


Cite this: *RSC Adv.*, 2020, 10, 42804

The application of “plug-in molecules” method in novel strobilurin fungicides screening†

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Based on the “plug-in molecular” method, a series of novel strobilurin derivatives with aryloxy-pyridinyl-1-ethanone oxime side chains were designed, synthesized, and screened. The biological activity experiment showed that they had an excellent fungicidal effect on plant pathogens, especially *Sclerotinia sclerotiorum*. Compounds **5-01** and **5-09** had significant fungicidal activity and broad fungicidal spectrum. The structure–activity relationship indicates that the *cis* configuration, increasing the number of pharmacophores, substitution of the 2 position of the pyridine ring, and the introduction of chlorine atom on the benzene ring were not conducive to the fungicidal activity of such compounds. The model of 3D-QSAR indicated the introduction of large electropositive groups at the 4 position of the benzene ring and the introduction of small electronegative groups at the 2 position of the benzene ring were beneficial to the fungicidal activity, and compounds **6** were designed. Compared with azoxystrobin, compound **6-02** had a more effective fungicidal effect against *Sclerotinia sclerotiorum* (Lib.) de Bary. Cytotoxicity test and transmission electron microscopy showed that the modification of strobilurins fungicide by the “plug-in molecular” method would not affect its toxicity and mechanism. The “plug-in molecular” method is an efficient method for screening highly active compounds, which has important guiding significance for creating new pesticide molecules.

Received 18th July 2020
Accepted 5th November 2020

DOI: 10.1039/d0ra06263d

rsc.li/rsc-advances

Introduction

The “plug-in molecular” method is a new pesticide molecular design method proposed by Qin *et al.*¹ It is mainly to obtain high-frequency active groups through screening and design them as easily derived “molecular plug-in” and then through simple chemical reactions to derive various highly active compounds. Based on the excellent biological activity of diaryl ether and pyridine, a series of aryloxy-pyridine compounds (compounds **3**) has been designed and synthesized as “molecular plug-in” for deriving highly active compounds.

Diaryl ether compounds are a regular class of organic compounds with a wide range of biological activities such as insecticidal,² bactericidal,³ and herbicidal activities. The most famous of these is the diphenyl ether herbicide such as fomesafen.^{4,5} Diphenyl ether herbicides,⁶ a protoporphyrinogen oxidase (PPO) inhibitor,⁷ have the advantages of high efficiency, broad-spectrum and safety to crops and the environment, as well as occupy an extremely significant position in the herbicide market. Compared with herbicidal activity, people paid less attention to the fungicidal and insecticidal activities of these

compounds. However, due to its unique physical and chemical properties and biological activity, diaryl ethers have been widely used as active groups in pesticide creation.^{8–11} For example, the introduction of diphenyl ether structure in the alcohol part of pyrethroid solved the problem of poor light stability.¹² Moreover, the introduction of diphenyl ether structure in benzoylurea insecticides reduced the toxicity to 50% of the original.¹³ At present, the diaryl ether structure has been applied to various pesticide varieties such as pyrethroid insecticides, carbamate insecticides and triazole fungicides, and has been important biologically active groups in creating new pesticides.

With the development of heterocyclic compounds, replacing benzene with pyridine has become an important research direction.^{14,15} Compared with benzene, pyridine has a lower hydrophobic constant,¹⁶ and the compounds where the benzene ring was replaced by a pyridine ring, as well as had a higher biological activity or higher stability or higher selectivity or lower toxicity. For example, pyriofenone, a metrafenone analog, has excellent fungicidal activity, especially for *Botrytis cinerea*. Pyriprole, a fipronil analog, still has good insecticidal activity. Bicyclopyrone has a significant herbicidal activity after the introduction of a pyridine structure.¹⁷

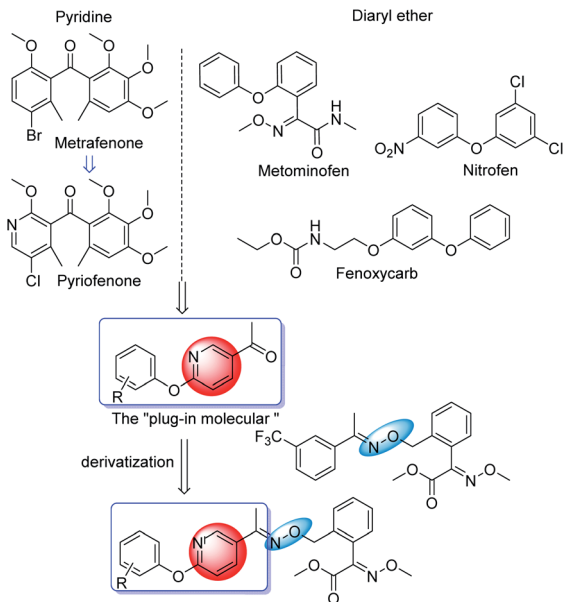
Strobilurins are a type of broad-spectrum fungicide, which has excellent fungicidal effects on almost all fungal diseases.^{18,19} Compared with other strobilurins, trifloxystrobin has the advantages of fast penetration, good systemic absorption, rapid distribution, resistance to rain washout, and long shelf life.^{20–23}

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra06263d

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Scheme 1 Strategies for the target compounds design.

To obtain highly active fungicides, a series of new compounds were synthesized by introducing the core structure of trifloxystrobin to the derivatize of the “plug-in molecular” of aryloxy pyridine (Scheme 1). Biological activity experiments showed that these compounds had excellent fungicidal activity.

Results and discussion

Chemistry

The synthetic route of targeted compounds **5** from commercially available starting materials is outlined in Scheme 2. As reported in the literature,^{24,25} precursor **4** was prepared from methyl (*E*)-2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate and *N*-hydroxyphthalimide by nucleophilic substitution and hydrazidation. The condensation reaction of compounds **3** and **4** formed a carbon–nitrogen double bond; however, due to the

steric hindrance, the products were mainly in *trans* configuration. Therefore, the targeted compounds **5** in this article were all in *trans* arrangement unless otherwise specified.

To explore the influence of configuration on the biological activity of compounds **5-26**, the *cis*-configuration compound **5-26b** was isolated and purified from the reaction system of compound **5-26**. The ¹H NMR spectra of compounds **5-26** (*E* configuration) and **5-26b** (*Z* configuration) displayed were not different, whereas the ¹³C NMR spectra showed a slight difference (Fig. S1†). In addition, the influence of the number of pharmacophores and the position of substituents on the pyridine ring with regards to the biological activity of the targeted compounds were studied, and the control drugs **5-01b** and **5-19b** were synthesized (Scheme 2b and S1†).

Structure–activity relationship (SAR)

A series of compounds were designed and synthesized by introducing the pharmacophore of strobilurins to the derivatize of the “molecular plug-in” of aryloxy pyridine by the “plug-in molecular” method, and their *in vitro* antifungal activities are shown in Tables 1 and 2. Targeted compounds **5** showed medium fungicidal activities against seven phytopathogens, except *Colletotrichum orbiculare* and *Rhizoctonia solani*, which was consistent with the lead compound trifloxystrobin. Most of these compounds had an excellent fungicidal activity to *Sclerotinia sclerotiorum*, and the inhibition rate was more than 90% at 50 μg mL^{−1}. Compounds **5-01**, **5-06**, **5-09** and **5-14** had a broad fungicidal spectrum and showed good fungicidal activity against *Rhizoctonia solani*, *Phytophthora infestans* (Mont.) de Bary (*Phytophthora infestans*), *Pycularia grisea*, *Botrytis cinerea*, and *Pythium aphanidermatum*. The fungicidal activity of compound **5-01b** was significantly lower than that of the other 4-substituted compounds, indicating that increasing the number of methoxyacrylate pharmacophores was detrimental to the fungicidal activity of these compounds (Fig. 1A). No significant difference of fungicidal activity between compounds **5-19** and **5-19b** was observed, which indicated that

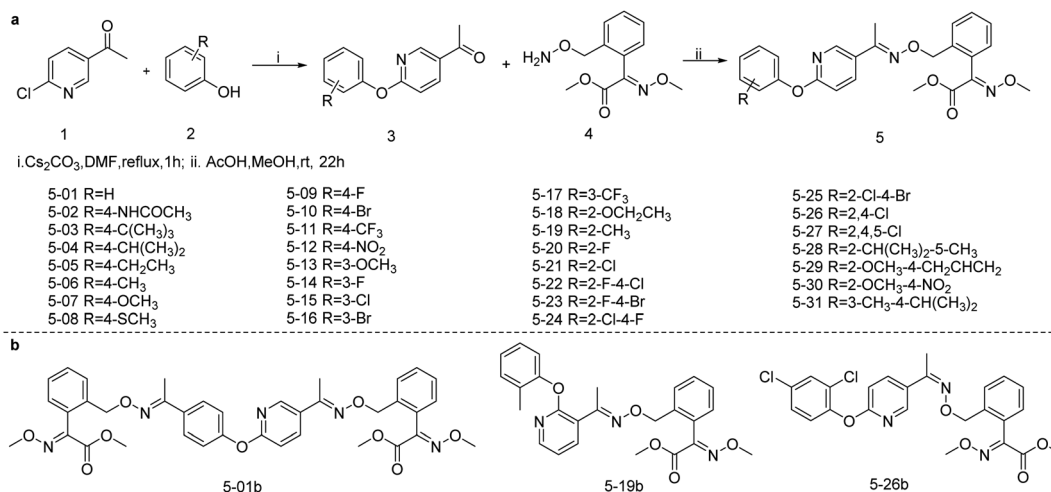
Scheme 2 Preparation of target compounds **5** (a) and control compounds (b).

Table 1 *In vitro* antifungal activity of the target compounds 5 against seven phytofungi (50 $\mu\text{g mL}^{-1}$)^a

Mycelium growth inhibitory rate (%) at 50 $\mu\text{g mL}^{-1}$								Mycelium growth inhibitory rate (%) at 50 $\mu\text{g mL}^{-1}$							
Compd	SS	BC	PI	PA	RS	PG	CO	Compd	SS	BC	PI	PA	RS	PG	CO
5-01	94.18	62.64	54.81	63.07	40.63	55.94	34.70	5-19	95.77	56.90	50.03	49.44	33.85	43.85	27.33
5-02	74.67	46.38	58.06	64.02	36.67	65.63	42.65	5-20	85.33	47.83	51.13	45.12	44.17	48.44	33.82
5-03	84.66	42.07	40.46	45.00	30.21	36.90	22.06	5-21	78.67	56.52	54.84	49.24	36.67	56.25	44.12
5-04	87.83	42.53	42.05	45.83	31.25	41.71	22.59	5-22	92.06	45.98	48.43	48.89	35.42	40.64	20.48
5-05	94.18	48.28	44.18	52.33	37.50	41.18	24.17	5-23	88.36	47.70	48.96	45.28	35.42	39.04	22.06
5-06	96.00	60.72	61.61	45.12	43.33	42.19	33.82	5-24	53.33	63.77	54.84	48.93	38.33	51.56	42.65
5-07	89.42	56.32	49.50	53.89	35.94	48.66	27.86	5-25	89.95	40.23	45.77	43.33	33.85	41.71	19.96
5-08	91.53	47.70	44.18	45.56	33.85	47.59	27.33	5-26	92.06	54.02	43.65	42.78	35.42	37.43	19.96
5-09	95.24	63.79	48.96	59.73	35.94	54.45	27.33	5-27	95.24	37.93	39.39	43.89	31.77	42.25	27.33
5-10	69.33	46.38	56.45	46.65	33.33	46.88	33.82	5-28	52.00	36.23	48.39	46.65	29.50	50.00	37.35
5-11	93.12	44.83	44.71	48.33	36.46	45.45	26.80	5-29	57.33	34.78	50.00	48.02	36.17	50.00	48.53
5-12	80.95	51.15	46.84	46.11	31.25	41.18	28.38	5-30	86.67	43.48	45.16	39.02	31.17	39.06	29.41
5-13	96.00	49.28	46.77	48.17	30.67	45.31	22.06	5-31	93.65	44.31	39.39	45.28	31.25	39.57	20.06
5-14	92.93	60.07	50.00	50.76	35.00	58.75	41.18	5-01b	51.85	30.46	36.20	39.45	26.04	39.57	31.02
5-15	96.83	48.28	45.24	50.00	31.77	42.25	24.70	5-19b	82.03	35.78	41.95	47.89	32.57	43.89	20.05
5-16	94.67	44.93	46.77	43.60	25.00	43.75	20.59	5-26b	56.08	47.70	42.05	45.00	27.60	35.29	20.48
5-17	93.33	42.03	46.77	42.68	28.33	40.63	26.47	Trifloxystrobin	100.00	70.12	52.68	63.33	40.63	62.78	24.17
5-18	46.67	56.52	54.84	54.88	39.50	55.31	49.12								

^a SS = *Sclerotinia sclerotiorum*; BC = *Botrytis cinerea*; PI = *Phytophthora infestans*; PA = *Pythium aphanidermatum*; RS = *Rhizoctonia solani*; PG = *Pyricularia grisea*; CO = *Colletotrichum orbiculare*.

the position of the substituent on the pyridine ring had no significant effect on the activity of these compounds (Fig. 1B). Compared with the *trans*-configuration compound 5-26, the *cis*-configuration compound 5-26b had lower fungicidal activity, especially against *Sclerotinia sclerotiorum*. For *Sclerotinia sclerotiorum*, the inhibition rate of compound 5-26 could reach 92%, and the inhibition rate of compound 5-26b was only 56% (Fig. 1C).

To further study the activities of the targeted compounds against *Sclerotinia sclerotiorum*, the EC₅₀ values of all the

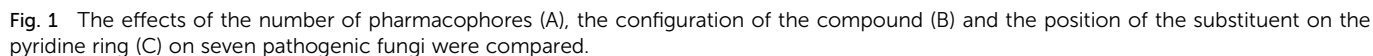
targeted compounds were tested. The number of substituents had a significant influence on the activity of the compounds. The reaction of bi-substituted compounds was worse than that of monosubstituted compounds, and the compounds containing two-electron substituents had the worst combination such as 5-28, 5-29, and 5-31. For monosubstituted compounds, the position of the substituent had no significant effect on the activity. Introducing a large substituent at the 3-position of the benzene ring instead of the 2-position was beneficial to the fungicidal activity of the compound. For the four substituted

Table 2 Experimental and predicted pEC₅₀ value of target compounds 5 against *Sclerotinia sclerotiorum*

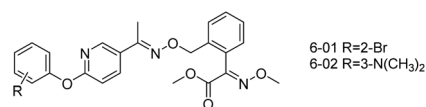
Compd	EC ₅₀ ($\mu\text{g mL}^{-1}$)	95% FL ($\mu\text{g mL}^{-1}$)	pEC ₅₀	Predicted pEC ₅₀		Compd	EC ₅₀ ($\mu\text{g mL}^{-1}$)	95% FL ($\mu\text{g mL}^{-1}$)	pEC ₅₀	Predicted pEC ₅₀	
				CoMFA	CoMSIA					CoMFA	CoMSIA
5-01	3.25	1.23–8.89	5.125	5.335	5.371	5-17	2.28	1.29–3.87	5.342	5.318	5.346
5-02	30.65	14.35–55.32	4.204	4.274	4.369	5-18	56.97	38.89–91.20	3.923	3.862	3.833
5-03	1.35	0.61–2.56	5.560	5.531	5.551	5-19	0.90	0.58–1.32	5.697	4.814	4.993
5-04	2.11	0.82–4.90	5.353	5.423	5.612	5-20	1.43	0.78–2.38	5.499	5.342	5.318
5-05	1.06	0.56–1.75	5.639	5.702	5.660	5-21	4.91	2.25–8.50	4.979	4.972	5.294
5-06	0.47	0.18–0.92	5.979	5.788	5.546	5-22	2.05	1.32–3.09	5.375	5.557	5.416
5-07	2.20	1.23–3.82	5.324	5.323	5.339	5-23	1.18	0.28–3.07	5.653	5.599	5.391
5-08	1.37	0.75–2.27	5.544	5.516	5.462	5-24	32.65	11.32–54.68	4.173	4.244	4.343
5-09	1.44	0.75–2.48	5.496	5.405	5.441	5-25	8.32	4.57–18.90	4.818	4.849	4.887
5-10	1.08	0.11–3.11	5.676	5.662	5.414	5-26	1.33	0.36–3.35	5.577	5.224	5.365
5-11	2.17	0.95–4.60	5.364	5.790	5.591	5-27	3.60	1.66–8.55	5.174	5.123	5.289
5-12	0.81	0.42–1.21	5.771	5.709	5.765	5-28	84.58	37.32–170.71	3.763	3.859	3.996
5-13	4.14	1.38–7.59	5.049	5.056	5.063	5-29	15.62	7.14–33.30	4.508	4.588	4.568
5-14	0.87	0.14–3.47	5.715	5.691	5.644	5-30	0.85	0.40–1.51	5.750	5.806	5.717
5-15	17.21	6.52–36.06	4.434	5.277	5.284	5-31	11.42	5.81–31.89	4.632	5.564	5.754
5-16	2.63	1.34–8.70	5.290	5.300	5.300	Trifloxystrobin	0.14	0.06–0.27	— ^a	—	—

^a Not determined.





Based on the analysis results of the above structure–activity relationship, some model compounds were designed. Their potential activities were predicted with the built QSAR models,



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Table 3 Predicted pEC₅₀ and actual fungicidal activity of ideal high-activity compounds **6** against *Sclerotinia sclerotiorum*

Compd	Predicted data		Measured data		
	CoMFA	CoMSIA	EC ₅₀ (μg mL ⁻¹)	95% FL (μg mL ⁻¹)	pEC ₅₀
5-06	5.788	5.546	0.47	0.18–0.92	5.979
6-01	5.843	5.781	0.68	0.17–1.50	5.877
6-02	6.686	6.539	0.08	0.01–0.23	6.775
Azoxystrobin	— ^a	—	0.79	0.45–1.44	—

^a Not determined.

Table 4 *In vitro* antifungal activity of the predicted compounds **6** against seven phyto-fungi (50 μg mL⁻¹)^a

Compd	Mycelium growth inhibitory rate (%) at 50 μg mL ⁻¹						
	SS	BC	PI	PA	RS	PG	CO
5-06	96.00	60.72	61.61	45.12	43.33	42.19	33.82
6-01	76.00	42.03	56.45	47.71	39.50	48.44	43.68
6-02	97.35	55.17	68.43	50.83	34.90	68.44	29.44
Azoxystrobin	97.88	81.61	58.53	61.67	41.15	64.39	38.92

^a SS = *Sclerotinia sclerotiorum*; BC = *Botrytis cinerea*; PI = *Phytophthora infestans*; PA = *Pythium aphanidermatum*; RS = *Rhizoctonia solani*; PG = *Pyricularia grisea*; CO = *Colletotrichum orbiculare*.

two compounds (compounds **6-01** and **6-02**) with better activity were selected for synthesis (Scheme 3 and S2†). The predicted data and experiment data of compounds **6** are shown in Table 3. Among them, compound **6-02** had a more excellent fungicidal effect on *Sclerotinia sclerotiorum* than compound **5-06**. The EC₅₀ value of compound **6-02** was 0.08 μg mL⁻¹, which was ten times lower than the commercial drug azoxystrobin (EC₅₀ = 0.79 μg mL⁻¹). Not only that, compounds **6-01** and **6-02** had a broad fungicidal spectrum and had a good inhibitory effect on seven plant pathogens at 50 μg mL⁻¹ (Table 4).

In addition, to screen the activities of the compounds, five compounds were selected for precise virulence measurements for six phyto-fungi, and their EC₅₀ values are shown in Table 5. These compounds had good antifungal activity on *Botrytis cinerea*, *Phytophthora infestans*, *Pythium aphanidermatum* and

Pyricularia grisea, especially on *Pyricularia grisea*. Among them, the EC₅₀ value of compound **5-01** against the four phytopathogens was generally <20 μg mL⁻¹. This indicated that compound **5-01** had a broader and better fungicidal spectrum than others. The EC₅₀ value of compound **5-09** against *Botrytis cinerea* was 6.59 μg mL⁻¹, which was better than that of commercial agents. The EC₅₀ values of compounds **5-01**, **5-06** and **6-02** against *Phytophthora infestans* were 17.29, 21.49 and 12.60 μg mL⁻¹, which were better than trifloxystrobin. The EC₅₀ values of compounds **5-01** and **5-09** against *Pythium aphanidermatum* were 18.14 and 20.30 μg mL⁻¹, respectively, which were better than azoxystrobin. The EC₅₀ values of compounds **5-06** and **6-02** against *Pyricularia grisea* were 8.42 and 6.86 μg mL⁻¹, which were comparable to those of control drugs.

To further verify the potential of the targeted compound as a commercial drug, we first assessed the potential cytotoxicity of **5-01** and **6-02** through CCK-8 assays. Hela cells were exposed to **5-01** or **6-02** for 24 h. Consistent with strobilurins fungicides, compounds **5-01** and **6-02** showed low cytotoxicity. At a dose of 100 μg mL⁻¹, compound **5-01** reduced cell viability to 52% of the control group. However, compound **6-02** showed significantly less cytotoxicity, *i.e.*, 100 μg mL⁻¹ dose showed ~92% cell viability (Fig. S4†). Moreover, the results of transmission electron microscopy showed that the mitochondria of *Sclerotinia sclerotiorum* mycelium were damaged when exposed to compound **5-01** at a dose of 50 μg mL⁻¹ (Fig. S5†). These results indicate that the compounds were expected to become potential fungicides, and the modification of strobilurins fungicide by the “plug-in molecular” method improves the activity of the compound without affecting its toxicity and mechanism.

Conclusions

A series of new compounds were synthesized by introducing the strobilurins pharmacophore to the derivatize of the “plug-in molecular” of aryloxy pyridine, and their antifungal activity experiments showed that they had excellent control effects on plant pathogens, especially on *Sclerotinia sclerotiorum*. The results of control experiments showed that the *trans* configuration of the compounds had superior fungicidal effects. Furthermore, the introduction of more pharmacophores in the compound or substitution at the 2-position of the pyridine ring rather than the 6-position were all not conducive to their fungicidal activities. The 3D-QSAR models indicated that large

Table 5 EC₅₀ values of target compounds **5** and predicted compounds **6** against six fungi (μg mL⁻¹)^a

Compd	BC	PI	PA	RS	PG	CO
5-01	14.16	17.29	18.14	>200	10.10	>200
5-06	20.57	21.49	131.90	>200	8.42	>200
5-09	6.59	72.75	20.30	>200	23.14	>200
5-14	23.61	63.29	63.13	>200	15.28	>200
6-02	29.66	12.60	43.92	>200	6.86	>200
Azoxystrobin	12.26	9.11	21.37	97.78	4.20	130.55
Trifloxystrobin	13.38	17.07	7.34	>200	3.35	>200

^a BC = *Botrytis cinerea*; PI = *Phytophthora infestans*; PA = *Pythium aphanidermatum*; RS = *Rhizoctonia solani*; PG = *Pyricularia grisea*; CO = *Colletotrichum orbiculare*.



electropositive groups were introduced into the 3 position and 4 position of the benzene rings, as well as a small electronegative group that was introduced into the 2 position of the benzene rings was beneficial to the fungicidal activity of the compounds. Based on this, the structures of high activity compounds were obtained. The result of the experiment indicated that predicted compounds **6-01** did show excellent fungicidal activity, and its fungicidal activity on *Sclerotinia sclerotiorum* was even ten times that of azoxystrobin while maintaining low cytotoxicity. Compounds **5-01** and **5-09** showed better fungicidal activity than the commercial drugs on some plant pathogens, highlighting that they might be potential fungicidal candidates. In general, it is feasible to obtain highly active compounds through the “plug-in molecular” method, which has important guiding significance for creating new pesticide molecules.

Experimental

Instrumentation and materials

^1H NMR and ^{13}C NMR spectra were obtained at 300 MHz using a Bruker Avance DPX300 spectrometer in CDCl_3 or $\text{DMSO}-d_6$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. High-resolution mass spectrometry data were obtained with an Accurate-Mass-Q-TOF MS 6520 system equipped with an electrospray ionization (ESI) source. Melting points were determined with a Cole-Parmer microscope melting point apparatus and were uncorrected. All reagents and solvents were commercially available and used directly without further purification. (*E*)-Methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino)acetate was obtained from Jiangsu Freychem Co. Intermediates **3** and **4** was synthesized according to literature reports. Experimental details are shown in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21877125).

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