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Synthesis and biological activity of novel *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines and their derivatives

Qingmin Wang and Runqiu Huang*

Research Institute of Elemento-Organic Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

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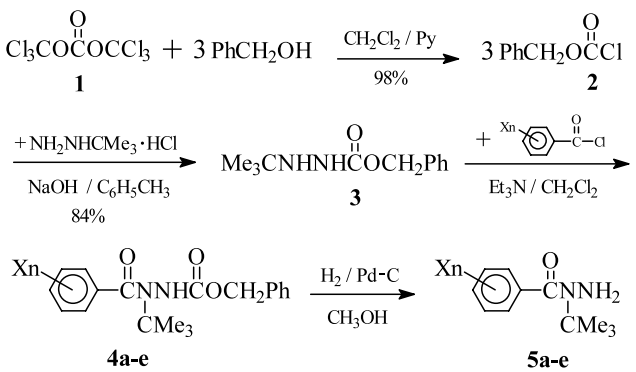
Abstract—Benzyl chloroformate was synthesised by the reaction of benzyl alcohol and triphosgene in good yield for the first time. *N-tert*-Butyl-*N*-substituted benzoylhydrazines were prepared in a new and convenient procedure with good yields. A series of novel *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines and their derivatives were synthesised and evaluated for molting hormone mimicking activity. The results of bioassays showed that the title compounds exhibit good larvicidal activities and toxicity assays indicated that the title compounds can induce a premature, abnormal and lethal larval molt. We have found that the title compounds possess potential anticancer activities.

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] Recently, a new class of insect growth regulators (IGR), the *N-tert*-butyl-*N*,*N′*-diacylhydrazines (BDAH), have been found to mimic the action of 20-hydroxyecdysone in activating the ecdysone receptor leading to lethal premature molting.[2] 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 favourable and *N-tert*-butyl-*N*-benzoylhydrazine is the biologically active unit.[3]



Scheme 1.

In general, structural similarity always results in similar biological activity, so designing a molecule that mimics the structural essentials of a bioactive unit is a shortcut to developing a lead compound with potential activity. In the study of novel IGRs, we combined the bioactive units of BDAH and BPU to design and synthesise novel *N′-tert*-butyl-*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.

Benzyl alcohol was treated with triphosgene [bis(trichloromethyl)carbonate] (**1**) to obtain benzyl chloroformate (**2**) in good yield for the first time.[4] This new and convenient synthesis of benzyl chloroformate avoids the use of phosgene gas and the complicated experimental set-up associated with it. Benzyl chloroformate (**2**) was condensed with *tert*-butylhydrazine hydrochloride to give *N-tert*-butyl-*N′*-benzyloxycarbonylhydrazine (**3**),[5] and subsequent acylation with substituted benzoyl chlorides yielded the *N-tert*-butyl-

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* Corresponding author. Tel.: 0086-022-23502673; fax: 0086-022-23503438; e-mail: wang98h@263.net

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N′-benzyloxycarbonyl-*N*-substituted benzoylhydrazines (**4**).[6] Further deprotection using 5% Pd–C as a catalyst provided *N*-*tert*-butyl-*N*-substituted benzoylhydrazines (**5**) in good yields, as shown in Scheme 1[7] and Table 1. This new and 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 yields, starting materials are cheap and easily prepared, the experimental procedure is very simple and this method may be applicable to large-scale production.

The reactions of the *N*-*tert*-butyl-*N*-substituted benzoylhydrazines (**5**) with substituted phenylisocyanates in 1,2-dichloroethane provided *N′*-*tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines (**6**), as shown in Scheme 2[8] and Table 2.

In order to increase the lipophilicity of compounds (**6**), treatment of the *N′*-*tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines (**6**) with oxalyl chloride gave the colourless crystalline products (**7**) in good yields (>70%), as shown in Scheme 3.[9] These compounds (**7**), with increased lipophilicity relative to the parent compounds (**6**), have higher biological activities because the increased lipophilicity facilitates penetration and transport as well as protection of the compound from metabolism.

The larvicidal activities of the title compounds (**6**) and (**7**) were evaluated using a previously reported procedure.[3c,10] The larvicidal activities were tested against armyworm by foliar application. 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.

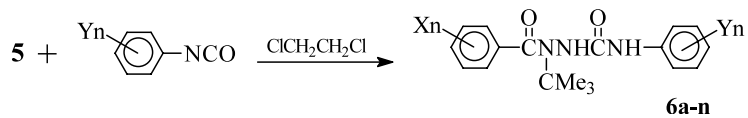
The larvicidal activities show that the title compounds (**6**) and (**7**) exhibit good larvicidal activities. For example, at 1000 μg/mL, the percent mortality of compound **6a** and **6b** is 75.0 and 82.5%, respectively. Toxicity assays indicated that the title compounds (**6**) and (**7**) can induce 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 potential anticancer activities. For example, at 10^{-4} mol/L, the inhibition rate of compound **6c** to P-388 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.

These results are promising. Further studies on larvicidal activities and anticancer activities of the title compounds (**6**) and (**7**) are underway and will be reported in due course.

Table 1.

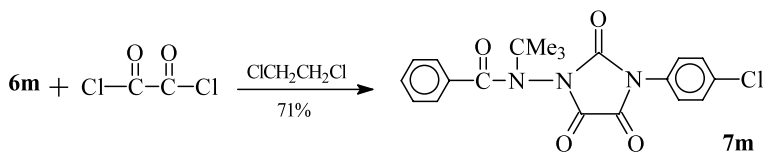
Entry	Xn	Isolated yield (%)	
		3→4a–e	**4a–e→5a–e**
a	H	90	96
b	3,5-Me_2	83	92
c	2-F	86	96
d	2-Cl	91	90
e	2,4-Cl_2	87	82



Scheme 2.

Table 2.

Entry	Xn	Yn	Yield (%)	Entry	Xn	Yn	Yield (%)
a	H	H	75	**h**	2-Cl	4-Cl	80
b	H	4-F	81	**i**	2-Cl	H	79
c	H	4-OMe	87	**j**	2,4-Cl_2	H	71
d	H	3,4-Cl_2	87	**k**	3,5-Me_2	4-F	80
e	H	2,6-Me_2	57	**l**	2-F	4-F	84
f	3,5-Me_2	4-Cl	87	**m**	H	4-Cl	75
g	2-F	4-Cl	69	**n**	H	4-Cl	71



Scheme 3.

Acknowledgements

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4. Benzyl chloroformate: yield 98%; $n_D^{20} = 1.5188$.
5. Compound **3**: yield 84%; mp 75–77°C; ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 9H, *t*-Bu), 5.16 (s, 2H, OCH_2), 5.02 (br., 2H, NHNH), 7.38 (m, 5H, Ph); IR (KBr) ν/cm^{-1}: 3264.0, 3240.0 (NHNH); 1713.4 (C=O); 1521.4, 1491.8, 1466.3 (Ph); 1406.2, 1381.8 (*t*-Bu); 1260.8 (C–O); 828.2, 716.1 (Ph).
6. Compound **4**: yield 90%; mp 150–152°C; ^{1}H NMR (DMSO): δ 1.40 (d, 9H, *t*-Bu), 4.80–5.05 (m, 2H, OCH_2), 6.84–7.37 (m, 10H, Ph), 9.83 (s, NH); IR (KBr) ν/cm^{-1}: 3219.5 (NH); 1742.5, 1622.0 (C=O); 1578.4, 1531.5, 1498.1 (Ph); 1403.3, 1382.3 (*t*-Bu); 738.6, 712.9 (Ph). Anal. calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.82; H, 6.85; N, 8.78%.
7. Compound **5a**: yield 96%; mp 127–129°C; ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H, *t*-Bu), 3.90 (s, 2H, NH_2), 7.28–7.56 (m, 5H, Ph); IR (KBr) ν/cm^{-1}: 3276.0 (NH_2); 1620.5 (C=O); 1573.1, 1529.5, 1508.8 (Ph); 1375.6, 1350.0 (*t*-Bu); 719.6, 696.7 (Ph).
8. General procedure for the preparation of *N′-tert*-butyl-*N′*-substituted benzoyl-*N*-(substituted phenyl)aminocarbonylhydrazines (**6**). To a stirred solution of the *N-tert*-butyl-*N*-substituted benzoylhydrazine (**5**) (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 stopped after complete consumption of **5**. The reaction mixture was diluted with petroleum ether (60–90°C) and filtered to afford a white solid. The crude solid was recrystallised from dimethylformamide to obtain an analytical sample of **6**. Compound **6f** (Xn = 3,5-Me_2, Yn = 4-Cl): yield 87%; mp 256–257°C; IR (KBr) ν/cm^{-1}: 3343, 3114, 2964, 1720, 1621, 1594, 1533, 1490, 1392, 1360, 1223, 1190, 1090, 852, 822, 757, 691, 618; ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9H, *t*-Bu), 2.20 (s, 6H, Me), 6.94–7.27 (m, 7H, Ph), 8.52 (s, 1H, NH), 8.56 (s, 1H, NH); MS (EI) *m*/*z* 373.20 (M, 2%), 317.25 (1%), 164.30 (6%), 153.20 (3%), 133.25 (100%), 105.25 (24%), 79.20 (8%). Anal. calcd for $C_{20}H_{24}ClN_3O_2$: C, 64.25; H, 6.47; N, 11.24. Found: C, 64.35; H, 6.44; N, 11.17%.
9. 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. Compound **7m** (Xn = H, Yn = Cl): yield 71%; mp 124–126°C; IR (KBr) ν/cm^{-1}: 3092, 2975, 1790, 1753, 1695, 1492, 1392, 1311, 1190, 804, 741, 699; ^{1}H NMR (DMSO): δ 1.59 (s, 9H, *t*-Bu), 7.01–7.38 (m, 9H, Ph); MS (EI): *m*/*z* 399.15 (M, 1.1%), 343.10 (16.5%), 105.05 (100%), 77.05 (9%). Anal. calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.86; H, 4.37; N, 10.74%.
10. Murphy, R. A.; Hsu, A. C. T. US Pat. 5,117,057.