

Syntheses and Biological Activities of Novel *N*-*tert*-butyl-*N'*-Alkoxy-carbonyl-*N*-Substituted Benzoylhydrazines and their Derivatives

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Abstract: A series of novel *N*-*tert*-butyl-*N'*-alkoxy-carbonyl-*N*-substituted benzoylhydrazines and their derivatives were synthesized. The results of bioassay showed that these title compounds exhibit moderate larvicidal activities, and toxicity assays indicated that these title compounds can induce a premature, abnormal and lethal larval molt. At the same time, we found by chance that these title compounds possess potential anticancer activities *in vitro*.

Keywords: *N*-*tert*-butyl-*N'*-alkoxy-carbonyl-*N*-substituted benzoylhydrazines, *N*-*tert*-butyl-*N*-benzoyl-hydrazine, benzyl chloroformate, Insect Growth Regulators (IGR), anticancer activities.

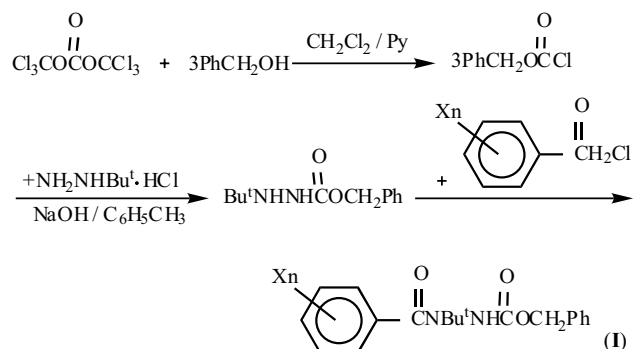
INTRODUCTION

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 [1-3]. Among nonsteroidal ecdysone agonists, *N*-*tert*-butyl-*N'*-(4-ethylbenzoyl)-3,5-dimethylbenzoylhydrazine (common name: tebufenozide, code name: RH-5992) has been the first to be commercialized as an 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 [4]. Relationships between the structure and biological activity of the *N*-*tert*-butyl-*N,N'*-dibenzoylhydrazine larvicides have been extensively investigated. The results indicated that *N*-*tert*-butyl-*N*-benzoylhydrazine is the biologically active unit [5-7]. Considering the wide application of these compounds and their potential to serve as insect growth regulators, we decided to reserve of bioactivity unit and replace of phenyl moiety by alkoxy in *N*-*tert*-butyl-*N,N'*-dibenzoylhydrazine, therefore, we designed and synthesized a series of novel *N*-*tert*-butyl-*N'*-alkoxy-carbonyl-*N*-substituted benzoylhydrazines and their derivatives.

RESULTS AND DISCUSSION

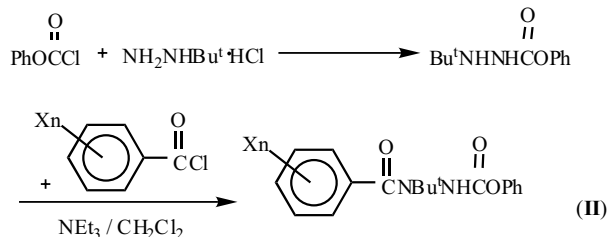
Benzyl alcohol was treated with triphosgene for the first time to obtain benzyl chloroformate in 98.0% yield. The new and convenient synthesis of benzyl chloroformate can avoid the use of phosgene gas due to the presence of the complicated experimental set up associated it. Then benzyl chloroformate was condensed with *tert*-butylhydrazine hydrochloride to give *N*-*tert*-butyl-*N'*-benzyloxycarbonylhydrazine. Subsequent acylation with appropriately

substituted benzoyl chloride yielded *N*-*tert*-butyl-*N'*-benzyloxycarbonyl-*N*-substituted benzoylhydrazines (**I**) in good yields as shown in Scheme 1.



Scheme 1.

Phenyl chloroformate was treated with *tert*-butylhydrazine hydrochloride to obtain *N*-*tert*-butyl-*N'*-phenyloxycarbonylhydrazine, and subsequent acylation with substituted benzoyl chloride yielded the *N*-*tert*-butyl-*N'*-phenyloxycarbonyl-*N*-substituted benzoylhydrazine (**II**) as shown in Scheme 2.



Scheme 2.

N-*tert*-Butyl-*N*-benzoylhydrazine is important intermediate 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 benzoyl chloride and deprotection

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using hydrochloric acid yielded *N-tert*-butyl-*N*-benzoylhydrazine in 38% yield [8]; (2) *N-tert*-Butylhydrazine was reacted with *N*-(9-fluorenylmethyl-carbonyl)succinimide to afford *N-tert*-butyl-*N'*-(9-fluorenylmethylcarbonyl)hydrazine, then acylation and deprotection using piperidine provided *N-tert*-butyl-*N*-benzoylhydrazine [9]; (3) *N-tert*-Butyl-*N'*-acetonehydrazine prepared from *N-tert*-butylhydrazine and acetone was condensation with benzoyl chloride, then deprotection using hydrochloric acid afforded *N-tert*-butyl-*N*-benzoylhydrazine [10]; 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-fluorenylmethyl-carbonyl) succinimide is used. Herein we report synthesis of *N-tert*-butyl-*N*-benzoylhydrazine by a novel procedure as shown in Scheme 3. Deprotection of *N-tert*-butyl-*N'*-benzyloxycarbonyl-*N*-benzoylhydrazines (**1a**) using 5% Pd-C as a catalyst provided *N-tert*-butyl-*N*-benzoylhydrazine in 96.4% yield, then condensation with ethyl chloroformate yielded *N-tert*-butyl-*N'*-ethoxycarbonyl-*N*-benzoylhydrazine (**III**) in 85.4% yield.

N-tert-Butyl-*N'*-benzyloxycarbonyl-*N*-benzoylhydrazines (**1a**) was reacted with benzyl bromide in the presence of sodium hydride to give *N-tert*-butyl-*N'*-benzyl-*N'*-benzyloxycarbonyl-*N*-benzoylhydrazine (**IV**) in 77.8% yield as shown in Scheme 4.

N-tert-Butyl-*N'*-benzyloxycarbonyl-*N*-substitutedbenzoylhydrazines (**I**) may undergo enolization as shown in Scheme 5. The hydrazine **A** may be converted into the enol form **B** at room temperature (24°C). The *tert*-butyl groups in **A** and **B** are magnetically nonequivalent, and therefore, the H atoms of the *tert*-butyl groups of the products show two single peaks. Owing to the unstability of the enol form **B**, it can be converted into the hydrazine **A** at higher temperature and the H atoms of the *tert*-butyl groups of the products obtained at 80°C exhibit a single peak.

Because the introduction of benzyl group to another nitrogen may cause the molecular rotations around the N-N

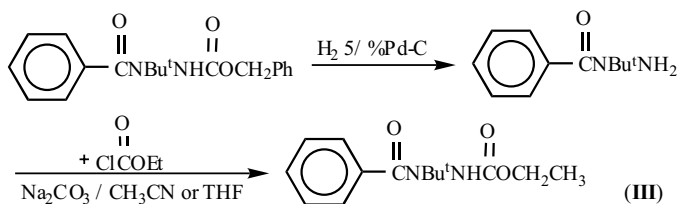
bond to be "frozen", there exist two conformational isomers in *N-tert*-butyl-*N'*-benzyl-*N'*-benzyloxycarbonyl-*N*-benzoylhydrazine (**IV**) and the H atoms of the *tert*-butyl groups of **IV** show two single peaks.

BIOLOGICAL ACTIVITIES

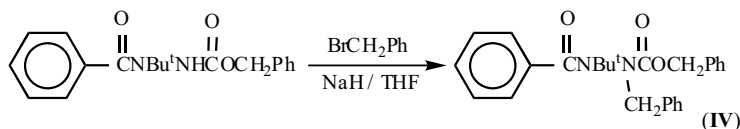
The larvicidal activities of these title compounds and *N-tert*-butyl-*N,N'*-dibenzoylhydrazine (**RH5849**) were evaluated using previously reported procedure [4, 8, 11-12]. The larvicidal activities were tested against Oriental armyworm (*Mythimna separata* (Walker)) by foliar application. For the 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 10 larvae of the 4th instar 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 4 days after treatment. Evaluations are based on a scale of 0-100 percent in which 0 equals no activity and 100 equals total kill. For comparative purposes, *N-tert*-butyl-*N,N'*-dibenzoylhydrazine (**RH5849**) was tested under the same conditions.

The results of larvicidal activities show that these title compounds exhibit moderate larvicidal activities. For example, at 1000 ug/mL, the percent mortality of compound **If**, **IIa** and **RH5849** is 70%, 50% and 100%, respectively. Toxicity assays indicated that these title compounds, like *N-tert*-butyl-*N,N'*-dibenzoylhydrazine (**RH5849**), can induce a premature, abnormal and lethal larval molt at 1000 ug/mL. Symptoms of toxicity included discoloration, weight loss, cessation of feeding, and developmentally premature, lethal molting at higher rates.

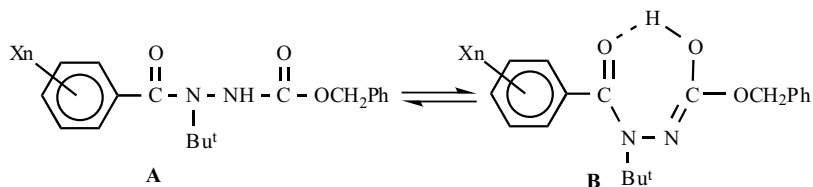
At the same time, we found that these title compounds possess potential anticancer activities *in vitro*. The anticancer activity was assayed by the MTT or SRB methods [13-16].



Scheme 3.



Scheme 4.



Scheme 5.

For example, at 10^{-4} mol/L, the inhibitory rate of compound **Ij** to HL-60 and BEL-7402 is 98.0% and 94.8%, respectively.

CONCLUSIONS

A series of novel N-tert-butyl-N'-alkoxy carbonyl-N-substituted benzoylhydrazines and their derivatives were synthesized. A novel synthesis of N-tert-butyl-N-benzoylhydrazine was described. Benzyl chloroformate was obtained by the reaction of benzyl alcohol and triphosgene in 98.0% yield for the first time. The results of bioassay showed that these title compounds exhibit moderate larvicidal activities, and toxicity assays indicated that these title compounds can induce a premature, abnormal and lethal larval molt. At the same time, we found by chance that these title compounds possess potential anticancer activities *in vitro*. These results are promising and have encouraged us to pursue the search of new and more effective analogs as pesticidal candidate and anticancer drug. Further studies on larvicidal activities and anticancer activities of the title compounds and its derivatives are underway and will be reported in due course.

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. ^1H 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.

Triphosgene was synthesized by chlorination of dimethylcarbonate in 96.0% yield [17-18], it melted at 79-81°C (literature, mp: 79-80°C), IR(KBr, cm^{-1}): 1820, 1178, 925, 810, 675, 517.

Benzyl Chloroformate

A solution of distilled benzyl alcohol (10.92 g, 0.101 mol) and distilled pyridine (11.98 g, 0.150 mol) in methylene dichloride (20 mL) was added dropwise to a solution of triphosgene (15 g, 0.050 mol) in methylene dichloride (30 mL) at -10°C . Then the resulting mixture was stirred at -10°C for 2 h, followed by 42 additional h of stirring at room temperature. After the solvent was removed under vacuum, the residue was distilled under reduced pressure yielding a colorless liquid (16.89 g) in 98.0% yield. bp: 42-49°C/5-6 mmHg, n_D^{20} : 1.5188. (literature [19], n_D^{20} : 1.5190)

N-tert-Butyl-N'-Benzoyloxycarbonylhydrazine

To a mechanically stirred suspension of tert-butylhydrazine hydrochloride (11.50 g, 0.092 mol) in toluene (100 mL) was added dropwise a solution of 10% aqueous sodium hydroxide (36.92 g, 0.092 mol) at room temperature. After 15 minutes, the reaction mixture was cooled to -15°C , and solutions of benzyl chloroformate (15 g, 0.088 mol) in toluene (30 mL) and 10% aqueous sodium

hydroxide (35.16 g, 0.088 mol) were added dropwise and simultaneously from separate addition funnels, while maintaining the temperature below -10°C . Following the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The water phase was extracted three times with 100 mL of chloroform. The extraction solvent was combined with the organic phase, and dried with 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 (16.33 g) in 83.6% yield: m.p. 75-77°C. ^1H NMR(CDCl_3 , 200 MHz) δ 1.11(s, 9H, Bu^t), 5.16(s, 2H, OCH_2), 5.02(br., 2H, NHNH), 7.38(m, 5H, Ph). IR(KBr): 3264.0, 3240.0 (NHNH); 1713.4 (C=O); 1521.4, 1491.8, 1466.3(Ph); 1406.2, 1381.8(Bu^t); 1260.8(C-O); 828.2, 716.1(Ph).

N-tert-Butyl-N'-Benzoyloxycarbonyl-N-Substituted benzoylhydrazine (I)

A solution of substituted benzoylchloride (0.054 mol) in methylene dichloride (15 mL) was added dropwise to a solution of N-tert-butyl-N'-benzyloxycarbonylhydrazine (12 g, 0.054 mol) and triethylamine (6.58 g, 0.065 mol) in methylene dichloride (40 mL) under magnetic stirring at 0°C , then the resulting mixture was stirred at room temperature for 2 h. Then the solid was filtered off and the filtrate was washed successively 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 recrystallized from ethanol to obtain a colorless crystalline solid (Scheme 1). The preparative and spectral data of **Ia-Ij** are listed in Tables 1-3.

N-tert-Butyl-N'-Phenyloxycarbonylhydrazine

To a mechanically stirred suspension of tert-butylhydrazine hydrochloride (0.092 mol) in toluene (100 mL) was added dropwise a solution of 10% aqueous sodium hydroxide (0.092 mol) at room temperature. After 15 minutes, the reaction mixture was cooled to -15°C , and solutions of phenyl chloroformate (0.088 mol) in toluene (30 mL) and 10% aqueous sodium hydroxide (0.088 mol) were added dropwise and simultaneously from separate addition funnels, while maintaining the temperature below -10°C . Following the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The water phase was extracted three times with 100 mL of chloroform. The extraction solvent was combined with the organic phase, and dried with 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 in 71% yield, mp 106-108°C. ^1H NMR(CDCl_3 , 200 MHz) δ : 1.12(s, 9H, Bu^t), 5.14(br., 2H, NHNH), 7.08-7.56(m, 5H, Ph).

N-tert-Butyl-N'-Phenyloxycarbonyl-N-Substituted benzoylhydrazine (II)

A solution of substituted benzoylchloride (0.054 mol) in methylene dichloride (15 mL) was added dropwise to a

solution of *N-tert-butyl-N'*-phenyloxycarbonylhydrazine (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 2 h. Then the solid was filtered off and the filtrate was washed successively 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 recrystallized from ethanol to obtain a colorless crystalline solid (Scheme 2). The preparative and spectral data of **IIa-IIIc** are listed in Tables 1-3.

Table 1. Experimental and Microanalytical Data for I^cII^oεIII and IV

No.	Xn	MP (°C)	Yield (%)	Elemental C	Analysis (%) H	Found (Calcd) N
Ia	H	150-152	89.6	69.82(69.92)	6.85(6.79)	8.78(8.58)
Ib	2-F	148-150	86.3	66.27(66.27)	6.15(6.15)	8.30(8.13)
Ic	2-Cl	143-144	91.3	63.27(63.24)	5.94(5.87)	8.01(7.76)
Id	2-I	128-130	70.5	50.40(50.46)	4.85(4.68)	6.33(6.19)
Ie	2-NO ₂	112-114	80.5	61.38(61.45)	5.68(5.70)	11.32(11.31)
If	3,5-Me ₂	134-136	82.9	70.98(71.16)	7.39(7.37)	8.14(7.90)
Ig	2,4-Cl ₂	159-161	87.3	57.67(57.73)	5.23(5.10)	7.22(7.09)
Ih	3,5-Cl ₂	153-155	83.5	57.83(57.73)	5.30(5.10)	7.15(7.09)
Ii	3,4-Cl ₂	84-86	83.5	57.46(57.73)	5.32(5.10)	7.33(7.09)
Ij	2,4,6-Cl ₃	129-130	63.1	52.9(53.11)	4.40(4.46)	6.76(6.52)
IIa	3-Me	150-151	76.5	69.61(69.92)	6.47(6.79)	8.74(8.58)
IIb	4-OMe	170-171	80.5	66.44(66.65)	6.23(6.48)	8.33(8.18)
IIc	2-OMe	163-164	75.6	66.61(66.65)	6.23(6.48)	8.43(8.18)
III	H	119-120	85.4	63.65(63.61)	7.71(7.62)	10.75(10.59)
IV	/	109-110	77.8	75.05(74.98)	6.61(6.78)	6.63(6.73)

Table 2. ¹H NMR Data for I^cII^oεIII and IV

No.		δ (ppm)
Ia	DMSO-d ₆	1.37(s), 1.42(s)(9H, Bu ^t); 4.80-5.05(m, 2H, CH ₂); 6.84-7.37(m, 10H, Ph); 9.40(s, OH); 9.83(s, NH)
Ib	CDCl ₃	1.45(s), 1.51(s)(9H, Bu ^t); 4.77-4.98(m, 2H, CH ₂); 6.88-7.47(m, 9H, Ph)
Ic	CDCl ₃	1.46(s), 1.52(s)(9H, Bu ^t); 4.78-5.03(m, 2H, CH ₂); 6.97-7.35(m, 9H, Ph);
Id	DMSO-d ₆	1.38(s), 1.45(s)(9H, Bu ^t); 4.85-5.09(m, 2H, CH ₂); 7.03-7.80(m, 9H, Ph); 9.31(s, OH); 9.76(s, NH)
Ie	DMSO-d ₆	1.38(s), 1.45(s)(9H, Bu ^t); 4.80-5.05(m, 2H, CH ₂); 6.98-8.20(m, 9H, Ph); 9.39(s, OH); 9.85(s, NH)
If	DMSO-d ₆	1.36(s), 1.40(s)(9H, Bu ^t); 2.21(s, 6H, Me); 4.80-5.09(m, 2H, CH ₂); 6.88-7.37(m, 8H, Ph); 9.33(s, OH); 9.77(s, NH)
Ig	CDCl ₃	1.46(s), 1.51(s) 9H, Bu ^t); 4.77-5.08(m, 2H, CH ₂); 6.80-7.42(m, 8H, Ph)
Ih	CDCl ₃	1.42(s), 1.48(s)(9H, Bu ^t); 4.86-5.12(m, 2H, CH ₂); 6.78-7.40(m, 8H, Ph)
Ii	CDCl ₃	1.10(s, 9H, Bu ^t); 5.07(s, 2H, CH ₂); 4.68(br., 1H, NH); 7.12-7.66(m, 8H, Ph)
Ij	CDCl ₃	1.43(s), 1.52(s)(9H, Bu ^t); 4.80-5.26(m, 2H, CH ₂); 6.73-7.38(m, 7H, Ph)
IIa	CDCl ₃	1.55(s), 1.58(s)(9H, Bu ^t); 2.34(s, 3H, Me); 6.70-7.27(m, 9H, Ph)
IIb	CDCl ₃	1.54(s), 1.57(s)(9H, Bu ^t); 3.80(s, 3H, Me); 6.79-7.49(m, 9H, Ph)
IIc	CDCl ₃	1.56(s), 1.59(s)(9H, Bu ^t); 3.91(s, 3H, Me); 6.57-7.42(m, 9H, Ph)
III	CDCl ₃	0.98(t, 3H, ³ J _{HH} =7.3Hz, Me); 1.50(s, 9H, Bu ^t); 3.88-4.00(m, 2H, CH ₂); 6.49(s, 1H, NH); 7.28-7.46(m, 5H, Ph)
IV	CDCl ₃	1.33(s), 1.43(s)(9H, Bu ^t); 4.32(m, 2H, NCH ₂); 5.33(m, 2H, OCH ₂); 7.02-7.39(m, 15H, Ph)

Table 3. IR Data for I^a–I^j and III and IV

No.	IR (cm ⁻¹) (KBr)
Ia	3219.0, 3022.5, 2875.5, 1742.4, 1621.9, 1600.3, 1578.8, 1532.0, 1498.1, 1404.3, 1382.3, 1359.9, 1251.5, 1211.8, 1060.1, 738.1, 712.8, 662.6
Ib	3222.0, 3015.5, 1737.4, 1637.6, 1614.2, 1584.4, 1526.6, 1489.5, 1453.1, 1405.9, 1281.6, 1252.4, 1222.3, 1189.6, 1058.3, 879.1, 782.3, 740.1, 693.6, 665.6, 641.9
Ic	3242.0, 3121.0, 2996.0, 1751.1, 1655.8, 1575.4, 1544.3, 1518.9, 1450.9, 1382.0, 1243.9, 1202.3, 1128.8, 1043.0, 875.9, 830.4, 742.9, 693.6, 622.0
Id	3237.5, 3077.0, 2965.5, 1727.9, 1716.0, 1644.7, 1592.4, 1559.9, 1515.5, 1394.6, 1366.5, 1252.0, 1214.1, 1077.8, 785.4, 694.4, 668.5, 638.7
Ie	3210.0, 2969.0, 1738.1, 1640.2, 1613.4, 1526.9, 1494.5, 1452.2, 1394.6, 1372.2, 1340.4, 1241.3, 1211.1, 1041.5, 850.6, 807.7, 735.5, 694.6
If	3253.5, 3055.0, 2922.5, 1733.5, 1639.8, 1599.6, 1523.6, 1495.6, 1472.9, 1399.4, 1365.4, 1251.0, 1212.8, 1054.1, 866.8, 788.1, 743.9, 693.9
Ig	3208.5, 3060.0, 1733.8, 1637.3, 1607.1, 1556.4, 1521.9, 1495.4, 1399.9, 1373.4, 1246.5, 1213.8, 1189.3, 1095.9, 1054.7, 876.2, 830.1, 763.4, 733.2, 692.4
Ih	3258.0, 2933.5, 1729.8, 1645.4, 1562.2, 1519.5, 1495.9, 1364.5, 1246.4, 1212.9, 1107.5, 1050.9, 804.0, 740.9, 716.0, 622.4
Ii	3271.0, 3030.5, 1723.5, 1695.1, 1606.3, 1513.1, 1451.9, 1382.0, 1262.0, 1222.1, 1157.3, 999.1, 746.5, 693.8
Ij	3258.0, 3079.5, 1734.6, 1641.7, 1592.4, 1568.3, 1520.3, 1453.0, 1401.8, 1361.9, 1277.4, 1247.1, 1210.0, 1047.5, 1025.2, 765.0, 737.1, 708.0, 639.6
IIa	3295.0, 3009.5, 1749.8, 1643.9, 1600.5, 1515.1, 1458.1, 1364.4, 1246.7, 1207.6, 1162.2, 1035.0, 804.1, 750.0, 693.7
III	3222.0, 2973.0, 1730.1, 1634.5, 1601.1, 1515.6, 1446.8, 1394.3, 1363.0, 1252.1, 1212.6, 1055.9, 796.4, 727.1
IV	3097.5, 2979.0, 1710.8, 1641.5, 1610.3, 1586.7, 1509.4, 1447.2, 1399.8, 1355.7, 1221.7, 1184.1, 1152.3, 1113.0, 1025.2, 791.1, 763.4, 727.9, 693.7

N-tert-Butyl-N-Benzoylhydrazine

To a solution of *N-tert-butyl-N'*-benzyloxycarbonyl-*N*-benzoylhydrazine **Ia** (13.50 g, 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 **Ia**. The solid was filtered off and the filtrate was concentrated under vacuum to obtain a white powder (7.67 g) in 96.4% yield: m.p. 127-129°C. (literature [8], yield: 38.0%, mp: 124-125°C) ¹H NMR(CDCl₃, 200 MHz) δ 1.48(s, 9H, Bu^t), 3.90(s, 2H, NH₂), 7.28-7.56(m, 5H, Ph). IR(KBr): 3276.0 (NH₂); 1620.5 (C=O); 1573.1, 1529.5, 1508.8 (Ph); 1375.6, 1350.0 (Bu^t); 719.6, 696.7 (Ph).

N-tert-Butyl-N'-Ethoxycarbonyl-N-Benzoylhydrazine (III)

The mixture of *N-tert-butyl-N*-benzoylhydrazine (1.56 mmol) ethyl chloroformate (1.87 mmol) potassium carbonate (1.87 mmol) and methyl-cyanide (20 mL) was stirred and fluxed for 22 h. The reaction was monitored by TLC and stopped after complete consumption of *N-tert-butyl-N*-benzoylhydrazine. The solid was filtered off and the filtrate was concentrated under vacuum to obtain a yellow solid. Methylene dichloride (20 mL) was added, then washed with distilled water, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was purified by column chromatography on a silica gel using a mixture of petroleum ether (60-90°C) and ethyl acetate as the eluent (Scheme 3). The preparative and spectral data of **III** are listed in Tables 1-3.

N-tert-Butyl-N'-Benzyl-N'-Benzyloxycarbonyl-N-Benzoylhydrazine (IV)

To a stirred solution of *N-tert-butyl-N'*-benzyloxy-carbonyl-*N*-benzoylhydrazines (**Ia**) (1.20 g, 3.68 mmol) in

anhydrous tetrahydrofuran (20 mL), was added portionwise sodium hydride (0.23 g, 50 percent purity, 4.78 mmol) at room temperature under nitrogen. The mixture was stirred at room temperature for 0.5 h and cooled to 0°C. Then benzyl bromide (0.82 g, 4.78 mmol) 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 5:1 petroleum ether (60-90°C) / ethyl acetate as the eluent. Finally, colorless crystals (**IV**) were obtained (Scheme 4). The preparative and spectral data of **IV** are listed in Tables 1-3.

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