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Synthesis and Fungicidal Activities of 4,5-Dihydro-7*H*-pyrano[3,4-*c*]isoxazole Derivatives

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4,5-Dihydro-7*H*-pyrano[3,4-*c*]isoxazoles (II and III) with an *o*-chlorophenyl or *p*-chlorophenyl group at C-7 were synthesized and the effect of substitution at C-3 of II and III on fungicidal activity was investigated *in vivo*. When the substituent at C-3 of II and III was CH_2Br, CH=NOMe, CH=NOEt or CH=NO-allyl, the fungicidal effect was significant and selectively high on wheat leaf rust and barley powdery mildew at 250 ppm. Compound IId with the CH_2Br substituent at C-7 showed high fungicidal activity against rice blast, providing more than 90% control of the disease at 2 ppm.

Key words: pyrano[3,4-*c*]isoxazole; fungicidal activity; plant pathogen; rice blast; wheat leaf rust

Many isoxazole derivatives are known to possess a variety of biological activities for medicine and agriculture.[1] For example, isoxazolylmethanols have anti-inflammatory and analgesic activities,[2,3] haloisoxazolylureas have acaricidal and insecticidal properties,[4] and 3-hydroxy-5-methylisoxazole shows high fungicidal activity.[5] In a recent report, we described the synthesis of *4H,6H*-furo[3,4-*c*]isoxazole derivatives (**I**) and their fungicidal activities against some plant pathogens.[6,7] Particularly, in the case of furo[3,4-*c*]isoxazole **I** with a *p*- or *o*-chlorophenyl substituent at C-6, the introduction of a methyl, alkoxymethyl, bromomethyl, (hydroxyimino) methyl or (alkoxyimino)methyl group at C-3 resulted in high fungicidal activity.[7]

Encouraged by these results, we considered that the preparation of a 4,5-dihydro-*7H*-pyrano[3,4-*c*]isoxazole (**II** and **III**) fused ring system might have fungicidal activities. Herein we report the synthesis and fungicidal activities of pyrano[3,4-*c*]isoxazole derivatives (**II** and **III**) with an *o*-chlorophenyl or *p*-chlorophenyl group at C-7.

The synthesis was accomplished by two reaction schemes: preparation of pyrano[3,4-*c*]isoxazoles **IIa** and **IIIb** having an *o*-chlorophenyl or *p*-chlorophenyl substituent at C-7 and a functional group at C-3 *via* the intramolecular nitrile oxide-alkyne cycloaddition reaction (Scheme 1), and conversion of the functional group at C-3 to afford **IIb-h** and **IIIb-h** (Scheme 2). Structural assignment of the synthesized compounds was based on their IR, NMR and mass spectra. According to the previously reported synthetic method,[9] 7-aryl substituted pyrano[3,4-*c*]isoxazoles **IIa** and **IIIa** were efficiently prepared from the corresponding aryl-substituted nitro ether (**4a** and **b**). Initially, alcohol **2**, which had been prepared from acetylide **1** and ethylene oxide, was treated with NaH and then reacted with the corresponding nitrostyrene (**3a** and **b**) to give a nitro ether (**4a** or **b**) in an 80% yield. These nitro ethers were readily cyclized into pyranoisoxazoles (**IIa** and **IIIa**) through a nitrile oxide intermediate (**5a** and **b**) in the presence of PhNCO and Et_3N.[8] Next, in order to introduce a variety of substituents at the 3-position of pyranoisoxazole, the tetrahydropyranyl (THP) groups of **IIa** and **IIIb** were simply removed by treating with *p*-toluenesulfonic acid in methanol to afford the corresponding alcohols (**IIb** and **IIIb**) in >92% isolated yield, which were transformed into various pyranoisoxazoles (**IIc-h** and **IIIc-h**) as illustrated in Scheme 2. Alcohols **IIb** and **IIIb** were reacted with phosphorous tribromide in Et_2O at 0°C to give corresponding bromo compounds **IId** and **IIId**, respectively. Aldehydes **IIc** and **IIIc** were readily obtained by the oxidation of **IIb** and **IIIb** with pyridinium chlorochromate in CH_2Cl_2. Various aldoxime derivatives, **IIe-h** and **IIIe-h**, were then prepared from the reaction of the corresponding aldehyde (**IIc** and **IIIc**) with the appropriate hydroxylamine or alkoxyamine in the presence of NaOAc in nearly quantitative yields. In those cases, oximes **IIe-h** and **IIIe-h** were formed as a mixture of geometric isomers (*E* and *Z*) which were inseparable by silica gel column chromatography. The assignment of the relative configurations of aldoximes was based on a comparison of their ^{1}H-NMR signals, and it was found that the (*E*)-isomer predominates, which is supported by the work of Karabatsos *et al.*[10,11] The ratio of isomers was thus determined by their ^{1}H-NMR analyses after chromatographic purification. Oxime **IIe** obtained was found to be a 71:29 (*E*/*Z*) mixture of isomers, while oxime ethers **IIf-h** were produced as a >84:16 (*E*/*Z*) mixture of isomers. This higher stereoselectivity for oxime ethers (**IIf-h**) is presumably due to the steric effect of the bulky OR' group of oxime. A similar result was apparent in the cases of **IIIe-h**. **IIIe** was obtained as an 88:22 mixture of isomers, whereas oxime ethers **IIIf-h** were formed as a >95:5 ratio of the isomeric mixture.

The synthesized compounds were examined *in vivo*

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Abbreviations: allyl, $-CH_2CH=CH_2$; THP, tetrahydropyran-2-yl; RCB, rice blast; RSB, rice sheath blight; CGM, cucumber gray mold; TLB, tomato late blight; WLR, wheat leaf rust; BPM, barley powdery mildew

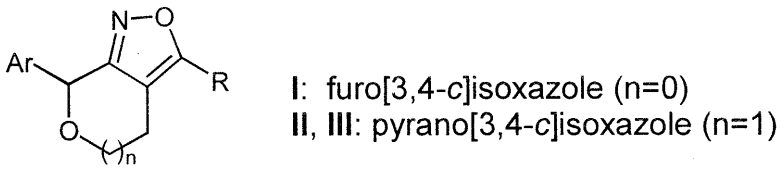
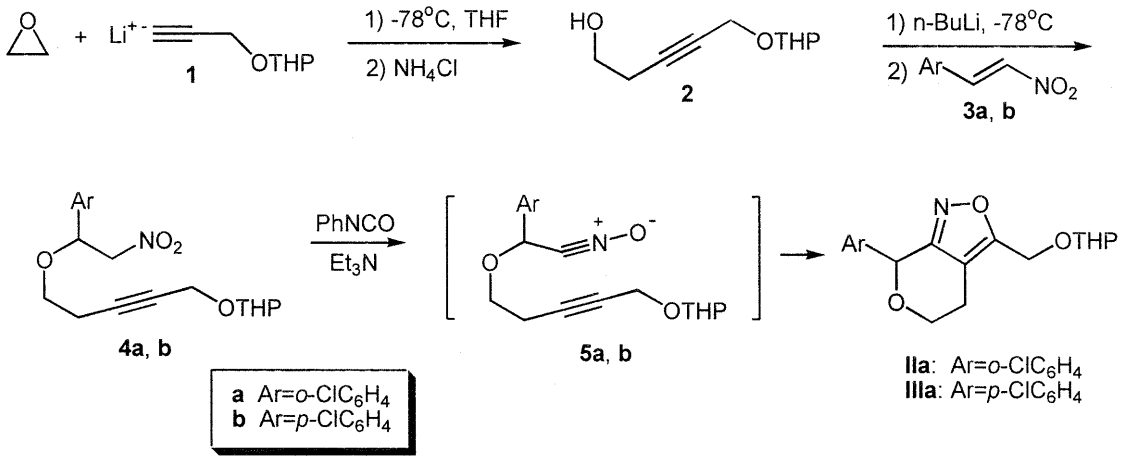
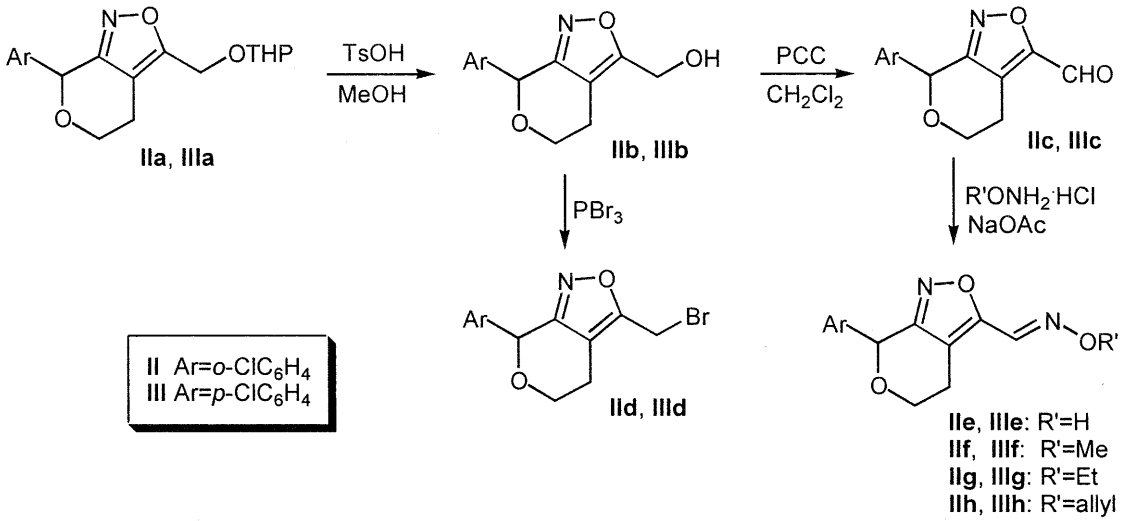


Fig.



Scheme 1.



Scheme 2.

for their fungicidal activities against six kinds of plant diseases such as rice blast (RCB; *Pyricularia oryzae*), rice sheath blight (RSB; *Rhizoctonia solani*), cucumber gray mold (CGM; *Botrytis cinerea*), tomato late blight (TLB; *Phytophthora infestants*), wheat leaf rust (WLR; *Puccinia recondita*), and barley powdery mildew (BPM; *Erysiphe graminis*). The results are summarized in Table 1. When R at C-3 of **II** and **III** was a CH_2Br, CH=NOMe, CH=NOEt or CH=NO-allyl, the fungicidal effects were significant and selectively high on RCB, WLR or BPM at a 250 ppm concentration. Of tested compounds **II** and **III**, the most active compounds, **IId** and **IIId**, were subjected to a confirmatory test at 250-2 ppm concentration. As shown in Table 2, compounds **IId** and **IIId** were both found to display strong fungicidal activity, being comparable to that of the commercial fungicides, tricyclazole or mancozeb. Compound **IId** showed high activity against RCB, providing more than 90% control of the disease even at a 2 ppm concentration. Compound **IIId** was active toward WLR with 90% control at 50 ppm but its activity decreased with dilution.

On the basis of the foregoing results, it can be concluded that the CH_2Br and CH=NOR' groups were effective as an R substituent in pyrano[3,4-*c*]isoxazoles **II** and **III** for high fungicidal activity.

Table 1. Substituent Effect on the Fungicidal Activities of Pyranoisoxazoles **II** and **III**[a,b,c]

Compound	Ar	R	RCB	RSB	CGM	TLB	WLR	BPM
IIa	*o*-C_6H_4	CH_2OTHP	0	47	0	0	86	16
IIb	*o*-C_6H_4	CH_2OH	0	0	0	0	10	0
IIc	*o*-C_6H_4	CHO	0	17	0	21	53	83
IId	*o*-C_6H_4	CH_2Br	100	41	52	7	97	16
IIe	*o*-C_6H_4	CH=NOH	41	52	5	42	0	0
IIf	*o*-C_6H_4	CH=NOMe	0	29	0	50	0	41
IIg	*o*-C_6H_4	CH=NOEt	0	64	5	78	76	91
IIh	*o*-C_6H_4	CH=NO-allyl	0	17	0	14	46	80
IIIa	*p*-C_6H_4	CH_2OTHP	0	0	0	9	0	0
IIIb	*p*-C_6H_4	CH_2OH	0	0	0	2	0	3
IIIc	*p*-C_6H_4	CHO	0	0	30	19	0	0
IIId	*p*-C_6H_4	CH_2Br	41	0	0	22	100	50
IIIe	*p*-C_6H_4	CH=NOH	0	45	0	10	86	0
IIIf	*p*-C_6H_4	CH=NOMe	0	65	28	0	12	96
IIIg	*p*-C_6H_4	CH=NOEt	0	55	10	14	52	81
IIIh	*p*-C_6H_4	CH=NO-allyl	0	75	10	7	96	100

[a] All activities were measured at 250 ppm.
[b] Control values are calculated by the equation [1-(percentage of disease area in treatment)/(percentage of disease area in untreated area)] × 100; 0 represents no activity and 100 means complete control of a disease.
[c] The activities of **IIe-h** and **IIIe-h** were measured without separating the isomers.

Table 2. Concentration Effect on the Fungicidal Activities of Pyranoisoxazoles **IId** and **IIId**

Compound	Pathogen	Concentration (ppm)			
		250	50	10	2
IId	RCB	100	99	96	91
Tricyclazole[a]	RCB	100	100	100	95
IIId	WLR	100	90	53	50
Mancozeb[b]	WLR	100	100	73	50

[a] This known fungicide was used as a standard; its IUPAC name is 5-methyl-1,2,4-triazolo[3,4-*b*]benzothiazole.
[b] This was a combination of *maneb* ([ethylenebis(dithiocarbarmato)]manganese) and *zineb* ([ethylenebis(dithiocarbarmato)]zinc).

Experimental

Melting point (mp) data are uncorrected. Infrared spectra were recorded with a Shimadzu IR-435 spectrophotometer, and ^{1}H-NMR and ^{13}C-NMR spectra were obtained with a Varian UNITY-300 Plus spectrometer in $CDCl_3$ at 300 MHz and 75.5 MHz, respectively. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane. Mass spectra were obtained with Shimadzu GCMS-QP5050 (low resolution) and Jeol JMX-DX303 (high resolution) mass spectrometers used in the electron impact mode at 70 eV. Column chromatography was performed with Merck Kieselgel 60 (70–230 mesh) as the stationary phase.

5-(Tetrahydropyran-2-yloxy)-3-pentyn-1-ol (**2**). To a stirred solution of 2-(prop-2-ynyloxy)-tetrahydropyran (14.2 g, 100 mmol) dissolved in THF (50 ml) was slowly added n-BuLi (62.5 ml of a 1.6 M n-hexane solution, 100 mmol) at −78°C. After stirring for 1 h, ethylene oxide (11 g, 250 mmol) was added at 0°C and then the mixture was stirred for 20 h at room temperature. A saturated NH_4Cl solution was added to the reaction mixture to separate the two layers. The aqueous layer was extracted with Et_2O, and the combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (hexane/EtOAc, 2:1) to give **2** (13.2 g, 72%). NMR δ_H: 1.68 (m, 6H, $CH_2CH_2CH_2$), 2.29 (bs, 1H, OH), 2.50 (tt, J=6.0, 2.1 Hz, 2H, CH_2CH_2OH), 3.54 (m, 1H, OC*H*HCH_2 of THP), 3.71 and 3.73 (t, 2H, J=6.0 Hz, CH_2CH_2OH), 3.84 (m, 1H, OCH*H*CH_2 of THP), 4.21 and 4.31 (dt, 2H, J=15.6, 2.1 Hz, CH_2OTHP), 4.81 (t, 1H, J=3.0 Hz, OC*H*-O).

2-{5-[1-(2-Chlorophenyl)-2-nitroethoxy]-pent-2-ynyloxy}-tetrahydropyran (**4a**). According to the reported method,[9] **2** (7.5 g, 40 mmol), NaH (960 mg, 40 mmol), 2-chloro-β-nitrostyrene (2.5 g, 13.6 mmol), and purification by column chromatography (hexane/EtOAc, 3:1) afforded **4a** (5.1 g, 79%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1556, 1346 (NO_2); NMR δ_H: 1.67 (m, 6H, $CH_2CH_2CH_2$), 2.49 (tt, J=6.9, 2.1 Hz, 2H, OCH_2CH_2), 3.54 (m, 3H, OCH_2CH_2 and OCH*H* of THP), 3.82 (ddd, J=11.7, 9.3, 3.0 Hz, 1H, OCH*H* (THP)), 4.18 and 4.29 (dt, J=15.6, 2.1 Hz, 2H, CH_2OTHP), 4.43 (dd, J=13.2, 3.0 Hz, 1H, C*H*HNO_2), 4.55 (dd, J=13.2, 9.6 Hz, 1H, CH*H*NO_2), 4.78 (t, J=2.94 Hz, 1H, OC*H*-O), 5.56 (dd, J=9.6, 3.0 Hz, 1H, OC*H*Ar), 7.47 (m, 4H, Ar); NMR δ_C: 18.79, 19.74, 25.01, 29.59, 54.05, 61.58, 67.93, 74.98, 77.10, 77.98, 82.24, 96.23, 127.39, 127.57, 129.60, 129.83, 132.25, 133.50.

2-{5-[1-(4-Chlorophenyl)-2-nitroethoxy]-pent-2-ynyloxy}-tetrahydropyran (**4b**). By a similar procedure, **4b** was prepared in an 80% yield. IR ν_{max} (neat) cm^{-1}: 1550, 1345 (NO_2); NMR δ_H: 1.70 (m, 6H, $CH_2CH_2CH_2$), 2.46 (tt, 2H, J=7.1, 2.1Hz, OCH_2CH_2), 3.51 (m, 3H, OCH_2CH_2 and OC*H*H of THP), 3.83(m, 1H, OCH*H* of THP), 4.16 and 4.27 (dt, 2H, J=15.3, 2.1 Hz, CH_2OTHP), 4.37 (dd, 1H, J=12.9, 3.5 Hz, C*H*HNO_2),

4.37 (dd, 1H, J=12.9, 9.9 Hz, CH*H*NO_2), 4.78 (t, 1H, J=3.1 Hz, OCHO), 5.09 (dd, 1H, J=9.9, 3.5 Hz, OC*H*Ar), 7.37 (m, 4H, Ar); NMR δ_C: 19.01, 20.03, 25.31, 30.20, 54.37, 61.90, 67.66, 77.29, 77.75, 79.93, 82.45, 96.67, 128.11, 129.28, 134.70, 135.02.

7-(2-Chlorophenyl)-3-(tetrahydropyran-2-yloxymethyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIa**). According to the reported method,[9] **4a** (7.11 g, 19.35 mmol), benzene (120 ml), PhNCO (5.77 g, 48.44 mmol), Et_3N (195 mg, 1.93 mmol), and purification by column chromatography (hexane/EtOAc, 10:1) gave **IIa** (3.76 g, 56%) as a colorless oil. IR ν_{max} (neat) cm^{-1}: 1640, 1476, 1442 (isoxazole); NMR δ_H: 1.71 (m, 6H, $CH_2CH_2CH_2$), 2.84 (m, 2H, H-4), 3.57 (m, 1H, OCH*H* of THP), 3.84 (m, 2H, H-5 and OC*H*H of THP), 4.23 (ddd, J=11.7, 5.4, 2.7 Hz, 1H, H-5), 4.65 (dd, J=13.5, 3.6 Hz, 1H, C*H*HOTHP), 4.74 (dd, J=7.20, 3.5 Hz, 1H, OC*H*O), 4.82 (d, J=13.5 Hz, 1H, CH*H*OTHP), 6.16 (s, 1H, H-7), 7.33 (M, 4H, Ar); NMR δ_C: 18.92, 20.19, 25.27, 30.15, 58.94, 61.93, 64.24, 72.84, 98.15, 110.73, 126.86, 129.58 129.86, 129.90, 133.90, 135.99, 160.51, 163.26; MS *m/z* (rel. intensity): 351 (M^++2, 1.8), 349 (M^+, 1.2), 260 (2), 248 (3), 85 (100); HRMS *m/z* (M^+): calcd. for $C_{18}H_{20}NO_4Cl$, 349.1081; found, 349.1080.

7-(4-Chlorophenyl)-3-(tetrahydropyran-2-yloxymethyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIa**). By a similar procedure, **IIIa** was prepared in a 76% yield. IR ν_{max} (neat) cm^{-1}: 1640, 1476, 1442 (isoxazole); NMR δ_H: 1.70 (m, 6H, $CH_2CH_2CH_2$), 2.79 (m, 2H, H-4), 3.56 (m, 1H, OCH*H* of THP), 3.83 (m, 2H, H-5 and OC*H*H of THP), 4.23 (ddd, 1H, J=11.7, 4.8, 3.0 Hz, H-5), 4.64 (dd, 1H, J=13.5, 3.0 Hz, C*H*HOTHP), 4.73 (dd, 1H, J=6.3, 3.0 Hz, OC*H*O), 4.81 (d, 1H, J=13.5 Hz, CH*H*OTHP), 5. 76 (s, 1H, H-7), 7.35 (m, 4H, Ar); NMR δ_C: 18.88, 20.15, 25.25, 30.11, 58.87, 61.95, 63.24, 74.39, 98.11, 110.41, 128.66, 128.98, 134.33, 136.60, 160.58, 163.26; MS *m/z* (rel. intensity): 352 (M^++2, 0.5), 349 (M^+, 1.5), 247 (25), 212 (29), 139 (16), 93 (91), 85 (100); HRMS *m/z* (M^+): calcd. for $C_{18}H_{20}NO_4Cl$, 349.1081; found, 349.1079.

7-(2-Chlorophenyl)-3-hydroxymethyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIb**). The mixture of **IIa** (3.75 g, 10.7 mmol) and TsOH hydrate (59.8 mg, 1.07 mmol) in MeOH (20 ml) was stirred for 2 h at 25°C. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 3:1) to give **IIb** (2.63 g, 92%) as an oil. IR ν^{max} (neat) cm^{-1}: 3438 (OH), 1639, 1475, 1440 (isoxazole); NMR δ_H: 2.65 (dt, J=15.9, 3.3 Hz, 1H, H-4), 2.82 (ddd, J=15.9, 10.2, 5.7 Hz, 1H, H-4), 3.60 (s, 1H, **OH**), 3.73 (ddd, J=11.7, 10.2, 4.2 Hz, 1H, H-5), 4.17 (ddd, J=11.7, 5.7, 2.7 Hz, 1H, H-5), 4.58 (s, 2H, CH_2OH), 6.11 (s, 1H, H-7), 7.48 (m, 4H, Ar); NMR δ_C: 19.74, 55.12, 64.11, 72.63, 109.62, 126.84, 129.44, 129.73, 129.93, 133.60, 135.73, 160.52, 165.11; MS *m/z* (rel. intensity): 267 (M^++2, 1.2), 265 (M^+, 3.2), 234 (1), 139 (30), 125 (100), 67 (58); HRMS *m/z* (M^+): calcd. for $C_{13}H_{12}NO_3Cl$, 265.0506; found, 265.0502.

7-(4-Chlorophenyl)-3-hydroxymethyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIb**). By a similar procedure, **IIIb** was prepared from **IIIa** in a 93% yield. Mp 109–111°C; IR ν_{max} (KBr) cm^{-1}: 3340 (OH); NMR δ_H: 2.21 (t, 1H, J=6.3 Hz, O*H*), 2.79 (m, 2H, H-4), 3.80 (ddd, 1H, J=12.6, 8.7, 4.8 Hz, H-5), 4.11 (ddd, 1H, J=12.6, 5.1, 4.2 Hz, H-5), 4.76 (d, 2H, J=6.3Hz, CH_2OH), 5.76 (s, 1H, H-7), 7.38 (m, 4H, Ar); NMR δ_C: 19.99, 55.65, 63.31, 74.46, 109.58, 128.71, 128.87, 134.34, 136.54, 160.78, 164.74; MS *m/z* (rel. intensity): 267 (M^++2, 2.5), 265 (M^+, 5.3), 230 (12), 141 (25), 139 (37), 125 (100), 111 (13), 94 (31); HRMS *m/z* (M^+): calcd. for $C_{13}H_{12}NO_3Cl$, 265.0506; found, 265.0505.

7-(2-Chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole-3-carboaldehyde (**IIc**). To a stirred solution of **IIb** (2.45 g, 9.37 mmol) in CH_2Cl_2 (20 ml) was added portionwise PCC (4.31 g, 20 mmol) and the mixture was stirred for 1 h at room temperature. Et_2O (20 ml) was added, the supernatant liquid was decanted, and the insoluble residue was washed with Et_2O (3×10 ml). The combined organic solution was passed through a short pad of Florisil. The solvent was evaporated, and the crude product was purified by column chromatography (hexane/EtOAc, 4:1) to give **IIc** (2.2 g, 90%). Mp 82–85°C; IR ν_{max} (KBr) cm^{-1}: 1695 (C=O), 1618, 1470, 1441, (isoxazole); NMR δ_H: 3.00 (ddd, J=17.7, 5.1, 2.7 Hz, 1H, H-4), 3.11 (ddd, J=17.7, 9.6, 5.7 Hz, 1H, H-4), 3.81 (ddd, J=11.7, 9.6, 5.1 Hz, 1H, H-5), 4.27 (ddd, J=11.7, 5.7, 2.7 Hz, 1H, H-5), 6.16 (s, 1H, H-7), 7.44 (m, 4H, Ar), 10.03 (s, 1H, C*H*O); NMR δ_C: 20.85, 63.57, 72.64, 118.48, 126.89, 129.25, 129.84, 130.09, 133.54, 135.24, 159.60, 161.51, 179.38; MS *m/z* (rel. intensity): 265 (M^++2, 2.4), 263 (M^+, 9.1), 234 (21), 123 (25), 94 (100), 77 (37), 66 (83); HRMS *m/z* (M^+): calcd. for $C_{13}H_{10}NO_3Cl$, 263.0349; found, 263.0350.

7-(4-Chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole-3-carboaldehyde (**IIIc**). By a similar procedure, **IIIc** was prepared from **IIIb** in an 89% yield as an oil. IR ν^{max} (neat) cm^{-1}: 1685 (C=O); NMR δ_H: 3.05 (m, 2H, H-4), 3.84 (ddd, 1H, J=12.6, 7.2, 6.0 Hz, H-5), 4.14 (ddd, 1H, J=12.6, 9.9, 4.8 Hz, H-5), 5.82 (s, 1H, H-7), 7.39 (m, 4H, Ar), 10.07 (s, 1H, C*H*O); NMR δ_C: 21.03, 62.63, 74.21, 118.26, 128.73, 128.83, 134.71, 135.80, 159.82, 161.72, 179.56; MS *m/z* (rel. intensity): 265 (M^++2, 4.2), 263 (M^+, 13.4), 234 (12), 228 (23), 139 (39), 123 (10), 111 (13), 94 (100), 66 (44); HRMS *m/z* (M^+): calcd. for $C_{13}H_{10}NO_3Cl$, 263.0349; found, 263.0344.

3-Bromomethyl-7-(2-chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IId**). To a stirred solution of **IIb** (400 mg, 1.5 mmol) in Et_2O (5 ml) was added PBr_3 (820 mg, 3.0 mmol) at 0°C. After being stirred for 1 h, the mixture was poured into cold water (10 ml) and the layers separated. The organic layer was washed with brine (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:1) to give **IId** (350 mg,

70%). Mp 72–75°C; IR ν_{max} (KBr) cm^{-1}: 1698, 1475, 1441 (isoxazole); NMR δ_H: 2.68 (ddd, J=15.9, 4.2, 2.7 Hz, 1H, H-4), 2.85 (ddd, J=15.9,10.2, 6 Hz, 1H, H-4), 3.81 (ddd, J=11.7, 10.2, 4.2 Hz, 1H, H-5), 4.25 (ddd, J=11.7, 6, 2.7 Hz, 1H, H-5), 4.46 (s, 2H, CH_2Br), 6.12 (s, 1H, H-7), 7.37 (m, 4H, Ar); NMR δ_C: 17.68, 20.04, 63.93, 72.80, 111.21, 126.92, 129.50, 129.88, 130.01, 133.84, 135.65, 160.96, 161.48; MS *m/z* (rel. intensity): 331 (M^++4, 25.3), 329 (M^++2, 21.8), 327 (M^+, 3.3), 292 (3), 248 (7), 216 (6); HRMS *m/z* (M^+): calcd. for $C_{13}H_{11}NO_2BrCl$, 326.9662; found, 326.9662.

3-Bromomethyl-7-(4-chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIId**). By a similar procedure, **IIId** was prepared from **IIIb** in a 72% yield as an oil. IR ν_{max} (neat) cm^{-1}: 1698, 1475, 1441 (isoxazole); NMR δ_H: 2.75 (m, 2H, H-4), 3.83 (ddd, 1H, J=11.7, 8.4, 4.8 Hz, H-5), 4.13 (ddd, 1H, J=11.7, 5.4, 4.2 Hz, H-5), 4.47 (s, 2H, CH_2Br), 5.57 (s, 1H, H-7), 7.39 (m, 4H, Ar); NMR δ_C: 17.63, 20.03, 63.01, 74.36, 110.92, 128.74, 128.82, 134.49, 136.20, 161.04, 161.57; MS *m/z* (rel. intensity): 331 (M^++4, 5.1), 329 (M^++2, 15.5), 327 (M^+, 13.7), 294 (53), 248 (18), 189 (46), 139 (65), 108 (100), 89 (28), 77 (33); HRMS *m/z* (M^+): calcd. for $C_{13}H_{11}NO_2BrCl$, 326.9662; found, 326.9665.

7-(2-chlorophenyl)-3-(hydroxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIe**). A mixture of **IIc** (336 mg, 1.28 mmol), $HONH_2 \cdot HCl$ (133 mg, 1.92 mmol) and NaOAc (157 mg, 1.92 mmol) dissolved in EtOH (5 ml) was stirred for 4 h at room temperature and then filtered. The filtrate was concentrated, and the crude product was purified by column chromatography (hexane/EtOAc, 2:1) to give **IIe** (340 mg, 96%) as an isomeric mixture (*E:Z*=71:29). Mp 145–150°C; IR ν_{max} (KBr) cm^{-1}: 3193 (OH), 1492, 1438 (isoxazole); MS *m/z* (rel. intensity): 280 (M^++2, 3.8), 278 (M^+, 5.3), 138 (100), 77 (28), 44 (36). (*E*)-**IIe**: NMR δ_H: 2.86 (ddd, J=16.8, 4.2, 3.0 Hz, 1H, H-4), 2.98 (ddd, J=16.8, 9.9, 6.0 Hz, 1H, H-4), 3.84 (ddd, J=11.7, 9.9, 4.2 Hz, 1H, H-5), 4.25 (ddd, 11.7, 6.0, 3.0 Hz, 1H, H-5), 6.18 (s, 1H, H-7), 7.35 (m, 4H, Ar), 7.93 (s, 1H, O*H*), 8.22 (s, 1H, C*H*=N); NMR δ_C: 21.22, 63.95, 72.75, 112.26, 126.95, 129.56, 129.95, 130.07, 133.91, 135.69, 139.61, 157.75, 161.09. (*Z*)-**IIe**: NMR δ_H ($CDCl_3$): 2.85 (m, 1H, H-4), 3.07 (m, 1H, H-4), 3.81 (m, 1H, H-5), 4.22 (m, 1H, H-5), 6.17 (s, 1H, H-7), 7.34 (m, 4H, Ar), 7.57 (s, 1H, O*H*), 7.93 (s, 1H, C*H*=N); NMR δ_C: 23.11, 29.69, 64.21, 114.94, 126.95, 129.52, 129.56, 129.95, 130.07, 132.86, 137.34, 155.85, 161.33; HRMS *m/z* (M^+): calcd. for $C_{13}H_{11}N_2O_3Cl$, 278.0458; found, 278.0455.

7-(4-chlorophenyl)-3-(hydroxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIe**) was prepared from **IIIc**, $HONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** in a 92% yield (*E:Z*=88:12). Mp 153–158°C; IR ν_{max} (KBr) cm^{-1}: 1485 (isoxazole); NMR δ_H: 2.87 (m, 2H, H-4), 3.83 (ddd, 1H, J=12.3, 8.1, 5.1 Hz, H-5), 4.12 (ddd, 1H, J=12.3, 4.8, 1.8 Hz, H-5), 5.79 (s, 1H, H-7), 7.39 (m, 4H, Ar), 8.03 (bs, 1H, N-O*H*), 8.21 (s, 1H, C*H*=N); NMR δ_C: 21.18, 63.00, 111.93, 128.77, 128.87, 134.55, 136.27, 139.50, 157.82, 161.24; MS *m/z* (rel. intensity): 280 (M^++2, 6.5), 278 (M^+, 18.3), 234 (28), 226 (10), 139 (67), 138 (100), 111 (27), 89 (25), 66 (28); HRMS *m/z* (M^+): calcd. for $C_{13}H_{11}N_2O_3Cl$, 278.0458; found, 278.0460.

7-(2-chlorophenyl)-3-(methoxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIf**) was prepared from **IIc**, $MeONH_2 \cdot HCl$ and NaOAc in the same manner as that described for IIe in an 85% yield (*E:Z*=89:11). Mp 83–88°C; IR ν_{max} (KBr) cm^{-1}: 1573, 1442 (isoxazole); MS *m/z* (rel. intensity): 294 (M^++2, 10.9), 292 (M^+, 25.1), 152 (100), 139 (51), 122 (48), 67 (73), 66 (59), 58 (58). (*E*)-**IIf**: NMR δ_H: 2.86 (ddd, J=16.8, 4.5, 3.1 Hz, 1H, H-4), 2.98 (ddd, 16.8, 9.9, 5.7 Hz, 1H, H-4), 3.82 (ddd, J=11.7, 9.9, 4.5 Hz, 1H, H-5), 4.03 (s, 3H, OCH_3), 4.23 (ddd, 11.7, 5.7, 3.1 Hz, 1H, H-5), 6.17 (s, 1H, H-7), 7.29 (m, 4H, Ar), 8.14 (s, 1H, C*H*=N); NMR δ_C: 21.33, 62.99, 63.88, 72.65, 111.96, 126.90, 129.58, 129.90, 130.01, 133.88, 135.73, 137.58, 157.83, 161.03. (*Z*)-**IIf**: NMR δ_H: 2.92 (m, 1H, *H*-4), 3.03 (m, 1H, *H*-4), 3.79 (m, 1H, H-5), 4.06 (s, 3H, OCH_3), 4.21 (m, 1H, H-5), 6.16 (s, 1H, H-7), 7.27 (m, 4H, Ar), 7.47 (s, 1H, C*H*=N); NMR δ_C: 23.02, 62.89, 64.14, 72.65, 114.71, 126.90, 129.58, 129.90, 133.12, 133.86, 130.01, 135.91, 156.14, 161.23; HRMS *m/z* (M^+): calcd. for $C_{14}H_{13}N_2O_3Cl$, 292.0615; found, 292.0614.

7-(4-chlorophenyl)-3-(methoxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIf**) was prepared from **IIIc**, $MeONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** in a 73% yield. Mp 74–76°C; IR δ_{max} (KBr) cm^{-1}: 1480 (isoxazole); NMR δ_H: 2.89 (m, 2H, H-4), 3.83 (ddd, 1H, J=12.3, 7.8, 5.1 Hz, H-5), 4.03 (s, 3H, OCH_3), 4.11 (ddd, 1H, J=12.3, 9.6, 4.8 Hz, H-5), 5.78 (s, 1H, H-7), 7.39 (m, 4H, Ar), 8.13 (s, 1H, C*H*=N); NMR δ_C: 21.32, 62.98, 63.03, 74.27, 111.65, 128.73, 128.88, 134.48, 136.36, 137.51, 157.91, 161.08; MS *m/z* (rel. intensity): 294 (M^++2, 14.4), 292 (M+, 41.2), 261 (3), 257 (17), 152 (100), 139 (40), 122 (23), 82 (12), 67 (30); HRMS *m/z* (M^+): calcd. for $C_{14}H_{13}N_2O_3Cl$, 292.0615; found, 292.0614.

7-(2-chlorophenyl)-3-(ethoxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIg**) was prepared from **IIc**, $EtONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** in a 97% yield (*E:Z*=84:16). IR ν_{max} (CCl_4) cm^{-1}: 1585, 1473, 1444 (isoxazole); MS *m/z* (rel. intensity): 308 M^++2, 5.5), 306 (M^+, 16.2), 166 (94), 138 (80), 67 (100), 66 (66), 56 (58), 44 (57). (*E*)-**IIg**: NMR δ_H: 1.32 (t, J=7.08 Hz, 3H, $NOCH_2CH_3$), 2.82 (ddd, J=16.8, 4.5, 3 Hz, 1H, H-4), 2.95 (ddd, J=16.8, 9.9, 5.7 Hz, 1H, H-4), 3.79 (ddd, J=11.7, 9.9, 4.5 Hz, 1H, H-5), 4.19 (ddd, J=11.7, 5.7, 3 Hz, 1H, H-5), 4.28 (q, J=7.08 Hz, 2H, $NOCH_2CH_3$), 6.15 (s, 1H, H-7), 7.32 (M, 4H, Ar), 8.12 (s, 1H, C*H*=N); NMR δ_C: 9.42, 16.35, 58.92, 66.00, 67.67, 106.82, 121.94, 124.65, 124.88, 125.02, 128.88, 130.88, 132.33, 153.15, 156.03. (*Z*)-**IIg**: NMR δ_H: 1.34 (t, J=7.08 Hz, 3H, CH_2CH_3), 2.87 (m, 1H, H-4), 3.02 (m, 1H, H-4), 3.77 (m, 1H, H-5), 4.16 (m, 1H, H-5), 4.22 (q, J=7.08 Hz, 2H, CH_2CH_3),

6.15 (s, 1H, H-7), 7.30 (M, 4H, Ar), 7.45 (s, 1H, C*H*=N); NMR δ_C: 9.58, 18.27, 48.51, 59.22, 66.23, 67.67, 109.50, 121.94, 124.61, 124.88, 127.83, 128.83, 131.09, 151.25, 156.28; HRMS *m/z* (M^+): calcd. for $C_{15}H_{15}N_2O_3Cl$, 306.0771; found, 306.0773.

7-(4-chlorophenyl)-3-(ethoxyimino)methyl-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIg**) was prepared from **IIIc**, $EtONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** in a 90% yield. Mp 88–89°C; IR ν_{max} (KBr) cm^{-1}: 1485 (isoxazole); NMR δ_H: 1.33 (t, 3H, J=7.2 Hz, $NOCH_2CH_3$), 2.89 (m, 2H, H-4), 3.83 (ddd, 1H, J=12.3, 8.1, 5.1 Hz, H-5), 4.11 (ddd, 1H, J=12.3, 9.9, 5.1 Hz, H-5), 4.27 (q, J=7.2 Hz, $NOCH_2CH_3$), 5.79 (s, 1H, H-7), 7.39 (m, 4H, Ar), 8.14 (s, 1H, C*H*=N); NMR δ_C: 14.38, 21.35, 63.01, 71.04, 74.28, 111.41, 128.74, 128.91, 134.48, 136.39, 137.27, 158.24, 161.07; MS *m/z* (rel. intensity): 308 (M^++2, 14.7), 306 (M^+, 53.9), 271 (16), 261 (5), 166 (74), 151 (30), 139 (57), 138 (100), 122 (38), 94 (27), 67 (19); HRMS *m/z* (M^+): calcd. for $C_{15}H_{15}N_2O_3Cl$, 306.0771; found, 306.0774.

3-(Allyloxyimino)methyl-7-(2-chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIh**) was prepared from **IIc**, $CH_2=CHCH_2ONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** in a 97% yield (*E*:*Z*=83:17). IR ν_{max} (CCl_4) cm^{-1}: 1637, 1585, 1439 (isoxazole); MS *m/z* (rel. intensity): 320 (M^++2, 0.7), 318 (M^+, 4.0), 151 (7), 123 (10), 66 (14), 41 (100). (*E*)-**IIh**: NMR δ_H: 2.84 (ddd, J=16.8, 4.5, 3.0 Hz, 1H, H-4), 2.97 (ddd, J=16.8, 9.9, 5.7 Hz, 1H, H-4), 3.82 (ddd, J=11.7, 9.9, 4.5 Hz, 1H, H-5), 4.22 (ddd, J=11.7, 5.7, 3.0 Hz, 1H, H-5), 4.71 (dt, J=6.0, 1.3 Hz, 2H, $NOCH_2CH$), 5.33 (m, 2H, $CH=CH_2$), 6.03 (m, 1H, $CH_2CH=CH_2$), 6.17 (s, 1H, H-7), 7.76 (m, 4H, Ar), 8.18 (s, 1H, C*H*=N); NMR δ_H: 21.32, 63.86, 72.62, 76.17, 111.97, 118.66, 126.88, 129.55, 129.87, 129.98, 133.10, 133.86, 135.72, 137.87, 157.90, 161.01. (*Z*)-**IIg**: NMR δ_H: 2.91 (m, 1H, H-4), 3.05 (m, 1H, H-4), 3.79 (m, 1H, H-5), 4.13 (m, 1H, H-5), 4.76 (dt, J=6, 1.29 Hz, 2H, $NOCH_2CH$), 5.34 (m, 2H, $CH=CH_2$), 6.04 (m, 1H, $CH_2CH=CH_2$), 6.16 (s, 1H, H-7), 7.75 (m, 4H, Ar), 7.50 (s, 1H, C*H*=N); NMR δ_C: 23.19, 64.15, 72.62, 76.39, 114.73, 118.97, 126.88, 129.52, 129.87, 129.96, 133.10, 133.37, 133.81, 135.92, 156.03, 161.24; HRMS *m/z* (M^+): calcd. for $C_{16}H_{15}N_2O_3Cl$; 318.0771. found, 318.0768.

3-(Allyloxyimino)methyl-7-(4-chlorophenyl)-4,5-dihydro-7H-pyrano[3,4-c]isoxazole (**IIIh**) was prepared from **IIIc**, $CH_2=CHCH_2ONH_2 \cdot HCl$ and NaOAc in the same manner as that described for **IIe** a 95% yield. IR ν_{max} (neat) cm^{-1}: 1637, 1483 (isoxazole); NMR δ^H: 2.87 (m, 2H, H-4), 3.82 (ddd, 1H, J=12.3, 7.5, 5.1 Hz, H-5), 4.11 (dt, 1H, J=12.3, 5.1 Hz, H-5), 4.71 (dt, 2H, 6.0, 1.2 Hz, $OCH_2CH=CH_2$), 5.32 (m, 2H, $CH=CH_2$), 5.78 (s, 1H, H-7), 6.02 (m, 1H, $CH_2CH=CH_2$), 7.39 (m, 4H, Ar), 8.18 (s, 1H, C*H*=N); NMR δ_C: 21.34, 62.98, 74.27, 76.23, 116.68, 118.75, 128.73, 128.89, 133.09, 134.48, 136.37, 137.82, 158.00, 161.09; MS *m/z* (rel. intensity): 320 (M^++2, 24.4), 318 (M^+, 82.7), 283 (19), 261 (7), 161 (21), 141 (61), 139 (100), 123 (79), 96 (59), 66 (48); HRMS *m/z* (M^+): calcd. for $C_{16}H_{15}N_2O_3Cl$, 318.0771; found, 318.0770.

Biological tests. The fungicidal activities of pyranoisoxazole derivatives **II** and **III** were measured against rice blast (*Pyricularia oryzae*), rice sheath blight (*Rhizoctonia solani*), cucumber gray mold (*Botrytis cinerea*), tomato late blight (*Phytophthora infestants*), wheat leaf rust (*Puccinia recondita*) and barley powdery mildew (*Erysiphe graminis*). Each test compound (12.5 mg) was readily dispersed in a standard formulation of acetone (5 ml) and a Tween 20 solution (45 ml) to give a 250 ppm concentration, and the resulting solution was evenly sprayed on to the plants. All tests were run in two-pot replicates according to the methods reported in our previous paper.[7]

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