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Synthesis and Evaluation *O*-Benzyl Oxime-ether Derivatives Containing *β*-Methoxyacrylate Moiety for Insecticidal and Fungicidal Activities

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In attempt to lead compounds exhibiting both insecticidal and fungicidal activities, a series of *O*-benzyl oxime-ether derivatives were designed and synthesized by introducing *β*-methoxyacrylate pharmacophore into a scaffold. The insecticidal activity against *Aphis fabae* and the fungicidal activity against *Erysiphe graminis* were screened. The title compounds exhibited remarkable insecticidal and fungicidal activities. The most potent compound **6d** was identified. Its insecticidal LC_{50} against *A. fabae* is 6.4 mg/L, which is lower than that of chlorfenapyr (19.4 mg/L) and even close to the level of imidacloprid (4.8 mg/L). Its fungicidal EC_{90} in preventive and curative treatment against *E. graminis* are 2.2 and 4.8 mg/L, respectively, which are lower than azoxystrobin (7.0 and 5.9 mg/L). These results indicate that compound **6d** can be considered as a lead for further developing new *O*-benzyl oxime-ether typed candidates with both fungicidal and insecticidal activities.

Key Words : *O*-Benzyl oxime-ether, *β*-Methoxyacrylate fungicides, Insecticide, Synthesis

Introduction

Oxime ether/ester derivatives with broad-spectrum of biological activities have received increasing attention recently.[1,2] Among them, *O*-benzyl oxime-ether is recognized as one of the most promising scaffolds. In the field of pesticides, *O*-benzyl oxime-ethers such as flucycloxuron as an insect growth regulator[3] and trifloxystrobin as a fungicide have been used successfully (Figure 1).

Strobilurins and oudemansins are naturally-existing *β*-methoxyacrylate fungicides. These are two important classes of agricultural fungicides, because of their high efficacy, broad spectrum, low toxicity to mammalian cells, and environment friendly profile.[4-7] Their primary action mechanism is the inhibition of mitochondrial respiration. So far, thousands of analogues have been synthesized,[8-13] leading to more than 10 commercial products, such as including metominostrobin, azoxystrobin and so on (Figure 1). However, their derivatives rarely have insecticidal activity. Therefore, new types of strobilurins should be developed to overcome this problem.

A series of *O*-benzyl oxime-ethers (Figure 1) possessing remarkable insecticidal activity have been identified in our earlier work, but their fungicidal activity is weak.[14-18] Later, a series of *O*-benzyl oxime-ether compounds containing *β*-methoxyacrylate moiety with high fungicidal activity and certain insecticidal activity were synthsized.[19] This achievement encourages us to search for novel lead compounds with both insecticidal and fungicidal activities. To continue investigation on the design and synthesis of bioactive compounds (Figure 2), the target compounds **6a**–**6w** were designed by introducing the essential pharmacophore from the strobilurin fungicides into the *O*-benzyl oxime-ether scaffold to possess both insecticidal and fungicidal activities.

So this paper mainly reports the synthesis, fungicidal

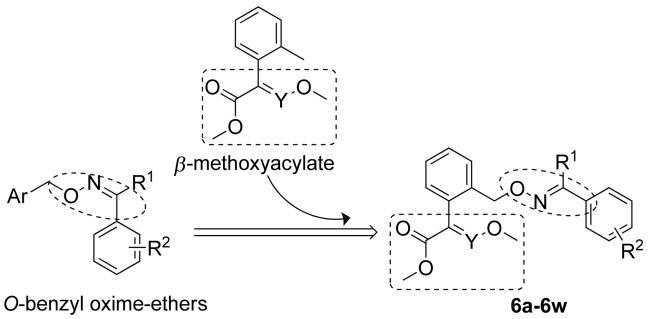


Figure 2. Design strategy of the title compounds.

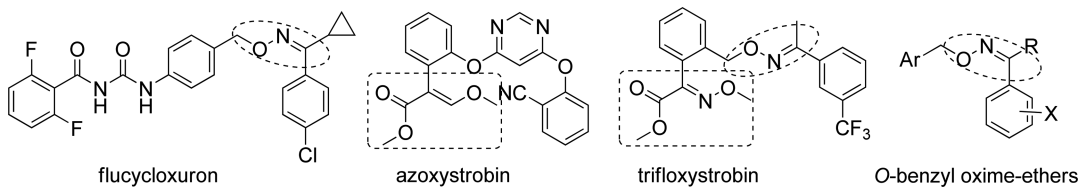


Figure 1. Structures of flucycloxuron, azoxystrobin, trifloxystrobin and *O*-benzyl oxime-ethers in our previous work.

acitivity, insecticidal activity, and the structure-activity relationship of *O*-benzyl Oxime-ether containing *β*-methoxyacrylate.

Experimental

Materials and Instruments. Unless otherwise noted, reagents and solvents were purchased from commercial suppliers. ^{1}H-NMR spectra were obtained with a Varian INOVA-300 spectrometer using tetramethylsilane (TMS) as the internal standard and deuterated chloroform ($CDCl_3$) as the solvent. Mass spectra (MS) were obtained with both Hewlett-Packard 6890-5973 GC/MS and Agilent 1100 Series LC/MS. Uncorrected melting points were taken on a WRS-1A digital melting point apparatus.

General Procedure for Synthesis of Target Compounds 6a–6g, 6j–6w. Intermediates **2**, **3**, **4** and **6** were prepared according to the reported methods.[19]

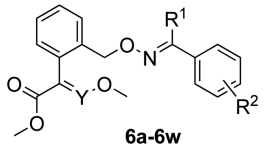
A solution of compound **4** (0.01 mol) in *N,N*-dimethylformamide (DMF) (3 mL) was added dropwise over a period of 0.5 h to a solution of KOH (0.84 g, 0.015 mol) in DMF (20 mL) at −5 to 0 °C. The mixture was stirred at −5 to 0 °C for 0.5 h and then a solution of compound **5** (0.01 mol) in DMF (3 mL) was added dropwise. The new mixture was stirred at 20-25 °C for 10-12 h, and then poured into ice-water and extracted with ethyl ether. The combined ether extracts were washed with water, dried (anhydrous magnesium sulfate) and filtered, and the solvent was removed. The residue was separated by silica gel column chromatography with petroleum ether-ethyl acetate (12:1, v/v) as eluent, and the yields of the target compounds were 22-53%.

6h and **6i** could be synthesized by the method described above from compound **2** instead of compound **4**.

Structures of **6a**–**6w** were supported by spectroscopic data shown in the supporting information.

Insecticidal Activity against *Aphis fabae* (*Bean Aphids*). The activity of compounds **6** against *A. fabae* (*Bean Aphids*) was evaluated according to the reported procedure.[20] *A. fabae* was dipped according to a slightly modified Food and Agriculture Organization (FAO) dip test. The tender shoots of soybean with healthy apterous third-instar nymphae were

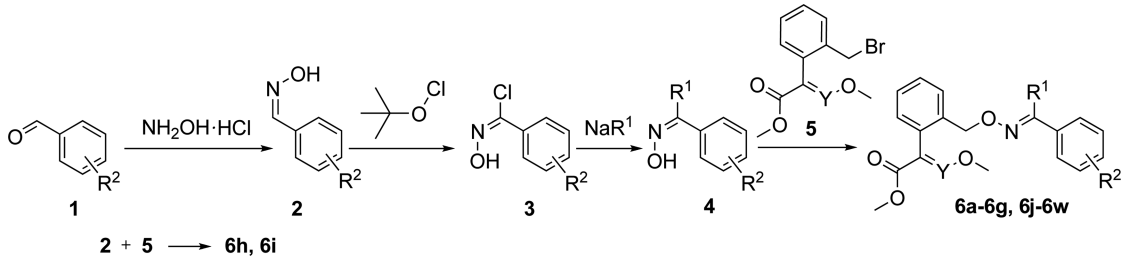
Table 1. Chemical structures, yield, fungicidal and insecticidal activities (%) of compounds **6a**–**6w**



6a-6w

No	Yield[a]	Y	R^1	R^2	*A. fabae* (mg/L)			*E. graminis* (mg/L)				
					500	100	LC_{50}	500	100	6.25	3.15	1.56
6a	28.3%	CH	SCH_3	4-OCF_3	100	100	4.4	100	50	20	NT[b]	NT
6b	32.8%	CH	SCH_2CH_3	4-OCF_3	65	NT	NT	80	NT	NT	NT	NT
6c	28.6%	CH	$SCH(CH_3)_2$	4-OCF_3	79	NT	NT	80	NT	NT	NT	NT
6d	29.5%	CH	OCH_3	4-OCF_3	100	100	6.4	100	100	100	95	90
6e	24.8%	CH	OCH_2CH_3	4-OCF_3	22	NT	NT	100	100	100	90	85
6f	22.5%	CH	$NHCH_3$	4-OCF_3	100	84	25.3	100	95	NT	NT	NT
6g	53.9%	CH	CN	4-OCF_3	0	NT	NT	95	80	NT	NT	NT
6h	39.4%	CH	H	4-OCF_3	17	NT	NT	100	90	NT	NT	NT
6i	38.5%	N	H	4-OCF_3	78	NT	NT	100	85	NT	NT	NT
6j	25.6%	N	SCH_3	4-OCF_3	86	NT	NT	100	85	NT	NT	NT
6k	24.5%	N	$SCH(CH_3)_2$	4-OCF_3	61	NT	NT	70	NT	NT	NT	NT
6l	32.9%	CH	SCH_3	4-F	100	61	NT	100	100	76	55	45
6m	37.1%	CH	SCH_2CH_3	4-F	100	58	NT	100	100	65	50	45
6n	26.0%	CH	$NHCH_3$	4-F	0	NT	NT	80	NT	NT	NT	NT
6o	29.6%	N	SCH_3	4-Cl	100	34	NT	95	80	25	NT	NT
6p	31.5%	CH	OCH_3	4-Cl	100	96	14.8	100	100	80	72	68
6q	25.3%	N	OCH_3	4-Cl	100	90	21.1	100	100	50	30	20
6r	28.0%	CH	OCH_3	4-CF_3	100	100	14.6	100	100	88	80	75
6s	31.9%	CH	OCH_3	3-CF_3	100	63	NT	100	100	100	100	92
6t	24.4%	N	OCH_3	3-CF_3	88	NT	NT	100	100	70	40.0	30
6u	36.3%	N	OCH_2CH_3	3-CF_3	100	60	NT	100	100	80	77	70
6v	26.0%	CH	SCH_2CH_3	3-CF_3	63	NT	NT	88	NT	NT	NT	NT
6w	35.7%	CH	SCH_3	3-CF_3	100	64	NT	100	100	80	75	70
			chlorfenapyr				19.4					
			imidacloprid				4.8					
			azoxystrobin					100	100	80	70	65

[a]Yield is determined after purification by column chromatography on silica gel. [b]Not tested.



Scheme 1. Synthetic pathways for the title compounds.

dipped into the diluted solutions of the compounds for 10 s, and the superfluous fluid was removed and the nymphae were placed in an air-conditioned room. Mortality was calculated 48 h after treatment. Each treatment was performed three times. Imidacloprid and chlorfenapyr were used as standards. The data for the mortality-regression lines of the compounds were used in probit analysis. The results of the median lethal concentrations (LC_{50}) of the derivative compounds, chlorfenapyr and imidacloprid against *A. fabae* are listed in Table 1.

Fungicidal Activity against *Erysiphe graminis*. The fungicidal activity of compounds **6** against *E. graminis* was evaluated according to the reported procedure.[19]

Results and Discussion

Synthesis. The synthetic route was shown in Scheme 1. Compund **2** was prepared starting from the substituted benzaldehyde **1** and hydroxylamine hydrochloride in methanol at reflux temperature in excellent yield, and then **2** reacted with *tert*-butyl hypochlorite in methanol at −5 to 0 °C to give **3**. The reaction of **3** with sodium alkoxide afforded corresponding intermediates **4**. Finally, the reaction of **4** with **5** in the presence of potassium hydroxide produced strobilurin derivatives **6a**–**6g** and **6j**–**6w**. Strobilurin derivatives of **6h** and **6i** were synthesized from **2** and **5** by the similar method. Their structures were confirmed by spectroscopy and LC-MS. Table 1 summarizes the chemical structures and yields of compounds **6a**–**6w**. Physical properties, MS and ^{1}H-NMR data are shown in the supporting information.

Insecticidal Activity. The activity of compounds **6** against *A. fabae* is shown in Table 1. The commercial insecticide chlorfenapyr and imidacloprid were used as standards.

Most of the target compounds **6** exhibited remarkable activity against *A. fabae*, some of them showed high insecticidal activity. For example, compounds **6a**, **6d**, **6f**, **6p**, **6q**, and **6r** possessed insecticidal activity 90% at 100 mg/L. Four compounds **6a**, **6d**, **6p** and **6r** exhibited promising lethal activity against *A. fabae*, with LC_{50} lower than 15 mg/L, which were better than chlorfenapyr (19.4 mg/L). In particular, compound **6a** owned the optimal LC_{50} of 4.4 mg/L, which was about equal to imidacloprid (4.48 mg/L).

Structure-Activity Relationship of Insecticidal Activity. Structural optimization of compounds **6** was carried out by modification of three primary substructures: R^1, R^2 and Y moieties. Variations of R^1, R^2 and Y moieties can significantly affect the insecticidal activity against *A. fabae* (Table 1).

Table 2. Preventive activities and curative actives of compounds **6d**, **6s** and azoxystrobin against *E. graminis* (14 d after treatment)

Method	Preventive activities		Curative activities	
Dose (mg/L)	EC_{50}	EC_{90}	EC_{50}	EC_{90}
6d	0.9	2.2	1.2	4.8
3 **6s**	1.0	2.4	1.1	2.6
azoxystrobin	1.7	7.0	1.7	5.9

When R^2 and Y were invariable, the insecticidal activity of the synthesized compounds **6** was influenced by the nature of group R^1. The modification of R^1 from electron-withdrawing group (CN, **6g**) to a hydrogen atom (**6h**) and then to electron-donating groups (*e.g.* SCH_3, **6a**; OCH_3, **6d**; NCH_3, **6f**) improved the insecticidal activity. When the methyl substituents in the heteroatoms of the R^1 group was changed to ethyl or isopropyl, the insecticidal activity of the corresponding compound decreased, for example, **6a** > **6b**, **6d** > **6e**, **6j** > **6k**, **6l** > **6m** and **6w** > **6v** (but **6u** < **6t**). The insecticidal activity of the corresponding compound decreased as **6a** > **6d** > **6f** and **6l** > **6n** when Y was kept as CH and R^2 was a moiety of *p*-substitute, but R^1 was changed from SCH_3 to OCH_3 and then to NCH_3. However, the insecticidal activity of **6s** was equal to **6w**'s when Y was kept as CH, R^2 was a moiety of *m*-substitute, and R^1 was changed from OCH_3 to SCH_3.

When R^1 and R^2 were kept unchangeably, the insecticidal activity of the synthesized compounds was influenced by group Y. When Y was varied from CH to N, the insecticidal activity of the corresponding compound decreased. It can be shown that **6a** > **6j**, **6p** > **6o**, **6s** > **6t**.

Similarily, the insecticidal activity of the synthesized compounds were also influenced by the nature of group R^2, when R^1 and Y were kept constant. The modification of R^2 from *m*-substitute to *p*-substitute increased the insecticidal activity, such as **6r** > **6s**. Additionally, the insecticidal activity of the corresponding compound decreased, When R^2 was changed from 4-OCF_3 to 4-CF_3, 4-Cl, or 4-F.

Overall, when R^1 was OCH_3 or SCH_3, most of the compounds had excellent insecticidal activity, particularly, **6a** and **6d** (Y is CH, R^2 is 4-OCF_3) possessed the optimal results.

Fungicidal Activity. Not only insecticidal activity but

also fungicidal activity is disscussed. Table 1 shows the preventive activity of compounds **6** against *E. graminis.* The commercial strobilurin fungicides azoxystrobin was used as standard.

As shown in Table 1, all the compounds **6** exhibited high fungicidal activity against *E. graminis*. In particular, **6a**, **6d**, **6e**, **6r**, **6s**, **6u** and **6w** showed fungicidal activity 80% at 6.25 mg/L, and **6d** and **6s** even had fungicidal activity 90% at 1.56 mg/L, while azoxystrobin only exhibited fungicidal activity of 65% at the same dose.

To further explore the more active compounds **6d** and **6s**, more accurate preventive and curative activities of **6d**, **6s** and azoxystrobin against were evaluated (Table 2). Clearly, **6d** and **6s** had higher preventive and curative activities than that of azoxystrobin.

Structure-Activity Relationship of Fungicidal Activity. Structural optimization of compounds **6** was also carried out by modification of three primary substructures: R^1, R^2 and Y moieties. Variations among R^1, R^2 and Y groups might greatly affect the fungicidal activity against *E. graminis* (Table 1).

Surprisingly, fungicidal activity and insecticidal activity have many similarities in structure-activity relationship: (1) When R^2 and Y were invariable, the modification of R^1 from electron-withdrawing group (CN, **6g**) to a hydrogen atom (**6h**) and then to electron-donating groups (*e.g.* SCH_3, **6a**; OCH_3, **6d**; NCH_3, **6f**) enhanced the fungicidal activity; (2) When the methyl substituents in the heteroatoms of the R^1 group was changed from methyl to ethyl or isopropyl, the fungicidal activity of the corresponding compound decreased; (3) When R^1 and R^2 were kept constant and Y was changed from CH to N, the fungicidal activity of the corresponding compound decreased.

However, fungicidal activity also had its peculiarity in structure-activity relationship: When R^2 and Y were kept constant, and R^1 was changed from OCH_3 to SCH_3 and then to NCH_3, the fungicidal activity of the corresponding compound decreased, for example, **6d** > **6a** > **6f**, **6q** > **6o**, **6s** > **6w**.

On the whole, when Y was CH and R^1 was OCH_3, most of the compounds also had good fungicidal activity, and especially, **6d** (R^2 is 4-OCF_3) and **6s** (R^2 is 3-CF_3) possessed the optimal results.

Conclusions

We successfully found that introduction of the β-methoxyacrylate pharmacophore lead *O*-benzyl oxime-ethers derivatives to exhibit both insecticidal and fungicidal activities. The insecticidal LC_{50} of the compounds **6a**, **6d**, **6p** and **6r** against *A. fabae* were 4.4, 6.4, 14.8 and 14.6 mg L^{-1}, respectively, which were all lower than that of chlorfenapyr (19.4 mg/L). In particular, compound **6a** possessed the optimal LC_{50} of 4.4 mg/L, which was about equal to imidacloprid (4.8 mg/L). Meanwhile, compound **6d** displayed high fungicidal activities in preventive and curative treatment against *E. graminis* with EC_{90} values of 2.2 and 4.8 mg/L, respectively, which were even better than that of azoxystrobin. These results indicate that **6d** can be used as a lead compound for further developing new *O*-benzyl oxime-ether type candidates with both fungicidal and insecticidal activities.

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