6356 J. Agric. Food Chem. 2009, 57, 6356–6361
DOI:10.1021/jf900882c

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

Design, Synthesis, and Bioactivity Study of Novel Benzoylpyridazyl Ureas

RANFENG SUN, YONGLIN ZHANG, FUCHUN BI, AND QINGMIN WANG*

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

A series of novel benzoylpyridazyl ureas were designed and synthesized from maleic anhydride and hydrazine monohydrate. These benzoylureas were identified by ^{1}H NMR spectroscopy and element analysis. The bioactivities of the new compounds were evaluated. These compounds exhibited larvicidal activities against oriental armyworm, and in particular, compound **13** displayed comparable activity to the commercial insecticide Hexaflumuron. Most of these compounds also had some larvicidal activities against mosquito. Interestingly, some compounds showed good plant growth regulatory activities.

KEYWORDS: Benzoylphenyl ureas (BPUs); benzoylurea; benzoylpyridazyl ureas; larvicidal activity; plant growth regulating activities; insect growth regulator

INTRODUCTION

The control of insects is of vital importance to the feeding of an ever-growing poplulation. It is well-known that insects at the larval stage, such as those belonging to the order of Lepidoptera, cause extensive damage to many crops (*1*). Benzoyl ureas represent a class of pesticide that act as insect growth regulators (IGRs), which act on the larval stages of most insects by inhibiting or blocking the synthesis of chitin, a vital and almost indestructible part of the insect exoskeleton during the molting stage; therefore, the failure to successfully cast off the old exoskeleton leads to the eventual death of the larvae (*2*, *3*). During the past decades, benzoylureas have attracted considerable attention (*4*−*11*).

L-7063 and EL-494 (**Figure 1**) are two commercial products of Eli Lilly Co., which contain pyrazinal groups. L-7063 displays excellent larvicidal activities against the order of Lepidoptera and shows good systemic activities (*1*). Aryloxyphenyl and (haloalkoxy)phenyl benzoylureas such as Flufenoxuron and Hexaflumuron (**Figure 1**) exhibited better larvicidal activities and had a broader spectrum of control of insects than diflubenzuron. For example, the larvicidal activity of Flufenoxuron against *Tetranychus cinnabarinus* was >100 times higher than that of Diflubenzuron (*12*, *13*). Bioisosterism is an effective way to design bioactive compounds and used in the design of benzoylurea compounds (*14*, *15*). Building on these developments (**Figure 1** and bioisosterism, which is a method for selecting molecular groups for drug design and lead-compound development, a series of novel benzoylpyridazyl ureas (**Figure 1**) were designed and synthesized. The bioactivities of the new compounds were evaluated.

MATERIALS AND METHODS

Instruments. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer or at 400 MHz using a Varian Mercury Plus 400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized.

General Synthesis. The reagents were all analytically or chemically pure. All anhydrous solvents were dried and purified by standard techniques prior to use. 2,6-Difluorobenzoyl isocyanate was prepared according to the literature method (*16*).

Synthesis of 1,2-Dihydropyridazine-3,6-dione (I-1). To a solution of hydrazine monohydrate (6.0 g, 120 mmol) in water (50 mL) cooled with an ice−water bath was slowly added concentrated hydrochloric acid (9.6 g), and then maleic anhydride (9.8 g, 100 mmol) was added. Then the mixture was heated under reflux for 3 h. When the mixture was cooled to room temperature, a white solid was separated out from the reaction solution, which was filtered and washed with water to obtain intermediate **I-1** (9.6 g, 86%): mp 301−302 °C [lit. 299−300 °C (*17*)].

Synthesis of 3,6-Dichloropyridazine (I-2). Phosphorus oxychloride (40 mL) was added to compound **I-1** (9.6 g, 85.7 mmol), and the mixture was heated at 90 °C for 4 h. Then the excess phosphorus oxychloride was removed under reduced pressure, and crushed ice (20 g) and water (20 mL) were added; sodium bicarbonate was slowly added to the mixture until the neutralization reaction was completed. The mixture was extracted by ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a crude product, which was purified by flash column chromatography on silica gel to give compound **I-2** (10.8 g, 85%) as a white solid: mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 2H).

Synthesis of 6-Chloropyridazin-3-amine (I-3). Ammonium was bubbled into the anhydrous ethanol (100 mL) below −15 °C to make an ammonia-saturated ethanol solution. This ammonia-saturated ethanol solution (100 mL) was added to intermediate **I-2** (13.6 g, 84.6 mmol) in an autoclave, and the mixture was heated at 130 °C for 20 h under sealed condition. Then the mixture was cooled to room temperature, and the solvent was removed under reduced pressure to give a crude product, which was dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated brine, dried over anhydrous sodium sulfate,

*Author to whom correspondence should be addressed [telephone +86-(0)22-23499842; fax +86-(0)22-23499842; e-mail wang98h@263.net or wangqm@nankai.edu.cn].

 Published on Web 06/23/2009

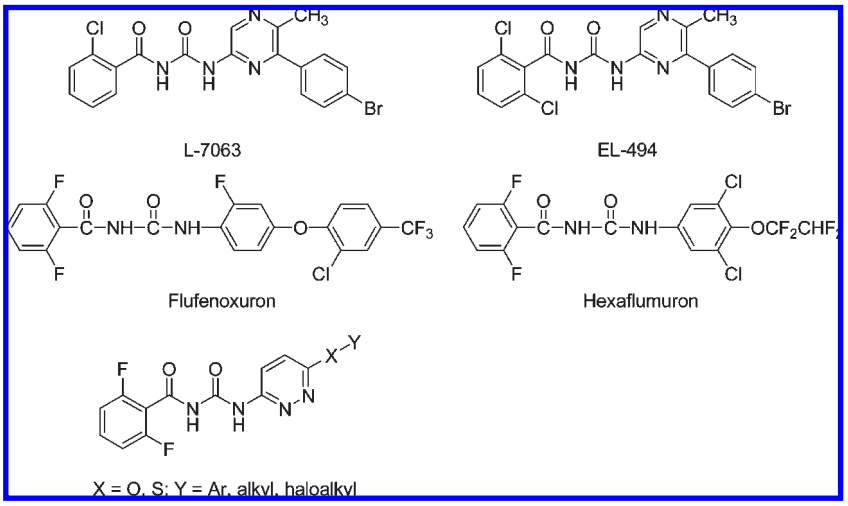
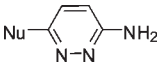
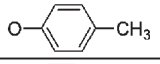
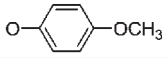
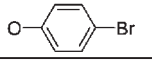
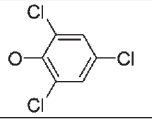
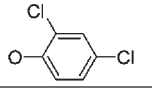
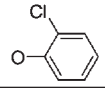
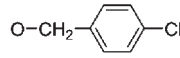


Figure 1. Commercial products of benzoylpyrizinyl ureas and benzoylphenyl ureas, designed benzoylpyridazyl ureas.

Table 1. Experimental Data of Compounds **I-4b**−**I-4m**[a]



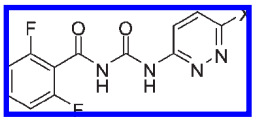
compd.	Nu	appearance	m.p. (°C)	yield (%)
I-4b		white solid	167-168	23
I-4c		white solid	166-167	58
I-4d		white solid,	177-183	17
I-4e		white solid	185-188	28
I-4f		white solid	136-138	21
I-4g		off-white solid	140-141	25
I-4h	OC_2H_5	white solid	163-166	67
I-4i		white solid	100-105	52
I-4j	$OCH(CH_3)_2$	pale yellow oil	/	47
I-4k	SC_4H_9-n	pale yellow solid	80-82	50
I-4l		yellow solid	140-141	67
I-4m	OCH_2CF_3	white solid	99-103	54

[a] /, not tested.

filtered, and concentrated in vacuo to give compound **I-3** (7.9 g, 67%) as a colorless crystal: mp 229−231 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (br s, 2H, NH_2), 6.75 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H), 7.22 (d, $^3J_{HH}$ = 9.2 Hz, 1H, Ar−H).

Synthesis of 6-(4-Chlorophenoxy)pyridazin-3-amine (I-4a). To a mixture of sodium hydroxide (0.31 g, 7.8 mmol) and 4-chlorophenol (1.00 g, 7.8 mmol) in water (10 mL) in the autoclave was added intermediate **I-3** (0.50 g, 3.9 mmol), and then the mixture was heated at 190 °C for 20 h under sealed condition. Then the mixture was cooled to room temperature and extracted by ethyl acetate. The organic extract was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo to give a crude product,

Table 2. Physical Properties and Elemental Analyses of Compounds **2**−**14**



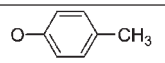
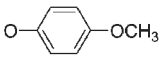
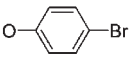
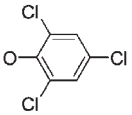
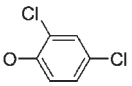
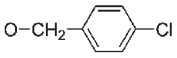
compd.	X	m.p. (°C)	yield (%)	Element analysis (%, calc.) C	H	N
2		211-212	67	59.34 (59.38)	3.85 (3.67)	14.62 (14.58)
3		198-200	54	57.05 (57.00)	3.75 (3.52)	14.02 (13.99)
4		203-205	24	48.21 (48.13)	2.59 (2.47)	12.37 (12.47)
5		218-220	90	45.59 (45.64)	2.06 (1.92)	11.56 (11.83)
6		186-188	58	49.01 (49.22)	2.35 (2.29)	13.00 (12.76)
7		194-195	84	53.31 (53.41)	2.53 (2.74)	13.99 (13.84)
8		206-207	82	54.52 (54.49)	3.00 (3.13)	13.36 (13.38)
9	OC_2H_5	181-183	82	52.46 (52.18)	3.52 (3.75)	17.35 (17.39)
10	$OCH(CH_3)_2$	128-130	90	53.50 (53.57)	4.02 (4.20)	16.41 (16.66)
11	SC_4H_9-n	150-151	54	52.33 (52.45)	4.46 (4.40)	15.39 (15.29)
12		151-152	84	55.88 (55.95)	3.11 (3.13)	14.89 (14.50)
13	OCH_2CF_3	200-202	83	44.42 (44.69)	2.78 (2.41)	14.89 (14.89)
14	CH_3	203-205	49	53.22 (53.43)	3.37 (3.45)	19.00 (19.17)

Table 3. ^{1}H NMR ($CDCl_3$) of Compounds **2**−**14**

compd	δ
2	2.36 (s, 3H, Ar*CH*$_3$), 7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.08 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar−H), 7.16 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.21 (d, $^3J_{HH}$ = 8.4 Hz, 2H, Ar−H), 7.46−7.58 (m, 1H, Ar−H), 8.26 (br, 1H, CONHAr), 8.33 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 11.11 (br, 1H, CONHCO)
3	3.82 (s, 3H, O*CH*$_3$), 6.93 (d, $^3J_{HH}$ = 9.0 Hz, 2H, Ar−H), 7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.13 (d, $^3J_{HH}$ = 9.0 Hz, 2H, Ar−H), 7.16 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.48−7.58 (m, 1H, Ar−H), 8.31 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.35 (br, 1H, CONHAr), 11.11 (br, 1H, CONHCO)
4	7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, 2H, Ar−H), 7.11 (d, $^3J_{HH}$ = 8.8 Hz, 2H, Ar−H), 7.21(d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 7.48−7.58 (m, 1H, Ar−H), 7.53 (d, $^3J_{HH}$ = 8.6 Hz, 2H, Ar−H), 8.31 (br, 1H, CONHAr), 8.37 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 11.16 (br, 1H, CONHCO)
5	7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ =8.4 Hz, 2H, Ar−H), 7.38(d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.42 (s, 2H, Ar−H), 7.48−7.58 (m, 1H, Ar−H), 8.20 (br, 1H), 8.46 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H, CONHAr), 11.16 (br, 1H, CONHCO)
6	7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.29−7.32 (m, 3H, Ar−H), 7.45(d, $^4J_{HH}$ = 2.2 Hz, 1H, Ar−H), 7.50−7.58 (m, 1H, Ar−H), 8.16 (br, 1H, CONHAr), 8.43 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 11.14 (br, 1H, CONHCO).
7	7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.18−7.39 (m, 4H, Ar−H), 7.46−7.58 (m, 2H, Ar−H), 8.36 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.45 (br, 1H, CONHAr), 11.14 (br, 1H, CONHCO)
8	5.12 (s, 2H, O*CH*$_2$Ar), 7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.3 Hz, 2H, Ar−H), 7.06 (d, $^3J_{HH}$ = 9.6 Hz, 1H, Ar−H), 7.36 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar−H), 7.44 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar−H), 7.48−7.58 (m, 1H, Ar−H), 8.27 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.28 (br, 1H, CONHAr), 11.13 (br, 1H, CONHCO)
9	1.45 (t, $^3J_{HH}$ = 7.0 Hz, 3H, *CH*$_3$CH$_2$), 4.56 (q, $^3J_{HH}$ = 7.0, 2H, CH$_3$*CH*$_2$O), 6.98 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.04 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.3 Hz, 2H, Ar−H), 7.46−7.58 (m, 1H, Ar−H), 8.19 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.63 (br, 1H, CONHAr), 11.18 (br, 1H, CONHCO)
10	1.41 (d, $^3J_{HH}$ = 6.1 Hz, 6H, OCH(*CH*$_3$)$_2$), 5.47−5.49 (m, 1H, O*CH*(CH$_3$)$_2$), 6.92 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.04 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.3 Hz, 2H, Ar−H), 7.46−7.56 (m, 1H, Ar−H), 8.15 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.70 (br, 1H, CONHAr), 11.15 (br, 1H, CONHCO)
11	1.44−1.54 (m, 5H, *CH*$_3$*CH*$_2$CH$_2$CH$_2$O), 1.72−1.79 (m, 2H, CH$_3$CH$_2$*CH*$_2$CH$_2$O), 3.32 (t, $^3J_{HH}$ = 7.4 Hz, 2H, CH$_3$CH$_2$CH$_2$*CH*$_2$O), 7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.32 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 7.50−7.57 (m, 1H, Ar−H), 8.10 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 8.36 (br, 1H, CONHAr), 11.15 (br, 1H, CONHCO)
12	7.04 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.09 (d, $^3J_{HH}$ = 9.4 Hz, 1H, Ar−H), 7.41−7.46 (m, 3H, Ar−H), 7.47−7.54 (m, 1H, Ar−H), 7.57−7.63 (m, 2H, Ar−H), 8.10 (d, $^3J_{HH}$ = 8.4 Hz, 1H, Ar−H), 8.43 (br, 1H, CONHAr), 11.20 (br, 1H, CONHCO)
13	4.90 (q, $^3J_{HF}$ = 8.3 Hz, 2H, CF$_3$*CH*$_2$O), 7.04 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.5 Hz, 2H, Ar−H), 7.15 (d, *J* = 9.5 Hz, 1H, Ar−H), 7.50−7.57 (m, 1H, Ar−H), 8.32 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 8.53 (br, 1H, CONHAr), 11.18 (br, 1H, CONHCO)
14	2.65 (s, 3H, Ar*CH*$_3$), 7.05 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, 2H, Ar−H), 7.34 (d, $^3J_{HH}$ = 9.1 Hz, 1H, Ar−H), 7.47−7.57 (m, 1H, Ar−H), 8.24 (d, $^3J_{HH}$ = 9.1 Hz, 1H, Ar−H), 8.59 (br, 1H, CONHAr), 11.44 (br, 1H, CONHCO)

which was purified by flash column chromatography on silica gel to give compound **I-4a** (0.39 g, 46%) as a white solid: mp 203−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (br s, 2H, NH_2), 6.85 (d, $^3J_{HH}$ = 9.3 Hz, 1H, Ar−H), 7.00 (d, $^3J_{HH}$ = 9.3 Hz, 1H, Ar−H), 7.10 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ph), 7.32 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ph).

Compounds **I-4b**−**I-4m** were prepared according to a method similar to that of compound **I-4a**. When sodium alkoxide was used as a nucleophile, the corresponding alkyl alcohol was used as the solvent. The experimental data of compounds **I-4b**−**I-4m** are listed in **Table 1**.

Synthesis of Target Compound 1. A solution of 2,6-difluorobenzoyl isocyanate (0.18 g, 1.0 mmol) in dichloromethane (5 mL) was added dropwise to a solution of compound **I-4a** (0.22 g, 1.0 mmol) in dichloromethane (10 mL) at room temperature, and the mixture was allowed to stand for 2 h. Then part of the solvent was removed in vacuo, and the precipitated solid was filtered to give a white solid (0.22 g, 55%): mp 208−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (t, $^3J_{HH}$ = $^3J_{HF}$ = 8.4 Hz, 2H, Ar−H), 7.16 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 7.22 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 7.38 (d, $^3J_{HH}$ = 8.9 Hz, 2H, Ar−H), 7.49−7.59 (m, 1H, Ar−H), 8.27 (br, 1H, CONHAr), 8.38 (d, $^3J_{HH}$ = 9.5 Hz, 1H, Ar−H), 11.15 (br, 1H, CONHCO). Anal. Calcd. for $C_{18}H_{11}ClF_2N_4O_3$: C, 53.41; H, 2.47; N, 13.84. Found: C, 53.35; H, 2.89; N, 13.85.

Compounds **2**−**14** were prepared according to a method similar to that of compound **1**. The physical properties, elemental analyses of title compounds **2**−**14**, and their ^{1}H NMR data are listed in **Tables 2** and **3**.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula (*18*). Evaluations are based on a percentage scale of 0−100, in which 0 = no activity and 100 = total kill. The deviation of values was ±5%.

Larvicidal Activity against Oriental Armyworm (*Mythimna separata*). The larvicidal activities of compounds **1**−**14** against oriental armyworm were evaluated by foliar application using the reported procedure (*19*−*21*). 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 (the test compound was resolved in acetone) and allowed to dry. The dishes were infested with 10 fourth-instar oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed three times. For comparative purposes, Hexaflumuron was tested under the same condition.

Larvicidal Activity against Mosquito (*Culex pipiens pallens*). The larvicidal activity of compounds **1**−**10**, **13**, and **14** was evaluated against mosquito according to the reported procedure (*22*). The test solutions were prepared by dissolving the compound in acetone and adding distilled water. Ten fourth-instar mosquito larvae were put into the 10 mL of the test solution and left for 8 days. The results are expressed as percentage mortality. For comparative purposes, Hexaflumuron was tested under the same condition.

Plant Growth Regulatory Activity Assay. The plant growth regulatory activities of compounds **1**−**7** and **14** were evaluated using previously reported procedures (*23*−*25*). Seeds of cucumber were incubated at 26 °C in the dark for 72 h, and 10 cotyledons were cut off. *N*,*N*-Dimethylformamide solutions of the test compounds were prepared at concentrations of 10 mg/L. The experiments were conducted in sterile Petri dishes (6 cm diameter) lined with a sheet of filter paper. To each dish was added 0.3 mL of the test solution, and the solvent was evaporated before the addition of 3 mL of water, followed by the above cotyledons. Assays were carried out at 26 °C in the dark in an incubator for 5 days. The number of roots was counted, and the growth regulatory activities were evaluated. Controls were performed under the same conditions, using only water. Each treatment was performed in triplicate. Hexaflumuron was tested under the same condition.

RESULTS AND DISSCUSSION

Synthesis. 1,2-Dihydropyridazine-3,6-dione (**I-1**) was synthesized from maleic anhydride and hydrazine monohydrate as shown in **Figure 2**. Then compound **I-1** was treated with phosphorus oxychloride to give intermediate **I-2**, which was reacted with ammonia to yield compound **I-3**. The nucleophilic substitution of intermediate **I-3** produced compounds **I-4a**−**I-4m**, which were combined with 2,6-difluorobenzoyl isocyanate to obtain the target compounds **1**−**13**. It was found that intermediate **I-1** was not obtained without hydrochloric acid, and the reaction temperature had an important effect on the yield of compound **I-3** because a lot of black byproducts were produced if the reaction temperature exceeded 95 °C. The nucleophilic aromatic substitution of intermediate **I-3** was accomplished in sealed condition because of the difficulty of substituting the chloride atom on the pyridazine ring in the presence of the amino group.

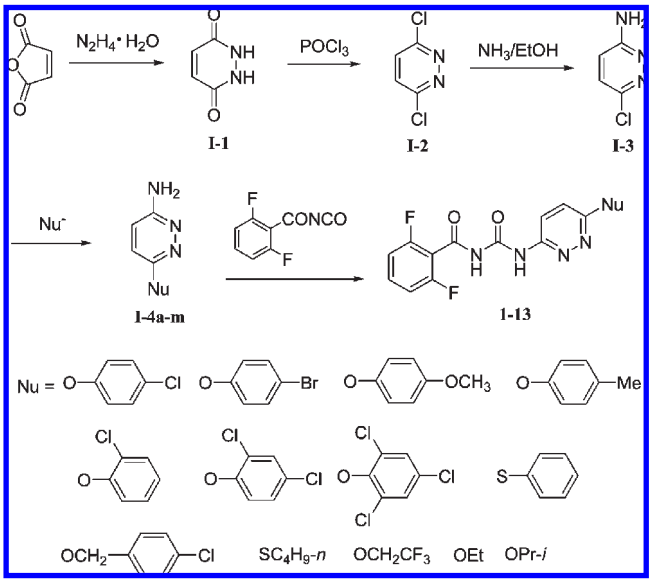


Figure 2. General synthetic procedure for compounds **1**−**13**.

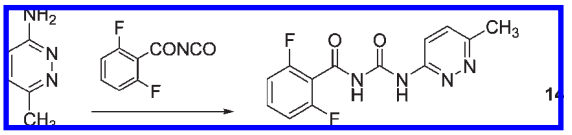
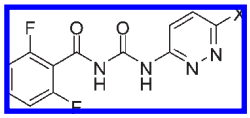


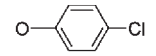
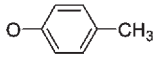
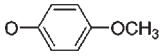
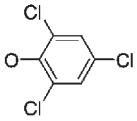
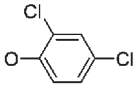
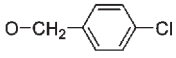
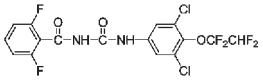
Figure 3. Synthetic procedure for compound **14**.

Compound **14** was obtained from the combination between 6-methylpyridazin-3-amine and 2,6-difluorobenzoyl isocyanate as shown in **Figure 3**.

Biological Activity. Table 4 shows the larvicidal activities of compounds **1**−**14** and Hexaflumuron against oriental armyworm and mosquito. The results indicate that most of the compounds **1**−**14** exhibited larvicidal activities against oriental armyworm and mosquito. One the whole, the larvicidal activities of the alkyloxy-substituted benzoylpyridazyl ureas against oriental armyworm were better than those of aryloxy-substituted compounds. For example, compounds **9**, **10**, and **13** displayed higher larvicidal activities against oriental armyworm than compounds **1**−**7**. In particular, compound **13** had 80% mortality on oriental armyworm at 10 mg L^{-1}, which exhibited comparable activity with commercial Hexaflumuron. Compound **4** exhibited best larvicidal activities against mosquito in the tested compounds, which had 90% mortality even at 1 mg L^{-1}, but was not as effective as Hexaflumuron, which showed 100% mortality at 0.25 mg L^{-1}. The plant growth regulatory activities of compounds **1**−**7** and **14** were evaluated, and their effects on the radicle growth of cucumber are shown in **Table 5**. Interestingly,

Table 4. Larvicidal Activities against Oriental Armyworm and Mosquito of Compounds **1**−**14** and Hexaflumuron[a]



compd.	X	Toxicities against Oriental armyworm		Toxicities against Mosquito	
		concentration (mg L^{-1})	*larvicidal activity (%)	concentration (mg L^{-1})	*larvicidal activity (%)
1		200	10	2	20
2		200	0	2	0
3		200	10	2	10
4		200	30	**2** **1**	**100** **90**
5		100	10	2	20
6		200	20	2	60
7		200	20	2	40
8		200	10	2	10
9	OC_2H_5	**200** **100** **50**	**100** **100** **80**	2	20
10	$OCH(CH_3)_2$	**200** **100** **50**	**100** **100** **70**	2	10
11	SC_4H_9-n	**200** **100** **50**	**100** **100** **90**	/	/
12		200	20	/	/
13	OCH_2CF_3	25 **10**	100 **80**	1	30
14	CH_3	200	10	2	20
Hexaflumuron		**10**	**80**	0.25	100

[a] *, Larivicidal activity was calculated according to the following equation: larvicidal activity (%) = numbers of dead insects × 100/numbers of total insects. /, not tested.

some compounds showed good stimulation of radicle growth of cucumber, such as compounds **5** and **7**, which, respectively, gave 130 and 105% promotion, whereas Hexaflumuron gave only 65% growth promotion.

In summary, a series of novel alkyloxy(thio)- or aryloxy-substituted benzoylpyridazyl ureas were designed and synthesized, and their structures were characterized by ^{1}H NMR and elemental analysis. The larvicidal activities against oriental armyworm and mosquito and plant growth regulatory activities of these benzoylpyridazyl ureas were evaluated. The results indicate that most of the compounds **1**−**14** exhibited larvicidal activities against oriental armyworm and mosquito. In particular, compound **13** exhibited activity against oriental armyworm comparable with that of the commercial Hexaflumuron. Interestingly, some compounds showed good stimulation of radicle growth of cucumber.

Table 5. Plant Growth Activities on the Radicle Growth of Cucumber

compd	plant growth regulatory activities at 10 mg L^{-1} (%)	rank[a]
1	30	+
2	50	+
3	30	+
4	50	+
5	130	++
6	65	+
7	105	++
14	−35	−
Hexaflumuron	65	+

[a] ++, ≥100%; +, ≥50%; −, <50%.

LITERATURE CITED

(1) Miesel, J. L. Novel 1-(mono-O-substituted benzoyl)-3-(substituted pyrazinyl) ureas. U.S. Patent, 4293552, **1981**.

(2) Oberlander, H.; Silhacek, D. L. New perspectives on the mode of action of benzoylphenyl urea insecticides. In *Insecticides with Novel Modes of Action: Mechanism and Application*, 1st ed.; Ishaaya, I., Degheele, D., Eds.; Springer-Verlag: Berlin, Germany, 1998; pp 92−105.

(3) Oberlander, H.; Silhacek, D. L. Mode of action of insect growth regulators in Lepidopteran tissue culture. *Pestic. Sci.* **1998**, *54*, 300–302.

(4) Xu, X. Y.; Qian, X. H.; Li, Z.; Huang, Q. C.; Chen, G. Synthesis and insecticidal activity of new substituted *N*-aryl-*N*′-benzoylthiourea compounds. *J. Fluorine Chem.* **2003**, *121*, 51–54.

(5) Qian, X. H. Quantitative studies on structure-activity relationship of sulfonylurea and benzoylphenylurea type pesticides and their substituents' bioisosterism using synthons' activity contribution. *J. Agric. Food Chem.* **1999**, *47*, 4415–4418.

(6) Yang, X. L.; Wang, D. Q.; Chen, F. H.; Zhang, Z. N. The synthesis and larvicidal activity of *N*-aroyl-*N*′-(5-aryl-2-furoyl)ureas. *Pestic. Sci.* **1998**, *52*, 282–286.

(7) Li, X. H.; Ling, Y.; Yang, X. L. Synthesis of novel benzoyl ureas containing thiadiazole and their insecticidal activity. *Huaxue Tongbao* **2003**, *66* (5), 333–336.

(8) Kubato, S.; Shono, Y.; Matsunaga, T.; Tsunoda, K. Laboratory evaluation of bistrifluron, a benzoylphenylurea compound, as a bait toxicant against *Coptotermes formosanus* (Isoptera: Rhinotermitidae). *J. Econ. Entomol.* **2006**, *99*, 1363–1368.

(9) Chen, L.; Ou, X. M.; Mao, C. H.; Shang, J.; Huang, R. Q.; Bi, F. C.; Wang, Q. M. Synthesis and bioassay evaluation of 1-(4-substitutedideneaminooxymethyl)-phenyl-3-(2,6-difluorobenzoyl)ureas. *Bioorg. Med. Chem.* **2007**, 3678–3683.

(10) Yoon, C.; Yang, J. O.; Kang, S. H.; Kim, G. H. Insecticidal properties of bistrifluron against sycamore lace bug, *Corythucha ciliata* (Hemiptera: Tingidae). *J. Pestic. Sci.* **2008**, *33*, 44–50.

(11) Wei, Z. Z; Pang, H. L.; Liu, A. P.; Cheng, H.; Lin, L. Z.; Liu, Y.; Hu, C. H.; Yang, G. F. Synthesis and biological activity of 1-(pyrimidin-4-yl)-3-(2,6-difluorobenzoyl)urea derivatives. *Chin. J. Org. Chem.* **2006**, *26* (8), 1120–1124.

(12) Rigterink, R. H.; Sbiagia, R. J. Substituted *N*-aroyl *N*′-phenyl urea compounds. EP 71279, **1983**.

(13) Anderson, M. Pesticidal benzoylurea compounds. EP161019, **1985**.

(14) Lima, L. M. A.; Barreiro, E. J. Bioisosterism: a useful strategy for molecular modification and drug design. *Curr. Med. Chem.* **2005**, *12* (1), 23–49.

(15) Sun, R. F.; Lü, M. Y.; Chen, L.; Li, Q. S.; Song, H. B.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. Design, synthesis, bioactivity, and structure−activity relationship (SAR) studies of novel benzoylphenylureas containing oxime ether group. *J. Agric. Food Chem.* **2008**, *56*, 11376–11391.

(16) Meazza, G.; Rama, F.; Bettarini, F. Synthesis and bioactivity of some fluorine-containing benzoyl arylureas. Part I: Insecticidalacaricidal products in which the aryl group bears a trifluoromethyl-substituted alkyl or alkenyl side chain. *Pestic. Sci.* **1992**, *35*, 137.

(17) Feuer, H.; White, E. H.; Wyman, J. E. The reactions of maleic anhydride with hydrazine hydrate. *J. Am. Chem. Soc.* **1958**, *80*, 3790–3792.

(18) Abbott, W. S. A method of computing the effectiveness of an insecticide. *J. Econ. Entomol.* **1925**, *18*, 265–267.

(19) Mao, C. H.; Wang, Q. H.; Huang, R. Q.; Bi, F. C.; Chen, L.; Liu, Y. X.; Shang, J. Synthesis and insecticidal evaluation of novel *N*-oxalyl derivatives of tebufenozide. *J. Agric. Food Chem.* **2004**, *52*, 6737–6741.

(20) Hsu, A. C.; Murphy, R. A.; Aller, H. E.; Hamp, D. W.; Weinstein, B. Insecticidal *N*′-substituted-*N*,*N*′-disubstitutedhydrazines. U.S. Patent 5117057, **1992**.

(21) Luo, Y. P.; Yang, G. F. Discovery of a new insecticide lead by optimizing a target-diverse scaffold: tetrazolinone derivatives. *Bioorg. Med. Chem.* **2007**, *15*, 1716–1724.

(22) Chen, L.; Huang, Z. Q.; Wang, Q. M.; Shang, J.; Huang, R. Q.; Bi, F. C. Insecticidal benzoylphenylurea-*S*-carbamate: a new propesticide with two effects of both benzoylphenylureas and carbamates. *J. Agric. Food Chem.* **2007**, *55*, 2659–2663.

(23) Liu, Y. X.; Cai, B. L.; Li, Y. H.; Song, H. B.; Huang, R. Q.; Wang, Q. M. Synthesis, crystal structure, and biological activities of 2-cyanoacrylates containing furan or tetrahydrofuran moieties. *J. Agric. Food Chem.* **2007**, *55*, 3011–3017.

(24) Einhellig, F. A.; Schan, M. K.; Rasmunsen, J. A. Synergistic effects of four cinnamic acid compounds on grain sorghum. *Plant Growth Regul.* **1983**, *1*, 251–258.

(25) Demuner, A. J.; Barbosa, L. C. A.; Veloso, D. P. New 8-oxabicyclo [3.2.1]oct-6-en-3-one derivatives with plant growth regulatory activity. *J. Agric. Food Chem.* **1998**, *46*, 1173–1176.

Received March 15, 2009. Revised manuscript received May 13, 2009. Accepted June 17, 2009. This work was supported by the National Natural Science Foundation of China (20672064).