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Synthesis of Novel Benzoylphenylurea Chitin Inhibitors from Chlorothalonil

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Abstract: Twenty-six novel benzoylphenylurea chitin inhibitor derivatives have been synthesized in over 30~50% yield from chlorothalonil **1** *via* sequential fluorine exchange, aminolysis, hydrolysis, decarboxylation and acylation reactions.

Keywords: Benzoylphenylureas, chitin inhibitor, chlorothalonil.

The insecticidal activity of benzoylphenylureas (BPUs) analogues, discovered in the early 1970s[1,2] , is connected with the process of moulting. The BPUs class of insect growth regulators (IGRs), interferes the chitin synthesis in target pests, causing death or abortive development, and is considered to be the third generation of insecticides and used as a novel material for insect control. BPUs type insecticides possess high selectivity, low acute toxicity for mammals, and high biological activity resulting in low application doses[3,4].

Our attention was focused on the emerging family of insect growth regulators consisting of two aromatic rings linked by a urea bridge. Despite a large number of BPUs derivatives reported so far[5-12], the preparation of multihalo-cyano-phenyl-containing or 2,3,5-trihalo-phenyl-containing BPUs have not been disclosed. The novel BPUs analogues **7a~p** and **9a~j** have been designed and synthesized, predisposing **7a~p** and **9a~j** to exhibit lasting fungicidal activity as well as the well-known IGR_S function.

Experimental

Chlorothalonil **1** was treated with anhydrous KF in DMF at 110°C to give the corresponding crystalline fluorine-containing 1,3-benzenedicarbonitrile **2a~c**, KF is used in equivalent to the number of chlorine atoms to be substituted[13], **2a~c** were subsequently reacted with ammonia[14] to provide **3a~f**. In addition, chlorothalonil **1** was subjected to direct aminolysis[1] with ammonia in THF at room temperature to afford **3g**. The structures and yields of **3a~g** were listed in **Table 1**.

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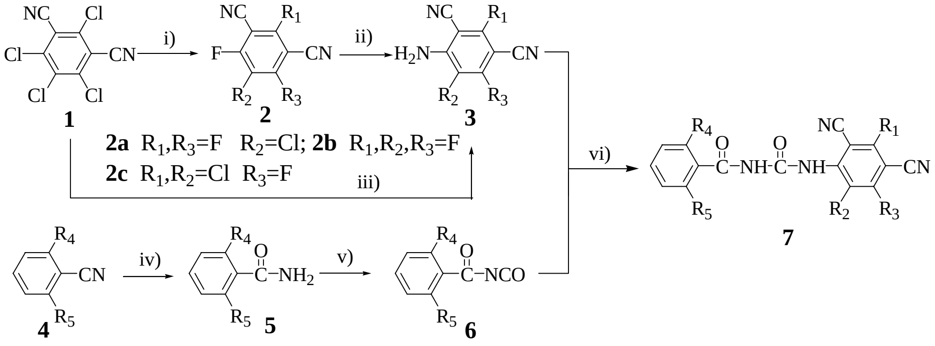
Table 1 The structures and yields of **3a~g**

Compound	R_1	R_2	R_3	Time(h)	Yield(%)
3a	F	Cl	F	2	72
3b	F	Cl	NH_2	6	68
3c	F	F	F	3	54
3d	F	F	NH_2	5	89
3e	Cl	Cl	F	3	84
3f	Cl	Cl	NH_2	8	52
3g	Cl	Cl	Cl	12	90

Halobenzenenitriles **4a~c** were hydrolyzed with 80% sulphuric acid to give benzamide derivatives **5a~c**, followed by refluxing with oxalyl chloride in anhydrous 1,2-dichloroethane (DCE) to yield benzoylisocyanates **6a~c**. Finally, sixteen novel BPUs chitin inhibitors **7a~p** (**Table 2**) were synthesized in over 90% yield *via* the selective reaction of **3a~g** with benzoylisocyanate derivatives **6a~c** (**Scheme 1**).

Scheme 1



4a-6a R_4=Cl R_5=H; **4b-6b** R_4=Cl R_5=Cl; **4c-6c** R_4=F R_5=F

Reagents and conditions: (i) KF, DMF, 110°C; (ii) $NH_3·H_2O$, DME; (iii) NH_3, THF; (iv) 80% H_2SO_4; (v) $(COCl)_2$, DCE; (vi) DCE, 0°C.

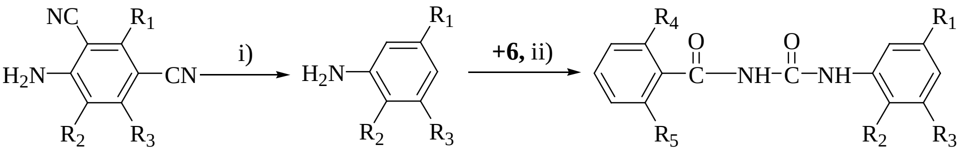
In addition, the 1,3-dicyanoanilines **3** were hydrolyzed and decarboxylated by heating with 80% sulphuric acid at 150°C for 8 hours affording trihalophenylamines **8a~d** in over 70% yield. Similarly, ten novel analogues of teflubenzuron **9a~j** (**Table 3**) were synthesized by the reaction of **8a~d** with benzoylisocyanate derivatives **6a~c** (**Scheme 2**).

In comparison to the commercial fungicide chlorothalonil **1**, compound **2a** exhibited increased fungicidal activity against *Piricuaria oryzac* and *Erysiphe cichoracearum*[15]. Some **7** and **9** showed potent insecticidal activity against *Plutellaxy Lostella, Culex pipens pallens, mythimna separata Walker.* A detailed investigation into the insecticidal and fungicidal properties of these novel BPUs is in progress.

Table 2 The structure, yields and m.p. of BPUs derivatives **7a~p**

Compound	R_1	R_2	R_3	R_4	R_5	yield (%)	m.p. (°C)
7a	F	Cl	F	Cl	H	91	234-237
7b	F	Cl	F	Cl	Cl	93	178-180
7c	F	Cl	F	F	F	91	183-185
7d	F	Cl	NH_2	Cl	H	93	246-247
7e	F	Cl	NH_2	F	F	92	222-226
7f	F	F	F	Cl	H	92	152-154
7g	F	F	F	F	F	94	156-160
7h	F	F	NH_2	Cl	H	94	160-162
7i	F	F	NH_2	F	F	93	165-167
7j	F	F	NH_2	Cl	Cl	90	206-208
7k	Cl	Cl	F	Cl	H	94	213-215
7l	Cl	Cl	NH_2	Cl	H	90	233-235
7m	Cl	Cl	NH_2	F	F	96	242-244
7n	Cl	Cl	Cl	Cl	H	93	207-208
7o	Cl	Cl	Cl	F	F	94	223-224
7p	Cl	Cl	Cl	Cl	Cl	91	232-234

Scheme 2



3 **8** **9**

8a R_1,R_3=F R_2=Cl; **8b** R_1=F R_2=Cl; R_3=NH_2 **8c** R_1,R_2=Cl R_3=F; **8d** R_1, R_2,R_3=Cl
Reagents and conditions: (i) 80% H_2SO_4; (ii) DCE, 0°C.

Table 3 The yields and m.p. of teflubenzuron derivatives **9a~j**

Compound	R_1	R_2	R_3	R_4	R_5	yield(%)	m.p. (°C)
9a	F	Cl	F	Cl	H	95	215-219
9b	F	Cl	F	Cl	Cl	90	230-234
9c	F	Cl	F	F	F	93	229-232
9d	Cl	Cl	Cl	Cl	H	92	232-234
9e	Cl	Cl	Cl	Cl	Cl	91	251-253
9f	Cl	Cl	Cl	F	F	93	242-245
9g	F	Cl	NH_2	Cl	H	91	215-217
9h	F	Cl	NH_2	Cl	Cl	90	294-296
9i	F	Cl	NH_2	F	F	91	260-262
9j	Cl	Cl	F	F	F	93	215-218

The analytic data including IR, ^{1}H NMR, ^{13}C NMR and HRMS of **7a~p** and **9a~f** were given[16,17].

Acknowledgments

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16\. Selected ^{1}H NMR (500 MHz, DMSO-d_6) and HRMS data of diflubenzuron derivatives **7a~e**: **7a**. ^{1}H NMR: δ 7.00-7.80 (m, 4H, aromatic), 10.46 (s, 1H, ArCON*H*), 10.72 (s, 1H, CON*H*CO)**;** HRMS (*m/z*): 393.9847 [M$^+$] (calcd. for $C_{16}H_6Cl_2F_2N_4O_2$, 393.9836). **7b**. ^{1}H NMR: δ 7.40-7.80 (m, 3H, aromatic), 11.29 (s, 1H, ArCON*H*), 11.30 (s, 1H, CON*H*CO)**;** HRMS (*m/z*): 427.9463 [M$^+$] (calcd. for $C_{16}H_5Cl_3F_2N_4O_2$, 427.9446). **7c**. ^{1}H NMR: δ 7.01-7.70 (m, 3H, aromatic), 11.03 (s, 1H, ArCON*H*), 11.08 (s, 1H, CON*H*CO)**;** HRMS (*m/z*): 396.0026 [M$^+$] (calcd. for $C_{16}H_5ClF_4N_4O_2$, 396.0037). **7d**. HRMS (*m/z*): 391.0040 [M$^+$] (calcd. for $C_{16}H_8Cl_2FN_5O_2$, 391.0039). **7e**. HRMS (*m/z*): 393.0256 [M$^+$] (calcd. for $C_{16}H_7ClF_3N_5O_2$, 393.0240).

16\. Selected ^{1}H NMR (500 MHz, DMSO-d_6) and HRMS data of teflubenzuron derivatives **9a~c: 9a**. ^{1}H NMR: δ 7.34-7.68 (m, 5H, aromatic), 8.06 (d, 1H, J=10 Hz, aromatic), 11.30 (s, 1H, ArCON*H*), 11.70 (s, 1H, CON*H*CO); HRMS (*m/z*): 343.9942 [M$^+$] (calcd for $C_{14}H_8Cl_2F_2N_2O_2$, 343.9931). **9b**. ^{1}H NMR: δ 7.34 (d, 1H, J=10 Hz, aromatic), 7.63-7.66 (m, 3H, aromatic), 8.11(d, 1H, J=10 Hz, aromatic), 11.22 (s, 1H, ArCON*H*), 12.10 (s, 1H, CON*H*CO); HRMS (*m/z*): 377.9560 [M$^+$] (calcd for $C_{14}H_7Cl_3F_2N_2O_2$, 377.9541). **9c**. ^{1}H NMR: δ 7.20-7.60 (m, 4H, aromatic), 7.93(d, 1H, J=10 Hz, aromatic), 10.92 (s, 1H, ArCON*H*), 11.88(s, 1H, CON*H*CO); HRMS (*m/z*): 346.0108 [M$^+$] (calcd. for $C_{14}H_7ClF_4N_2O_2$, 346.0132).

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