Bioorganic & Medicinal Chemistry Letters 24 (2014) 2173–2176

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and fungicidal activities of novel benzothiophene-substituted oxime ether strobilurins

Song Tu *, Ya-Qiang Xie, Si-Zhe Gui, Li-Yi Ye, Zi-Long Huang, Yi-Bing Huang, Li-Ming Che

Department of Chemical and Biochemical Engineering, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, People's Republic of China

ARTICLE INFO

Article history:
Received 28 January 2014
Revised 6 March 2014
Accepted 8 March 2014
Available online 26 March 2014

Keywords:
Benzothiophene
Oxime ether
Strobilurins
Fungicide
Fungicidal activities

ABSTRACT

Twenty-one novel benzothiophene-substituted oxime ether strobilurins, which employed a benzothiophene group to stabilise the *E*-styryl group in Enoxastrobin (an unsaturated oxime strobilurin fungicide developed by Shenyang Research Institute of Chemical Industry, China) were designed and synthesised. The biological assay indicated that most compounds exhibited good or excellent fungicidal activities, especially against *Colletotrichum lagenarium* and *Puccinia sorghi* Schw. In addition, methyl 3-methoxypropenoate oxime ethers and *N*-methoxy-carbamic acid methyl esters exhibited good in vivo fungicidal activities against *Erysiphe graminis*, *Colletotrichum lagenarium* and *Puccinia sorghi* Schw. under the tested concentrations. Notably, (*E*,*E*)-methyl 3-methoxy-2-(2-((((6-chloro-1-(1*H*-benzo[*b*]thien-2-yl)ethylidene)amino)oxy)methyl)phenyl)propenoate (**5E**) exhibited more potent in vivo fungicidal activities against nearly all of the tested fungi at a concentration of 0.39 mg/L compared to Enoxastrobin.

Strobilurins are naturally occurring derivatives of β-methoxyacrylic acid that comprise an important class of agricultural fungicides.[1–4] However, these compounds are natural, and they could not be used directly due to insufficient photochemical stability and volatility.[2,5] To date, several chemists have published synthetic analogues of strobilurin **A** (Fig. 1) to stabilise the triene structure of the compound.[6–14]

Compounds **I** (Fig. 1), which were discovered by the Rohm and Haas Company [the 4-Cl-substituted derivatives of compounds **I** were developed by Shenyang Research Institute of Chemical Industry and named Enoxastrobin (Fig. 1)[10]], contain an unsaturated oxime ether group and exhibit effective fungicidal activities.[7] In addition, novel arylcyclopropyl oxime ether compounds **II** (Fig. 1), which replace the *E*-styryl group in compounds **I** with a *trans*-arylcyclopropyl group, have been reported. These compounds exhibit excellent fungicidal activities.[8] In our previous study, we synthesised a series of novel indene–substituted oxime ethers **III** (Fig. 1) to study the structure–activity relationships of this type of compound.[12,15] A benzopentatomic ring structure was used to stabilise the *E*-styryl group in Enoxastrobin. Most of the indene–substituted oxime ethers (**III**) exhibited effective fungicidal activity. In addition, the fungicidal activities of some compounds (**III**) were better than those of Enoxastrobin.

Many heterocyclic compounds have shown good insecticidal or fungicidal activities, increasing their importance in pesticide discovery.[16–21] The heterocyclic scaffold of a crop protection agent often has a positive effect on its synthetic accessibility and its physicochemical properties, driving values, such as lipophilicity and solubility toward the optimal balanced range for uptake and bioavailability.[16] Heterocycles are deemed to be perfect bioisosteres of other carba- or heterocyclic rings as well as of several different functional groups which deliver equal or even better biological efficacy through their similarity in structural shape and electronic distribution.[16,20] In addition, the substitution of a heteroaryl group (i.e., pyridine or furane) with one of the aryl residues of the compound results in increased biological activity.[21] More importantly, environmental compatibility of the synthesised organic compounds is enhanced when heteroatoms are introduced into the carba-rings.[16,19,20]

Based on these facts, a series of novel benzothiophene-substituted oxime ethers **5** (Fig. 1) utilising a benzothiophene group as a bioisostere to replace the *E*-styryl group in Enoxastrobin was synthesised in this Letter. The target compounds (**5**) were predicted to retain or further enhance their biological activity and simultaneously improve their environmental compatibility. The structure–activity relationship of this type of compound was also studied. The biological assay indicated that most compounds (**5**) maintained or enhanced their fungicidal activities compared to Enoxastrobin.

The synthetic route for the target compounds is outlined in Scheme 1, and the reaction yields were not optimised.

The 2-(ethylthio)-benzaldehyde intermediates (**2**) were prepared according to a previously published protocol.[22] the

* Corresponding author. Tel./fax: +86 592 2183751.
E-mail address: tusong@xmu.edu.cn (S. Tu).

http://dx.doi.org/10.1016/j.bmcl.2014.03.024
0960-894X/

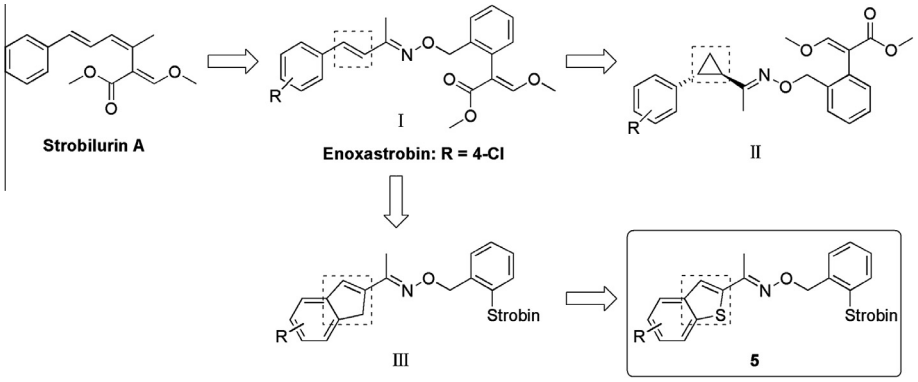


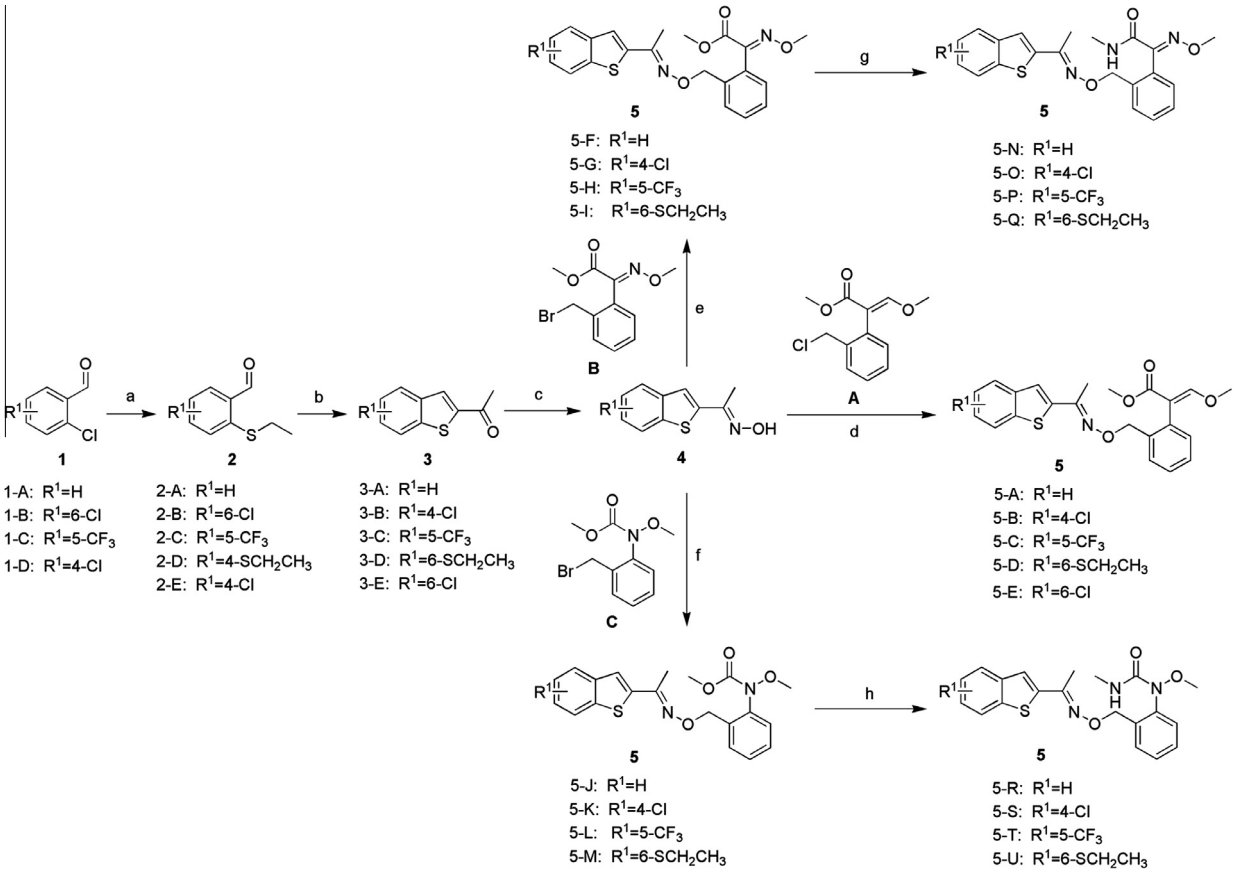
Figure 1. Structure of strobilurin **A** and its analogues.

2-chlorobenzaldehydes (**1**) were reacted with 1.4 equiv of ethanethiol in the presence of 1.4 equiv of sodium hydroxide and 0.03 equiv of tetrabutylammonium bromide at 82 °C for 4.0–6.0 h to afford 2-(ethylthio)-benzaldehydes (**2A**, **2B**, **2C** and **2E**). 2,4-Dichlorobenzaldehyde was reacted with 2.8 equiv of ethanethiol in the presence of 2.8 equiv of sodium hydroxide and 0.06 equiv of tetrabutylammonium bromide at 82 °C for 2.5 h to yield 2,4-bis(ethylthio)benzaldehyde (**2D**). When 2,4-dichlorobenzaldehyde (R^1 = 4-Cl) was used to synthesis **2E**, significant byproduct, presumably from the reaction of 4-Cl in 2,4-dichlorobenzaldehyde with ethanethiol, made isolation of the product difficult. Due to the low yielding nature of this reaction and difficulties with purification, only one derivative where R^1 = 6-Cl (**5E**) were synthesized.

Second, according to the literature,[22] the 2-(ethylthio)-benzaldehydes (**2**) were reacted with 1.25 equiv of 1-chloropropan-2-one in the presence of 1.25 equiv of potassium carbonate at 59 °C to afford 1-(benzo[*b*]thiophen-2-yl)ethanones (**3**) in good yields.

Then, according to a previously described method,[23] the 1-(benzo[*b*]thiophen-2-yl)ethanones (**3**) were reacted with 1.5 equiv of hydroxylamine hydrochloride and 1.5 equiv of sodium acetate trihydrate in the presence of a 2:1 (v/v) mixture of ethanol and water under reflux to produce (*E*)-1-(1*H*-benzo[*b*]thien-2-yl)ethanoneoximes (**4**) in high yields.

Next, the target compounds (**5A**–**M**) were obtained by reaction of ethanone oximes (**4**) with (*E*)-methyl 2-(2-(chloromethyl)phenyl)-3-methoxypropenoate (**A**), (*E*)-methyl 2-(2-(bromomethyl)



Scheme 1. General synthetic route for the target compounds **5**. Reagents and conditions: (a) NaOH, H_2O, tetrabutylammonium bromide, ethanethiol, 82 °C, 4.0–6.0 h; (b) 1-chloropropan-2-one, CaO, acetone, 59 °C, 10.0–14.0 h; (c) hydroxylamine hydrochloride, sodium acetate, 2:1 (v/v) mixture of ethanol and H_2O, reflux, 0.5–9.5 h; (d–f) K_2CO_3, anhydrous acetonitrile, reflux, 5.0–14.5 h; (g and h) CH_3NH_2, methanol, reflux, 0.5–18.0 h.