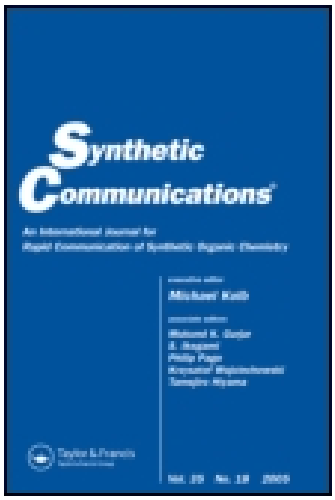

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A Convenient Synthesis of Novel N′-tert-Butyl-N′-Substituted Benzoyl-N-(Substituted Phenyl)aminocarbonylhydrazines and Their Derivatives

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A Convenient Synthesis of Novel *N′-tert*-Butyl-*N′*-Substituted Benzoyl-*N*-(Substituted Phenyl)aminocarbonylhydrazines and Their Derivatives

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ABSTRACT

N-tert-butyl-*N*-substituted benzoylhydrazines were prepared in two convenient procedures with good yields, subsequent reaction with substituted phenylisocyanates in 1,2-dichloroethane provided a series of novel *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines. Further treatment with oxalyl chloride gave their derivatives in good yields. The title compounds exhibit moderate larvicidal activities and anticancer activities.

Key Words: *N′-tert*-Butyl-*N′*-substituted benzoylhydrazine; Phenylisocyanate; Benzoylphenylurea; Insect growth regulators.

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In contrast to traditional pesticides, benzoylphenylurea (BPU) and its derivatives mainly control the growth and development process of insects by interfering with chitin biosynthesis and breeding, and the activities of BPUs are attributed to the structures of the urea linkage.[1,2] Moreover, *N-tert*-butyl-*N*,*N*′-diacylhydrazines (TBDH) as a new class of insect growth regulators (IGR) have been found to mimic the action of 20-hydroxyecdysone to activate the ecdysone receptor, leading to lethal premature molting.[3–7] Relationships between the structure and biological activity of the *N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine larvicides have been extensively investigated. The results indicated that the molecular hydrophobicity is favorable to insecticidal activity and *N-tert*-butyl-*N*-benzoylhydrazine is the biologically active unit.[8–12]

In the course of our studies on diacylhydrazine as novel IGRs,[13–15] we combined the bioactive units of TBDH and BPU to design and synthesize novel *N-tert*-buty1-*N*′-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines and their derivatives in order to find a new lead compound with unusual biological properties and a different spectrum of activities.

N-tert-Butyl-*N*-substituted benzoylhydrazines are important intermediates in synthesis of *N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine derivatives and three synthesis methods of such compound have been published as exemplified below. (1) *N-tert*-Butylhydrazine was reacted with di-tert-butyldicarbonate to afford *N-tert*-butyloxycarbonyl-*N*′-*tert*-butylhydrazine, then condensation with benzoylchloride and deprotection using hydrochloric acid yielded *N-tert*-butyl-*N*-benzoylhydrazine in 38% yield;[16] (2) *N-tert*-butylhydrazine was reacted with *N*-(9-fluorenylmethylcarbonyl)succinimide to afford *N-tert*-butyl-*N*-(9-fluorenylmethylcarbonyl)hydrazine, then acylation and deprotection using piperidine provided *N-tert*-butyl-*N*-substituted benzoylhydrazine;[8] and (3) *N-tert*-butyl-*N*′-acetonehydrazine prepared from *N-tert*-butylhydrazine and acetone was condensation with substituted benzoylchloride, then deprotection using hydrochloric acid afforded *N-tert*-butyl-*N*-substituted benzoylhydrazine.[17] However, all of these methods have some respective problems. In the methods (1) and (3), the yields are low ($<50\%$). The method (2) is not economically profitable, because an expensive *N*-(9-fluorenylmethycarbonyl)succinimide is used. Herein we report the syntheses of *N-tert*-butyl-*N*-substituted benzoylhydrazines by two novel procedures as shown in Schs. 1 and 2.

Method 1. Benzyl alcohol was treated with triphosgene [bis(trichloromethyl)carbonate] to obtain benzyl chloroformate in good yield. This convenient synthesis of benzyl chloroformate avoids the use of phosgene gas and the complicated experimental set-up associated with it. Benzyl chloroformate was condensed with *tert*-butylhydrazine hydrochloride to give *N-tert*-butyl-*N*′-benzyloxycarbonylhydrazine (**1**), and subsequent acylation with

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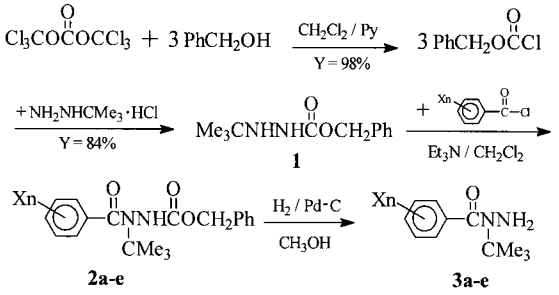
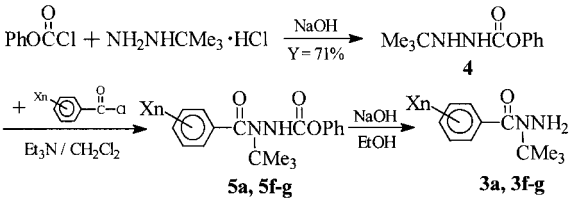


Scheme 1.



Scheme 2.

substituted benzoyl chlorides yielded the *N-tert*-butyl-*N*′-benzyloxycarbonyl-*N*-substituted benzoylhydrazines (**2**). Further deprotection using 5% Pd-C as a catalyst provided *N-tert*-butyl-*N*-substituted benzoylhydrazines (**3**) in good yields as shown in Scheme 1 and Table 1. This highly efficient method for the synthesis of *N-tert*-butyl-*N*-substituted benzoylhydrazines enjoys a number of advantages in that the reaction is carried out under mild conditions in good

Table 1. *N-tert*-butyl-*N*-substituted benzoylhydrazine yield using 5% Pd-C catalyst.

		Isolated yield (%)	
Entry	Xn	**1** → **2a–e**	**2a–e** → **3a–e**
a	H	90	96
b	3,5-Me_2	83	92
c	2-F	86	96
d	2-Cl	91	90
e	2,4-Cl_2	87	82

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Table 2. *N-tert*-butyl-*N*-substituted benzoylhydrazine yield using sodium hydroxide.

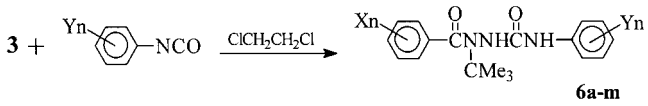
		Isolated yield (%)	
Entry	Xn	**4** → **5a**, **5f**–**g**	**5a**, **5f**–**g** → **3a**, **3f**–**g**
a	H	81	76
f	3-Me	77	73
g	4-OMe	81	78

yields, the starting materials are cheap a easily prepared, the experimental procedure is very simple and this method may be applicable to large scale production.

Method 2. Phenyl chloroformate was treated with *tert*-butylhydrazine hydrochloride to obtain *N-tert*-butyl-*N′*-phenyloxycarbonylhydrazine (**4**), and subsequent acylation with substituted benzoyl chloride yielded the *N-tert*-butyl-*N′*-phenyloxycarbonyl-*N*-substituted benzoylhydrazines (**5**). Further deprotection using sodium hydroxide provided *N-tert*-butyl-*N′*-substituted benzoylhydrazines (**3**) as shown in Scheme 2 and Table 2. As a consequence of its practical simplicity and high efficiency, this new method has already been applied to the preparation of *N-tert*-butyl-*N*-substituted benzoylhydrazines in our laboratory.

The reactions of the *N-tert*-butyl-*N*-substituted benzoylhydrazines (**3**) with substituted phenylisocyanates in 1,2-dichloroethane provided *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines (**6**) as shown in Sch. 3 and Tables 3–5. The structures of the title compounds **6** were confirmed by ^{1}H NMR and IR and mass spectra and elemental analysis. For example, for **6f**, 3343 cm^{-1} (s) corresponds to an N–H stretching absorption band, 1720 cm^{-1} (s) and 1621 cm^{-1} (s) to C=O stretching absorption bands, 1392 cm^{-1} (s) and 1360 cm^{-1} (s) to the C–H absorption bands in the Bu^t group. The EI-MS of the title compound **6f** gives the molecular ion peaks (373.20, M^+) and those of the main fragments.

Treatment of the *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines (**6**) with oxalyl chloride gave the colorless



6a-m

Scheme 3.

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Table 3. Experimental and microanalytical data for **6a–m** and **7m**.

Entry	Xn	Yn	Yield (%)	MP (°C)	Elemental Analysis (%) C	H	Found (calcd.) N
6a	H	H	75	259–260	69.49(69.43)	6.72(6.80)	13.58(13.49)
6b	H	4-F	81	251–253	65.41(65.64)	6.11(6.12)	12.73(12.76)
6c	H	4-OMe	87	205–207	66.47(66.84)	6.67(6.79)	12.32(12.31)
6d	H	r	87	212–214	57.04(56.85)	5.04(5.04)	10.86(11.05)
6e	H	3,4-Cl2	57	239–240	70.68(70.77)	7.36(7.42)	12.20(12.38)
6f	3,5-Me2	2,6-Me2	87	256–257	64.35(64.25)	6.44(6.47)	11.17(11.24)
6g	2-F	4-Cl	69	218–219	59.49(59.42)	5.26(5.26)	11.44(11.55)
6h	2-Cl	4-Cl	80	245–246	56.75(56.85)	4.93(5.04)	10.95(11.05)
6i	2-Cl	4-Cl	79	226–227	62.61(62.52)	5.75(5.83)	12.02(12.15)
6j	2,4-Cl2	H	71	174–175	56.99(56.85)	5.31(5.04)	11.05(11.05)
6k	3,5-Me2	H	80	237–238	66.99(67.21)	6.50(6.77)	12.04(11.76)
6l	2-F	4-F	84	233–235	62.25(62.24)	5.46(5.51)	12.20(12.10)
6m	H	4-F	75	243–245	62.49(62.52)	5.77(5.83)	11.98(12.15)
7m	H	4-Cl	71	124–126	59.86(60.08)	4.37(4.54)	10.74(10.51)

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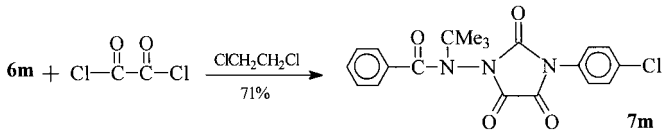
Table 4. ^{1}H NMR data for **6a–m** and **7m**.

Entry	δ (ppm) (DMSO-d_6)
6a	1.46(s, 9H, Bu^t), 6.84–7.50(m, 10H, Ph), 8.39(s, 1H, NH), 8.54(s, 1H, NH).
6b	1.45(s, 9H, Bu^t), 6.97–7.72(m, 9H, Ph), 8.44(s, 1H, NH), 8.56(s, 1H, NH).
6c	1.45(s, 9H, Bu^t), 3.66(s, 3H, OMe), 6.74–7.44(m, 9H, Ph), 8.17(s, 1H, NH), 8.44(s, 1H, NH).
6d	1.45(s, 9H, Bu^t), 7.13–7.63(m, 8H, Ph), 8.77(s, 1H, NH), 8.86(s, 1H, NH).
6e	1.46(s, 9H, Bu^t), 1.83(s, 6H, Me), 6.96–7.39(m, 8H, Ph), 8.66(br., 1H, NH).
6f	1.44(s, 9H, Bu^t), 2.20(s, 6H, Me), 6.94–7.27(m, 7H, Ph), 8.52(s, 1H, NH), 8.56(s, 1H, NH).
6g	1.52(s, 9H, Bu^t), 7.00–7.64(m, 8H, Ph), 8.34(s, 1H, NH), 8.56(s, 1H, NH).
6h	1.52(s, 9H, Bu^t), 7.04–7.52(m, 8H, Ph), 8.32(s, 1H, NH), 8.42(s, 1H, NH).
6i	1.52(s, 9H, Bu^t), 6.80–7.52(m, 9H, Ph), 8.20(s, 1H, NH), 8.40(s, 1H, NH).
6j	1.46(s, 9H, Bu^t), 6.86–7.94(m, 8H, Ph), 8.34(s, 1H, NH), 8.61(s, 1H, NH).
6k	1.52(s, 9H, Bu^t), 2.26(s, 6H, Me), 6.56–7.44(m, 7H, Ph), 8.22(s, 1H, NH), 8.40(s, 1H, NH).
6l	1.50(s, 9H, Bu^t), 6.72–7.60(m, 8H, Ph), 8.20(s, 1H, NH), 8.48(s, 1H, NH).
6m	1.45(s, 9H, Bu^t), 7.16–7.42(m, 9H, Ph), 8.36(s, 1H, NH), 8.6 1(s, 1H, NH).
7m	1.59(s, 9H, Bu^t), 7.01–7.38(m, 9H, Ph).

Table 5. IR data for **6a–m** and **7m**.

Entry	IR (cm^{-1}) (KBr)
6f	3343, 3114, 2964, 1720, 1621, 1594, 1533, 1490, 1392, 1360, 1223, 1190, 1090, 852, 822, 757, 691, 618.
6m	3371, 3255, 2995, 1691, 1626, 1590, 1532, 1501, 1395, 1366, 1218, 1197, 824, 706, 699, 604.
7m	3092, 2975, 1790, 1753, 1695, 1492, 1392, 1311, 1190, 804, 741, 699.

crystalline products (**7**) in good yields (>70%) as shown in Sch. 4. The structures of the title compounds **7** were confirmed by ^{1}H NMR and IR and mass spectra and elemental analysis. For example, for **7m**, 1790 cm^{-1} (s), 1753 cm^{-1} (S) and 1695 cm^{-1} (s) to C=O stretching absorption bands,



Scheme 4.

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1392 cm^{-1} (s) and 1311 cm^{-1} (s) to the C–H absorption bands in the Bu^t group. The EI-MS of the title compound **7m** gives the molecular ion peaks (399.15, M^+) and those of the main fragments.

The larvicidal activities of the title compounds (**6**) and (**7**) and *N-tert*-butyl-*N*,*N*′-dibenzoylhydrazine (**RH5849**) were evaluated using previously reported procedure.[7,16,18,19] The larvicidal activities show that the title compounds (**6**) and (**7**) exhibit moderate larvicidal activities. For example, at 1000 ppm, the percent mortality of compounds **6f**, **6k** and **RH5849** is 75.0%, 82.5% and 100%, respectively. Toxicity assays indicated that the title compounds (**6**) and (**7**) can induce a premature, abnormal and lethal larval molt. The symptoms of toxicity included discoloration, weight loss, cessation of feeding, and developmentally premature, lethal molting at higher rates.

We have found that the title compounds (**6**) possess anticancer activities in vitro. The anticancer activity was assayed by the MTT or SRB methods.[20–23] For example, at 1000 μM, the inhibition rate of compound **6c** to P388 and A-549 is 29.8% and 29.2%, respectively. The inhibition rate of compound **6b** to HL-60 and BEL-7402 is 33.3% and 21.6%, respectively.

EXPERIMENTAL

All the melting points were determined with Thomas-Hoover melting point apparatus, the thermometer was not standardized. IR spectra were recorded with a Shimadzu-435. ^{1}H NMR spectra were recorded with Bruker AC-P200 using tetramethylsilane as an internal standard. Mass spectra were recorded with HP5988A spectrometer using the EI method. Elemental analysis was carried out with a Yanaco CHN Corder MT-3 elemental analyzer.

***N-tert*-Butyl-*N*-substituted benzoylhydrazines 3a–e**. To a solution of *N-tert*-butyl-*N*-benzyloxycarbonyl-*N*-substituted benzoylhydrazine **2a–e** (41.40 mmol) in methanol (100 mL) was added 5% Pd-C. Hydrogen gas was then admitted to the solution. The reaction was monitored by TLC and stopped after complete consumption of **2a–e**. The solid was filtered off and the filtrate was concentrated under vacuum to obtain a white powder.

3a. m.p. 127–129°C. (literature m.p.: 124–125°C)[16] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (s, 9H, Bu^t), 3.90 (s, 2H, NH_2), 7.28–7.56 (m, 5H, Ph).

3b. m.p. 128–130°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48 (s, 9H, Bu^t), 2.34 (s, 6H, Me), 4.08 (s, 2H, NH_2), 7.00–7.20 (m, 3H, Ph).

3c. m.p. 106–107°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 9H, Bu^t), 4.06 (s, 2H, NH_2), 6.96–7.60 (m, 4H, Ph).

3d. m.p. 59–61°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 9H, Bu^t), 4.00 (s, 2H, NH_2), 7.20–7.60 (m, 4H, Ph).

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3e. m.p. 103–105°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 9H, Bu^t), 3.88 (s, 2H, NH_2), 7.20–7.50 (m, 3H, Ph).

N-tert-Butyl-*N*-Substituted Benzoylhydrazines 3a, 3f–g

N-tert-Butyl-*N*′-phenyloxycarbonyl-*N*-substituted benzoylhydrazine (8.00 mmol) was dissolved in lukewarm ethanol (40 mL). While the reaction mixture was stirred, a 15% aqueous solution of sodium hydroxide (50 mL) was added. Following the addition, the mixture was stirred at 60°C for 1 hr, then cooled, and extracted three times with 100 mL of chloroform. The extraction solvent was dried over anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from isopropanol and petroleum ether to obtain a colorless crystalline solid.

3a. m.p. 127–129°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.48 (s, 9H, Bu^t), 3.90 (s, 2H, NH_2), 7.28–7.56 (m, 5H, Ph). IR (KBr): 3276.0 (NH_2), 1620.5 (C═O), 1573.1, 1529.5, 1508.8 (Ph), 1375.6, 1350.0 (Bu^t), 719.6, 696.7 (Ph) cm^{-1}.

3f. m.p. 98–100°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.45 (s, 9H, Bu^t), 2.36 (s, 3H, Me), 3.78 (br., 2H, NH_2), 7.28 (m, 4H, Ph). Anal. Calcd. for $C_{12}H_{18}N_2O$ (%): C, 69.87; H, 8.79; N, 13.58. Found: C, 69.85; H, 8.88; N, 13.56.

3g. m.p. 151–152°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.45 (s, 9H, Bu^t), 3.80 (s, 3H, OMe), 4.00 (br., 2H, NH_2), 6.85, 7.48 (dd, 4H, $^3J_{HH} = 8.4$ Hz, Ph). Anal. Calcd. for $C_{12}H_{18}N_2O$ (%): C, 64.84; H, 8.16; N, 12.60. Found: C, 64.42; H, 8.42; N, 12.78.

General Procedure for the Preparation of *N*′-*tert*-Butyl-*N*′-Substituted Benzoyl-*N*-(Substituted Phenyl)-aminocarbonylhydrazines (6a–m)

To a stirred solution of the *N-tert*-butyl-*N*-substituted benzoylhydrazine (**3**) (2.17 mmol) in 1,2-dichloroethane (10 mL) was added dropwise a solution of a substituted phenylisocyanate (2.17 mmol) in 1,2-dichloroethane (5 mL) at room temperature. After the addition, the resulting mixture was stirred at reflux temperature. The reaction was monitored by TLC and stoped after complete consumption of **3**. The reaction mixture was diluted with petroleum ether (60–90°C) and filtered to afford a white solid. The crude solid was recrystallized from dimethylformamide to obtain an analytical sample of **6a–m**. The preparative and spectral data of **6a–m** are listed in Tables 3–5.

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General Procedure for the Preparation of the Compounds (7)

N′-tert-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazine (**6**) (3.27 mmol) and oxalyl chloride (0.50 g) were dissolved in 25 mL of 1,2-dichloroethane and boiled for 24 hr. The solvent was removed under vacuum, 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. Finally, the colourless crystalline (**7**) was obtained. The preparative and spectral data of **7m** are listed in Tables 3–5.

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