A New Method for the Synthesis and Herbicidal Activity of 3-Phenoxy-6-(*1H*-(substituted)pyrazol-1-yl) Pyridazines

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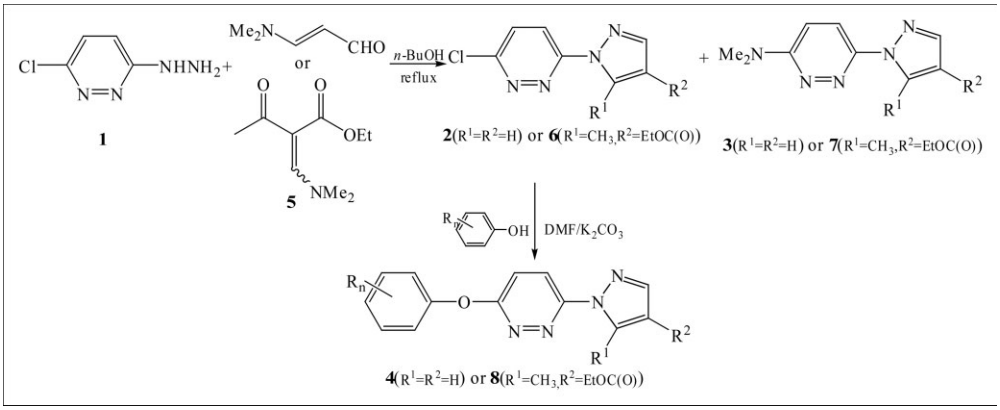

A series of 3-substituted phenoxy-6-((substituted)*1H*-pyrazol-1-yl) pyridazines were synthesized from the condensation of various phenols and 3-chloro-6-(*1H*-pyrazol-1-yl) pyridazine **2** or 3-chloro-6-(5′-methyl-4-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazine **6** in N,N-dimethylformamide (DMF) at 120°C with K_2CO_3 as an acid receptor. The intermediates **2** or **6** were obtained from the cyclization of 3-chloro-6-hydrazinyl pyridazine **1** with 3-dimethylamino-acrylaldehyde or ethyl 2-((dimethylamino) methylene)-3-oxobutanoate in *n*-butanol under reflux, respectively, and side products **3** or **7** were also generated. All of the title compounds were confirmed by ^{1}H NMR, infrared spectometry (IR) and elemental analyses. Preliminary bioassay indicated that some of the title compounds showed high inhibitory activity against *Brassica campestris L. (B. campestris)* and moderate inhibitory activity against *Echinochloa crusgalli*. For example, the inhibition percentages of compound **4b** and **4c** against *B. campestris* were both 94% at 10 μg/mL.

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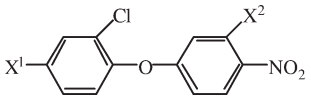
INTRODUCTION

Protoporphyrinogen IX oxidase (Protox, EC 1.3.3.4) is the key enzyme in chlorophyll biosynthesis pathways in plants, which catalyzes the oxidative O_2-dependent aromatization of the colorless protoporphyrinogen IX to the highly conjugated protoporphyrin IX. The phytotoxicity of Protox inhibitors is light dependent and involves intracellular peroxidation caused by protoporphyrin IX, chlorophyll precursor, leading to accumulation of protoporphyrin IX in plant mitochondria and plant chloroplasts. Abnormal accumulated protoporphyrin IX in plant tissue is assumed to cause light-induced formation of active oxygen, which induces disruption of membranes, chlorophyll degradation, and desiccation of plants in the light [1].

So far, several structurally distinct classes of compounds, cyclic imides, phenyltriazolinones, diphenyl ethers (DPEs), etc, targeted at Protox, have been used as herbicides for several decades [2]. DPEs are one of the important Protox inhibitors, and numerous diphenylether compounds have been developed as commercial herbicides (Fig. 1), for example, nitrofen, chlomethoxynil, bifenox, oxyfluorfen, acifluorfen, fluoroglycofen-ethyl, fomesafen, and lactofen.

According to the commercialized Protox inhibitors, DPEs, a pharmacophore of Protox, and its inhibitors were established in our group [3], which indicated that two phenyl rings in DPEs, connected by an oxygen atom as a hydrogen-bonding acceptor, play important roles in their herbicidal activity. In addition, it is deduced from the Protox pharmacophore that a molecule bearing three aromatic rings connected directly or by oxygen atoms or nitrogen atoms maybe also shows good inhibition against Protox.

Heterocyclic rings are the classic phenyl-ring equivalents according to the bioisosterism [4], especially nitrogen-containing heterocyclic rings. So, it is reasonable to



nitrofen(X^1=Cl, X^2=H),

chlomethanoxynil (X^1=Cl, X^2=OMe),

bifenox(X^1=Cl, X^2=CO_2Me),

oxyfluorfen(X^1=CF_3, X^2=OEt),

acifluorfen (X^1= CF_3, X^2=COONa),

fluoroglyfen-ethyl(X^1=CF_3, X^2=$CO_2CH_2CO_2$Et),

fomesafen (X^1= CF_3, X^2=$CONHSO_2$Me),

lactofen (X^1= CF_3, X^2=CH(Me)CO_2Et).

Figure 1. Commercialized herbicides of diphenyl ethers.

use a heterocyclic ring to replace one of the phenyl rings in DPEs. Pyridazine ring is an important moiety in some pharmaceuticals and agrochemicals [5–7]. In our previous work, we synthesized numerous 3-phenoxy-6-dimethylamino pyridazines, and some of them showed inhibitory activity against *Brassica campestris L. (B. campestris)* and *Echinochloacrus-galli (E. crus-galli)* (Fig. 2, X^3 = H, Cl, CF_3, etc) [8]. However, after treatment of above weeds using the synthesized phenoxy pyridazines, *B. campestris* and *E. crus-galli* were desiccated but not killed completely. Ten days later after ''desiccation,'' these two weeds can grow again, which may be attributed to the loss of dimethylamino moiety of phenoxy-pyridazines in above weeds in the light [9]. To get new phenoxy pyridazines, which can be tolerated in above two weeds, we synthesized 3-aryloxy-6-fluoro pyridaiznes and found that they can inhibit the growth of *B. campestris* and *E. crus-galli* to some extent (Fig. 3, X^4 = Cl, OMe, NO_2, etc.) [10]. It was excited that they can be well tolerated in these two weeds. Currently, pyrazole ring is an important moiety in the pesticide researches [11–13]. We introduced pyrazole ring into phenoxy pyridazines because pyrazol-yl moiety has electron-withdrawing characteristic in pyrazolyl pyridazines as nitro group in DPEs (Fig. 4). In addition, the structures in Figure 4 almost meet the requirement of the deducation from Protox pharmacophore. So, we synthesized 3-aryloxy-6-(3′,5′-dimethyl-*1H*-pyrazol-1-yl) pyridazines (Fig. 4, X^5 = Cl, Br, Me, etc.), which

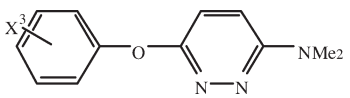


Figure 2. 3-Aryloxy-6-substituted pyridazines.

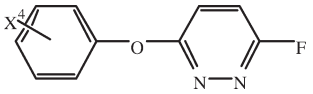


Figure 3. 3-Aryloxy-6-fluoro pyridazines.

showed inhibitory activity against *B. campestris* and *E. crus-galli* to some extent [14].

In continuation on our research program for the synthesis of novel pyrazolyl-pyridazine derivatives and study on the relationship of structure and herbicidal activity, we design 3-substituted phenoxy-6-(*1H*-pyrazol-1-yl)pyridazines **4** and 3-substituted phenoxy-6-(5′-methyl-4′-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazines **8**, which were synthesized from the condensation of various phenols and 3-chloro-6-(1*H*-pyrazol-1-yl) pyridazine or 3-chloro-6-(5′-methyl-4′-ethoxycarbonyl-1*H*-pyrazol-1-yl) pyridazine in DMF at 120°C using K_2CO_3 as an acid acceptor(Scheme 1). All novel compounds were characterized by ^{1}H NMR, IR, and elemental analyses. Preliminary bioassay indicated that some of the title compounds showed high inhibitory activity against *B. campestris* and moderate inhibitory activity against *E. crus-galli*. Moreover, the title compounds are well tolerated in above weeds during the bioassay procedure.

RESULTS AND DISCUSSION

Synthesis. The synthetic procedure of the title compounds is shown in Scheme 1. The intermediate **2** was achieved from the cyclization of starting materials **1** and 3-(dimethylamino)-acrylaldehyde. When this reaction was carried out in anhydrous ethanol under reflux, side product **3**, rather than the desired compound **2**, was obtained in high yield. However, compound **1** was treated with 3-(dimethylamino)acrylaldehyde in *iso*-propanol or *n*-butanol under reflux to afford compound **2** in 20% and 80% yield, respectively. Steiner *et al*., [15] Steel and Constable, [16] and Blake *et al*. [17] have previously obtained **2** in 53–74% yield by treatment of pyrazole and 3,6-dichloropyridazine in DMF with NaH as a base. However, side product, 3,6-bis(*1H*-pyrazol-1-yl) pyridazine, was not avoidable.

As such, treatment of starting materials **1** and ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **5** under reflux in *n*-butanol furnished the desired intermediate **6**

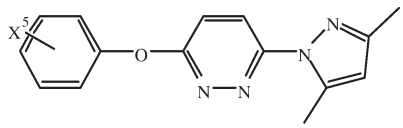
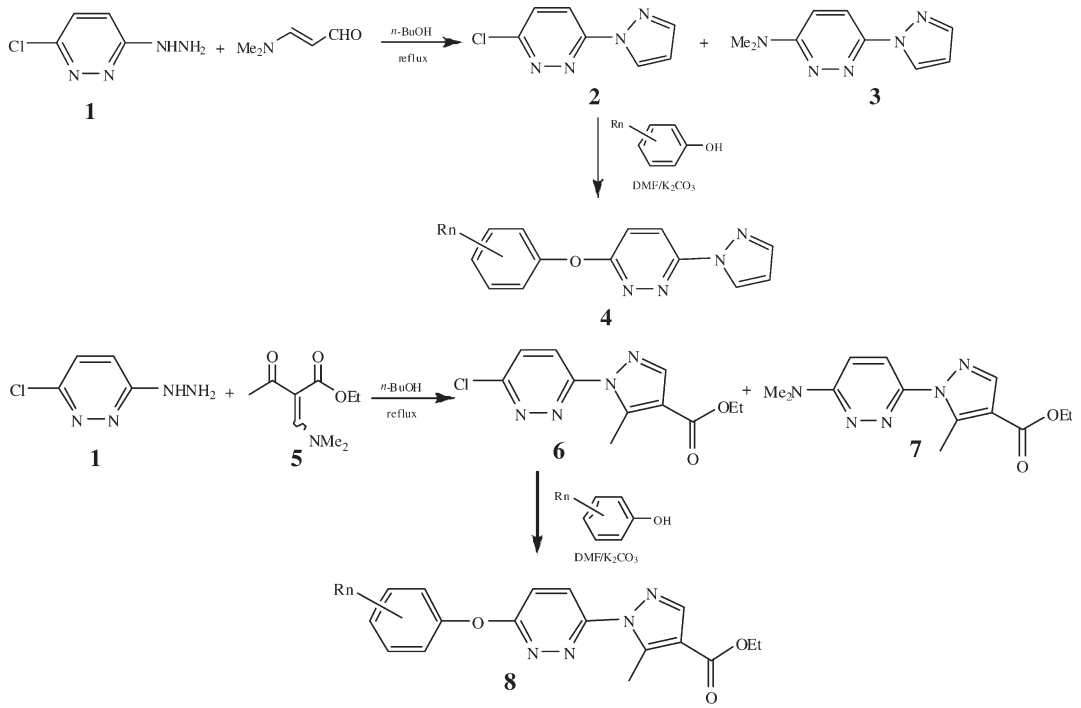


Figure 4. Structure of 3-aryloxy-6-(3′,5′-dimethyl-*1H*-pyrazol-1-yl) pyridazines.

Scheme 1. General procedure for the synthesis of the title compounds.



4a(R_n=3-Cl), **4b**(R_n=4-Cl), **4c**(R_n=4-CH_3), **4d**(R_n=3,4-Cl_2), **4e**(R_n=3-CF_3), **4f**(R_n 4-$CH_3OC(O)$).

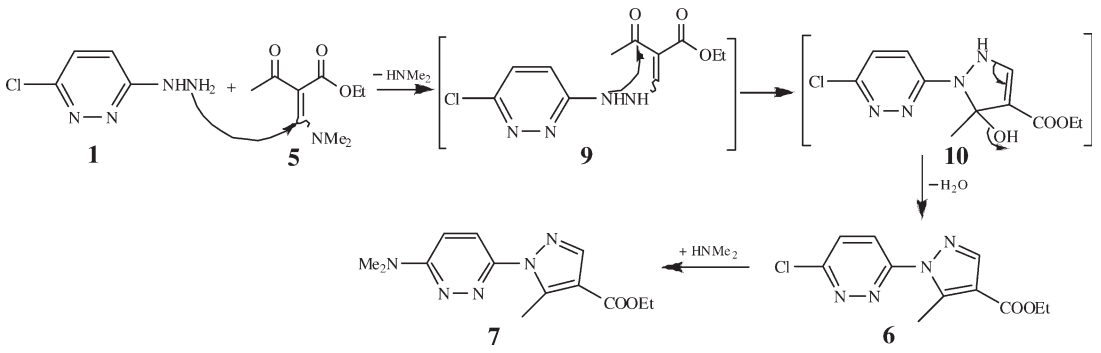
8a(R_n=4-CH_3), **8b**(R_n=3,5-$(CH_3)_2$), **8c**(R_n=2-$CH_3OC(O)$), **8d**(R_n=4-Cl), **8e**(R_n=3-Cl), **8f**(R_n=3,4-Cl_2), **8g**(R_n=4-$CH_3OC(O)$), **8h**(R_n=3-CF_3).

and side product **7** in the yields of 60% and 10%, respectively. Compound **6** was first synthesized by Bagrov [18] from the reaction of ethyl 2-(ethoxymethylene)-3-oxobutanoate with **1**.

A proposed mechanism of the generation of **6** and **7** is shown in Scheme 2. First, the hydrazinyl group in compound **1** attacks the carbon nucleus, which is linked to the dimethylamino moiety, to generate intermediate **9** with elimination of dimethylamine. **9** proceeds the intramolecular cyclization to furnish intermediate **10**, which is dehydrated to give **6**. **7** is obtained through the condensation of **6** and dimethylamine, which is produced from the cyclization of starting materials **1** and **5**. **7** is conformed by X-ray diffraction (Fig. 5) [19], indicating that methyl group is at 5th position and ethoxycarbonyl moiety is at 4th position in the pyrazole ring.

The title compounds **4** or **8** were obtained from the treatment of intermediates **2** or **6** and substituted phenols in DMF at 120°C for several hours until **2** or **6** was consumed completely as indicated by thin layer chromatography. After the reactions were over, the resulting mixtures were poured into cold water, and crude solids were filtrated, which were recrystallized with ethanol and cyclohexane to give pure products. All of the title

Scheme 2. Proposed mechanisms for the generation of **6** and **7**.



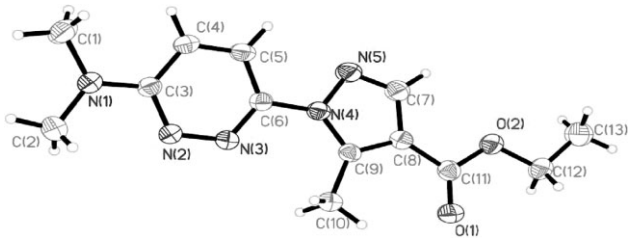


Figure 5. Crystal structure of compound **7**.

compounds were confirmed by ^{1}H NMR, IR, and elemental analyses.

Herbicidal activities. The title compounds were screened for herbicidal activity against *B. campestris* and *E. crus-galli* using a previously reported procedure [20,21], and the data of herbicidal activity were listed in Table 1. It was found that the title compounds are well tolerated in two weeds during the bioassay procedure. Most of compounds **8**, containing a methyl group at 5th position and an ethylcarbony moiety at 4th position in pyrazole ring, have no or slight herbicidal activity against *B. Campestris* and *E. crus-galli*. Compounds **4a–d**, which only have H-atoms at 4th and 5th positions in pyrazole ring, showed high inhibitory activity against *B. Campestris* and moderate inhibitory activity against *E. crus-galli*. at the concentration of 100 and 10 μg/mL, respectively. Compounds **4b** (R_n = 4-Cl) and **4c** (R_n = 4-Me) both showed high inhibitory activity against *B. Campestris*, which indicates that electron-donating groups or weak electron-withdrawing groups at 4th position in phenyl rings are favorable to the increase of herbicidal activity. However, compounds **4e** (R_n = 3-CF_3) and **4f** (R_n = 4-$CH_3OC(O)$) have no herbicidal activity against *B. Campestris*, indicating that strong electron-withdrawing groups at 3rd or 4th positions in phenyl rings are unfavorable to the enhancement of herbicidal activity. When R_n = 3,4-Cl_2, inhibitory activity of compound **4d** against *B. Campestris* decreased slightly compared with that of **4b**, suggesting that introduction of chlorine at 3rd position in phenyl ring be unfavorable to the increase of herbicidal activity. Compound **4a** with chlorine atom at 3rd position in phenyl ring has lower herbicidal activity against *B. Campestris* and *E. crus-galli* than compound **4b** with chlorine atom at 4th position in phenyl ring.

CONCLUSION

In conclusion, a series of 3-substituted phenoxy 6-(substituted pyrazol-yl)pyridazines were obtained from the condensation of various phenols and 3-chloro-6-(*1H*-pyrazol-1-yl) pyridazine or 3-chloro-6-(5′-methyl-4-ethoxycarbonyl-*1H*-pyrazol-1-yl) pyridazine in DMF at 120°C with K_2CO_3 as an acid receptor. The title compounds were screened for herbicidal activity against *B. Campestris* and *E. crus-galli*. Preliminary bioassay indicated that some of title compounds show high inhibitory activity against *B. Campestris* and moderate inhibitory activity against *E. crus-galli* at 10 and 100 μg/mL, respectively. Further study of structure-activity relationship of modified 3-phenoxy 6-substituted pyrazolyl pyridazines is now under investigation.

EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and chemical shift values (δ) were given in parts per million downfield of internal tetramethylsilane. ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 MHz spectrometer (100 MHz) using $CDCl_3$ as a solvent, and chemical shift values (δ) were reported in parts per million relative to the residual chloroform (77.00 ppm) and was obtained with ^{1}H decoupling. IR spectra were recorded on a MAGNA-560 FTIR (Nicolet Company) spectrometer using KBr plates (thin film). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were not corrected. Elemental analyses were performed on a Yanaca CHN Corder MT-3 elemental analyzer. All anhydrous solvents were dried and purified by standard techniques just before use. 3-Chloro-6-hydrazinylpyridazine **1** was prepared according to the literature procedure [22], and 3-(dimethylamino)acrylaldehyde and 3-((dimethylamino) methylene)-1-ethoxy-pentane-2,4-dione **5** were both available commercially.

Synthesis of 3-chloro-6(1H-pyrazol-1-yl) pyridazine 2 and 3-dimethylamino-6(1H-pyrazol-1-yl) pyridazine 3. A mixture of 3-(dimethylamino)acrylaldehyde (1.09 g, 11.00 mmol) and 3-chloro-6-hydrazinyl pyridazine **1** (1.45 g, 10.00 mmol) in *n*-butanol(20mL) was refluxed for half an hour. When the

Table 1

Herbicidal activity against *B. campestris* and *E. crus-galli* of the title compounds (inhibition percentage, %).

Compounds	R_n	*B. campestris*		*E. crusgalli*	
		100 μg/mL	10 μg/mL	100 μg/mL	10 μg/mL
4a	3-ClC_6H_4	62	54	0	0
4b	4-ClC_6H_4	97	94	65	42
4c	4-$CH_3C_6H_4$	97	94	84	40
4d	3,4-$Cl_2C_6H_3$	83	79	26	19
4e	3-$CF_3C_6H_4$	0	0	0	0
4f	4-$CH_3OC(O)$ C_6H_4	0	0	0	0
8a	4-$CH_3C_6H_4$	54	38	0	0
8b	3,5-$(CH_3)_2C_6H_3$	0	0	14	0
8c	2-$CH_3OC(O)C_6H_4$	0	0	16	0
8d	4-ClC_6H_4	0	0	0	0
8e	3-ClC_6H_4	34	0	9	0
8f	3,4-$Cl_2C_6H_3$	0	0	0	0
8g	4-$CH_3OC(O)$ C_6H_4	0	0	0	0

starting materials were consumed completely as indicated by thin layer chromatography, the reaction mixture was allowed to cool to room temperature. After removal of the solution under pressure, the resulting residue was subjected to flash column chromatography on silica gel to give compound **2** (1.50 g) as a white crystal (eluent: petroleum ether: ethyl acetate=4:1 (*V/V*) in 80% yield, mp.143–144°C (ref.: mp. 124–126°C[15]). ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.54–6.56 (m, 1H, pyrazole-H), 7.63 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.81 (d, J = 2.0 Hz, 1H, pyrazole-H), 8.22 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.73 (d, J = 2.8 Hz, 1H, pyrazole-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 109.18, 119.92, 127.40, 130.43, 143.28, 153.62, 154.23; IR (KBr) ν (cm^{-1}): 3129, 1635, 1575, 1523, 1448, 1402, 1143, 1016, 860, 765.

Side product 3-dimethylamino-6(1*H*-pyrazol-1-yl) pyridazine **3** was also obtained in 15% yield, mp. 147–149°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.21 (s, 6H, NMe_2), 6.47 (m, 1H, pyrazole-H), 7.00 (d, J=9.6 Hz, 1H, pyridazine-H), 7.73 (d, J=2.0 Hz, 1H, pyrazole-H), 7.97 (d, J=9.6 Hz, 1H, pyridazine-H), 8.62 (d, J=2.4 Hz, 1H, pyrazole-H). GC-MS(EI, m/z(%)): 189.09 (M+, 40), 160.10(100). ^{13}C NMR($CDCl_3$, 100 MHz), δ: 38.38, 107.86, 119.40, 126.26, 141.48, 147.77, 159.08. Anal. calcd. for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01; found: C, 57.18; H, 5.72; N, 36.89.

General Procedure for the Synthesis of 3-aryloxy-6-(1H-pyrazol-1-yl) pyridazine 4. A 25-mL three-necked round bottom flask equipped with a thermometer, magnetic stir bar, and a dropping addition funnel was charged sequentially with new distilled DMF (7 mL), compounds **2** (2.00 mmol), substituted phenols (2.00 mmol), anhydrous potassium carbonate 0.29 g (2.10 mmol). The resulting mixture was heated at 120°C. After stirring for 12 h, the reaction mixture was allowed to cool to room temperature, poured into 30 mL of ice water, and filtrated to give the crude product. The resulting precipitate was washed with water (5 mL). The collected solid was dried overnight under vacuum to give a white powder, which was recrystallized from ethanol/cyclohexane (1/3: (*V/V*) to generate pure compounds **4**.

3-(3-chlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4a). White solid, yield 86%, mp.130–131°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.51–6.52 (m, 1H, pyrazole-H), 7.15 (dd, J_1=8.8Hz, J_2=2.0Hz, 1H, ArH), 7.22–7.29 (m, 2H, ArH), 7.35 (s, 1H, ArH), 7.37 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.77 (d, J=2.0Hz, 1H, pyrazole-H), 8.30 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.40 (d, J=2.4Hz, 1H, pyrazole-H). IR (KBr) ν (cm^{-1}): 3136, 3093, 3021, 1578, 1523, 1469, 1418, 1290, 1197, 1126, 1085, 1046, 1018, 909, 858, 768. Anal. calcd for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55; found: C, 57.36; H, 3.21; N, 20.31.

3-(4-chlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4b). White solid, yield 85%, m.p. 151–152°C.^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.51–6.52 (m, 1H, pyrazole-H), 7.19 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 9.2 Hz, 1H, pyridazine-H), 7.40 (d, J = 8.8 Hz, 2H, ArH), 7.77 (d, J = 2.0Hz, 1H, pyrazole-H), 8.28 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.4 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3150, 3006, 1571, 1530, 1498, 1459, 1408, 1299, 1254, 1200, 1171, 1136, 1043, 1008, 934, 838, 762; Anal. calcd for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55; found: C, 57.01; H, 3.48; N, 20.58.

3-(4-methylphenoxy)-6-(1H-pyrazol-1-yl)pyridazine(4c). White solid, yield 70%, mp. 131–132°C.^{1}H NMR ($CDCl_3$, 400 MHz) δ:2.37 (s, 3H, $ArCH_3$), 6.50–6.51 (m, 1H, pyrazole-H), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.31 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.76 (d, J = 2.0Hz, 1H, pyrazole-H), 8.23 (d, J = 9.2 Hz, 1H, pyridazine-H) 8.63 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3093, 3042, 1581, 1514, 1459, 1411, 1296, 1258, 1203, 1133, 1104, 1032, 1014, 931, 861, 762; Anal. calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; found: C, 66.78; H, 4.89; N, 22.45.

3-(3,4-dichlorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine (4d). White solid, yield 87%, mp.158–159°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.52–6.56 (m, 1H, pyrazole-H), 7.14 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H, ArH), 7.37 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.40 (d, J = 2.8 Hz, 1H, ArH), 7.50 (d, J = 8.8 Hz, 1H, ArH), 7.77 (d, J=2.0Hz, 1H, pyrazole-H), 8.30 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.4 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3143, 3084, 3056, 3028, 1568, 1530, 1469, 1418, 1398, 1299, 1261, 1206, 1120, 1043, 1018, 918, 864, 810, 755; Anal. calcd. for $C_{13}H_8Cl_2N_4O$: C, 50.84; H, 2.63; N, 18.24; found: C, 50.62; H, 2.83; N, 18.34.

3-(3-trifluorophenoxy)-6-(1H-pyrazol-1-yl)pyridazine (4e). White solid, yield 80%, mp. 160–161°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.51–6.53 (m, 1H, pyrazole-H), 7.40 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.46 (d, J = 7.6 Hz, 1H, ArH), 7.51–7.59 (m, 3H, ArH), 7.77(d, J=2.0Hz, 1H, pyrazole-H), 7.82 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.63 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3086, 3035, 1574, 1523, 1459, 1408, 1325, 1286, 1206, 1162, 1136, 1068, 1018, 909, 864 762; Anal. calcd. for $C_{14}H_9F_3N_4O$: C, 54.91; H, 2.96; N, 18.29; found: C, 54.98; H, 2.94; N, 18.29.

3-(4-methoxycarbonylphenoxy)-6-(1H-pyrazol-1-yl) pyridazine (4f). White solid, yield 80%; mp. 187–188°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.93 (s, 3H, $COOCH_3$), 6.51–6.52 (m, 1H, pyrazole-H), 7.31 (d, J = 8.0 Hz, 2H, ArH), 7.39 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.77 (d, J = 2.0 Hz, 1H, pyrazole-H), 8.13 (d, J = 8.0 Hz, 2H, ArH), 8.31 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.64 (d, J = 2.0 Hz, 1H, pyrazole-H); IR (KBr) ν (cm^{-1}): 3136, 3093, 3028, 2958, 1725, 1597, 1517, 1456, 1408, 1283, 1197, 1158, 1110, 1046, 1014, 931, 861, 774; Anal. calcd. for $C_{15}H_{12}N_4O_3$: C, 60.78; H, 4.08; N, 18.91; found: C, 60.78; H, 4.02; N, 18.92.

Synthesis of 3-chloro-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine 6 and 3-dimethylamin-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine 7. A mixture of ethyl 2-((dimethylamino)methylene)-3-oxobutanoate **5** (1.50 g, 8.10 mmol) and 3-chloro-6- hydrazinyl pyridazine **1**(1.16 g, 8.00 mmol) in *n*-butanol (20mL) was refluxed. When the starting materials were consumed completely as indicated by thin layer chromatography, the workup of reaction mixture was the same as that of compound **2** to give compound **6** (1.52 g) as a white crystal in 60% yield, mp. 140–141°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.39 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 3.05 (s, 3H, pyrazole-CH_3), 4.35 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.69 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.10 (s, 1H, pyrazole-H), 8.14 (d, J = 9.2 Hz, 1H, pyridazine-H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ: 13.73, 14.55, 60.53, 115.59, 124.14, 130.73, 143.91, 146.59, 155.38, 156.06, 163.31; LC-MS: 267 (M^+, 100), 269 (33); IR (KBr) ν (cm^{-1}): 3131, 1633, 1448, 1402, 1089, 1018, 860, 765. Anal. calcd. for $C_{11}H_{11}ClN_4O_2$: C, 49.54; H, 4.16; N, 21.01; found: C, 49.28; H, 4.26; N, 20.98.

Side product 3-dimethylamin-6-(4-ethoxycarbonyl-5-methyl-*1H*-pyrazol-1-yl) pyridazine **7** was also obtained in 10% yield.

mp. 102–104°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.92 (s, 3H, pyrazole-CH_3), 3.24(s, 6H, $N(CH_3)_2$), 4.33 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 6.98((d, J = 10.0 Hz, 1H, pyridazine-H), 7.34 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.04 (s, 1H, pyrazole-H). Anal. calcd. for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44; found: C, 56.77; H, 6.27; N, 25.41. Compound **7** was further confimred by X-ray diffraction (Fig. 5).

3-(4-methylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl)pyridazine(8a). White solid, yield 41%, mp. 110–111°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.38 (s, 3H, Ar—CH_3), 2.95 (s, 3H, pyrazole-CH_3), 4.33 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.12 (d, J = 8.4 Hz, 2H, ArH), 7.25 (d, J = 8.4 Hz, 2H, ArH), 7.34 (d, J = 9.2 Hz, 1H, pyridazine-H), 8.06 (s, 1H, pyrazole-H), 8.11 (d, J = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3114, 3035, 1710, 1545, 1446, 1402, 1302, 1251, 1184, 1085, 1018, 934, 880, 842, 771; Anal. calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56; found: C, 63.92; H, 5.41; N 16.49.

3-(3,5-dimethylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8b). White solid, yield 80%, mp. 119–120°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.34 (s, 6H, Ar—$(CH_3)_2$), 2.95 (s, 3H, pyrazole-CH_3), 4.34 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 6.83 (s, 2H, ArH), 6.90 (s, 1H, ArH), 7.33 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.06 (s, 1H, pyrazole-H), 8.10 (d, J = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}):3114, 3035, 2985, 2934,1718,1619, 1555, 1443, 1402, 1296, 1251, 1184, 1133, 1094, 1034, 934, 835, 784; Anal. calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90; found: C, 64.56; H, 6.00; N, 15.97.

3-(2-methoxycarbonylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8c). White solid, yield 75%, mp. 130–131°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.93 (s, 3H, pyrazole-CH_3), 3.74 (s, 3H, $COOCH_3$), 4.33 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.37 (t, J = 7.6 Hz, 1H, ArH), 7.45 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.65 (t, J = 7.6 Hz, 1H, ArH), 8.06 (s, 1H, pyrazole-H), 8.09 (d, J = 7.6 Hz, 1H, ArH), 8.17 (d, J = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3122, 2992, 1710, 1602, 1552, 1478, 1446, 1402, 1299, 1258, 1184, 1133, 1091, 1034, 931, 880, 835, 774; Anal. calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65; found: C, 59.70; H, 4.61; N, 14.69.

3-(4-chlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8d). White solid, yield 80%, mp. 175–176°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.95 (s, 3H, pyrazole-CH_3), 4.33 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.19 (d, J = 8.8 Hz, 2H, ArH), 7.38 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.41 (d, J = 8.8Hz, 2H, ArH), 8.06(s, 1H, pyrazole-H), 8.16 (d, J = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3134, 3012, 1716, 1578, 1552, 1443, 1402, 1285, 1254, 1168, 1041, 1087, 848, 772; Anal. calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62; found: C, 56.73; H, 4.34; N, 15.90.

3-(3-chlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8e). White solid, yield 72%, mp. 130–131°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.38 (t, J =7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.97 (s, 3H, pyrazole-CH_3), 4.34 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.16(dd, J=1.6Hz, 6.8Hz, 1H, ArH), 7.27–7.30(m, 2H, ArH), 7.38–7.42 (m, 2H, pyridazine-H + ArH), 8.07 (s, 1H, pyrazole-H), 8.18 (d, J = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3136, 3035, 1718, 1584, 1562, 1442, 1402, 1290, 1248, 1187, 1040, 1094, 854, 778; Anal. calcd. for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62; found: C, 57.32; H, 4.05; N, 15. 44.

3-(3,4-dichlorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8f). White solid, yield 58%, mp. 145–146°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.97 (s, 3H, pyrazole-CH_3), 4.34 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.14 (dd, J_1 = 8.8Hz, J_2 = 2.8Hz, 1H, ArH), 7.36–7.42 (m, 2H, ArH+ pyridazine-H), 7.52 (d, J = 8.8 Hz, 1H, ArH), 8.07 (s, 1H, pyrazole-H), 8.20 (d, J = 9.2 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3114, 3021, 1718, 1552, 1443, 1402, 1296, 1246, 1187, 1094, 1037, 922, 890, 838, 771; Anal. calcd. for $C_{17}H_{14}Cl_2N_4O_3$: C, 51.93; H, 3.59; N, 14.25; found: C, 52.11; H, 4.05; N, 14.03.

3-(4-methoxycarbonylphenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8g). White solid, yield 52%, mp. 129–130°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.96 (s, 3H, pyrazole-CH_3), 3.94(s, 3H, $COOCH_3$), 4.33 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.32(d, J = 8.8 Hz, 2H, ArH), 7.42 (d, J = 9.6 Hz, 1H, pyridazine-H), 8.07 (s, 1H, pyrazole-H), 8.14 (d, J = 8.8 Hz, 2H, ArH), 8.19 (d, J = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3136, 3013, 2025, 1723, 1606, 1590, 1554, 1506, 1481, 1456, 1435, 1412, 1400, 1298, 1245, 1206, 1184, 1168, 1098, 1042, 1016, 935, 877, 771; Anal. calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65; found: C, 59.64; H, 4.55; N, 14.45.

3-(3-trifluorophenoxy)-6-(4-ethoxycarbonyl-5-methyl-1H-pyrazol-1-yl) pyridazine(8h). White solid, yield 80%, mp.: 133–134°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (t, J = 7.2 Hz, 3H, $CH_2\mathbf{CH}_3$), 2.96 (s, 3H, pyrazole-CH_3), 4.34 (q, J = 7.2 Hz, 2H, $\mathbf{CH}_2CH_3$), 7.43 (d, J = 9.6 Hz, 1H, pyridazine-H), 7.47 (d, J = 8.0 Hz, 1H, ArH), 7.52 (s, 1H, ArH), 7.54 (d, J = 8.0 Hz, 1H, ArH), 7.58 (t, J = 7.6 Hz, 1H, ArH), 8.08 (s, 1H, pyrazole-H), 8.20 (d, J = 9.6 Hz, 1H, pyridazine-H); IR (KBr) ν (cm^{-1}): 3181, 3145, 3060, 2992, 2931,1718, 1648, 1581, 1554, 1474, 1444, 1380, 771, 691; Anal. calcd. for $C_{18}H_{15}F_3N_4O_3$: C, 55.10; H, 3.85; N, 14.28; found: C, 55.24; H, 4.05; N, 14.39.

Herbicidal activity tests [20,21]. ***Inhibition of the root-growth of rape (Brassica campestris L.).*** The compounds to be tested are made into emulsions to aid dissolution. Rape seeds are soaked in distilled water for 5 h before being placed on a filter paper in a 6-cm Petri plate, to which 2 ml of inhibitor solution had been added in advance. Usually, 15 seeds are used on each plate. The plate is placed in a dark room and allowed to germinate for 72 h at 28(±1)°C. The lengths of 10 rape roots selected from each plate are measured and the means are calculated. The inhibition percentage is calculated relative to controls using distilled water instead of the inhibitor solution. There were two replicates for each treatment. The data of herbicidal activity are listed in Table 1.

Inhibition of the seedling growth of barnyard grass (Echinochloa crusgalli (L.) Beauv.). The compounds to be evaluated are made into emulsions to aid dissolution. Ten baryard grass seeds are placed into a 50-mL cup covered with a layer of grass beads (diameter = 0.5cm) and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup is placed in a bright room, and the seeds were allowed to germinate for 72 h at 28(±1)°C. The height of the above-ground parts of the seedlings in each cup

is measured and the means calculated. The inhibition percentage is calculated relative to controls using distilled water instead of the inhibitor solution. There were two replicates for each treatment. The data of herbicidal activity are listed in Table 1.

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REFERENCES AND NOTES

[1] Arnould, S.; Camadro, J. M. Proc Natl Acad Sci USA 1998, 95, 10553.

[2] Hirai, K. In Peroxidizing Herbicides; Boger, P.;Wakabayashi, K., Eds.; Springer-Verlag: Berlin Herdelberg, 1999; p 15–70.

[3] Chen, K. PhD Thesis; Nankai University: Tianjin, China, 2001.

[4] Patani, G. A.; Lavoie, E. J. Chem Rev 1996, 96, 3147.

[5] Heinisch, G.; Kopelent F. H. Prog Med Chem 1992, 29, 141.

[6] Jojima, T.; Yoshimura, N.; Takematsu, T.; Tamura, S. Agric Bio Chem 1969, 33, 96.

[7] Tsukamoto, Y.; Komai, H.; Kadotani, J.; Koi, K.; Mio, S.; Takeshiba, H. World Patent 200316286, 2003. Chem Abstr 2003, 138, 187781.

[8] Yang, H.-Z.; Wang, X.; Hu, F.-Z; Yang, X.-F. Chem J Chinese Univ 2002, 23, 2261 (in Chinese).

[9] Hancock, K. G.; Uriarte, A. K.; Dickinson, D. A. J Am Chem Soc 1973, 95, 6980.

[10] Wang, Z.-P.; Hu, F.-Z.; Zou, X.-M.; Yang, X.-F.; Yang, H.-Z. Chinese J Pesticide Sci 2004, 6, 15 (in Chinese).

[11] Trofimov, B. A.; Malkina, A. G.; Borisova, A. P.; Nosyreva, V. V.; Shemyakina, O. A.; Kazheva, O. N.; Shilov, G. A.; Dyachenko, O. A. Tetrahedron Lett, 2008, 49, 3104, and the references cited therein.

[12] Ren, X.-L.; Hu, F.-Z.; Zou, X.-M.; Yang, H.-Z. Pesticides 2003, 42, 17 (in Chinese).

[13] Chen, H.-S; Li, Z.-M.; Li, J.-F. Chem J Chinese Univ 2000, 21, 1520 (in Chinese).

[14] Hu, F. Z.; Zhang, G. F.; Zou, X. M.; Liu, B.; Zhu, Y. Q.; Yang, H. Z. Chin J Org Chem 2008, 28, 1227 (in Chinese).

[15] Steiner, G.; Gries, J.; Lenke, D. J Med Chem 1981, 24, 59.

[16] Steel, P.; Constable, E. C. J Chem Res (S) 1989, 7, 189.

[17] Blake, A. J.; Hubberstey, P.; Li, W. S.; Russell, C. E.; Smith, B. J.; Wraith, L. D. J Chem Soc Dalton Transactions: Inorg Chem 1998, 4, 647.

[18] Bagrov, F. V. Russian J Org Chem 2000, 36, 191.

[19] Hu, F. Z.; Zhang, G. F.; Zhu, Y. Q.; Yang, H. Z. Acta Crystallogr 2006, E62, o4638.

[20] Wang, B. L.; Duggleby, R. G.; Li, Z. M.; Wang, J. G.; Li, Y. H.; Wang, S. H.; Song, H. B. Pest Management Sci 2005, 61, 407.

[21] Zhu, Y. Q.; Zou, X. M., Hu, F. Z.; Yao, C. S.; Liu, B.; Li, Y. H.; Yang, H. Z. J Agric Food Chem 2005, 53, 9566.

[22] Carlo, F.; Riccardo, M.; Mario, P. Org Prep Proc Int 1989, 21, 125.