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Synthesis, spectroscopy and biological activity of novel acylhydrazines containing ferrocenyl moiety

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Abstract

In a search for new insect growth regulators, we replaced the phenyl moiety by ferrocenyl in *N*-*tert*-butyl-*N*,*N*′-dibenzoylhydrazine and synthesized the novel *N*-*tert*-butyl-*N*′-ferrocenoyl-*N*-substitutedbenzoylhydrazines by the reaction of ferrocenoyl chloride with *N*-*tert*-butyl-*N*-substituted benzoylhydrazines in dry tetrahydrofuran using triethylamine as the acid acceptor. The *N*-*tert*-butyl-*N*-ferrocenoyl-*N*′-substituted benzoylhydrazines were prepared similarly. Then, the treatment of *N*-*tert*-butyl-*N*′-ferrocenoyl-*N*-benzoylhydrazine with alkylmethyl(chlorosulfenyl)carbamates in the presence of sodium hydride afforded the novel acylhydrazines containing the ferrocenyl moiety. The title compounds were identified by IR spectroscopy, ^{1}H-NMR spectroscopy, EIMS and elemental analyses. The results of bioassay showed that some of the title compounds exhibit excellent larvicidal activities. Toxicity assays indicated that the title compounds could induce a premature, abnormal and lethal larval molt. We found by chance that one of the title compounds possesses good anti-TMV (Tobacco Mosaic Virus) activity. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ferrocene; Ferrocenecarboxylic anhydride; Diacylhydrazine; Insect growth regulators; Lethal larval molt

1. Introduction

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 molting [1]. Relationships between the structure and biological activity of *N*-*tert*-butyl-*N*,*N*′-dibenzoylhydrazine larvicides have been extensively investigated [2]. The results indicated that the molecular hydrophobicity is favorable. In addition, ferrocene is ideal for use in drug design because of the low toxicity of the molecule containing a ferrocenyl moiety and the ease of substitution of a conventional phenyl or heteroaromatic group with a ferrocene moiety. Moreover, ferrocene-containing compounds often possess unexpected biological activity [3]. Indeed, ferrocenyl groups have already been shown to advantageously replace phenyl moieties in biologically active compounds [4]. The substitution of a phenyl group by a ferrocenyl group in a bioactive compound was expected to induce great changes in molecular properties, such as the solubility and hydrophobicity. Hence, in a search for new insect growth regulators, we thought that the replacement of the phenyl moiety by ferrocenyl in *N*-*tert*-butyl-*N*,*N*′-dibenzoylhydrazine would enhance their larvicidial activities to a significant degree. Therefore, we designed and synthesized the novel ferrocenoyl acylhydrazines **3** and **4**.

It has been reported that biscarbamoyl sulfide derivatives of methylcarbamate insecticides still retained the good insecticidal activity of the parent methylcarbamate but were substantially less toxic to the white mouse [5]. Encouraged by the reports, we developed the idea that the introduction of carbamate into *N*-*tert*-butyl-*N*′-ferrocenoyl-*N*-benzoylhydrazine, which has excellent insect growth regulators' activity, would retain the good insecticidal activity of the parent methylcarbamate and *N*-*tert*-butyl-*N*′-ferrocenoyl-*N*-benzoylhydrazine, while the toxicity of methylcarbamate would be reduced at the same time. Therefore, we designed and synthesized the title products **5**.

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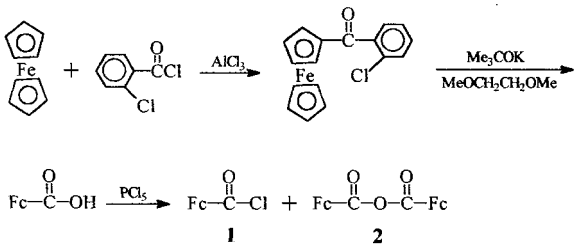
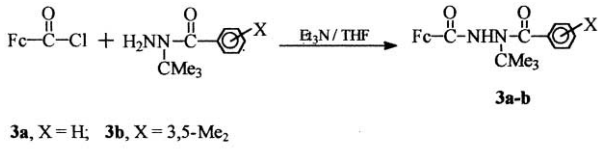
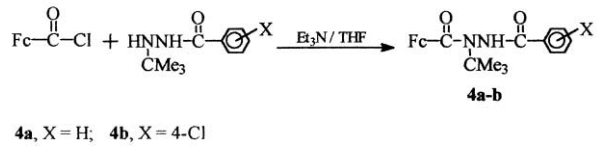


Scheme 1.

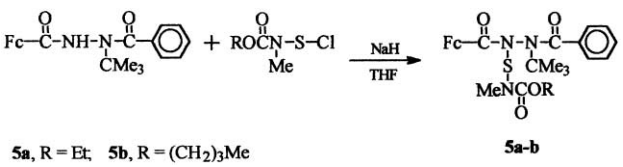


3a, X = H; **3b**, X = 3,5-Me_2



4a, X = H; **4b**, X = 4-Cl

Scheme 2.



5a, R = Et; **5b**, R = $(CH_2)_3Me$

Scheme 3.

2. Results and discussion

Treatment of ferrocene with 2-chlorobenzoyl chloride afforded 2-chlorobenzoylferrocene, and subsequent reaction with potassium *tert*-butoxide yielded ferrocene carboxylic acid in high yield [6]. Then, ferrocene carboxylic acid reacted with phosphorus pentachloride to give ferrocenoyl chloride in 48% yield [7]. We found that the above reaction under the reported condition [7] afforded two compounds, as shown in Scheme 1. The major product was found to be the expected ferrocenoyl chloride **1** in ca. 48% yield, and ferrocenecarboxylic anhydride **2** was isolated in 29–47% yield. The anhydride was identified by IR and ^{1}H-NMR spectroscopy, EIMS and elemental analyses. The characteristic bands of the ferrocenyl group in the IR spectra of the anhydride appear at 3112, 1442, 1242, 1102, 1065, 1008, 899, 821 and 755 cm^{-1}. The formation of the anhydride was the reason for the low yield of ferrocenoyl chloride prepared from ferrocene carboxylic acid and phosphorus pentachloride. According to the literature [8], anhydrides are good acylating agents. However, our attempts to prepare *N-tert*-butyl-*N'*-ferrocenoyl-*N*-benzoylhydrazine from ferrocenecarboxylic anhydride **2** and *N-tert*-butyl-*N*-benzoylhydrazine were unsuccessful. It is interesting to note that the ferrocenecarboxylic anhydride **2** cannot react with any primary or secondary amines or hydrazine. This is due to the effect of steric hindrance of ferrocenoyl and the conjugative effect of the ferrocene group with carbonyl.

The ferrocenoyl chloride **1** reacted with *N-tert*-butyl-*N*-substituted benzoylhydrazines in dry tetrahydrofuran using triethylamine as the acid acceptor to yield *N-tert*-butyl-*N'*-ferrocenoyl-*N*-substituted benzoylhydrazines in ca. 48% yield. The *N-tert*-butyl-*N*-ferrocenoyl-*N'*-substituted benzoylhydrazines **4** were similarly prepared, as shown in Scheme 2.

We found that the treatment of *N-tert*-butyl-*N'*-ferrocenoyl-*N*-benzoylhydrazine with alkylmethyl(chlorosulfenyl)carbamates in the presence of sodium hydride afforded the title compounds **5**, as shown in Scheme 3.

The title compounds **3**–**5** were characterized by IR and ^{1}H-NMR spectroscopy, EIMS and elemental analyses. The results are in accordance with the expected structures. The ^{1}H-NMR spectra of **3** and **4** are characteristic: the ferrocenyl substituent gives rise to a five-proton singlet in the range of 3.83–4.38 ppm for the unsubstituted cyclopentadienyl ring and two multiplets at 4.27–4.89 ppm for the monosubstituted ring.

The results of larvicidal activities given in Table 1 show that the title compounds **3** and **5** exhibit excellent larvicidal activities whereas the title compounds **4** have low activities. These results suggested that the benzoyl moiety located closer to the *tert*-butyl group is important for retaining high activity, and another phenyl can be replaced by the ferrocene group without losing much of the larvicidal activities. Toxicity assays indicated that the title compounds **3** and **5**, like *N-tert*-butyl-*N*,*N'*-dibenzoylhydrazine (RH5849), can induce a premature, abnormal and lethal larval molt. Symptoms of toxicity included discoloration, weight loss, cessation of feeding, and developmentally premature, lethal molting at higher rates. Therefore, the presence of the ferrocene group in title compounds **3** and **5** has been considered to play an important role in insect growth regulator activity.

We found by chance that the title compound **3b** possesses good anti-TMV (Tobacco Mosaic Virus) activity. For example, at 500 ppm, the inhibitory rate of compound **3b** to TMV attains 30%. To the best of our knowledge, this is the first report on anti-TMV activity of ferrocene derivatives. This result is promising. Further studies on anti-TMV activities of the ferrocenoyl acylhydrazines are underway.

Table 1
Larvicidal activities of products **3**–**5**

No.	Compound		Larvicidal activity (%)			
	X	R	1000 ppm	200 ppm	100 ppm	50 ppm
3a	H	–	100	100	90	70
3b	3,5-Me_2	–	100	100	80	70
4a	H	–	0	0	0	0
4b	4-Cl	–	50	20	10	0
5a	–	Et	100	100	10	–
5b	–	^{n}Bu	100	100	10	–
	RH5849		100	100	100	95

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

3. Experimental

3.1. Instruments

All reactions were carried out under N_2 atmosphere with the exclusion of moisture. ^{1}H-NMR spectra were obtained at 200 MHz using a Bruker AC-P 200 spectrometer. Chemical shift values (δ) are given in ppm. Infrared spectra were recorded on a Shimadzu-435 spectrometer. Elemental analyses were determined on an MT-3 elemental analyzer. Melting points were taken on a Thomas–Hoover melting-point apparatus and are uncorrected. Mass spectra were recorded with a HP 5988A spectrometer using the EI method.

3.2. Synthesis

Ferrocene carboxylic acid was obtained according to a previous report [6]. Alkyl methyl(chlorosulfenyl)-carbamates were prepared by the reaction between carbamate and sulfur dichloride in CH_2Cl_2, using Py as the acid acceptor [9]. *N-tert*-Butyl-*N*-substituted benzoylhydrazines and *N-tert*-butyl-*N*′-substituted benzoylhydrazines were synthesized according to the reported procedure [10].

3.2.1. General procedure for the preparation of products *3*, *4* and byproduct *2*

To a solution of ferrocene carboxylic acid (4.35 mmol) in dry C_6H_6 (15 ml) under N_2, PCl_5 (4.35 mmol) was added in small portions. After the addition, the resulting mixture was stirred for 3 h at room temperature (r.t.). The solvent and phosphorus oxychloride were evaporated at reduced pressure, and the residue was dissolved in anhydrous THF. It was used for the following reactions directly, without any further purification.

The above solution of ferrocenoyl chloride in anhydrous THF was added dropwise to a solution of *N-tert*-butyl-*N*(or *N*′)-substituted benzoylhydrazine (4.35 mmol) and distilled Et_3N (5.22 mmol) in anhydrous THF (20 mL) under N_2 at 0 °C, then the resulting mixture was stirred at r.t. for 8 h. Then the solid was filtered off and the filtrate was concentrated under vacuum and chromatographed on a silica gel column using a mixture of petroleum ether (60–90 °C) and EtOAc as the eluent. Finally, the desired compound **3** or **4** was obtained and ferrocenecarboxylic anhydride **2** was isolated as the byproduct.

*3.2.1.1. Ferrocenecarboxylic anhydride (**2**).* Red crystalline solid, m.p. 145–146 °C. IR (KBr): 3112, 1760, 1702, 1442, 1242, 1102, 1065, 1008, 899, 821 and 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 4.36 (s, 10H, C_5H_5), 4.55 (s, 4H, C_5H_4), 4.89 (s, 4H, C_5H_4). EIMS; *m*/*z* (%): 442.20 ($[M]^+$, 42). Anal. Found: C, 59.68; H, 4.29. Calc. for $C_{22}H_{18}Fe_2O_3$: C, 59.77; H, 4.10%.

*3.2.1.2. N-tert-Butyl-N′-ferrocenoyl-N-benzoylhydrazine (**3a**).* Red crystalline solid, yield 48.0%, m.p. 235–236 °C. ^{1}H-NMR ($CDCl_3$): δ 1.54 (s, 9H, ^{t}Bu), 3.84 (s, 5H, C_5H_5), 4.28 (m, 2H, C_5H_4), 4.56 (m, 2H, C_5H_4), 7.29–7.60 (m, 5H, Ph). Anal. Found: C, 65.09; H, 5.73; N, 6.91. Calc. for $C_{22}H_{24}N_2O_2Fe$: C, 65.36; H, 5.98; N, 6.93%.

*3.2.1.3. N-tert-Butyl-N′-ferrocenoyl-N-(3,5-dimethyl)-benzoylhydrazine (**3b**).* Red crystalline solid, yield 47.4%, m.p. 238–239 °C. IR (KBr): 3380, 3105, 2993, 1665, 1652, 1603, 1509, 1446, 1421, 1392, 1357, 1272, 1238, 1212, 1104, 1000, 844, 823, 758, 700 and 617 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9H, ^{t}Bu), 2.29 (s, 6H, Me), 3.83 (s, 5H, C_5H_5), 4.27 (m, 2H, C_5H_4), 4.60 (m, 2H, C_5H_4), 7.00 (s, 1H, Ph), 7.12 (s, 2H, Ph), 7.32 (br., 1H, NH). EIMS; *m*/*z* (%): 432.35 ($[M]^+$, 19), 213.20 (61), 185.25 (20) and 120.25 (2). Anal. Found: C, 66.54; H, 6.39; N, 6.69. Calc. for $C_{24}H_{28}N_2O_2Fe$: C, 66.68; H, 6.53; N, 6.48%.

*3.2.1.4. N-tert-Butyl-N-ferrocenoyl-N′-benzoylhydrazine (**4a**).* Red crystalline solid, yield 47.2%, m.p. 245–246 °C. ^{1}H-NMR ($CDCl_3$): δ 1.50 (s, 9H, ^{t}Bu), 4.38 (s,

5H, C_5H_5), 4.89 (m, 4H, C_5H_4), 7.31–7.74 (m, 5H, Ph). Anal. Found: C, 65.24; H, 5.76; N, 7.05. Calc. for $C_{22}H_{24}N_2O_2Fe$: C, 65.36; H, 5.98; N, 6.93%.

*3.2.1.5. N-tert-Butyl-N-ferrocenoyl-N′-(4-Cl)benzoylhydrazine (**4b**).* Yellow crystalline solid, yield 40.8%, m.p. 254–256 °C. ^{1}H-NMR ($CDCl_3$): δ 1.50 (s, 9H, ^{t}Bu), 4.38 (s, 5H, C_5H_5), 4.77 (m, 4H, C_5H_4), 7.31–7.74 (m, 5H, Ph). Anal. Found: C, 60.25; H, 5.07; N, 6.60. Calc. for $C_{22}H_{23}ClN_2O_2Fe$: C, 60.23; H, 5.28; N, 6.38%.

*3.2.2. General procedure for the preparation of compound **5***

To a stirred solution of *N-tert*-butyl-*N′*-ferrocenoyl-*N*-benzoylhydrazine (**3a**) (2.6 mmol) in anhydrous THF (30 ml) at r.t. under N_2 was added NaH portionwise (2.6 mmol). The mixture was stirred at r.t. for 0.5 h and cooled to 0 °C. Then a solution of alkyl methyl(chlorosulfenyl)carbamates (2.6 mmol) in anhydrous THF (5 ml) was added dropwise. After the addition, the reaction mixture was stirred for 8 h at r.t. 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 a mixture of petroleum ether (60–90 °C) and EtOAc as the eluent. Finally, the desired compound **5** was obtained.

*3.2.2.1. Compound **5a**.* Red crystalline solid, yield 55.7%, m.p. 118–120 °C. IR (KBr): 2973, 1713, 1668, 1641, 1389, 1365 and 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.54 (br., 12H, ^{t}Bu, CMe), 2.6 (br., 3H, NMe), 4.27–4.66 (m, 11H, C_5H_5, C_5H_4, OCH_2), 7.25 (br., 5H, Ph). EIMS; *m/z* (%): 537.30 ($[M]^+$, 4). Anal. Found: C, 58.14; H, 5.87; N, 7.75. Calc. for $C_{26}H_{31}N_3SO_4Fe$: C, 58.10; H, 5.81; N, 7.82%.

*3.2.2.2. Compound **5b**.* Yellow crystalline solid, yield 83.4%, m.p. 112–113 °C. ^{1}H-NMR ($CDCl_3$): δ 0.95 (s, 3H, CMe), 1.56 (br., 9H, ^{t}Bu), 2.02 (m, 4H, CH_2CH_2), 2.51 (br., 3H, NMe), 4.17–4.62 (m, 11H, C_5H_5, C_5H_4, OCH_2), 7.24 (br., 5H, Ph). Anal. Found: C, 59.35; H, 6.27; N, 7.51. Calc. for $C_{28}H_{35}N_3SO_4Fe$: C, 59.47; H, 6.24; N, 7.43%.

3.3. Larvicidal activity tests

The larvicidal activities of the title compounds and *N-tert*-butyl-*N,N′*-dibenzoylhydrazine (RH5849) were evaluated using a previously reported procedure [11]. Solutions of the compounds to be tested were prepared by dissolving the appropriate weight of the compound in Me_2CO.

The larvicidal activities were tested against armyworm 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 fourth instar larvae of the Southern armyworm. 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 h 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 and RH5849 are summarized in Table 1. Armyworm foliar results are 96-h observations and reported as percent mortality.

Toxicity assays indicated that the title compounds **3** and **5** induces a premature, abnormal, and lethal molt in the fourth instar larvae of armyworm. Symptoms of toxicity included discoloration, weight loss, cessation of feeding, and developmentally premature, lethal molting at higher rates.

Acknowledgements

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