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Synthesis and Insecticidal Evaluation of Propesticides of Benzoylphenylureas

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Two series of benzoylphenylurea derivatives were synthesized as candidate propesticides by a nucleophilic addition reaction between 2,6-difluronbenzoyl isocyanate and N-substitutedaniline. The new compounds were identified by ^{1}H NMR spectroscopy, electron ionization−mass spectrometry, and elemental analyses. The bioactivities of the new compounds were evaluated. All of the propesticides reported here were soluble in most organic solvents, and their hydrophobicities were improved obviously. The result of the bioactivities of the new compounds against Oriental armyworm showed that some of the new compounds are good as compared to diflubenzuron and penfluron.

KEYWORDS: Propesticide; benzoylphenylurea; larvicidal activity; hydrophobicity; solubility; parent compounds

INTRODUCTION

Chitin is the most abundant organic skeletal component in the cuticle of insects, but it is absent in vertebrates (including mammals) and higher plants. Thus, the development of selective insecticides based on interference with chitin formation has become one of the aims in new pesticide design (*1*). Benzoylphenylureas (BPUs), discovered in the 1970s, are known well as commercial chitin formation inhibitors. In contrast to traditional pesticides, BPU and its derivatives mainly control the growth and development process of insects by interfering with chitin biosynthesis and breeding (*2*−*4*). Consequently, the toxicity of BPUs to vertebrates and environmental impact is very low and a high insecticidal selectivity is achieved.

On the other hand, BPUs are only very slightly soluble in solvents generally used in pesticide formulations (*5*). Consequently, they have to be formulated in the solid state. The particle size of the active material in the formulation has a considerable influence on the biological activity and the rate of degradation of the compound in soil.

It has been reported that N,N′-thiodicarbamates of N-methylcarbamate insecticides retain the good insecticidal activity of the parent methylcarbamate (*6*, *7*) and N-sulfenylated derivatives of diacylhydrazines exhibit excellent larvicidal activities (*8*, *9*). Encouraged by the reports, we developed an idea that substitution of the hydrogen on the nitrogen atom of BPUs with carbamylosulfenyl or formate could retain the insecticidal activity of parent BPUs, and solubility and hydrophobicity of these BPU derivatives would be improved at the same time. In this paper, we describe the synthesis and larvicidal activities of some lipid soluble derivatives of BPUs.

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EXPERIMENTAL PROCEDURES

Instruments. The title compounds were synthesized under a nitrogen atmosphere. Proton NMR spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer in $CDCl_3$ solution with tetramethylsilance as the internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. MS were recorded with a VG ZAB-HS spectrometer using the electron ionization (EI) method. Melting points were taken on a Thomas-Hoover melting-point apparatus and were uncorrected. Yields were not optimized.

General Synthesis. Solvents were dried by standard methods and distilled prior to use. 2,6-Diflurobenzoyl isocyanate was synthesized by the method of literature (*10*). Sulfur dichloride was prepared by the reaction of sulfur monochloride with chlorine (*11*). Pyridine was distilled over sodium hydroxide pellets and kept dry by storing with the same reagent. Ethyl N-methylcarbamate and benzyl N-methylcarbamate were synthesized by the method of literature (*12*) and purified by distillation under vacuum. N-Chlorosulfenyl-carbamates were obtained according to a reported procedure (*7*). Compounds **1a**−**d** and **3a**−**c** were synthesized as the literature (*13*) described.

General Synthetic Procedure for 1a−**d.** Chloroformate (10 mmol) was added dropwise to a solution of aniline (10 mmol) and pyridine (10 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to yield **1a**−**d**.

General Synthetic Procedure for 1e,f. Sodium hydroxide (10 mmol) in water (10 mL) was added to aniline (10 mmol) in dioxane (10 mL). The mixture was cooled to −10 °C. Then, di-*tert*-butyl dicarbonate (10 mmol) was added dropwise to the mixture. The mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to yield **2a**,**b**.

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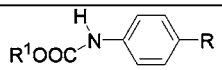
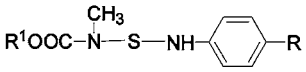
Table 1. Melting Points and Yields of Compounds **1a**–**f** and **3a**–**c**

Compd.	R	R^1	m.p. (°C)	Yield (%)
				
1a	Cl	C_2H_5	66-67	86.8
1b	Cl	$CH_2C_6H_5$	110-111	61.1
1c	CF_3	C_2H_5	107-108	71.7
1d	CF_3	$CH_2C_6H_5$	124-125	80.3
1e	Cl	$C(CH_3)_3$	105-105	51.6
1f	CF_3	$C(CH_3)_3$	115-117	63.0
				
3a	Cl	C_2H_5	55-56	69.0
3b	CF_3	C_2H_5	77-78	72.1
3c	CF_3	$C(CH_3)_3$	119-120	53.5

General Synthetic Procedure for 2a−f. A solution of N-formate-aniline (3 mmol) (**1a**−**f**) and 2,6-difluronbenzoyl isocyanate (6 mmol) in 20 mL of 1,2-dichloroethane was boiled for 10−48 h. The solvent was evaporated off under reduced pressure, and the residue was purified by vacuum column chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate as the eluent to yield **2a**−**f**.

General Synthetic Procedure for 3a−c. A solution of N-chloro-sulfenyl-carbamate (10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added dropwise to a solution of substituted aniline (10 mmol) and pyridine in tetrahydrofuran (20 mL). The mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate as the eluent to give **3a**−**c** as white crystals.

General Synthetic Procedure for 4a−c. 2,6-Difluronbenzoyl isocyanate (3 mmol) was added dropwise to a solution of **3a**−**c** (3 mmol) in 20 mL of 1,2-dichloroethane. The mixture was stirred at room temperature for 3 h. The solvent was evaporated off under reduced pressure, and the residue was purified by vacuum column chromatography on silica gel using petroleum ether (60−90 °C) and ethyl acetate as the eluent to yield **4a**−**c**.

The melting points and yields of compounds **1e**−**f** and **3a**−**c** are listed in **Table 1**. The melting points, yields, and elemental analyses of compounds **2a**−**f** and **4a**−**d** are listed in **Table 2**. The ^{1}H NMR of compounds **2a**−**f** and **4a**−**d** are listed in **Table 3**. The EI-MS (%) of compounds **2c** and **4d** are as follows. Compound **2c**: *m*/*z* 411.3 (M, 8), 355.2 (17), 311.2 (22), 158.1 (36), 57.6 (100), 41.4 (24). Compound **4d**: *m*/*z* 506.2 (M^+, 16), 341.2 (10), 322.2 (8), 91.5 (100), respectively.

Biological Assay. The larvicidal activities of the title compounds (**2a**−**f** and **4a**−**d**) and the parent compounds, diflubenzuron [1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea] and penfluron [1-(4-trifluoro-phenyl)-3-(2,6-difluorobenzoyl)urea], were evaluated using a previously reported procedure (*14*). The larvicidal activity was tested against Oriental armyworm [*Mythimna* (= *Pseudaletia*) *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 4th-instar armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Evaluations are based on a percentage scale of 0−100 in which 0 = no activity and 100 = total kill. For comparative purposes, the parent compounds, diflubenzuron and penfluron, were tested under the same conditions. The larvicidal activity is summarized in **Table 4**.

RESULTS AND DISCUSSION

Preparations. Compounds **1a**−**d** and **3a**−**c** were prepared in good yields as shown in **Scheme 1** and **Scheme 4**. It is a new method to synthesize **1e**,**f** by reacting di-*tert*-butyl dicarbonate with aniline as shown in **Scheme 2**. The reaction time of compounds **1a**−**f** reacted with 2,6-diflurobenzoyl isocyanates to give products **2a**−**f** (**Scheme 3**) is different for different compounds from 10 to 48 h. A small amount of diflubenzuron and penfluron was isolated as byproduct for compounds **2c**,**f**. So the yields of compounds **2c**,**f** were lower than **2a**,**b**,**d**,**e**. A small amount of diflubenzuron and penfluron was isolated as byproduct for products **4a**−**d** also. This result shows that there

Table 2. Melting Points, Yields, and Elemental Analysis of Compounds **2a**–**f** and **4a**–**d**

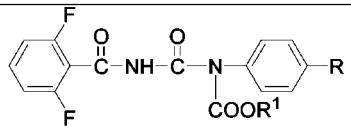
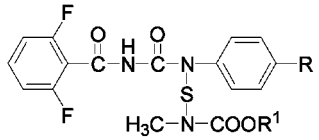
	R	R^1	m.p. (°C)	Yield (%)	Formula for calc.	Elemental analysis (%, calc.)		
						C	H	N
								
2a	Cl	C_2H_5	80-82	78.3	$C_{17}H_{13}ClF_2N_2O_4$	53.37 (53.35)	3.34 (3.42)	7.23 (7.32)
2b	Cl	$CH_2C_6H_5$	81-82	70.0	$C_{22}H_{15}ClF_2N_2O_4$	59.34 (59.40)	3.24 (3.40)	6.40 (6.30)
2c	Cl	$C(CH_3)_3$	133-136	59.0	$C_{22}H_{15}ClF_2N_2O_4$	55.67 (55.55)	4.07 (4.17)	6.89 (6.82)
2d	CF_3	C_2H_5	66-69	63.2	$C_{18}H_{13}F_5N_2O_4$	52.06 (51.93)	3.22 (3.15)	6.67 (6.73)
2e	CF_3	$CH_2C_6H_5$	88-90	68.4	$C_{23}H_{15}F_5N_2O_4$	57.55 (57.75)	3.30 (3.16)	5.85 (5.86)
2f	CF_3	$C(CH_3)_3$	138-140	40.0	$C_{20}H_{17}F_5N_2O_4$	54.10 (54.06)	3.94 (3.86)	6.27 (6.30)
								
4a	Cl	C_2H_5	147-148	60.1	$C_{18}H_{16}ClF_2N_3O_4S$	48.87 (48.71)	3.49 (3.63)	9.51 (9.47)
4b	CF_3	C_2H_5	Amorphous	57.3	$C_{19}H_{16}F_5N_3O_4S$	47.77 (47.80)	3.45 (3.45)	8.95 (8.80)
4c	CF_3	$C(CH_3)_3$	Amorphous	33.8	$C_{21}H_{20}F_5N_3O_4S$	49.90 (49.90)	4.07 (3.99)	8.21 (8.31)
4d	Cl	$CH_2C_6H_5$	114-116	11.9	$C_{23}H_{18}ClF_2N_3O_4S$	54.43 (54.60)	3.44 (3.59)	8.36 (8.31)

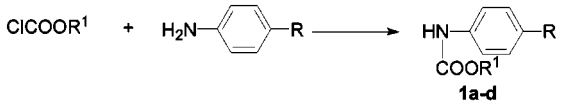
Table 3. ^{1}H NMR of Compounds **2a**–**f** and **4a**–**d**

compd	δ (ppm)
2a	1.21 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 4.25 (q, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2), 6.92–6.97 (m, 2H, Ph), 7.12 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 736–7.44 (m, 3H, Ph), 11.92 (s, 1H, NH)
2b	5.21 (s, 2H, CH_2), 6.91–6.97 ((m, 2H, Ph), 7.10–7.41 (m, 10H, Ph), 11.84 (s, 1H, NH)
2c	1.40 (s, 9H, $(CH_3)_3$), 6.91–6.96 (m, 2H, Ph), 7.08 (d, 2H, $^3J_{HH}$ = Hz, Ph), 7.32–7.42 (m, 3H, Ph), 11.94 (s,1H, NH)
2d	1.11 (t, 3H, $^3J_{HH}$ = 6.6 Hz, CH_3), 4.17 (q, 2H, $^3J_{HH}$ = 6.6 Hz, CH_2), 6.83–6.88 (m, 2H, Ph), 7.22–7.35 (m, 3H, Ph), 7.60 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 11.82 (s, 1H, NH)
2e	5.21 (s, 2H, CH_2), 6.92–6.98 (m, 2H, Ph), 7.16 (d, 2H, J = 8.1 Hz, Ph), 7.28–7.44 (m, 6H, Ph), 7.70 (d, 2H, J = 8.1 Hz, Ph), 11.82 (s, 1H, NH)
2f	1.40 (s, 9H, $(CH_3)_3$), 6.91–6.97 (m, 2H, Ph), 7.29 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 7.33–7.43 (m, 1H, Ph), 7.67 (d, 2H, $^3J_{HH}$ = 7.5 Hz, Ph), 11.93 (s,1H, NH)
4a	1.27 (t, 3H, $^3J_{HH}$ = 7.5 Hz, CH_3), 3.06 (s, 3H, NCH_3), 4.26 (q, 2H, $^3J_{HH}$ = 6.9 Hz, CH_2), 6.81–6.86 (m, 2H, Ph), 7.12 (d, 2H, $^3J_{HH}$ = 9.0 Hz, Ph), 7.22–7.32 (m, 3H, Ph), 11.51 (s, 1H, NH)
4b	1.27 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 3.05 (s, 3H, NCH_3), 4.26 (q, 2H, $^3J_{HH}$ = 7.5 Hz,CH_2), 6.81–6.86 (m, 2H, Ph), 7.22–7.34 (m, 3H, Ph), 7.57 (d, 2H, $^3J_{HH}$ = =8.4 Hz, Ph), 11.62 (s, 1H, NH)
4c	1.40 (s, 9H, $(CH_3)_3$), 3.01 (s, 3H, NCH_3), 6.83–6.88 (m, 2H, Ph), 7.25–7.35 (m, 3H, Ph), 7.58 (d, 2H, $^3J_{HH}$ = 8.4 Hz, Ph), 11.93 (s,1H, NH)
4d	3.16 (s, 3H, NCH_3), 5.29 (s, 2H, CH_2), 6.91–6.97 (m, 2H, Ph), 7.18 (d, 2H, $^3J_{HH}$ = 8.1 Hz, Ph), 7.33–7.40 (m, 8H, Ph), 11.67 (s, 1H, NH)

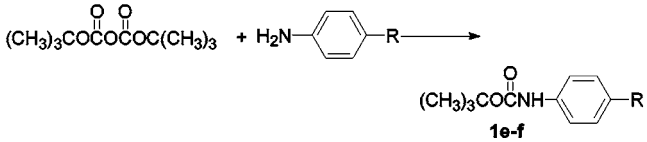
Table 4. Larvicidal Activities of Compounds **2a**–**f**, **4a**–**d**, and Parent Compounds

	larvicidal activity (%) at concentration (mg kg^{-1})										
compd	500	200	100	50	25	10	5	1	0.5	0.2	0.1
2a	100	100	100	100	100	0	0	0	0	0	
2b	100	100	70	0	0	0	0	0	0	0	
2c	100	100	100	100	100	100	95	5	0	0	
2d	100	100	100	100	5	0	0	0	0	0	
2e	100	30	0	0	0	0	0	0	0	0	
2f	100	100	100	100	100	100	75	0	0	0	
4a	100	100	100	100	100	100	100	20		5	0
4b	100	100	100	100	100	100	100	100	95	85	0
4c	100	100	100	100	100	100	100	100	100	35	0
4d	100	100	100	100	100	100	100	85	55	0	0
diflubenzuron	100	100	100	100	100	100	100	100	100	45	0
penfluron	100	100	100	100	100	100	100	100	100	95	0

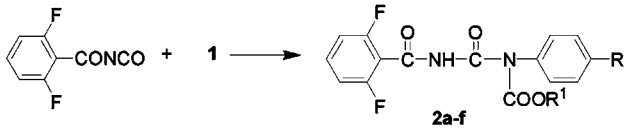
Scheme 1



Scheme 2

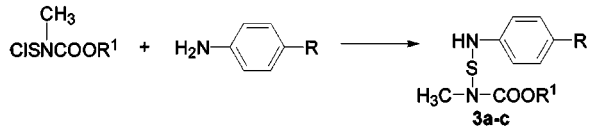


Scheme 3

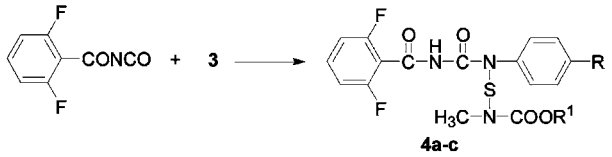


is bond cleavage during the reactions. We did not isolate benzyl N-(4-chlorophenyl)aminothio-carbamate and used a pot reaction method to prepare compound **4d** from the reaction of benzyl N-methylcarbamate with sulfur dichloride, so the yield of compound **4d** is only 11.9% from benzyl N-methylcarbamate. Although the N-substituted BPUs were pure, some of them did not crystallize readily, and they were obtained in amorphous forms.

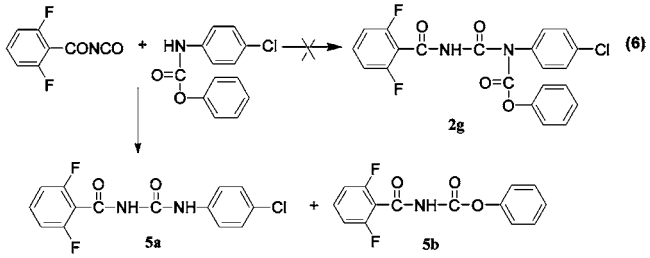
Scheme 4



Scheme 5



Scheme 6



We also try to react phenyl N-(4-chlorophenyl)carbamate with 2,6-diflurobenzoyl isocyanates to obtain compound **2g**, as shown in **Scheme 6**. However, only compounds **5a**,**b** were isolated. This result showed that phenyl N-(4-chlorophenyl)carbamate decomposed more easily than compound **1e**,**f** under the reaction condition.

Bioassay. The results of larvicidal activity tests given in **Table 4** show that some of the title compounds are good as compared to diflubenzuron and penfluron. For example, at the concentration of 0.2 mg kg^{-1}, the larvicidal activities of **4b**,**c**, diflubenzuron, and penfluronare are 85, 35, 45, and 95%, respectively. Toxicity assays indicated that the title compounds, like the parent compounds (diflubenzuron and penfluron), can interfere with chitin biosynthesis of armyworm. Symptoms of

Table 5. R_f of Compounds **2a**–**f**, **4a**–**d**, and Parent Compounds

compd	R_f	compd	R_f	compd	R_f
2a	0.40	**2e**	0.42	**4c**	0.40
2b	0.38	**2f**	0.50	**4d**	0.33
2c	0.47	**4a**	0.32	diflubenzuron	0.26
2d	0.43	**4b**	0.35	penfluron	0.27

toxicity included discoloration, weight loss, cessation of feeding, and death. Assuming that in vivo release of the toxic parent BPUs (diflubenzuron and penfluron) is responsible for toxicity of the compounds **2a**−**f** and **4a**−**d**, the nearly equal toxicities observed within compound **4b** suggest that nearly equal amounts of parent BPUs are produced from compound **4b**, and conversion of the derivatives to the BPUs is rapid in vivo. On the other hand, N-sulfenylated BPUs (**4a**−**d**) show apparently higher larvicidal activities than N-acylbenzoylphenylureas (**2a**−**f**). This may be because compounds (**4a**−**d**) can easily regenerate the parent compounds in vivo.

BPU insecticides have very low solubility in water and limited solubility in common organic solvents, so application of such BPUs in water and as emulsifiable concentrates is not ordinarily feasible. Therefore, the discovery of new propesticides of BPUs reported here is expected to lead to compounds with better biological activities and characteristics. We found that the title compounds have a better solubility than the parent BPUs in organic solvents such as methylene dichloride, chloroform, 1,2-dichloroethane, toluene, and xylene, which should make them easier to use.

On the other hand, the R_f of all of the title compounds (including diflubenzuron and penfluron) was detected by using a thin-layer chromatographic plate and 3:1 *n*-hexane/ethyl acetate as the developer. The R_f is listed in **Table 5**. As compared to the parent compounds, the hydrophobicities of the BPU derivatives reported here were improved obviously. The hydrophobicities of *tert*-butyl derivatives (**2c**,**f** and **4c**) were improved more than other corresponding derivatives.

In summary, two series of new propesticides of BPUs were prepared by the reaction of N-substitutedaniline with 2,6-diflurobenzoyl isocyanates. All of the propesticides reported here were soluble in most organic solvents, and the hydrophobicities of them were improved obviously. The result of the bioactivities of the new compounds against Oriental armyworm showed that some of the new compounds are good as compared to diflubenzuron and penfluron.

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