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RESEARCH ARTICLE

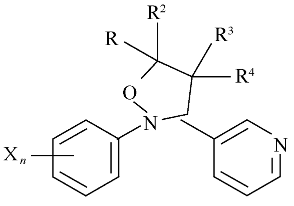
**Cheng Chunsheng, Li Zhinian, Shu Jinyan, Li Tao,
Zhang Baoyan**

Synthesis of isoxazolidines by 1,3-dipolar cycloaddition and their bioactivity

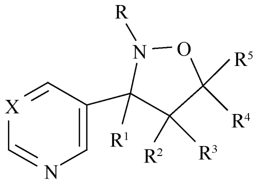
Abstract A series of new isoxazolidines was prepared by 1,3-dipolar cycloaddition of different mono-substituted styrenes with 1,3-dipolar compounds that were prepared by the reaction of *N*-methylhydroxylamine sulfate with aromatic carbonyl substances. This synthetic pathway for the preparation of isoxazolidines was an ideal process of green chemistry. The synthetic products were 5-substituted isoxazolidines and their structures were characterized by mass and NMR (^{1}H-, ^{13}C-, COSY, HSQC, and DEPT) spectrometry, and their bioactivity was investigated indicating that some new compounds inhibited *Botrytis cinerea* effectively.

Keywords 1,3-dipolar cycloaddition, isoxazolidine, NMR, MS, bioactivity

Isoxazolidines are very useful organic compounds because of their application as medicines or insecticides. Besides, they provide a convenient path for the synthesis of natural base and natural compounds containing N and O atoms in the molecules. Thus, they can be used as intermediates to synthesize natural base. For example, compounds A and B being possibly used as fungicide were synthesized by Clive B.C. Boyce et al. in 1979 [1] and Lixin Zhang et al. in 1999 [2], respectively.



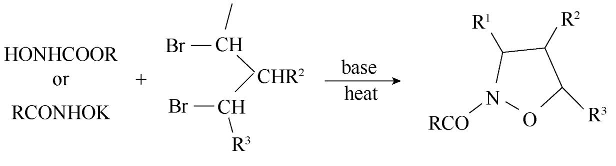
A



B

There are three methods for the synthesis of isoxazolidines.

(1) The method for the synthesis of *N*-unsubstituted isoxazolidines in very early times involves the reaction of *N*-hydroxyurethanes or hydroxamic acids and their salts with 1,3-dihalo compounds in an alkaline medium (Scheme 1). This reaction is especially valuable for the synthesis of 3- or 5-mono-, and 3,5-disubstituted isoxazolidines, but the yields were not high [3, 4, 5].



Scheme 1

(2) 1,3-Dipolar cycloaddition of 1,3-dipoles with olefins represents the main method of isoxazolidine synthesis of green chemical reactions [6] (Scheme 2). Nitrones are perhaps the most extensively studied 1,3-dipoles and can be prepared by condensation of aldehydes or ketones with *N*-monosubstituted hydroxylamines. 5-Substituted stereoisomeric isoxazolidines were obtained when nitrones reacted with mono-substituted olefins [7].

(3) Isoxazolidinium salts can be prepared by intramolecular cyclization of long chain nitrones that are obtained by oxidation of tertiary amines with peracetic acid (Scheme 3), but this method is rarely used [8].

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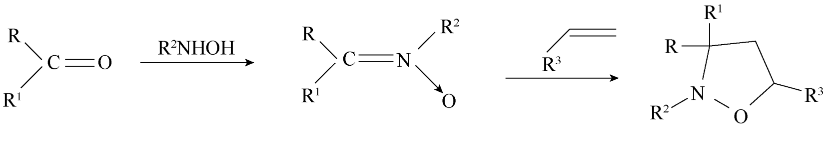
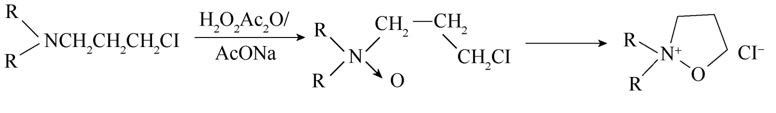
Cheng Chunsheng, Zhang Baoyan(✉)
School of Sciences, Northeastern University, Shenyang 110004, China
E-mail: chunshengcheng@163.com

Cheng Chunsheng, Li Zhinian, Shu Jinyan, Li Tao
Shenyang Research Institute of Chemical Industry,
Shenyang 110021, China



Scheme 2



Scheme 3

In the present study, a series of new isoxazolidinium compounds was synthesized by method (2). Most of the nitrone and olefin intermediates were also synthesized in our laboratory [9]. The chemical structures of these products were characterized by IR, NMR, and mass spectra and their bioactivity was investigated revealing that some new isoxazolidinium compounds inhibited *Botrytis cinerea* effectively.

1 Experimental

1.1 Reagents

C,*N*-dimethyl-C-benzyl-nitrone(97.5%)[9],*C*,*N*-dimethyl-*C*-(*p*-chloro-benzyl)-nitrone(98.1%)[9],*N*-methyl-*C*-(*p*-methoxy-benzyl)-nitrone(98.0%)[9], *p*-chloro-vinylbenzene (98%) [10], *m*-nitro-vinylbenzene (98%)[10], *m*-methoxy- vinylbenzene (98%)[10], 4-pyridyl-ethylene (98%) [10] were prepared according to reported methods [9, 10]. Toluene (99.5%) and benzene (99.5%) were obtained from comercial production.

1.2 General procedures

^{1}H-NMR and ^{13}C-NMR spectra were measured on a BRUKER ARX-300 spectrometer with tetramethylsilane as internal standard. Chemical shifts are reported in δ.

The purity of the products was determined by HPLC with a UV detector and an ODS (C18 5 μm) 250 mm × 4.6 mm (i.d.) column.

Mass spectra were recorded on an LC-MSD-Trap-SL mass spectrometer.

Elemental analyses were recorded on an EA-1108 instrument.

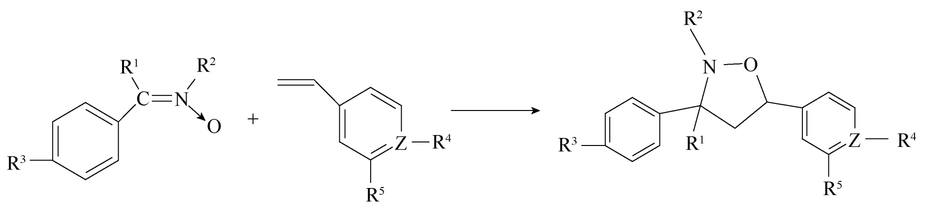
1.3 The synthesis of isoxazolidinium compounds [11–15]

A series of new isoxazolidines was prepared as shown in Table 1 by the following reaction (Scheme 4).

Table 1 The list of different compounds

Item	Compound	R^1	R^2	R^3	R^4	R^5	Z
I	a	CH_3	CH_3	H	Cl	H	C
	b			Cl	Cl	H	
	g			Cl	H	OCH_3	
	f			H	H	H	N
II	j	CH_3	CH_3	Cl	H	NO_2	C
	h			Cl	H	H	
	i			NO_2	H	H	N
III	c	H	CH_3	OCH_3	H	H	N
	d				Cl	H	C
	e				H	OCH_3	

General synthetic method A: To a stirred solution of *p*-tertbutyl-pyrocatechol (2 mg) in toluene (30 mL), nitrone (0.02 mol) was added. After heating to reflux, mono-substituted styrenes (0.021 mol) were added within 15 min. Reflux was maintained for 6–8 h, the reaction was finished as indicated by the <1% content of nitrone analyzed by HPLC. The mixture was cooled down to room temperature and washed with aqueous $NaHCO_3$ (2%) for two times. The organic layer was separated and aqueous HCl (20 mL, 10%) was added. Aqueous phase was separated and neutralized with aqueous NaOH (30%) to pH 10–11. The mixture was extracted with toluene and combined organic layers were concentrated. The residue was purified by column chromatography on silica gel or recrystalizing with petroleum ether to give the products.



Scheme 4

1.3.1 a: 2,3-Dimethyl-3-benzyl-5-(p-chloro)benzylisoxazolidine

Pale yellow crystals 5.3 g (95.8%), yield: 88.3%. m.p. 45-52°C, ^{1}H-NMR (CDCl$_3$, 300MHz):δ1.558, 1.608 (2S, 3H), 2.618, 2.624 (2S, 3H), 2.329, 2.922 (2m, 1H), 2.827, 2.577 (2m, 1H), 5.237, 5.071 (2q, 1H), 7.2–7.5(m, 9H). ^{13}C-NMR (CDCl$_3$, 300 MHz): 22.57, 38.87, 51.58, 69.07, 77.96, 126.25, 126.86, 127.42, 128.18, 128.43, 133.02, 139.92, 144.45. IR(KBr): 3000, 2940, 1500, 1100, 920, 710 cm^{-1}. MS *m/z* (%): 288 ([M^{+}+1], 100), 268(4), 241(4), 170(12), 150(3).

1.3.2 b: 2,3-Dimethyl-3,5-di (p-chloro)benzyl isoxazolidine

Yellow crystals 7.3 g (80.1%), yield: 90.8%. The product was purified and separated by column chromatography on silica gel to give endo- and exo- isomers.

For endo-isomer: pale yellow crystals 2.6g, m.p.83−84°C, ^{1}H-NMR(CDCl$_3$, 300 MHz): δ 1.52 (S, 3H), 2.61 (S, 3H), 2.30 (q, *J* = 8.1 Hz, 12.6 Hz, 1H), 2.92 (q, *J* = 7.8 Hz, 12.6 Hz, 1H), 5.00 (t, *J* = 8.1 Hz, 1H), 7.31 (S, 4H), 7.33 (m, 2H), 7.53(m, 2H)

^{13}C-NMR(CDCl$_3$, 300 MHz): 22.2, 39.0, 51.7, 68.8, 78.2, 127.5, 127.8, 128.4, 128.6, 132.8, 133.3, 139.7, 143.2. For exo-isomer: pale yellow crystal 3.1g，m.p.88–90°C, ^{1}H-NMR (CDCl$_3$, 300 MHz): δ1.56 (S, 3H), 2.58 (S, 3H), 2.53 (q, *J* = 7.2 Hz, 12.6 Hz, 1H), 2.82 (q, *J* = 9.0 Hz, 12.6 Hz, 1H), 5.22 (q, *J* = 8.7 Hz, 7.2 Hz, 1H), 7.15–7.18 (m, 2H), 7.23–7.30 (m, 2H), 7.23-7.30 (m, 2H), 7.41-7.45 (m, 2H).

^{13}C-NMR(CDCl$_3$, 300 MHz): 21.1, 38.3, 52.6, 69.4, 77.6, 127.4, 128.0, 128.4, 128.5, 132.8, 133.0, 141.4, 143.1.

IR(KBr): 3000, 2940, 1500, 1100, 1020，920, 840, 540, cm^{-1}.

MS *m/z* (%): 322([M^{+}+1], 100), 302 (16), 286 (7), 194 (4), 170 (12).

Anal. calcd for C$_{17}$H$_{18}$ClNO: C 70.96, H 6.26, O 5.56, N 4.87; found C 70.66, H 6.36, O 5.66, N 4.90.

1.3.3 c: 2-Methyl-3-(p-methoxy)benzyl-5-(4-pyridyl)isoxazolidine

Yellow oil 4.9 g (95.2%), yield: 86.4%. ^{1}H-NMR (CDCl$_3$, 300 MHz): δ 2.66, 2.70 (2S, 3H), 3.78, 3.81 (2S, 3H), 2.26–2.35, 3.11-3.21 (2m, 1H), 2.48–2.54, 2.70-2.84 (2m, 1H), 3.65 (m, 1H), 5.20 (q *J* = 6.6 Hz, 8.4 Hz, 1H), 6.84, 6.90 (2dd, *J* = 8.7 Hz, 2H), 7.20, 7.30 (2dd, *J* = 8.7 Hz, 2H), 7.26–7.39(m, 2H), 8.58–8.61(m, 2H).

^{13}C-NMR(CDCl$_3$, 300 MHz): 43.06, 47.3(48.0), 55.18, 72.23(73.35), 76.17(76.91), 114.1, 120.7, 122.7, 129.9, 130.3, 150.0, 159.3.

IR(NaCl): 2980, 2920, 1600, 1520, 1250, 1040, 840 cm^{-1}.

MS *m/z* (%): 271([M^{+}+1], 64), 166 (100), 106 (8), 240 (4).

1.3.4 d: 2-Methyl-3-(p-methoxy)benzyl-5-(p-chloro)benzyl isoxazolidine

Pale yellow crystal 5.4g (96.8%), yield: 86.1%，m.p. 80–90°C.

^{1}H-NMR (CDCl$_3$, 300 MHz): δ 2.3-2.36, 3.04-3.13(2m, 1H), 2.47-2.56, 2.65-2.77 (2m, 1H), 2.66, 2.67 (2S, 3H), 3.65–3.7(m, 1H), 3.78, 3.81 (2S, 3H), 5.22 (t, *J* = 8.4 Hz, 1H), 6.86, 6.90(2dd, *J* = 8.7 Hz, 2H), 7.24–7.30(m 2H), 7.30–7.43(m 4H).

^{13}C-NMR (CDCl$_3$, 300 MHz): 42.99 (43.35), 47.50 (48.52), 55.15, 72.68 (73.35), 77.25 (77.90), 114.00, 127.23, 127.84, 128.46, 128.53, 128.70, 128.77, 130.39, 130.73, 132.77, 133.41.

IR(KBr): 2980, 2920, 1620, 1520, 1300, 1260, 1180, 1040, 830 cm^{-1}.

MS *m/z* (%): 304([M^{+}+1], 100), 286(3), 257(7), 170(10).

Anal. calcd for C$_{17}$H$_{18}$ClNO$_2$: C 67.22, H 5.93, O 10.54, N 4.61; found C 67.19, H 5.96, O 10.58, N 4.57.

1.3.5 e: 2-Methyl-3-(p-methoxy)benzyl-5-(m-methoxy)benzyl isoxazolidine

Colorless oil 5.2g (98.8%), yield: 85.9%.

^{1}H-NMR (CDCl$_3$, 300 MHz): δ2.68 (S, 3H), 3.81 (S, 3H), 3.83 (S, 3H), 2.36–2.44, 2.99–3.08(2m, 1H), 2.54–2.59, 2.60–2.72 (2m, 1H), 5.21 (t, *J* = 7.8 Hz, 1H), 3.78 (m, 1H), 6.84 (m, 1H), 6.90 (m, 1H), 7.00 (m, 1H), 7.04 (m, 1H), 7.29 (m, 3H).

^{13}C-NMR (CDCl$_3$, 300 MHz): 42.96 (43.46), 48.38, 55.05, 72.59 (73.20), 77.85 (78.43), 111.3, 112.9, 114.2, 118.7, 128.6, 129.3, 130.7, 142.7(144.9), 159.1, 159.6. IR(NaCl): 2980, 2920, 1620, 1520, 1250, 1040, 840 cm^{-1}.

MS *m/z* (%): 300([M^{+}+1]，100), 253 (6), 166 (6), 150 (8).

Anal. calcd for C$_{18}$H$_{21}$NO$_3$: C 72.24, H 7.02, O 16.05, N 4.68; found C 72.00, H 7.26, O 16.08, N 4.64.

1.3.6 f: 2,3-Dimethyl-3-benzyl-5-(4-pyridinyl) isoxazolidine

Pale yellow oil 4.7g(95.8%), yield 88.6%.

^{1}H-NMR (CDCl$_3$, 300 MHz): 1.50, 1.58 (2S, 3H), 2.61, 2.66 (2S, 3H), 2.31, 3.08 (2dd, *J* = 7.8 Hz, 12.0 Hz, 1H), 2.86, 2.54 (2dd, *J* = 8.7 Hz, 12.3 Hz, 1H), 5.05(t), 5.19 (q, *J* = 7.2 Hz, 8.1 Hz, 1H), 7.19–7.41(m, 5H), 7.44–7.46, 7.56–7.58 (2m, 2H), 8.49–8.51, 8.56–8.68 (2m, 2H).

^{13}C-NMR(CDCl$_3$, 300 MHz): 20.64 (22.58), 39.04, 50.61 (52.34), 69.20, 76.37, 120.52, 126.4, 127.0, 128.2, 149.6, 143.46 (143.91), 150.86 (152.49).

IR(NaCl): 2980, 2940, 1600, 1510, 760，700 cm^{-1}.

MS *m/z* (%): 255 ([M^{+}+1],72), 150 (100), 226 (4), 106 (8).

1.3.7 g: 2,3-Dimethyl-3-(p-chloro)benzyl-5-(m-methoxy) benzyl isoxazolidine

Yellow crystals 7.0 g (81%), yield: 89.3%. The product was purified and separated by column chromatography on silica gel to give exo-isomer 2.1 g.

^{1}H-NMR(CDCl$_3$, 300 MHz): 1.58 (S, 3H), 2.61 (S, 3H), 3.65 (S, 3H), 2.84, 2.61 (2dd, J = 8.7 Hz, 12.6 Hz, 2H), 5.25 (q, J = 7.2 Hz, 8.7 Hz, 1H), 6.67 (S, 1H), 6.74 (dd, J = 8.7 Hz, 1H), 6.82(d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 8.4 Hz 2H), 7.47(d, J = 8.7 Hz, 2H).

^{13}C-NMR(CDCl$_3$, 300MHz): 22.07, 38.57, 51.85, 54.97, 69.62, 78.48, 111.0, 113.4, 118.5, 132, 132.3, 128.3, 129.3, 159.7, 132.5, 143.8 (144).

IR(KBr): 2990, 2970, 1600, 1490, 1470, 1270，1100, 1020, 790, 700 cm^{-1}.

MS *m/z* (%): 318([M$^+$+1],100), 286(4), 271(3), 166(12).

Anal. calcd for $C_{18}H_{20}ClNO_2$: C 68.03, H 6.30, O 10.08, N 4.41; found: C 68.08, H 6.28, O 10.12, N 4.32.

General synthetic method B: To a stirred solution of p-tertbutyl-pyrocatechol (1 mg) in benzene, nitrone (0.02 mol) and mono-substituted styrenes (0.021 mol) were added. After heating the solution under reflux for 10–12 h, the reaction was complete as indicated by the <2% content of nitrone analyzed by HPLC. The mixture was cooled down to room temperature and washed with aqueous NaHCO$_3$ (2%) for two times. The organic layer was separated and aqueous HCl (20 mL, 10%) was added. Aqueous phase was separated and neutralized with aqueous NaOH (30%) to pH 10–11. The mixture was extracted with chloroform and combined organic layers were concentrated. The residue was purified by column chromatography on silica gel to give the products.

1.3.8 h: 2,3-Dimethyl-3-(p-chloro)benzyl-5-4-pyridinyl) isoxazolidine

Yellow oil 5.6 g (96%), yield: 93.2%.

^{1}H-NMR(CDCl$_3$, 300 MHz): 1.49 (S, 3H), 2.61 (S, 3H), 2.51, 2.87 (2dd, J = 9.0 Hz, 12.6 Hz, 1H), 2.31, 3.02(2dd, J = 8.1 Hz, 12.6 Hz, 1H), 5.01 (t, J = 7.1 Hz), 5.20 (dd, J = 8.7 Hz, 6.9 Hz, 1H), 7.19–7.30 (2dd, 2H), 7.34 (dd, J = 9.3 Hz 2H), 7.52 (d, J = 8.7 Hz 2H), 8.51, 8.57 (2dd, J = 6.0Hz, 2H).

^{13}C-NMR(CDCl$_3$, 300 MHz): 22.46, 39.18, 50.70, 68.90, 77.18, 127.75, 128.40, 132.87, 142.69, 149.8, 150.75.

IR(NaCl): 2980, 2940, 1600, 1490, 1320，910, 820 cm^{-1}.

MS *m/z* (%): 318([M$^+$+1],100)，286(4)，271(3)，166(12).

1.3.9 i: 2,3-Dimethyl-3-(p-nitro)benzyl-5-(4-pyridinyl)isoxazolidine

Yellow oil 5.4 g (95.2%), yield: 85.9%.

^{1}H-NMR (CDCl$_3$, 300MHz): 1.55, 1.61 (2S, 3H), 2.66, 2.68 (2S, 3H), 4.97 (t, J = 8.3 Hz), 5.28 (q, J = 6.0 Hz, 9.0 Hz, 1H), 2.40 (dd, J = 8.1 Hz, 12.9 Hz), 3.06 (dd, J = 8.4 Hz, 12.4 Hz, 1H), 2.55 (dd, J = 9.3 Hz, 12.6Hz), 2.98 (dd, J = 6.0 Hz, 12.0Hz, 1H), 7.14, 7.29(2m, 2H), 7.66, 7.80 (2dd, J = 8.7 Hz, 9.0 Hz, 2H), 8.15, 8.23(2dd, J = 8.7 Hz, 9.0 Hz, 2H), 8.49, 8.59 (2dd, J = 6.0 Hz, 6.3 Hz, 2H).

^{13}C-NMR (CDCl$_3$, 300 MHz): 20.78 (22.00), 38.01 (39.51), 50.38 (51.99), 69.34 (69.57), 76.40, 120.50, 123.45, 127.29, 149.78, 146.8, 151.64, 152.05.

IR(NaCl): 3000, 2960, 1600, 1520, 1350，860, 710 cm^{-1}.

MS *m/z* (%): 300([M$^+$+1],100), 106 (36), 271 (6).

1.3.10 j: 2,3-Dimethyl-3-(p-Chloro)benzyl-5-(3-Nitro) enzyl-Isoxazolidine

Yellow oil 7.2 g (80.8%), yield: 87.5%. The product was purified and separated by column chromatography on silica gel to give exo- isomer 3.1 g as pale yellow oil. ^{1}H-NMR (CDCl$_3$，300 MHz): δ1.58 (S, 3H), 2.61 (S, 3H), 2.54 (dd, J = 6.3 Hz, 12.6 Hz, 1H), 2.92 (dd, J = 9.3 Hz, 12.6 Hz, 1H), 5.31(q, J = 6.3 Hz, 8.7 Hz, 1H), 7.27 (m, 2H)，7.42 (m, 2H)，7.45(t, 1H), 7.60(d, J = 7.5 Hz, 1H), 8.05 (d, 1H), 8.13 (d ,1H).

^{13}C-NMR(CDCl$_3$, 300MHz): 20.45, 37.92, 52.61, 69.19, 77.42, 120.8, 122.0, 127.8, 128.3, 129.2, 131.8, 132.7, 142.3, 145.5, 148.1.

IR(NaCl): 3000, 2940, 1600, 1540, 1360，1100, 920, 740 cm^{-1}.

MS *m/z* (%): 333([M$^+$+1],100), 300(27), 321(17), 286(14), 150(8).

Anal. calcd for $C_{17}H_{17}ClN_2O_3$: C 61.35, H 5.11, O 14.44, N 8.42; found C 60.88, H 5.01, O 14.68, N 8.38.

2 Biological part of novel compounds

2.1 Materials and methods

The novel analogs (Tech. 90%) of isoxazolidines were screened in the test. Commercial Azoxystrobin (Tech. 90%), Dingjunezuo (Tech. 96%), and sumilex (Tech. 98%) were used as the standard chemicals. The targets were cucumber downy mildew (*Pseudoperonospora cubensis*), vegetable gray mold (*Botrytis cinerea*), rice blast (*Pyricularia oryzae*), wheat powdery mildew (*Blumeria graminis*). Cucumber seedling, wheat seedling, and rice seedling in pots cultivated in a greenhouse were the host plants.

According to the test design, the novel compounds and the standard chemicals were weighed and dissolved in the proper quantity of acetone. After dissolution, the samples were brought to the distilled water with 0.1% Tween-80. Through 2-fold dilution, a low concentration of the compound was obtained and used in the next screen procedure. The solution of each sample contained 10% acetone.

Plants were sprayed at the same time with the use of a turntable sprayer. The spraying pressure was 1.5 kg/cm^2 and the spraying volume was 20 mL for eight pots. The two-nozzle sprayer enabled the test plants to acquire a whole

Table 2 Disease control of isoxazolidium compounds against vegetable gray mold

Compounds	Disease control/%		
	200 μg/mL	100 μg/mL	50 μg/ mL
c	85	75	50
d	70	65	50
e	100	100	100
f	60	10	0
g	70	70	60
h	90	80	75
i	95	80	60
Dingjunezuo	100	100	100
Sumilex	100	100	65

body protectant of pesticide. Sprayed plants were kept in the spraying room to dry. After 24 h, the plants were separated into different groups by pathogens and inoculated with four kinds of spore in the inoculating room. The inoculated plants were in different conditional rooms that were according to the disease. Plants were assessed when disease symptoms had developed on control plants treated only with the carrier solvent. Percent disease control was determined by comparison of visually seen pathogens on the tested samples with that on the control plants.

2.2 Biological activity result of compounds

The novel analogs of isoxazolidines demonstrated good activity against vegetable gray mold in only four screen targets as shown in Table 2.

3 Results and discussion

3.1 Influence factors for the reaction

The activity for the reaction of nitrone with mono- substituted styrene was increased when the polarity of the solvent was decreased as shown in the experimental result. Toluene and benzene were ideal reaction solvents. The yield was lower and the reaction time was longer when the reaction was carried out in ethanol compared with that in toluene or benzene. The quality of nitrone was the most important influencing factor for the reaction. The yields were above 85% when the reaction was carried out in toluene or benzene. The polymerization inhibitor was used in the reaction in order to avoid the polymerization of mono-substituted styrene. The ideal polymerization inhibitor was *p-tert*-butyl-pyrocatechol. The influence of solvents on the synthesis of compound ***a*** was shown in Table 3.

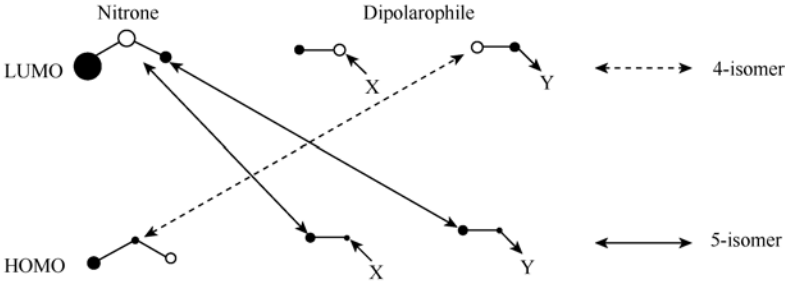
3.2 Regioselectivity

The result of the cycloaddition reaction between nitrones and dipolarophiles depends on both electronic and steric effects based on frontier molecular orbital theory. The reaction may be classified as a thermally allowed [$\pi\,^4S+\pi\,^2S$] process. Its electronic nature has been investigated. It is found that both the energy levels and the coefficients associated with the reacting atoms of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reactants are the most important factors in determining reactivity and regioselectivity of the reaction. In the present study, it was found that the regioselectivity was usually the formation of only 5-substituted isoxazolidine rather than 4-substituted isoxazolidine in the product when nitrones reacted with mono-substituted styrenes because of the dominant interaction of LUMO (nitrone) with HOMO (mono-substituted styrene). The reaction activity is higher for electron-poor dipolarophiles compared with electron-rich ones because of the energy similarity of LUMO (nitrone) and HOMO (mono-substituted styrene) (Scheme 5). For example, the synthesis of 2,3-dimethyl-3-(*p*-chloro) benzyl-5-(*m*-nitro) benzyl-isoxazolidine was easier than the synthesis of 2,3-dimethyl-3-(*p*-chloro)benzyl-5-(*m*-methoxy) benzyl-isoxazolidine .

Table 3 The influence of solvents on the reaction (Synthesis of compound ***a***)

Solvent	Reaction time/h	Yield/%
ethanol	28	68
benzene	22	89
toluene	13	88

The mixture of diastereoisomers was often obtained since the two reagents can approach each other through an endo- or exo-transition state. Trans-isoxazolidine was obtained through an exo-addition while the cis isomer was obtained through an endo-addition. Trans isomer was always having a fixed configuration no matter what substituting group existed in the nitrones or dipolarophiles.



Scheme 5

3.3 Nuclear magnetic resonance spectra

The chemical structure of the products prepared in this paper were characterized by NMR (^{1}H-, ^{13}C-, COSY, HSQC, and DEPT) spectrometry. The explanation for their Nuclear Magnetic Resonance Spectra was based on new compound **a**.

The CH_3 at position 2 connected with N showed two absorptions at δ 2.618 and 2.624 as singlet, respectively. The CH_3 at position 3 connected with C showed two absorptions at δ 1.558 and 1.608 as singlet also. The benzene ring protons showed absorptions at δ 7.2–7.5 as multiplet.

The proton at position 5 received stronger deshielding effect because the atom C at position 5 connected with atom O and benzene ring. One proton at position 5 and two protons at position 4 showed a quartet or a triplet at δ 5.237, δ 5.071 and four quartets at δ 2.827, 2.577, 2.329, 2.229, respectively, based on the experiment of H-H COSY.

The ring of isoxazolidine existed as a plane and the substituting groups at positions 3, 4 and 5 will exist at the up or down side of this plane. Trans-isoxazolidine was obtained through an exo-addition and the cis isomer was obtained through an endo-addition. The proton at position 4 at the same side of aromatic nucleus received stronger deshielding effect in cis isomer, so its resonance peak shifted to downfield. The peak of proton at position 4 at the opposite side in the cis isomer shifted to upfield. The proton 4 resonance peaks were between downfield and upfield in the trans isomer.

In ^{13}C-NMR and DEPT analysis, the six carbons in benzene ring showed the absorptions at δ 126.25—144.45, the tertiary carbon at position 5 appeared at δ 77.96, the quaternary carbon at position 3 appeared at δ69.07, the secondary carbon at position 4 appeared at δ 51.58, the primary carbons appeared at δ 38.87 and δ 22.57, the carbon of CH_3 at position 2 connected with N appeared at δ 38.87, and the carbon of CH_3 at position 3 appeared at δ 22.57.

It was found that the absorption strength of the carbon of CH_3 at position 3 in ^{13}C-NMR spectrum was very weak and it was only observed with the aid of HSQC analysis. The reason for this phenomenon will be explained in our further research.

3.4 Biological activity of compounds

The novel compounds showed good activity against vegetable gray mold (*Botrytis cinerea*) in the general screen and primary screen procedures. The activity of compound ***e*** was the same as that of Dingjunezuo at 50 μg/mL to 200 μg/mL, which is a new fungicide. The activity of this compound was higher than that of sumilex at 50 μg/mL, which is a commercial standard chemical. Thus, we will do further research work for the new isoxazolidium compounds. It is our wish that a new pesticide will be discovered.

4 Conclusion

Ten kinds of new isoxazolidines were prepared and the cycloaddition of different mono-substituted styrenes with new 1,3-dipolar compounds including the influence of solvents on the reaction was studied . This synthetic pathway for synthesis of isoxazolidines was an ideal process of green chemistry. The synthetic products were 5-substituted isoxazolidines. The products were purified and their chemical structures were characterized by IR, NMR, EA, and MS. Their bioactivity was studied and it was revealed that some new compounds inhibited *Botrytis cinerea* effectively. It is our wish to discover a new kind of insecticide through further research.

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