the reports, we developed the idea that the introduction of carbamate into *N*-*tert*-butyl-N′,N-diacylhydrazine would retain the good insecticidal activity of the parent methylcarbamate and *N*-*tert*-butyl-N′,N-diacylhydrazine, while toxicity of methylcarbamate would be reduced at the same time. Therefore, in a search for new insect growth regulators with improved biological properties and different activity spectrum, we designed and synthesised a series of new N-sulfenylated derivatives of diacylhydrazines as shown in Scheme 1.

The results of larvicidal activities given in Table 1 show that the title compounds (**3**) exhibit excellent larvicidal activities. Toxicity assays indicated that the title compounds (**3**), like *N*-*tert*-butyl-*N*,*N*′-dibenzoylhydrazine (RH5849), can induce a premature, abnormal and lethal larval moult. Symptoms of toxicity included discoloration, weight loss, cessation of feeding, and developmentally premature, lethal moulting at higher rates.



Scheme 1

Experimental

Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Infrared spectra were recorded on a Shimadu-435 spectrometer. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting-point apparatus and are uncorrected.

Ethyl methyl(chlorosulfenyl)carbamate (**1**) was prepared by reaction between carbamate and sulfur dichloride in dichloromethane, using pyridine as the acid acceptor.[4] *N*-*tert*-butyl-*N*′-benzoylhydrazine was synthesised according to the reported procedure.[5]

General procedure for the preparation of N-tert-butyl-N′-benzoyl-N-substitutedbenzoylhydrazines (**2**): a solution of substituted benzoly chloride (0.054 mol) in methylene dichloride (15 ml) was added dropwise to a solution of *N*-*tert*-butyl-N′-benzoylhydrazine (0.054 mol) and triethylamine (0.065 mol) in methylene dichloride (40 ml) under magnetic stirring at 0°C, then the resulting mixture was stirred at room temperature for 4 h. Then the solid was filtered off and the filtrate was washed successfively with 2% aqueous hydrochloric acid and 10% aqueous sodium bicarbonate, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallised from isopropanol to obtain a colourless crystalline solid.

2a *(X = H)*. Yield: 94.5%. m.p. 173–175 °C (literature reference,[6a] m.p. = 174–176 °C.) ^{1}H NMR($CDCl_3$) δ 1.59(s, 9H, Bu^t); 7.25–7.41(m, 10H, Ph); 7.84(s, 1H, NH).

2b *(X = 3, 5-Me$_2$)*. Yield: 86.3%. m.p. 202–204 °C. ^{1}H NMR($CDCl_3$) δ 1.56(s, 9H, Bu^t); 2.20(s, 6H, Ph-Me); 6.86–7.40(m, 8H, pH); 7.92(s, 1H, NH). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.36; Found: C, 74.23; H, 7.19; N, 8.07.

General procedure for the preparation of the title products (**3**): To a stirred solution of *N*-*tert*-butyl-*N*′-benzoyl-*N*-substituted benzoylhydrazines (**2**) (4.05 mmol) in anhydrous tetrahydrofuran (40 ml) at room temperature under nitrogen was added portionwise sodium hydride (0.114 g, 85% purity, 4.05 mmol). The mixture was stirred at room temperature for 0.5 h and coooled to 0 °C. Then ethyl methyl(chlorosulfenyl) carbamate (**1**) (4.05 mmol) was added dropwise. After the addition, the reaction mixture was stirred for 5 h at room temperature. Then the solid was filtered off and the filtrate was concentrated under vaccum. The residue was purified by column chromatography on a silica gel using 5:1 petroleum ether (60–90 °C)/ethyl acetate as the eluent. Finally, the colourless crystalline (**3**) was obtained.

3a *(X = H)*. Yield: 91.3%. m.p. 111–112 °C. IR (KBr) ν/cm^{-1} 2965, 1719, 1679, 1648, 1390, 1351, 1265, 1194, 1116, 1064, 1023, 969, 791, 763, 701. ^{1}H NMR($CDCl_3$) δ 1.31(t, 3H, CMe); 1.66(s, 9H, Bu^t); 2.03(s, 3H, NMe); 4.21(m, 2H, OCH_2); 7.11–7.42(m, 10H, Ph). Anal.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 1 Larvicidal activities of the title compounds

No.	Larvicidal activity (%) 500ppm	200ppm	100ppm	50ppm
3a	100	95	90	15
3b	100	100	100	100
RH5849	–	–	100	95

RH5849: *N-tert*-butyl-*N, N′*-dibenzoylhydrazine.

Calcd for $C_{22}H_{27}N_3O_4S$: C, 61.52; H, 6.34; N, 9.78; Found: C, 61.51; H, 6.46; N, 10.01.

3b *(X = 3, 5-Me$_2$)*. Yield: 60.0%. m.p. 115–116 °C. IR (KBr) ν/cm^{-1} 2968, 1723, 1680, 1642, 1391, 1351, 1195, 1079, 1022, 865, 787, 735, 702. ^{1}H NMR($CDCl_3$) δ 1.33(t, 3H, CMe); 1.64(s, 9H, Bu^t); 2.24(s, 3H, NMe); 2.32(s, 6H, Ph-Me); 4.24(q, 2H, OCH_2); 7.00–7.42(m, 8H, Ph). Anal. Calcd for $C_{24}H_{31}N_3O_4S$: C, 63.00; H, 6.83; N, 9.18; Found: C, 62.84; H, 6.66; N, 9.24, MS (EI, 70eV) *m/z* 324.30 (4%). 268.20 (1%), 133.25 (100%, 105.25 (72%).

Larvicidal activity tests: The larvicidal activities of the title compounds (**3**) and *N-tert*-butyl-*N-N′*-dibenzoylhydrazine (RH5849) were evaluated using previously reported procedure.[6] Solutions of the compounds to be tested were prepared by dissolving the appropriate weight of the compound in acetone.

The larvicidal activities were tested against arymworm 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 10 4th instar larvae of the Southern armyworn. The dishes were then covered with the lid and held for 3 days at which time the percent control (mortality) was determined. Percent mortalities for the armyworm evaluations were determined 96 hours after treatment. Evaluations are based on a scale of 0–100 % in which 0 equals no activity and 100 equals total kill.

The larvicidal activities of the title compounds (**3**) and RH5849 are summarised in Table 1. Armyworm foliar results are 96 hour observations and reported as percent mortality.

Toxicity assays indicated that the title compounds (**3**) induces a premature, abnormal, and lethal moult in 4th instar larvae of armyworm.

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