Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# A Facile Synthesis of 3,4-Disubstituted Isoxazole Derivatives by Regioselective Cleavage of Pyrano[3,4-C]Isoxazoles with Boron Trihalide

Hyung JinKim [a] & Young JuLee [a]
[a] Department of Chemical Technology , Chonnam National University , Kwangju, 500-757, Korea
Published online: 22 Aug 2006.

To cite this article: Hyung JinKim & Young JuLee (1998) A Facile Synthesis of 3,4-Disubstituted Isoxazole Derivatives by Regioselective Cleavage of Pyrano[3,4-C]Isoxazoles with Boron Trihalide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:19, 3527-3537, DOI: 10.1080/00397919808004899

To link to this article: http://dx.doi.org/10.1080/00397919808004899

SYNTHETIC COMMUNICATIONS, 28(19), 3527-3537 (1998)

# A FACILE SYNTHESIS OF 3,4-DISUBSTITUTED ISOXAZOLE DERIVATIVES BY REGIOSELECTIVE CLEAVAGE OF PYRANO[3,4-*C*]ISOXAZOLES WITH BORON TRIHALIDE

Hyung Jin Kim* and Young Ju Lee

Department of Chemical Technology, Chonnam National University, Kwangju, 500-757, Korea.



**Abstract**: 4,5-Dihydro-7*H*-pyrano[3,4-*c*]isoxazoles **4** were efficiently prepared by the intramolecular nitrile oxide-alkyne cycloaddition following the Michael addition of sodium alkoxide to nitroalkene. Reaction of pyrano[3,4-*c*]isoxazole **4** with boron trihalide resulted in regioselective benzylic C-O bond cleavage to furnish a 3,4-disubstituted isoxazole (**5**, **6**) in high yield.

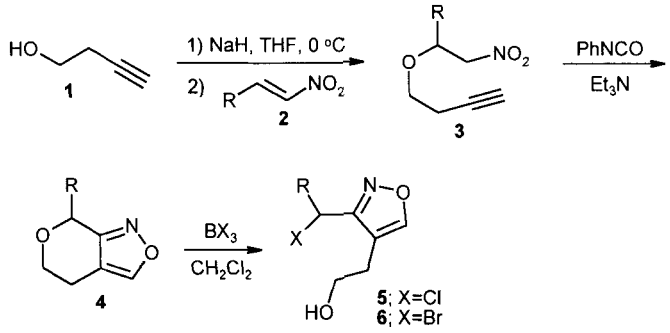
Synthesis of substituted isoxazole derivatives is particularly important because a lot of compounds containing isoxazole ring is known to have a variety of biological activities in pharmaceutical and agricultural areas.[1] Since Claisen's report in 1891,[2] many methods have been developed for the preparation of substituted isoxazoles which can generally be divided into two synthetic routes. The first involves the condensation reaction of a hydroxylamine with a carbonyl compound and provides easy access to 3,5-disubstituted isoxazoles.[1] However, introduction of a substituent at C-4 by this method is not convenient. The second route involves the 1,3-dipolar cycloaddition of a nitrile oxide with an alkyne. In this transformation, nitrile oxides react intermolecularly with monosubstituted alkynes to again give a preponderance of 3,5-disubstituted isoxazoles[3] and furoxan is a significant byproduct.

Recently, we developed the convenient preparation of 3,4-disubstituted isoxazole derivatives by boron trihalide mediated C-O bond cleavage of 4*H*,6*H*-furo[3,4-*c*]isoxazoles and their applications to the preparation of novel fused isoxazoles.[4] As a part of ongoing this research for accessing 3,4-disubstituted isoxazoles, we have examined a similar synthetic methodology on [6,5] fused ring system, pyrano[3,4-*c*]isoxazole derivatives **4**. Herein we report a selective C-O bond cleavage reaction of 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles along with their transformations into novel 3,4-disubstituted isoxazoles.

Previously developed synthetic methodology was successfully applied to the preparation of 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles: the intramolecular nitrile oxide-alkyne cycloaddition following the Michael addition of alkoxide to nitroalkene.[4,5] Thus, various pyranoisoxazoles **4** were prepared from the corresponding substituted nitroalkene in good yields. For instance, 3-butyn-1-ol **1** was treated with NaH in THF at low temperature, and then nitroalkene **2** was added. A subsequent acidic workup afforded nitro ether **3** in high yields. The ether **3** was readily cyclized into 4,5-dihydro-7*H*-pyranoisoxazole **4** in the presence of PhNCO and a catalytic amount of $Et_3N$.[6]

We then examined the cleavage reaction with boron trihalide on 4,5-dihydro-7*H*-pyranoisoxazole **4** and found that the reaction proceeded smoothly through regioselective C-O bond cleavage to furnish a 3,4-disubstituted isoxazole as shown in Scheme 1. For example, treating a methylene chloride solution of pyranoisoxazole **4a** with an equimolar amount of boron trihalide delivered either isoxazole **5a** (X=Cl) from reaction with boron trichloride or isoxazole **6a** (X=Br) from reaction with boron tribromide in nearly quantitative yield. In both cases, it is noteworthy that the isoxazole moiety is never damaged and benzylic C-O bond cleavage is observed. All reactions proceed cleanly at 0 °C in an hour but the reaction with boron trichloride takes longer than that with boron tribromide. After a simple aqueous work up, the crude product was essentially pure and could be used in subsequent reactions. Pyranoisoxazole **4d** with alkyl substituent at C-7, upon treatment with $BBr_3$, also gave **6d** in quantitative yield. However, the

**Scheme 1**




| | | %Yield[b] | | | |
|---|---|---|---|---|---|
| Entry[a] | R | **1 + 2 → 3** | **3 → 4** | **4 → 5** | **4 → 6** |
| **a** | $C_6H_5$ | 87 | 75 | 82 | 92 |
| **b** | *o*-$ClC_6H_4$ | 89 | 71 | 84 | 98 |
| **c** | *p*-$ClC_6H_4$ | 80 | 70 | 85 | 96 |
| **d** | *i*-Pr | 76 | 89 | 0 [c] | 98 |

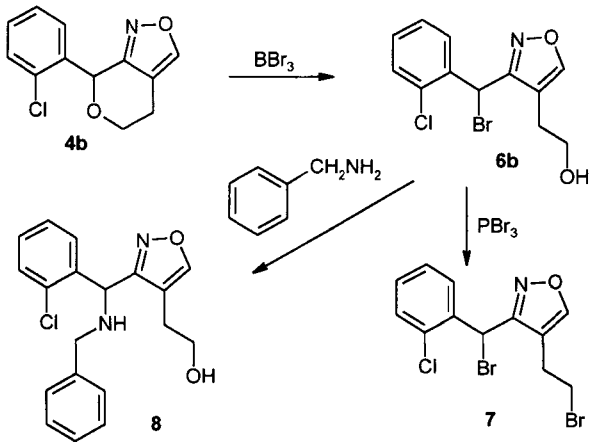
[a] All compounds were fully characterized by IR, $^1$H NMR, $^{13}$C NMR, and MS data.
[b] Purified yields by column chromatography.
[c] No reaction occurred.

reaction of **4d** with $BCl_3$ did not proceed even at refluxing temperature and the starting material was mostly recovered.

In addition, the various functionalities of isoxazoles **5** and **6** provide numerous opportunities for further chemical elaboration. For example, upon treatment with $PBr_3$ ($Et_2O$, 0 °C), **6b** was converted to dibromoisoxazole **7** in 96% yield. Nucleophilic substitution of the benzylic bromide of **6b** by benzyl amine produced amine derivative **8** in 95% yield. Therefore, the chemical transformations outlined in Scheme 2 establish that isoxazolopyran **4** is a versatile substrate to provide easy access to unusual 3,4-disubstituted isoxazoles such as **5**, **6**, **7** and **8**.

In summary, we have shown that 4,5-dihydro-7*H*-pyrano[3,4-*c*]isoxazoles with alkyl or aryl substituents at C-7 are utilized for the preparation of unusual

**Scheme 2**




3,4-disubsituted isoxazoles **5** and **6** from the reaction with boron trihalide. Isoxazoles **5** and **6** could be converted into novel isoxazoles by chemical transformations of the functionalities at C-3 and/or C-4 of isoxazole ring. Their synthetic applications to develop a new bioactive compound are in progress and will be reported elsewhere.

## Experimental Section

IR spectra were obtained on a Shimadzu IR-435 spectrophotometer. $^{1}H$ NMR and $^{13}C$ NMR spectra were measured in $CDCl_3$ at 300 and 75.5 MHz, respectively. Mass spectra were obtained using the EI (70 eV) method.

**General procedure for the preparation of nitroethers 3**: Sodium hydride (60% suspension in oil, 3 mmol) was washed with dry hexane (10mL × 2), dried with a stream of $N_2$, and suspended in dry THF (25mL). A solution of 3-butyn-1-ol (3 mmol) in THF (5mL) was slowly added, and the resulting mixture was stirred at rt for 30 min and cooled to –40 °C. A solution of nitroolefin **2** (1.0 mmol) in THF (5mL) was added dropwise, and the mixture was warmed to 0 °C

and stirred for an additional 3 h. The reaction was quenched by addition of 1 N HCl (10 mL) solution. The organic and aqueous layers were separated and the aqueous layer was extracted with $Et_2O$ (20mL × 3). The combined organic layers were then washed with water and brine, dried ($MgSO_4$), and concentrated in reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 15:1).

**1-(3-Butynyloxy)-2-nitro-1-phenylethane (3a)**: Colorless oil. IR (KBr) 1550 ($NO_2$) $cm^{-1}$; $^1H$ NMR δ 1.93 (t, *J*=2.6 Hz, 1H), 2.35 (dt, *J*=6.9, 2.6 Hz, 2H), 3.45 (m, 2H), 4.36 (dd, *J*=9.8, 3.4 Hz, 1H), 4.57 (dd, *J*=13.0, 9.8 Hz, 1H), 5.10 (dd, *J*=10.1, 3.4 Hz, 1H), 7.37 (m, 5H); $^{13}C$ NMR ($CDCl_3$) δ 19.3, 67.0, 69.5, 78.1, 79.8, 80.6, 126.5, 128.7, 128.8, 135.9; Ms (m/z, rel. intensity) 219 ($M^+$, 0.6), 145 (59.9), 104 (100), 91 (38.5), 77 (11.8); HRMS calcd for $C_{12}H_{13}NO_3$ 219.0895, found 219.0896.

**1-(3-Butynyloxy)-1-(2-chlorophenyl)-2-nitroethane (3b)**: Colorless oil. IR (KBr) 1550 ($NO_2$) $cm^{-1}$; $^1H$ NMR δ 1.98 (t, *J*=2.6 Hz, 1H), 2.45 (dt, *J*=6.6, 2.6 Hz, 2H), 3.56 (m, 2H), 4.51 (m, 2H), 5.56 (dd, *J*=9.8, 3.0 Hz, 1H), 7.37 (m, 3H), 7.61 (dd, *J*=2.09, 7.3 Hz, 1H); $^{13}C$ NMR δ 19.5, 68.0, 69.6, 75.2, 78.1, 80.5, 127.5, 127.7, 129.8, 130.0, 132.4, 133.6; Ms (m/z, rel. intensity) 255 ($M^+$+2, 0.7), 253 ($M^+$, 1.9), 186 (91.6), 171 (100), 141 (100); HRMS calcd for $C_{12}H_{12}ClNO_3$ 253.0506, found 253.0510.

**1-(3-Butynyloxy)-1-(4-chlorophenyl)-2-nitroethane (3c)**: Colorless oil. IR (KBr) 1550 ($NO_2$) $cm^{-1}$; $^1H$ NMR δ 1.96 (t, *J*=2.6 Hz, 1H), 2.43(dt, *J*=6.8, 2.6 Hz, 2H), 3.50 (ddd, *J*=13.1, 6.8, 2.5 Hz, 2H), 4.37 (dd, *J*=13.1, 3.5 Hz, 1H), 4.61 (dd, *J*=13.1, 9.8 Hz, 1H), 5.10 (dd, *J*=3.5, 9.8 Hz, 1H), 7.37 (m, 4H); $^{13}C$ NMR δ 19.7, 67.6, 69.6, 77.8, 79.9, 80.5, 128.1, 129.3, 134.6, 135.1; Ms (m/z, rel. intensity) 255 ($M^+$ +2, 1.0), 253 ($M^+$, 2.5), 163 (100), 140 (67.6), 138 (100); HRMS calcd for $C_{12}H_{12}ClNO_3$ 253.0506, found 253.0504.

**1-(3-Butynyloxy)-1-isopropyl-2-nitroethane (3d)**: Colorless oil. IR (KBr) 1555 ($NO_2$) $cm^{-1}$; $^1H$ NMR δ 0.97 (d, *J*=6.9 Hz, 3H), 0.99 (d, *J*=6.9 Hz, 3H),

1.97 (m, 2H), 2.42 (dt, *J*=6.9, 2.7 Hz, 2H), 3.64 (m, 2H), 3.91 (m, 1H), 4.43 (m, 2H), 7.37(m, 4H); $^{13}$C NMR δ 17.7, 17.8, 20.0, 30.3, 69.3, 69.4, 77.0, 80.8, 81.7; HRMS calcd for $C_9H_{15}NO_3$ 185.1052, found 185.1052.

**General procedure for the preparation of 4,5-Dihydro-7*H*-pyranoisoxazole 4**: To a solution of nitroether **3** (5 mmol) dissolved in dry benzene (30 mL) was added phenyl isocyanate (25 mmol) and $Et_3N$ (0.5 mmol), and 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 ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel using a *n*-hexane/EtOAc eluent (10:1).

**4,5-Dihydro-7-phenyl-7*H*-pyrano[3,4-*c*]isoxazole (4a)**: Yellow solid (mp 43-45 °C). IR (KBr) 1450, 1495, 1610 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.77 (dtd, *J*=15.6, 4.6, 0.6 Hz, 1H), 2.82 (dddd, *J*=15.6, 8.6, 5.5, 1.3 Hz, 1H), 3.79 (ddd, *J*=11.8, 8.6, 4.8 Hz, 1H), 4.09 (ddd, *J*=11.8, 5.5, 4.4 Hz, 1H), 5.81 (s, 1H), 7.39 (m, 5H, Ar), 8.21 (br s, 1H); $^{13}$C NMR δ 18.8, 62.4, 74.2, 111.4, 126.8, 127.6, 137.8, 152.9, 159.2; Ms (m/z, rel. intensity) 201 ($M^+$, 24.2), 200 ($M^+$-1, 21.5), 172 (100), 173 (89.6), 105 (100), 95 (100); HRMS calcd for $C_{12}H_{11}NO_2$ 201.0790, found 201.0793.

**4,5-Dihydro-7-(2-chlorophenyl)-7*H*-pyrano[3,4-*c*]isoxazole (4b)**: Yellow oil. IR (neat) 1610, 1500, 1440 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.70 (dt, *J*=15.7, 3.3 Hz, 1H), 2.88 (dddd, *J*=15.7, 10.4, 5.8, 1.3 Hz, 1H), 3.78 (dddd, *J*=11.8, 10.4, 4.1, 1.3 Hz, 1H), 4.19 (ddd, *J*=11.8, 5.8, 2.8 Hz, 1H), 6.18 (s, 1H), 7.32 (m, 4H), 8.22 (s, 1H); $^{13}$C NMR δ 18.6, 63.2, 71.8, 111.4, 126.0, 128.1, 129.0, 135.4, 152.9, 158.6; Ms (m/z, rel. intensity) 237 ($M^+$+2, 3.7), 235 ($M^+$, 11), 141 (95), 95 (100), 65 (89), 67 (73); HRMS calcd for $C_{12}H_{10}ClNO_2$ 235.0400, found 235.0399.

**4,5-Dihydro-7-(4-chlorophenyl)-7*H*-pyrano[3,4-*c*]isoxazole(4c)**: Yellow solid (mp 41-42 °C). IR (KBr) 1610, 1490, 1405 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.73 (dt,

*J*=15.8, 4.4 Hz, 1H), 2.85 (dddd, *J*=15.8, 8.6, 5.3, 0.7 Hz, 1H), 3.79 (ddd, *J*=11.7, 8.6, 4.5 Hz, 1H), 4.09 (ddd, *J*=11.7, 5.3, 4.3 Hz, 1H), 5.80 (s,1H), 7.33-7.44 (m, 4H), 8.24 (br s,1H); $^{13}$C NMR δ 19.0, 62.7, 73.6, 111.4, 127.8, 133.3, 136.4, 153.1, 159.0; Ms (m/z, rel. intensity) 237 ($M^+$ +2, 3.5), 235 ($M^+$, 9.6), 200 (87.9), 141 (23.6), 95 (100); HRMS calcd for $C_{12}H_{10}ClNO_2$ 235.0400, found 235.0398.

**4,5-Dihydro-7-isopropyl-7*H*-pyrano[3,4-*c*]isoxazole (4d)**: Yellow oil. IR (neat) 1610, 1490, 1410 (isoxazole) cm$^{-1}$; $^1$H NMR δ 0.98 (d, *J*=6.9 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 2.34 (m, 1H), 2.60 (dddd, *J*=15.6, 3.8, 2.0, 0.9 Hz, 1H), 2.75 (dddd, *J*=15.6, 11.2, 5.4, 1.1 Hz, 1H), 3.55 (ddd, *J*=11.4, 11.2, 3.8 Hz, 1H), 4.10 (ddd, *J*=11.4, 5.4, 2.0 Hz, 1H), 4.55 (d, *J*=3.9 Hz, 1H), 8.18 (dd, *J*=0.9, 1.1 Hz, 1H); $^{13}$C NMR δ 16.7, 18.5, 19.9, 32.1, 63.9, 78.3,112.7, 153.0, 160.2; Ms (m/z, rel. intensity) 166 ($M^+$, 5.4), 124 (97), 95 (100), 43 (74); HRMS calcd for $C_9H_{13}NO_2$ 167.0946, found 167.0947.

**General procedure for reaction of 4 with $BX_3$**: To a cooled solution of **5** (2 mmol) in dry $CH_2Cl_2$ (2 mL) at 0 °C was added a solution of $BX_3$ (2 mmol), and the mixture was stirred until the reaction was completed. $Et_2O$ (10 mL) was added, and the resulting solution was poured into cold water (5 mL) with good stirring, the organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (2 × 10 mL). The combined organic solution was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1). The reaction times were 2 h for $BCl_3$ and 30 min for $BBr_3$, respectively.

**3-[Chloro(phenyl)methyl]-4-(2-hydroxyethyl)isoxazole (5a)**: Brown oil. IR (neat) 3400 (OH), 1610, 1500, 1440 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.10 (br s, 1H), 2.45 (dt, *J*=15.6, 6.3 Hz, 1H), 2.56 (dt, *J*=15.6, 5.8 Hz, 1H), 3.59 (dt, *J*=10.5, 6.3 Hz, 1H), 3.64 (dt, *J*=10.5, 5.8 Hz, 1H), 6.26 (s, 1H), 7.40 (m, 5H), 8.30 (br s, 1H);

$^{13}$C NMR δ 25.0, 54.0, 61.0, 115.0, 127.4, 128.6, 128.7, 136.8, 157.5, 161.5 ; Ms (m/z, rel. intensity) 284 ($M^+$+2, 1.7), 282 ($M^+$, 5.2), 202 (100), 91(95); HRMS calcd for $C_{12}H_{12}ClNO_2$ 236.0478, found 236.0480.

**3-[Chloro(2-chlorophenyl)methyl]-4-(2-hydroxyethyl)isoxazole (5b)**: Brown oil. IR (neat) 3400 (OH), 1600, 1440 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.59 (t, *J*=6.1 Hz, 2H), 2.95 (br s, 1H), 3.70 (t, *J*=6.1 Hz, 2H), 6.58 (s, 1H), 7.32 (m, 3H), 7.69 (d, *J*=7.44 Hz, 1H), 8.31 (br s, 1H); $^{13}$C NMR δ 24.7, 50.1, 60.8, 115.1, 127.3, 129.4, 130.1, 132.4, 134.5, 157.3, 160.7; Ms (m/z, rel. intensity) 273 ($M^+$+2, 1.4), $M^+$ (271, 2.1), 206 (100), 89 (87); HRMS calcd for $C_{12}H_{11}Cl_2NO_2$ 271.0167, found 271.0165.

**3-[Chloro(4-chlorophenyl)methyl]-4-(2-hydroxyethyl)isoxazole (5c)**: Brown oil. IR (neat) 3420 (OH), 1600, 1490 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.36 (br s, 1H), 2.47 (dtd, *J*=15.2, 6.8, 0.9 Hz, 1H), 2.59 (dtd, *J*= 15.2, 6.5, 0.8 Hz,1H), 3.65 (dt, *J*=11.3, 6.8 Hz, 1H), 3.70 (dt, *J*=11.3, 6.5 Hz, 1H), 6.22 (s, 1H), 7.37 (m, 4H), 8.33 (br s, 1H); $^{13}$C NMR δ 24.9, 53.2, 61.0, 115.1, 128.8, 128.9. 134.6, 135.4, 157.6, 161.2; Ms (m/z, rel. intensity) 273 ($M^+$+2, 1.5), 271 ($M^+$, 2.2), 159 (69), 125 (100), 89 (82.5); HRMS calcd for $C_{12}H_{11}Cl_2NO_2$ 271.0167, found 271.0165.

**3-[Bromo(phenyl)methyl]-4-(2-hydroxyethyl)isoxazole (6a)**: Brown solid (mp 72-74 °C ). IR (neat) 3390 (OH), 1605, 1410 (isoxazole) cm$^{-1}$; $^1$H NMR δ 2.01 (br s, 1H), 2.54 (dtd, *J*=15.5, 6.3, 0.9 Hz, 1H), 2.62 (dtd, *J*= 15.5, 6.6, 0.9 Hz, 1H), 3.70 (dt, *J*=9.0, 6.3 Hz, 1H), 3.72 (dt, *J*=9.0, 6.3 Hz, 1H), 6.27 (s, 1H), 7.35 (m, 3H), 7.52 (m, 2H), 8.34 (br s, 1H); $^{13}$C NMR δ 25.2, 42.4, 61.3, 115.1, 128.4, 128.7, 128.81, 137.2, 157.4; Ms (m/z, rel. intensity) 284 ( $M^+$+ 2, 4.7), 282 ($M^+$ , 5.2), 202 (100), 91 (95); HRMS calcd for $C_{12}H_{12}BrNO_2$ 281.0051, found 281.0050.

**3-[Bromo(2-chlorophenyl)methyl]-4-(2-hydroxyethyl)isoxazole (6b)**: Brown oil. IR (neat) 3340 (OH), 1600, 1440 (isoxazole) $cm^{-1}$; $^1H$ NMR δ 2.55 (t, *J*=6.0 Hz, 2H), 3.07 (br s, 1H), 3.66 (dt, *J*=10.5, 6.0 Hz, 1H), 3.71 (dt, *J*=10.5, 6.0 Hz, 1H), 6.59 (s, 1H), 7.29 (m, 3H), 7.72 (dd, *J*=7.2, 2.4, 1H), 8.34 (br s, 1H); $^{13}C$ NMR δ 24.8, 37.5, 60.8, 114.9, 127.4, 129.4, 130.1, 131.1, 132.1, 134.9, 157.3, 160.8; Ms (m/z, rel. intensity) 318 ( $M^+$+ 2, 2.5), 316 ($M^+$, 2.2), 236 (93), 125 (100); HRMS calcd for $C_{12}H_{11}BrClNO_2$ 314.9662, found 314.9661.

**3-[Bromo(4-chlorophenyl)methyl]-4-(2-hydroxyethyl)isoxazole (6c)**: Brown solid (mp 82-83 °C ). IR (neat) 3410 (OH), 1550, 1490 (isoxazole) $cm^{-1}$; $^1H$ NMR δ 1.69 (br s, 1H), 2.56 (dtd, *J*=15.6, 6.0, 0.9 Hz, 3H), 2.65 (dtd, *J*=15.6, 6.0, 0.9 Hz, 1H), 3.74 (dt, *J*=10.5, 6.0 Hz, 1H), 3.79 (dt, *J*=10.5, 6.0 Hz, 1H), 6.22 (s, 1H), 7.34 (d, *J*=8.7 Hz, 2H), 7.49 (d, *J*= 8.7, 2H), 8.36 (br s, 1H); $^{13}C$ NMR δ 25.1, 41.3, 61.4, 115.1, 128.9, 129.9, 134.8, 135.8, 157.4, 161.3; Ms (m/z, rel. intensity) 310 [( $M^+$+ 2)-$H_2O$, 6.6], 298 ($M^+$- $H_2O$, 6.8), 236 (85), 125 (100); Anal. Calcd for $C_{12}H_{11}BrClNO_2$: C, 45.53; H, 3.53; N, 4.42. Found: C, 45.61; H, 3.66; N, 4.38.

**3-[Bromo(isopropyl)methyl]-4-(2-hydroxyethyl)isoxazole (6d)**: Brown oil. IR (neat) 3440 (OH), 1550, 1420 (isoxazole) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.96 (d, *J*=6.6, 3H), 1.25 (d, *J*=6.6, 3H), 2.46 (m, 1H), 2.64-2.80 (m, 2H), 4.78 (d, *J*=9.0, 1H), 8.33 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 20.4, 21.5, 25.2, 33.6, 50.19, 61.1, 115.1, 156.9, 161.9; Ms (m/z, rel. intensity) 250 ($MH^+$+2, 5.4), 248 ($MH^+$, 6.5), 168 (100), 96 (74), 55 (90); Anal. Calcd for $C_9H_{14}BrNO_2$: C, 43.57; H, 5.69; N, 5.65. Found: C, 43.69; H, 5.61; N, 5.47.

**4-(2-Bromoethyl)-3-[bromo(isopropyl)methyl]isoxazole (7)**. To a stirred solution of alcohol **6b** (3.16 g, 10 mmol) dissolved in dry $CH_2Cl_2$ (20 mL) was

slowly added $PBr_3$ (3.25 g, 12 mmol) at 0 °C, and the mixture was stirred for 30 min. The reaction mixture was poured into cold water (20 mL) and the layers separated. The organic solution was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using an eluent *n*-hexane/EtOAc () to give **7** in 96% yield (3.63 g) as a yellowish oil. IR (neat) 1600, 1560, 1470 (isoxazole) $cm^{-1}$; $^1H$ NMR δ 2.9 (t, *J*=6.9 Hz, 2H), 3.35 (m, 2H), 6.58 (s, 1H), 7.25 (m, 4H), 7.72 (m, 1H), 8.41 (s, 1H)); $^{13}C$ NMR δ 25.4, 30.4, 37.1, 115.0, 127.6, 129.6, 130.3, 131.6, 132.2, 134.8, 157.3, 160.5; Ms (m/z, rel. intensity) 302 ($M^+$+4-Br, 27), 300 ($M^+$+2-Br, 100), 298 ($M^+$-Br, 74), 300 ($M^+$-Br-Cl, 7.4), 266 ($M^+$+2-Br-Cl, 7.0), 127 (22), 125 (34); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 37.98; H, 2.66; N. 3.69. Found: C, 38.12; H, 2.71; N, 3.75.

**3-[(2-Chlorophenyl)(benzamino)methyl]-4-(2-hydroxyethyl)isoxazole (8).** To a stirred mixture of bromoalcohol **6b** (633 mg, 2 mmol) and anhydrous $K_2CO_3$ (276 mg, 2 mmol) in dry DMF (4 mL) was added benzylamine (236 mg, 2.2 mmol). After being stirred for 2 h at rt, the reaction mixture was poured into water (5 mL) and extracted with $Et_2O$ (10 mL × 2). The extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 4:1) to give **8** in 95% yield (653 mg) as a pale yellow oil. IR (neat) 3400 (NH), 3350 (OH), 1600, 1440 (isoxazole) $cm^{-1}$; $^1H$ NMR δ 2.44 (t, *J*=11.7 Hz, 2H), 2.74 (br, 2H), 3.52 (m, 2H), 3.69 (s, 2H), 5.42 (s, 1H), 7.15-7.49 (m, 9H), 8.12 (br s,1H); $^{13}C$ NMR δ 25.0, 51.4, 54.1, 62.0, 115.6, 127.3, 127.3, 128.4, 128.5, 128.9, 129.1, 129.8, 133.9, 136.3, 138.3, 138.7, 156.7, 156.5, 162.2; Ms (m/z, rel. intensity) 345 ($MH^+$+2, 1.0), 343 ($MH^+$, 3.6), 313 (2.3), 311(4.9), 253 (1.8), 251 (4.7), 106

(100), 91 (100); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 66.57; H, 5.59; N, 8.17. Found: C, 66.64; H, 5.63; N, 8.09.

**Acknowledgements:** This work was supported by the Korea Science and Engineering Foundation (961-0302-021-2).

**References and Notes:**

1. (a) For a review: Lang, A. and Lin, Y. -i. "*Comprehensive Heterocyclic Chemistry*", Katrizky, A. R., Ed., Pergamon Press, Oxford, **1984**; Vol. 6, pp. 1-130. For recent our works: (b) Kim, H. J., Hwang, K. –J. and Lee, J. H., *Biosci. Biotech. Biochem.* **1994**, *58*, 1191. (c) Hwang, K. –J., Kim, H. J. and Lee, J. H., *Korean J. Med. Chem.* **1994**, *4*, 2. (d) Kim, H. J., Hwang, K. –J. and Lee, J. H., *Bull. Korean Chem. Soc.* **1997**, *18*, 534.
2. Claisen, L., *Ber.* **1981**, *24*, 3900.
3. Caramella, P. and Grunanger, P. "*1,3-Dipolar Cycloaddition Chemistry*", Padwa, A., Ed., John Wiley and Sons, New York, **1984**; Vol. 1, pp. 291-392.
4. (a) Kim, H. J., Lee, J. H., Olmstead, M. M. and Kurth, M. J., *J. Org. Chem.* **1992**, *57*, 6513. (b) Kim, H. J. and Lee, J. H., *Heterocycles,* **1994**, *38*, 1383.
5. (a) Duffy, J. L., Kurth, J. A. and Kurth, M. J., *Tetrahedron Lett.,* **1993**, *34*, 1259. (b) Duffy, J. L. and Kurth, M. J., *J. Org. Chem.* **1994**, *59*, 3783.
6. Mukayama, T. and Hoshino, T., *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(Received in Japan 6 February 1998)