

- D. J. *Biomol. Str. Dyn.* 1986, 3, 667.
20. Htun, H.; Dahlberg, J. E. *Science* 1988, 241, 1791.
 21. Johnston, B. H. *Science* 1988, 241, 1800.
 22. Takasugi, M.; Guendouz, A.; Chassignol, M.; Decout, J. L.; Lhomme, J.; Thuong, N. T.; Hélène, C. *Proc. Natl. Acad. Sci. USA* 1991, 88, 5602.
 23. Giovannangeli, C.; Thuong, N. T.; Hélène, C. *Proc. Natl. Acad. Sci. USA* 1993, 90, 10013.
 24. Sun, J. S.; François, J. C.; Montenay-Garestier, T.; Saison-Behmoaras, T.; Roig, V.; Thuong, N. T.; Hélène, C. *Proc. Natl. Acad. Sci. USA* 1989, 86, 9198.
 25. Mergny, J. L.; Duval-Valentine, G.; Nguyen, C. H.; Perrouault, L.; Faucon, B.; Rougée, M.; Montenay-Garestier, T.; Bisagni, E.; Hélène, C. *Science* 1992, 256, 1681.
 26. Lee, J. S.; Latimer, L. J. P.; Hampel, K. J. *Biochemistry* 1993, 32, 5591.
 27. Pilch, D. S.; Martin, M. T.; Nguyen, C. H.; Sun, J. S.; Bisagni, E.; Montenay-Garestier, T.; Hélène, C. *J. Am. Chem. Soc.* 1993, 115, 9942.
 28. Pilch, D. S.; Waring, M. J.; Sun, J. S.; Roug, M.; Nguyen, C. H.; Montenay-Garestier, T.; Hélène, C. *J. Mol. Biol.* 1993, 232, 926.
 29. Wilson, W. D.; Taniou, F. A.; Mizan, S.; Yao, S.; Kiselyov, A. S.; Zon, G.; Strekowski, L. *Biochemistry* 1993, 32, 10614.
 30. Scaria, P. V.; Shafer, R. H. *J. Biol. Chem.* 1991, 266, 5417.
 31. Tuite, E.; Nordén, B. *Bioorg. Med. Chem.* 1995, 3, 701.
 32. Kim, H.-K.; Kim, J.-M.; Kim, S. K.; Rodgér, A.; Nordén, B. *Biochemistry* 1996, 35, 1187.
 33. Howard, F. B.; Todd Miles, H.; Liu, K.; Frazier, J.; Raghunathan, G.; Sasisekharan, V. *Biochemistry* 1992, 31, 10671.
 34. Umamoto, K.; Sarma, M. H.; Gupta, G.; Luo, J.; Sarma, R. H. *J. Am. Chem. Soc.* 1990, 112, 4539.
 35. Durand, M.; Thuong, N. T.; Maurizot, J. C. *J. Biol. Chem.* 1992, 267, 24394.
 36. Durand, M.; Thuong, N. T.; Maurizot, J. C. *J. Biomol. Str. Dyn.* 1994, 11, 1191.
 37. Kim, S. K.; Nordén, B. *FEBS Lett.* 1993, 315, 61.
 38. Tuite, E.; Nordén, B. *J. Chem. Soc., Chem. Commun.* 1995b, 53.
 39. Lyng, R.; Rodger, A.; Nordén, B. *Biopolymer* 1991, 31, 1709.
 40. Lyng, R.; Rodger, A.; Nordén, B. *Biopolymer* 1992, 32, 1201.
 41. Nordén, B.; Kubista, M.; Kurucsev, T. *Q. Rev. Biophys.* 1992, 25, 51.
 42. Nordén, B.; Seth, S. *Appl. Spectrosc.* 1985, 39, 647.
 43. Nordén, B.; Kurucsev, T. *J. Mol. Recognit.* 1994, 7, 141.
 44. Matsuoka, Y.; Nordén, B. *Chem. Phys. Lett.* 1982, 85, 302.
 45. Fornasiero, D.; Kurucsev, T. *Chem. Phys. Lett.* 1985, 117, 176.
 46. Swenberg, C. E.; Carberry, S. E.; Geacintov, N. E. *Biopolymers* 1990, 29, 1735.

Synthesis of 4*H*,6*H*-Furo[3,4-*c*]isoxazole Derivatives as New Potent Fungicides and Their Structure Activity Relationship

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Received March 5, 1997

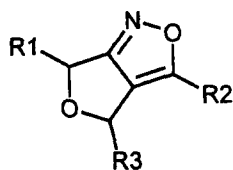
4*H*,6*H*-Furo[3,4-*c*]isoxazoles (I-IV), potential fungicides, have been designed and synthesized *via* intramolecular [2+3] cycloaddition of nitroalkyne 3 as a key step. The broad spectrum of fungicidal activities of furoisoxazoles (I-IV) were observed on plant pathogens at 250 ppm. Furoisoxazoles II, III with chlorophenyl at 6-position and methyl or alkylated oxime group at 3-position gave effective control of plant diseases. The furoisoxazole IV with a chlorophenyl group at 4-position also resulted in high fungicidal activities.

Introduction

In an effort to find a new lead compound as a plant fungicide, we were interested in the isoxazole derivatives. Many isoxazole derivatives show diverse medicinal and agricultural activities such as herbicidal, fungicidal, analgesic, anti-inflammatory, anti-microbial and CNS depression effect.¹⁻⁸ After consideration of synthetic aspect, we have designed furo[3,4-*c*]isoxazoles (I-IV), in which the fused isoxazole

nucleus might provide potential fungicidal activity. Our preliminary research showed that furoisoxazoles I with *o*- or *p*-chlorophenyl substituent on 6-position and methyl on 3-position have a broad spectrum of fungicidal activities against representative six plant fungi.^{9,10} Based on these results, we have continued further structural derivatization of furoisoxazole I to study structure activity relationship and eventually to enhance its fungicidal activity. Here, we report an efficient preparation of novel bicyclic isoxazole derivatives

I-IV with various substituents on the 3-, 4- and 6-positions, and the substituent effect on their fungicidal activities.



- I R²=CH₃, R³=H
 II R¹=*o*-ClC₆H₄, R³=H
 III R¹=*p*-ClC₆H₄, R³=H
 IV R²=CH₃, R³=*o*-ClC₆H₄

Results and Discussion

Synthesis. Previously developed synthetic methodology was applied to the preparation of 6-aryl substituted 4*H*,6*H*-furo[3,4-*c*]isoxazole I: the intramolecular nitrile oxide-alkyne cycloaddition following the Michael addition of alkoxide to nitroolefin (Scheme 1).¹⁰ Thus, various furoisoxazoles Ia-1 were prepared from the corresponding aryl substituted nitroalkene 2 in good yields. Initially, 2-butyn-1-ol 1 was treated with *n*-BuLi in THF at low temperature, and then nitroalkene 2 was added. A subsequent acidic workup afforded nitro ether 3 in overall 95% yield. The ether 3 was readily cyclized into furoisoxazole I via a nitrile oxide intermediate 4 in the presence of phenyl isocyanate and a catalytic amount of Et₃N.¹¹ The nitroalkene 2 was easily formed by a condensation of the corresponding aldehyde (R¹-CHO) with nitromethane.¹²

In order to introduce a variety of R² substituents on the 3-position of furoisoxazole, 3-hydroxymethylfuroisoxazoles IIb and IIIb were prepared. After monoprotection of 2-butyn-1,4-diol 5 by reaction with dihydropyran under a usual reaction condition,¹³ the Michael addition of its lithium alkoxide to the nitrostyrene 6 (Ar=*o*-ClC₆H₄ or *p*-ClC₆H₄) afforded the nitro ether 7 in good yield. Under the phenyl isocyanate mediated dehydration condition,¹¹ the nitro ether 7 was cyclized spontaneously to the furo[3,4-*c*]isoxazoles IIa and IIIa in high yields (see Scheme 2). Starting from furoisoxazoles IIa and IIIa, further functionalization of R² substituent on 3-position was proceeded smoothly to give furoisoxazoles IIb-i and IIIb-i as described in Scheme 2.

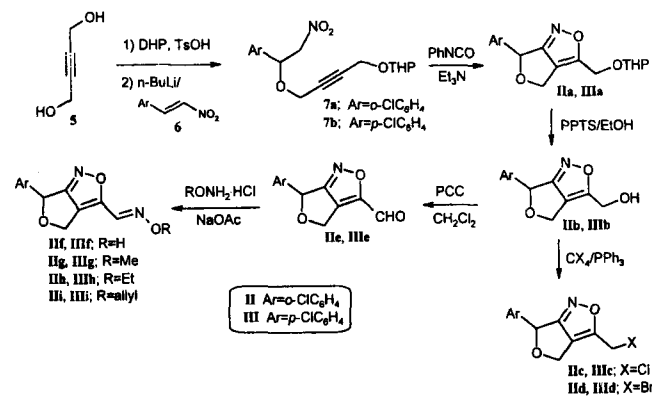
Tetrahydropyranyl ether of furoisoxazoles IIa and IIIa were deprotected by the reaction with pyridinium *p*-toluenesulfonate in ethanol¹⁴ to afford the corresponding alcohols IIb and IIIb quantitatively. Subsequent oxidation of the alcohols IIb and IIIb by using pyridinium chlorochromate in CH₂Cl₂ readily afforded the aldehydes (IIe and IIIe). The oximes (IIf and IIIf) or oxime ethers (IIg-i and IIIg-i) were prepared from the aldehydes (IIe and IIIe)

by the reaction with the corresponding hydroxyl amine or various alkoxyamine hydrochlorides in the presence of an equimolar sodium acetate. The geometric isomers (*trans* and *cis*) of oximes II*f*-i and III*f*-i were inseparable by silica gel column chromatography. Treatment of the alcohols (IIb and IIIb) with carbon tetrahalide in the presence of triphenyl phosphine readily gave halogen-substituted isoxazoles II and III (c, X=Cl; d, X=Br).

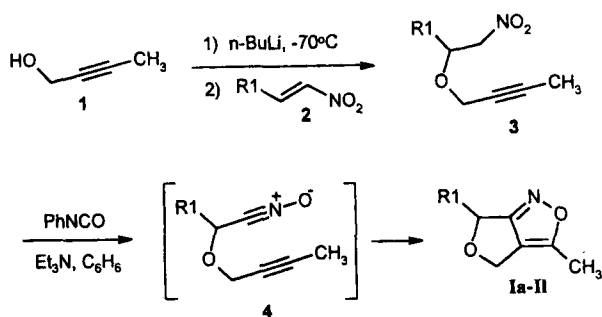
To prepare furoisoxazole IV with *o*-chlorophenyl on C-4 and methyl on C-3, we initially prepared the alkynol 8 from the reaction of 2-chlorobenzaldehyde with lithium acetylide followed by the methylation (*n*-BuLi/MeI). Treatment of the alkynol 8 with *n*-BuLi followed by the addition to nitrostyrene 6 gave the nitroalkyne 9. The intramolecular cycloaddition of 9 using PhNCO/Et₃N readily furnished a bicyclic isoxazole IV (see Scheme 3).

Fungicidal activity. More than 60 furoisoxazoles I-IV were prepared and their antifungal activity was tested against the six plant fungal diseases such as rice blast (RCB; *Pyricularia oryzae*), rice sheath blight (RSB; *Rhizoctonia solani*), cucumber gray mold (CGM; *Botrytis cineria*), tomato late blight (TLB; *Phytophthora infestans*), wheat leaf rust (WLR; *Puccinia recondita*) and barley powdery mildew (BPM; *Erysiphe graminis*).¹⁵ The selected examples and their results are summarized in the Table 1. The control values were calculated by the equation [1-(% of diseased area with treatment)/% of untreated diseased area] × 100. The structure activity relationship (SAR) of furoisoxazoles I-IV was studied on the level of fungicidal activity and disease selectivity.

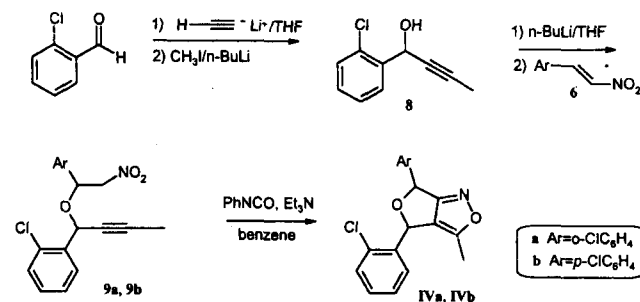
R¹ substituent effect. For the systematic examination of SAR of furoisoxazoles, the R¹ substituent was



Scheme 2.



Scheme 1.



Scheme 3.

Table 1. Substituent Effect on the Fungicidal Activities of Furoisoxazole Derivatives I-IV^{ab}

Compound ^c	R ¹	R ²	R ³	RCB	RSB	CGM	TLB	WLR	BPM
Ia	isopropyl	CH ₃	H	15	10	0	27	0	7
Ib	<i>o</i> -ClC ₆ H ₄	CH ₃	H	99	31	81	55	0	20
Ic	<i>m</i> -ClC ₆ H ₄	CH ₃	H	0	11	29	57	0	31
Id	<i>p</i> -ClC ₆ H ₄	CH ₃	H	0	20	90	0	0	0
Ie	<i>o,p</i> -Cl ₂ C ₆ H ₃	CH ₃	H	91	0	4	7	0	0
If	<i>m,p</i> -Cl ₂ C ₆ H ₃	CH ₃	H	0	5	57	27	0	0
Ig	<i>o</i> -FC ₆ H ₄	CH ₃	H	0	12	8	0	0	27
Ih	<i>p</i> -FC ₆ H ₄	CH ₃	H	0	15	23	24	0	0
Ii	<i>o</i> -CF ₃ C ₆ H ₄	CH ₃	H	0	32	89	81	0	0
Ij	<i>p</i> -CF ₃ C ₆ H ₄	CH ₃	H	0	25	10	15	0	0
Ik	<i>o</i> -CH ₃ C ₆ H ₄	CH ₃	H	7	24	38	0	0	16
II	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃	H	0	6	46	0	0	23
IIa	<i>o</i> -ClC ₆ H ₄	CH ₂ OTHP	H	94	89	19	86	0	0
IIb	<i>o</i> -ClC ₆ H ₄	CH ₂ OH	H	0	10	44	3	53	30
IIc	<i>o</i> -ClC ₆ H ₄	CH ₂ Cl	H	0	45	11	10	0	63
IId	<i>o</i> -ClC ₆ H ₄	CH ₂ Br	H	99	90	41	28	53	13
IIe	<i>o</i> -ClC ₆ H ₄	CHO	H	50	0	8	27	73	6
IIf	<i>o</i> -ClC ₆ H ₄	CH=NOH	H	91	65	80	43	0	96
IIg	<i>o</i> -ClC ₆ H ₄	CH=NOCH ₃	H	0	80	10	0	27	30
IIh	<i>o</i> -ClC ₆ H ₄	CH=NOEt	H	0	15	14	0	27	98
IIi	<i>o</i> -ClC ₆ H ₄	CH=NO-allyl	H	43	50	15	0	0	79
IIIa	<i>p</i> -ClC ₆ H ₄	CH ₂ OTHP	H	0	25	0	73	68	35
IIIb	<i>p</i> -ClC ₆ H ₄	CH ₂ OH	H	0	5	0	31	60	0
IIIc	<i>p</i> -ClC ₆ H ₄	CH ₂ Cl	H	0	20	0	10	27	11
IIId	<i>p</i> -ClC ₆ H ₄	CH ₂ Br	H	7	45	90	38	53	36
IIIe	<i>p</i> -ClC ₆ H ₄	CHO	H	43	5	14	59	0	11
IIIf	<i>p</i> -ClC ₆ H ₄	CH=NOH	H	75	50	15	48	53	34
IIIg	<i>p</i> -ClC ₆ H ₄	CH=NOCH ₃	H	0	55	20	38	0	96
IIIh	<i>p</i> -ClC ₆ H ₄	CH=NOEt	H	0	40	12	0	0	49
IIIi	<i>p</i> -ClC ₆ H ₄	CH=NO-allyl	H	7	50	4	0	0	61
Ib	<i>o</i> -ClC ₆ H ₄	CH ₃	H	99	31	81	55	0	27
IVa	<i>o</i> -ClC ₆ H ₄	CH ₃	<i>o</i> -ClC ₆ H ₄	99	0	71	45	0	40
Id	<i>p</i> -ClC ₆ H ₄	CH ₃	H	0	20	90	0	0	0
IVb	<i>p</i> -ClC ₆ H ₄	CH ₃	<i>o</i> -ClC ₆ H ₄	90	0	35	32	0	40

^aAll activities were measured at 250 ppm against RCB (Rice Blast, *Pyricularia oryzae*), RSB (Rice Sheath Blight, *Rhizoctonia solani*), CGM (Cucumber Gray Mold, *Botrytis cinerea*), TLB (Tomato Late Blight, *Phytophthora infestans*), WLR (Wheat Leaf Rust, *Puccinia recondita*) and BPM (Barley Powdery Mildew, *Erysiphe graminis*). ^bControl values are calculated by the equation: [1-(percent of disease area in treatment)/(percent of disease area in untreated area)] × 100; 0 represents no activity and 100 means complete control of a disease. ^cThe data for furoisoxazoles Ia-I are from the reference 9; for IVa, b from the reference 16.

varied after substituent R² was fixed with CH₃ group (Ia-I). As shown in the Table 1, relatively high fungicidal activity on RCB (>90% control) was observed by the substitution of chlorophenyl group for R¹ (Ib, Ie). Chlorine atom at *ortho* position of the phenyl ring at C-6 of a furoisoxazole was essential for high fungicidal activity. With *m*-ClPh group, the activity was decreased, especially against RCB as in case of isoxazole Ic. Other *ortho*-substituents on the phenyl ring at R¹ such as F (Ig), CF₃ (Ii) and CH₃ (Ik) were not effective at all against RCB. However, *o*-CF₃ group showed the high activity on CGM with ~90% control as in case of furoisoxazole (Ii). Substitution of alkyl group, instead of phenyl group, for R¹ in a furoisoxazole decreased the activity (Ia).

R² substituent effect. Because a chlorophenyl group at 6-position of furoisoxazole showed the best fungicidal activity, the R¹ substituent was fixed with *o*-ClPh or *p*-ClPh group as in isoxazoles II and III, respectively. Then, sub-

stituent R² was modified for SAR analysis as shown in the cases of IIa-i and IIIa-i. With *o*-ClPh as R¹ substituent, the R² substituents such as CH₃ (Ib), CH₂OTHP (IIa), CH₂Br (IId) and CH=NOH (IIf) showed more than 90% control against RCB. Considering the similar physicochemical properties of CH₂Br and CH₂Cl, different activities of isoxazoles IIc and IId were quite interesting. In contrast to the CH₂Br group (IId), the CH₂Cl substituent (IIc) gave lower activity than that of former isoxazole. It was initially assumed that this discrepancy was originated from the extent of proton-halogen exchange of allyl halide during the bioassay. Because the allyl bromide is chemically more reactive than allyl chloride, the isoxazole IId might be easily converted to the isoxazole Ib: thereby resulting in relatively high activity. However, it was not sufficient to explain different disease selectivity of isoxazoles Ib and IId: Ib was effective on RCB and CGM whereas IId was on RCB and RSB. The high activity by CH=NOH substituent (IIf) could

not be satisfactorily explained by hydrogen bonding. Because the CH₂OH group (**IIb**), being capable of acting as hydrogen bonding donor or acceptor like CH=NOH group, did not give high activity. The high fungicidal activity of isoxazole **IIa** was considered to be derived from the certain size of bulk of CH₂OTHP group. The size effect could explain well the high activities of isoxazoles **IIg-i** containing the substituent CH=N-OR. With CH=N-OEt group (**IIh**), the BPM was perfectly controlled at 250 ppm.

The similar R² substituent effect on the fungicidal activity was observed in cases of isoxazoles **IIIa-i** containing *p*-CIPh group as R¹ substituent. When R² was CH₂OTHP (**IIIa**), CH₂Br (**IIIc**), CH=NOH (**IIIe**), and CH=NOMe (**IIIg**), the fungicidal activities of these isoxazoles were quite high. However, the disease selectivity of isoxazoles **IIIa-i** were different from that of isoxazoles **IIa-i** containing *o*-CIPh group as R¹ substituent. For instance, isoxazoles **IIc** and **IIe** (both R²=CH₂Br) were effective on TLB and RCB, respectively. Furoisoxazoles **IIg** and **IIh** (both R³=CH=NOCH₃) effectively controlled RSB and BPM, respectively depending on the R¹ substituent.

R³ substituent effect. The R³ substituent effect on the fungicidal activities of furoisoxazole derivatives was studied using the furoisoxazoles containing the CIPh and CH₃ groups as R¹ and R² substituents, respectively. Introduction of *o*-CIPh as R³ substituent to the isoxazole **Ib** resulted in the similar fungicidal activity as shown in the case **IVa**. As shown in cases of isoxazoles **IVb** and **Id**, the substitution of *o*-CIPh for R³ group shifted the high activity from CGM to RCB. In general, the *o*-CIPh group as R³ substituent at 4-position of furoisoxazole gave high fungicidal activity on RCB.

In conclusion, we designed 4*H*,6*H*-furo[3,4-*c*]isoxazole, a novel fused heterocycle, as potent fungicide and developed efficient synthetic route for the diverse furoisoxazoles **I-IV** containing various substituents on the 3-, 4- and 6-positions. They exhibited *in vivo* fungicidal activity against six representative plant pathogens. The highest activity was observed with isoxazoles **Ib** and **Id** which controlled 50% of RCB and CGM even at 10 ppm, respectively.⁹ The structure activity relationship of furoisoxazoles was also systematically studied. When the R¹ substituents of furoisoxazole were *ortho* or *para* substituted chlorophenyl groups, the high fungicidal activities were observed. The groups CH₃, CH₂Br and CH=N-OR were essential as a R² substituent for the high fungicidal activity. The groups *o*-CIPh or H as R³ substituent, both gave similar fungicidal activities suggesting that the bulky *o*-chlorophenyl group is well accommodated by a biomolecule such as an enzyme or a receptor.¹⁶

Experimental Section

Chemical synthesis

Melting points are uncorrected. Mass spectra were recorded on a Shimadzu QP-1000 spectrometer using the electron impact mode at 25 eV. Infrared spectra were obtained on a Shimadzu IR-435 spectrophotometer. ¹H NMR were recorded in CDCl₃ at 60 or 200 MHz. Chemical shifts were reported in ppm (δ) relative to tetramethylsilane. Column chromatography was performed using Merck Kiesegel 60

(230-400 mesh) as the stationary phase.

General procedure for the preparation of nitro ethers 3, 7 and 9. To a stirred solution of alkynol **1** (10 mmol) dissolved in THF (10 mL) was slowly added *n*-BuLi (6.3 mL of 1.6 M *n*-hexane solution, 10 mmol) at -78 °C. The reaction solution was allowed to warm to 0 °C and then treated dropwise with nitroalkene **2** (5 mmol) in THF (1 mL) and stirred for 4 h at rt. Aqueous acetic acid (12 mL of a 1 N solution) was added to the reaction mixture with stirring, and the resulting two layers were separated. The aqueous layer was extracted with Et₂O (2×10 mL), and the combined organic solution was washed with saturated NaCl solution (10 mL), dried over MgSO₄, and concentrated. The crude product was purified by column chromatography on silica gel.

1-(2-Butynyloxy)-1-isopropyl-2-nitroethane (**3a**).

Yield 96%: IR (neat) 1555, 1375 (NO₂) cm⁻¹; ¹H NMR 1.0 (d, 6H, CH(CH₃)₂), 1.8 (t, 3H, CC-CH₃), 1.9 (m, 1H, CH(CH₃)₂), 4.2 (m, 3H, CHOCH₂), 4.5 (m, 2H, CH₂NO₂).

1-(2-Butynyloxy)-1-(3-chlorophenyl)-2-nitroethane (**3b**).

Yield 68%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.8 (dd, 1H, OCHAr), 7.4 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(3-chlorophenyl)-2-nitroethane (**3c**).

Yield 25%: IR (neat) 1545, 1370 (NO₂) cm⁻¹; ¹H NMR 1.9 (t, 3H, CH₃), 4.0 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.3 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-chlorophenyl)-2-nitroethane (**3d**).

Yield 60%: mp 72-74 °C; IR (CCl₄) 1540, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 4.0 (m, 2H, OCH₂), 4.5 (m, 2H, CH₂NO₂), 5.2 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2,4-dichlorophenyl)-2-nitroethane (**3e**).

Yield 87%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.5 (m, 2H, CH₂NO₂), 5.7 (dd, 1H, OCHAr), 7.4 (m, 3H, Ar).

1-(2-Butynyloxy)-1-(3,4-dichlorophenyl)-2-nitroethane (**3f**).

Yield 38%: IR (neat) 1545, 1370 (NO₂) cm⁻¹; ¹H NMR 1.9 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.7 (m, 2H, CH₂NO₂), 5.5 (dd, 1H, OCH), 7.7 (m, 3H, Ar).

1-(2-Butynyloxy)-1-(2-fluorophenyl)-2-nitroethane (**3g**).

Yield 67%: IR (neat) 1545, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.7 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-fluorophenyl)-2-nitroethane (**3h**).

Yield 55%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.9 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.3 (dd, 1H, OCH), 7.3 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2-trifluoromethylphenyl)-2-nitroethane (**3i**).

Yield 54%: IR (neat) 1550, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 3.0 (m, 2H, OCH₂), 4.4 (s, 1H, CHHNO₂), 4.5 (d, 1H, CHHNO₂), 5.8 (dd, 1H, OCH), 7.8 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-trifluoromethylphenyl)-2-nitroethane (**3j**).

Yield 46%: IR (neat) 1540, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.7 (m, 2H, CH₂NO₂), 5.5 (dd, 1H, OCH), 7.8 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(2-methylphenyl)-2-nitroethane (**3k**).

Yield 70%: IR (neat) 1540, 1370 (NO₂) cm⁻¹; ¹H NMR 1.9 (t, 3H, CH₃), 2.5 (s, 3H, CH₃), 4.1 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.7 (dd, 1H, OCH), 7.4 (m, 4H, Ar).

1-(2-Butynyloxy)-1-(4-methylphenyl)-2-nitroethane (3I). Yield 83%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.8 (t, 3H, CH₃), 2.4 (s, 3H, CH₃), 4.0 (m, 2H, OCH₂), 4.6 (m, 2H, CH₂NO₂), 5.3 (dd, 1H, OCH), 7.2 (m, 4H, Ar).

2-{4-[1-(2-Chlorophenyl)-2-nitroethoxy]-but-2-ynyl-oxy}-tetrahydrofuran (7a). Yield 63%: IR (neat) 1550, 1370 (NO₂) cm⁻¹; ¹H NMR 1.7 (m, 6H, CH₂CH₂CH₂), 3.7 (m, 2H, OCH₂CH₂), 4.2 (m, 4H, OCH₂CC and CH₂OTHP), 4.5 (d, 1H, OCHO), 4.6 (s, 1H, CHHNO₂), 4.8 (br s, 1H, CHHNO₂), 5.8 (dd, 1H, OCHAr), 7.3 (m, 4H, Ar).

2-{4-[1-(4-Chlorophenyl)-2-nitroethoxy]-but-2-ynyl-oxy}-tetrahydrofuran (7b). Yield 60%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.7 (m, 6H, CH₂CH₂CH₂), 3.7 (m, 2H, OCH₂CH₂), 4.1 (m, 4H, OCH₂CC and CH₂OTHP), 4.4 (m, 1H, OCHO), 4.6 (m, 1H, CHHNO₂), 4.8 (br s, 1H, CHHNO₂), 5.4 (dd, 1H, OCHAr), 7.4 (m, 4H, Ar).

1-(2-Chlorophenyl)-1-[1-(2-chlorophenyl)-2-nitro]ethoxy-but-2-yne (9a). Yield 65%: IR (neat) 1555, 1370 (NO₂) cm⁻¹; ¹H NMR 1.72 (d, 3H, CH₃), 4.44-4.57 (m, 2H, CH₂NO₂), 5.59 (q, 1H, OCHCC), 5.67 (dd, 1H, OCHCH₂), 7.23-7.38 (m, 6H, Ar), 7.60-7.68 (m, 2H, Ar).

1-(4-Chlorophenyl)-1-[1-(2-chlorophenyl)-2-nitro]ethoxy-but-2-yne (9b). Yield 57%: IR (neat) 1540, 1370 (NO₂) cm⁻¹; ¹H NMR 1.77 (d, 3H, CH₃), 1.90 (d, 3H, CH₃), 4.35-4.78 (m, 2H, CH₂NO₂), 5.15-5.77 (m, 2H, CHAr), 7.35-7.57 (m, 8H, ArH).

General procedure for the preparation of furoisoxazoles I, IIa, IIIa and IV. To a mixture of nitro ether **3** (5 mmol) and phenyl isocyanate (12.5 mmol) dissolved in dry benzene (30 mL) was added Et₃N (0.5 mmol), and the resulting mixture was stirred overnight at rt. Water (1 mL) was added, and the mixture was stirred for 2 h at which time the solids were removed by vacuum filtration. The filtrate was dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using an *n*-hexane/EtOAc eluent.

6-Isopropyl-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ia). Yield 70%: MS M⁺ m/z 167; IR (neat) 1665, 1460, 1380 (isoxazole) cm⁻¹; ¹H NMR 1.0 (dd, 6H, CH(CH₃)₂), 2.0 (m, 1H, CH(CH₃)₂), 2.4 (s, 3H, CH₃), 4.8 (m, 3H, CHOCH₂).

6-(2-Chlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ib). Yield 86%: mp 88-89 °C; MS M⁺ m/z 235, 237; IR (CCl₄) 1660, 1435, 1410 (isoxazole) cm⁻¹; ¹H NMR 2.4 (br s, 3H, CH₃), 4.9 (m, 2H, CH₂O), 6.4 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(3-Chlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ic). Yield 64%: MS M⁺ m/z 235, 237; IR (neat) 1660, 1465, 1410 (isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 4.9 (s, 2H, CH₂O), 6.0 (s, 1H, OCH), 7.3 (m, 3H, Ar), 7.5 (m, 1H, Ar).

6-(4-Chlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Id). Yield 75%: mp 62-63 °C; MS M⁺ m/z 235, 237; IR (CCl₄) 1660, 1485, 1400 (isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 4.9 (s, 2H, CH₂O), 6.0 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(2,4-Dichlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ie). Yield 55%: mp 106.5-107 °C; MS M⁺ m/z 269, 271, 273; IR (CCl₄) 1660, 1460, 1430

(isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 4.9 (s, 2H, CH₂O), 6.2 (s, 1H,), 7.3 (m, 3H, Ar).

6-(3,4-Dichlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (If). Yield 86%: MS M⁺ m/z 269, 271, 273; IR (neat) 1660, 1465, 1415 (isoxazole) cm⁻¹; ¹H NMR 2.5 (s, 3H, CH₃), 4.9 (m, 2H, CH₂O), 6.0 (s, 1H, OCH), 7.5 (m, 2H,), 7.6 (m, 1H, Ar).

6-(2-Fluorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ig). Yield 66%: MS M⁺ m/z 219; IR (neat) 1660, 1480, 1415 (isoxazole) cm⁻¹; ¹H NMR 2.5 (m, 3H, CH₃), 5.0 (m, 2H, CH₂O), 6.3 (s, 1H, OCH), 7.3 (m, 4H, Ar).

6-(4-Fluorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ih). Yield 87%: MS M⁺ m/z 219; IR (neat) 1660, 1500, 1405 (isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 5.9 (s, 2H, CH₂O), 6.0 (s, 1H, OCH), 6.9-7.6 (m, 4H, Ar).

6-(2-Trifluoromethylphenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ii). Yield 66%: MS M⁺ m/z 269; IR (neat) 1660, 1415 (isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 5.0 (m, 2H, CH₂O), 6.4 (s, 1H, OCH), 7.5 (m, 4H, Ar).

6-(4-Trifluoromethylphenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ij). Yield 69%: MS M⁺ m/z 269; IR (neat) 1660, 1405 (isoxazole) cm⁻¹; 2.4 (s, 3H, CH₃), 4.9 (s, 2H, CH₂O), 6.1 (s, 1H, OCH), 7.6 (m, 4H, Ar).

6-(2-Methylphenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Ik). Yield 81%: mp 48-49 °C; MS M⁺ m/z 215; IR (neat) 1660, 1455, 1410 (isoxazole) cm⁻¹; ¹H NMR 2.4 (s, 3H, CH₃), 2.5 (s, 3H, CH₃), 5.9 (m, 2H, CH₂O), 6.2 (s, 1H, OCH), 7.2 (m, 4H, Ar).

6-(4-Methylphenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (Il). Yield 89%: mp 44-46.5 °C; MS M⁺ m/z 215; IR (CCl₄) 1660, 1505, 1405 (isoxazole) cm⁻¹; ¹H NMR 2.3 (s, 3H, CH₃), 2.4 (s, 3H, CH₃), 4.9 (s, 2H, CH₂O), 6.0 (s, 1H, OCH), 7.2 (m, 4H, Ar).

6-(2-Chlorophenyl)-3-(tetrahydropyran-2-yloxy-methyl)-4H,6H-furo[3,4-c]isoxazole (IIa). Yield 95%: MS M⁺ m/z 335, 337; IR (neat) 1660, 1460, 1435 (isoxazole) cm⁻¹; ¹H NMR 1.6 (m, 6H, CH₂CH₂CH₂), 3.6 (m, 2H, OCH₂CH₂), 4.7 (m, 3H, CH₂OTHP and OCHO), 5.0 (s, 2H, OCH₂), 6.4 (s, 1H, OCHAr), 7.3 (m, 4H, Ar).

6-(4-Chlorophenyl)-3-(tetrahydropyran-2-yloxy-methyl)-4H,6H-furo[3,4-c]isoxazole (IIIa). Yield 90%: MS M⁺ m/z 335, 337; IR (neat) 1660, 1460, 1435 (isoxazole) cm⁻¹; ¹H NMR 1.6 (m, 6H, CH₂CH₂CH₂), 3.7 (m, 2H, OCH₂CH₂), 4.8 (m, 3H, CH₂OTHP and OCHO), 5.0 (s, 2H, OCH₂), 6.0 (s, 1H, OCHAr), 7.5 (m, 4H, Ar).

6-(2-Chlorophenyl)-3-hydroxymethyl-4H,6H-furo[3,4-c]isoxazole (IIb). The mixture of **IIa** (28.70 g, 85.5 mmol) and TsOH hydrate (813 mg, 4.28 mmol) in ethanol (20 mL) was stirred overnight at 50 °C. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 2:1) to give **IIb** (19.15 g, 89% yield): mp 85-86 °C; MS M⁺ m/z 251, 253; IR (CCl₄) 2905 (OH), 1660, 1480, 1415 (isoxazole) cm⁻¹; ¹H NMR 2.6 (s, 1H, OH), 4.8 (m, 2H, CH₂OH), 5.0 (m, 2H, OCH₂), 6.4 (s, 1H, OCHAr), 7.3 (m, 4H, Ar).

3-Chloromethyl-6-(2-chlorophenyl)-4H,6H-furo[3,4-c]isoxazole (IIc). The mixture of **IIb** (605 mg, 2.40 mmol) and Ph₃P (1.89 g, 7.21 mmol) dissolved in dry CCl₄ (10 mL) was refluxed for 30 min. After being cooled, the

reaction mixture was filtered and the filtrate was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to give **IIc** as a white solid (421 mg, 65% yield): mp 55-55.5 °C; MS M^+ *m/z* 269, 271, 273; IR (CCl₄) 1665, 1430 (isoxazole) cm^{-1} ; ¹H NMR 4.6 (m, 2H, CH₂Cl), 5.1 (m, 2H, OCH₂), 6.5 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

3-Bromomethyl-6-(2-chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole (IIId). To a stirred mixture of **IIb** (620 mg, 2.46 mmol) and Ph₃P (1.94 g, 7.39 mmol) dissolved in dry CH₂Cl₂ (5 mL) at 0 °C was added portionwise CBr₄ (1.14 g, 7.39 mmol), and the mixture was stirred for 2 h at rt. Et₂O (5 mL) was added and the mixture was filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to give **IIId** as a solid (505 mg, 65% yield): mp 90-91 °C; MS M^+ *m/z* 313, 315, 317; IR (CCl₄) 1660, 1435 (isoxazole) cm^{-1} ; ¹H NMR 4.5 (s, 2H, CH₂Cl), 5.1 (s, 2H, OCH₂), 6.5 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

6-(2-Chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole-3-carbaldehyde (IIe). To a stirred solution of **IIb** (6.98 g, 27.80 mmol) in CH₂Cl₂ (30 mL) was added portionwise PCC (8.99 g, 41.70 mmol) and the mixture was stirred for 2 h at rt. Et₂O (30 mL) was added, the supernatant liquid was decanted, and the insoluble residue was washed with Et₂O (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 (*n*-hexane/EtOAc, 4:1) to give **IIe** as an oil (3.28 g, 48% yield): MS M^+ *m/z* 249, 251; IR (neat) 1690 (C=O) cm^{-1} ; ¹H NMR 5.2 (m, 2H, OCH₂), 6.5 (s, 1H, OCHAr), 7.5 (m, 4H, Ar), 9.9 (s, 1H, CHO).

6-(2-Chlorophenyl)-3-(hydroxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIf). The mixture of **IIb** (392 mg, 1.57 mmol), HONH₂ HCl (164 mg, 2.36 mmol) and NaOAc (193 mg, 2.36 mmol) dissolved in EtOH (10 mL) was stirred for 8 h at rt and then filtered. The filtrate was concentrated and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to give **IIIf** (400 mg, 96% yield) as an isomeric mixture (*trans*:*cis*=7:1): MS M^+ *m/z* 264, 266; IR (CCl₄) 3150 (OH) cm^{-1} ; ¹H NMR (CDCl₃+DMSO-*d*₆) 2.7 (br, 1H, OH), 5.2 and 5.3 (m, 2H, OCH₂), 6.5 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, CH=NOH).

6-(2-Chlorophenyl)-3-(methoxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIg) was prepared from **IIb**, MeONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 95%: mp 107-115 °C; MS M^+ *m/z* 278, 280; IR (KBr) 1650, 1435 (isoxazole) cm^{-1} ; ¹H NMR 4.1 and 4.2 (s, 3H, OCH₃), 5.1 and 5.2 (s, 2H, OCH₂), 6.6 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, CH=NOMe).

6-(2-Chlorophenyl)-3-(ethoxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIf) was prepared from **IIb**, EtONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 93%: MS M^+ *m/z* 292, 294; IR (neat) 1650, 1460, 1435 (isoxazole) cm^{-1} ; ¹H NMR 1.4 and 1.45 (t, 3H, CH₂CH₃), 4.4 and 4.5 (q, 2H, OCH₂CH₃), 5.3 and 5.4 (s, 2H, OCH₂), 6.6 (s, 1H, OCHAr), 7.5 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, CH=NOEt).

3-(2-Allyloxyimino)methyl-6-(2-chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole (IIIi) was prepared from

IIb, CH₂=CHCH₂ONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 95%: MS M^+ *m/z* 304, 306; IR (neat) 1650, 1450 (isoxazole) cm^{-1} ; ¹H NMR 4.8 (m, 2H, OCH₂CH), 5.1 and 5.2 (s, 2H, OCH₂), 5.5 (m, 2H, CH=CH₂), 5.8-6.2 (m, 1H, CH=CH₂), 6.5 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, CH=NOCH₂).

6-(4-Chlorophenyl)-3-hydroxymethyl-4H,6H-furo[3,4-*c*]isoxazole (IIIb) was prepared from **IIIa** in a same manner to that described for **IIb**. Yield 91%: MS M^+ *m/z* 251, 253; IR (neat) 3370 (OH) 1660, 1485, 1400 (isoxazole) cm^{-1} ; ¹H NMR 2.7 (s, 1H, OH), 4.8 (m, 2H, CH₂OH), 5.0 (m, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

3-Chloromethyl-6-(4-chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole (IIIc) was prepared from **IIIb** in a same manner to that described for **IIc**. Yield 61%: MS M^+ *m/z* 269, 271, 273; IR (neat) 1665, 1430 (isoxazole) cm^{-1} ; ¹H NMR 4.6 (m, 2H, CH₂Cl), 5.1 (m, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

3-Bromomethyl-6-(4-chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole (IIIId) was prepared from **IIIb** in a same manner to that described for **IIId**. Yield 60%: MS M^+ *m/z* 313, 315, 317; IR (neat) 1660, 1485 (isoxazole) cm^{-1} ; ¹H NMR 4.6 (s, 2H, CH₂Br), 5.0 (s, 2H, OCH₂), 6.0 (s, 1H, OCHAr), 7.4 (m, 4H, Ar).

6-(4-Chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole-3-carbaldehyde (IIIe) was prepared from **IIIb** in a same manner to that described for **IIe**. Yield 48%: MS M^+ *m/z* 249, 251; IR (neat) 1695 (C=O) cm^{-1} ; ¹H NMR 5.2 (m, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.5 (m, 4H, Ar), 10.0 (s, 1H, CHO).

6-(4-Chlorophenyl)-3-(hydroxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIIf) was prepared from **IIIe** in a same manner to that described for **IIIf**. Yield 85%: MS M^+ *m/z* 264, 266; mp 134-140 °C; IR (KBr) 3100 (OH) cm^{-1} ; ¹H NMR 2.8 (br, 1H, OH), 5.1 and 5.2 (m, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.5 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, CH=NOH).

6-(4-Chlorophenyl)-3-(methoxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIIf) was prepared from **IIIb**, MeONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 94%: mp 77-80 °C; MS M^+ *m/z* 278, 280; IR (CCl₄) 1650, 1480 (isoxazole) cm^{-1} ; ¹H NMR 4.0 and 4.1 (s, 3H, OCH₃), 5.1 and 5.2 (s, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, CH=NOMe).

6-(4-Chlorophenyl)-3-(ethoxyimino)methyl-4H,6H-furo[3,4-*c*]isoxazole (IIIIf) was prepared from **IIIe**, EtONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 94%: MS M^+ *m/z* 292, 294; IR (neat) 1650, 1485, 1435 (isoxazole) cm^{-1} ; ¹H NMR 1.3 and 1.4 (t, 3H, CH₂CH₃), 4.2 and 4.3 (q, 2H, OCH₂CH₃), 5.1 and 5.2 (s, 2H, OCH₂), 6.1 (s, 1H, OCHAr), 7.4 (m, 4H, Ar), 7.6 and 8.1 (s, 1H, CH=NOEt).

3-(2-Allyloxyimino)methyl-6-(4-chlorophenyl)-4H,6H-furo[3,4-*c*]isoxazole (IIIi) was prepared from **IIIe**, CH₂=CHCH₂ONH₂ HCl and NaOAc in a same manner to that described for **IIIf**. Yield 94%: MS M^+ *m/z* 304, 306; IR (neat) 1650, 1485 (isoxazole) cm^{-1} ; ¹H NMR 4.8 (m, 2H, OCH₂CH), 5.1 and 5.2 (s, 2H, OCH₂), 5.2-5.6 (m, 2H, CH=CH₂), 5.8-6.1 (m, 1H, CH=CH₂), 6.1 (s, 1H, OCHAr),

7.4 (m, 4H, Ar), 7.6 and 8.2 (s, 1H, CH=NOCH₂).

4,6-Bis(2-chlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (IVa). Yield 75%: MS M⁺ m/z 345, 347, 349; IR (CCl₄) 1660, 1435, 1410 (isoxazole) cm⁻¹; ¹H NMR 2.32 (s, 3H, CH₃), 6.16 (s, 1H, ArCH), 6.20 (s, 1H, ArCH), 7.25-7.58 (m, 8H, Ar).

4-(2-Chlorophenyl)-6-(4-chlorophenyl)-3-methyl-4H,6H-furo[3,4-c]isoxazole (IVb). Yield 70%: MS M⁺ m/z 345, 347, 349; IR (CCl₄) 1660, 1485, 1400 (isoxazole) cm⁻¹; ¹H NMR 2.35 (s, 3H, CH₃), 6.38 (s, 1H, ArCH), 6.60 (s, 1H, ArCH), 7.32-7.60 (m, 8H, Ar).

Biological tests

All the test furo[3,4-c]isoxazole (I-IV) compounds (12.5 mg) were readily dispersed in a standard formulation of 5 mL of acetone and 45 mL of Tween 20 solution (250 ppm). The resulting solution was evenly sprayed onto plants while rotated on a turntable, and all tests were run in two-pot replicates.

Test 1. Evaluation of activity against rice blast was done by foliage spray onto rice plants (second leaf stage) grown in 5-cm pots. After the spray deposit had dried, the plants were inoculated with a suspension of conidia in water (1 × 10⁶ spores/mL) and placed in a dew chamber at 25 °C for 24 h. For inoculum preparation, rice blast fungus (*Pyricularia oryzae*) was incubated on rice polish agar medium at 26 °C for 2 weeks and then scratched aerial mycelia with rubber and irradiated with near UV light for 2 d. The plants were then held in lighted growth chamber (26 ± 2 °C) for an additional 5 d and rated on the disease severity.

Test 2. Evaluation of activity against rice sheath blast was done by foliage spray onto rice plants (third leaf stage) grown in 5-cm pots. After the spray deposit had dried, the treated plants were inoculated by injecting inoculum (incubated in wheat bran medium at 25 °C for 7 d). The plants were then held in lighted dew chamber (28 °C) for 5 d and rated on the disease severity.

Test 3. Evaluation of activity against cucumber gray mold was done by foliage spray onto cucumber plants (first leaf stage) grown in 5-cm pots. After the spray deposit had dried for 1 day, the treated cucumber foliage was inoculated with conidia (1 × 10⁶ spores/mL) of *Botrytis cinerea* (incubated on potato dextrose agar medium at 25 °C for 15 d) by leaf spray all sides until just before runoff. The plants were then held in lighted dew chamber (20 ± 2 °C) for an additional 4-5 d and rated on the disease severity.

Test 4. Evaluation of activity against tomato late blight was done by foliage spray to run off onto 14-day-old tomato plants grown in 5-cm polyvinyl pots. After the spray deposit had dried for 1 day, the treated plants were inoculated by spraying with a suspension of zoospores (1 × 10⁵ zoospores/mL; incubated on V-8 juice agar medium at 20 °C for 2 weeks). The plants were then held in lighted dew chamber (20 ± 2 °C) for an additional 4 d and rated on the disease severity.

Test 5. Evaluation of activity against wheat leaf rust was made by foliage spray of the first leaf of wheat (cultivar; Chokwang) grown in polyvinyl pots (diameter, 5 cm) for 7 d. After the spray deposit dried, plants were dusted with a uredospores colonized on the second leaf and placed in a moist chamber at 20 °C for 24 h. One day after inoculation,

plant were moved to the plant growth chamber (20 °C, 70% relative humidity) to induce disease. The plants were then held in growth chamber (20 ± 2 °C) for an additional 10 d and rated on the disease severity.

Test 6. Evaluation of activity against barley powdery mildew was done by foliage spray onto the first leaf of 7-day-old barley (cultivar, Allbori) grown in 5-cm polyvinyl pots. After spray deposit had dried for 1 day, the treated plants were dusted with conidia of *Erysiphe graminis* (formed on the primary leaf of barley). The inoculated plants were then placed in a growth chamber (20 ± 2 °C) for an additional 7 day and rated on the disease severity.

Acknowledgment. We are grateful to the CNU Research Foundation for partial support of this research and thank the Agrochemical Screening Center of KRICT for the bioassay.

References

- Lang, A.; Lin, Y. In *Comprehensive Heterocyclic Chemistry*; Katritky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol 6; p 1.
- Isloxazolylurea (a herbicide); see Sumitomo, S.; Ishizuka, I.; Sugita, J.; Yukinaga, H. *Japan Kokai* 1979, 7946779; (*Chem. Abstr.* 1979, 91, 140834).
- 3-Hydroxy-5-methylisoxazole (a fungicide); see Tomita, K. *Sankyo Kenkyusho Nempo* 1973, 25, 3.
- Isloxazolyl methanol (analgesic, antiinflammation); see (a) Hashimoto, S.; Shizu, M.; Takahashi, S. *Chem. Pharm. Bull.* 1976, 24, 1757. (b) Kano, H.; Takahashi, S. *Japan Kokai* 1979, 7934728; (*Chem. Abstr.* 1980, 93, 150236).
- Haloisoxazolyl urea (an acaricide); see Sumitomo, S.; Yukinaga, H.; Ishizuka, I.; Sugita, J. *Japan Kokai* 1976, 7659858; (*Chem. Abstr.* 1976, 85, 192703).
- For CNS depression, see Iijima, I.; Miyazaki, M.; Tanaka, T. *Japan Kokai* 1974, 7480062; (*Chem. Abstr.* 1975, 82, 156261).
- For antimicrobial activity, see Thakar, K. A.; Bhawal, B. M. *J. Indian Chem. Soc.* 1977, 54, 875.
- For pesticidal activity, see Lorenz, W.; Boeshagen, H.; Hammann, I.; Stendel, W. *Ger. Offen.* 1972, 2049691; (*Chem. Abstr.* 1972, 77, 34483).
- Kim, H. J.; Hwang, K.-J.; Lee, J. H. *Biosci. Biotech. Biochem.* 1994, 58, 1191.
- Kim, H. J.; Lee, J. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* 1992, 57, 6513.
- Mukayama, T.; Hoshino, T. *J. Am. Chem. Soc.* 1960, 82, 5339.
- (a) Campbell, N.; Anderson, W.; Gilmore, J. *J. Chem. Soc. (London)* 1940, 446. (b) Sanno, Y.; Kurita, A.; Imai, K. *J. Pharm. Soc. Jpn.* 1955, 75, 1461.
- Bernady, K. F.; Floyd, M. B.; Poletto, J. F.; Weiss, M. J. *J. Org. Chem.* 1979, 44, 1438.
- Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* 1977, 42, 3772.
- Shephard, M. C. *Ann. Rev. Phytopathol.* 1987, 25, 189.
- Hwang, K.-J.; Kim, H. J.; Lee, J. H. *Korean J. Med. Chem.* 1994, 4, 2.