Synthesis of 2-Cyanomethyl-3-hydroxy-5-iodomethyltetrahydrofuran from Various Isoxazolines: Effects of 3-Substituents in the Diastereoselective Iodoetheration Reactions of Isoxazolines

Hyoung Cheul Kim, Min Jung Seo, Jung Ki Kim, Jae-Don Lee,† Zaesung No, and Hyoung Rae Kim*

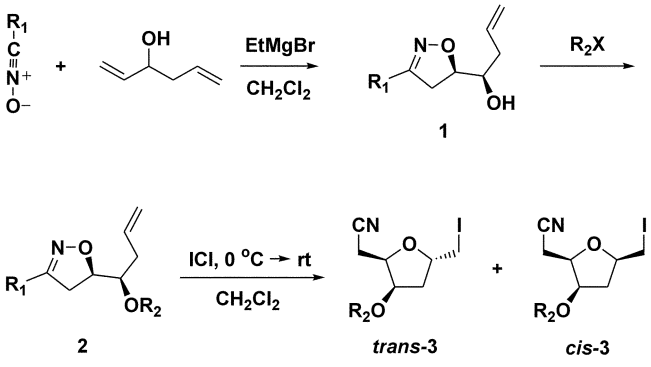
Medicinal Science Division, Korea Research Institute of Chemical Technology, P. O. Box 107, Yusong, Daejeon 305-600, Korea
†Bioneer Cooperation, High Tech Park, 124 Chuckbook-Rhi, Namee-Myun, Cheongwon-Kun, Chungbuk 363-810, Korea
Received October 2, 2003

Key Words : 2-Cyanomethyl-3-hydroxy-5-iodomethyltetrahydrofuran, Nitrile oxide-olefin cycloaddition, Iodoetheration, Diphenylmethylhydroximoyl chloride

Highly substituted tetrahydrofuran derivatives were prepared from isoxazolines by electrophilic iodoetheration using iodine or iodine monochloride.[1,2] In the mechanism of the iodoetheration reaction, the cationic stabilities of the 3-substituents (R_1) in the isoxazolines (**1**) were very important because the 3-substituents should detach from the isoxazoline ring as cations to form 2-cyanomethyl-3-hydroxy-5-iodomethyltetrahydrofurans (**3**)[2] as shown in Scheme 1. In general, trityl group or α-silyloxylbenzyl group was applied as R_1 groups and both of them afforded good results in the iodoetheration. However, we found these groups were not convenient to be prepared. The triphenylacetonitrile oxide (trityl group)[3] was prepared through silver fulminate that was a very explosive intermediate, and was too dangerous for us to prepare.

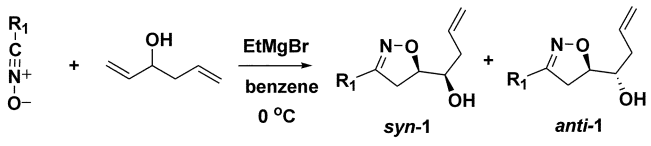
2-*t*-Butyldimethylsilyloxy-2-phenylacetohydroximoyl chloride,[2] a precursor of 2-*t*-butyldimethylsilyloxy-2-phenylacetonitrile oxide (α-silyloxylbenzyl group) was prepared from mandelic acid in several steps. The compound was not stable enough to store even in a refrigerator, moreover the chiral center in mandelic acid only made the reaction to be complicated and was not necessary in the iodoetheration reaction. In order to find a better group for R_1, we examined diphenylmethyl and 4-methoxybenzyl groups. Diphenylacetohydroximoyl chloride[4] was prepared from commercially available diphenylacetaldehyde and could be easily converted to diphenylacetonitrile oxide by triethylamine or ethylmagnesium bromide. 4-Methoxyphenylacetohydroximoyl chloride could not be prepared from 4-methoxyphenylacetaldehyde because the oxidation of 4-methoxyphenethyl alcohol afforded only 4-methoxybenzaldehyde. Thus, 4-methoxyphenylacetohydroximoyl chloride[5] was prepared from 4-methoxy-β-nitrostyrene by titanium tetrachloride and triethylsilane in low yield, and the purification of 4-methoxyphenylacetohydroximoyl chloride was a very hard job because of its instability. Interestingly, diphenylacetohydroximoyl chloride had low solubility in organic solvents such as hexane and dichloromethane and we could easily isolate it as a white solid by washing the crude compound with solvent (hexane/dichloromethane = 1/1). Moreover diphenylacetohydroximoyl chloride was so stable enough to store several month at room temperature, while 4-methoxyphenylacetohydroximoyl chloride was unstable and had to be used immediately. Four kinds of nitrile oxides were examined in the cycloaddition reactions[6] and the results were summarized in Table 1.

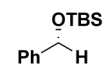
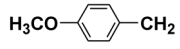
Triphenylacetonitrile oxide and diphenylacetonitrile oxide were used as isolated forms (Entry 1 and 2), and 2-*t*-butyldimethylsilyloxy-2-phenylacetonitrile oxide and 4-methoxyphenylacetonitrile oxide were generated from (2-*t*-



Scheme 1

Table 1. Diastereoselectivity in the Nitrile Oxide-Olefin Cycloaddition Reaction of Various Nitrile Oxides with 1,5-Hexadien-3-ol

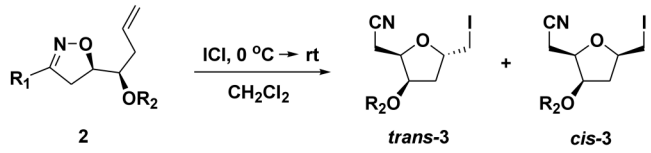


Entry	R_1	Yield (%)[a]	syn:anti[b]
1	Ph_3C	75	18 : 1
2	Ph_2CH	76	24 : 1
3		71	25 : 1
4		44	22 : 1

[a]Isolated yields. [b]The ratio were determined by HPLC.

*Corresponding author. E-mail: hyungrk@krict.re.kr

Table 2. Iodoetheration Reaction of 3-Substituted-*syn*-5-[1-(Protectedhydroxy)-3-butenyl]isoxazolines



2 ***trans*-3** ***cis*-3**

Entry	R_1	R_2	Yield (%)[a]	*trans:cis*[b]
1	Ph_3C	TBDMS	79	5 : 1
2		MPM	70	29 : 1
3	Ph_2CH	TBDMS	74	3 : 1
4		MPM	73	25 : 1
5	OTBS, Ph, H	TBDMS	74	3 : 1
6		MPM	69	2 : 1
7	H_3CO–C$_6$H$_4$–CH_2	TBDMS	71	2 : 1
8		MPM	68	3 : 1

[a]Isolated yields. [b]The ratios were determined by GC/MS.

butyldimethylsilyloxy-2-phenylacetohydroximoyl chloride and 4-methoxyphenylacetohydroximoyl chloride with excess ethylmagnesium bromide because of their instability (Entry 3 and 4). Diphenylacetonitrile oxide was generated from diphenylacetohydroximoyl chloride by triethylamine in dichloromethane and was separated by extraction. The resulting diphenylacetonitrile oxide was stable and soluble in dichloromethane and benzene but it easily underwent nucleophilic addition of ethylmagnesium bromide to form 1,1,-diphenyl-2-hydroximinobutane. As shown in Table 1, the reaction of diphenylacetonitrile oxide gave good yield with good diastereoselectivity (Entry 2). In case of 4-methoxyphenylacetonitrile oxide, relatively low yield was observed with low diastereoselectivity (Entry 4). The *syn*-isomers of isoxazolines (**1**) were isolated and the hydroxyl groups were protected with TBDMS and MPM groups. The protected isoxazolines (**2**) were reacted with iodine monochloride and converted to the *O*-protected 2-cyanomethyl-3-hydroxy-5-iodomethyltetrahydrofurans (**3**).[2] The results were summarized in Table 2.

All kinds of substituents in 3-position (R_1) gave good yields in iodoetheration, however the ratios of diastereomers were different. In the iodoetheration reaction of **2**, protecting groups attached on the hydroxyl group (R_2) were important because of their influences on the diastereoselectivity. The ratio of diastereomers **3** varied depending upon the protection groups. MPM protected isoxazolines showed much better diastereoselectivity than TBDMS protected ones. Trityl group gave the best result (Entry 2), but diphenylmethyl group also showed good diastereoselectivity (Entry 4).

In conclusion, diphenylacetohydroximoyl chloride was the most useful precursor in the nitrile oxide-olefin cycloaddition reaction owing to its easy preparation and good stability, and iodoetheration of the resulting *O*-protected isoxazolines gave considerable results with good diastereoselectivity.

Experimental Section

General. Unless otherwise specified, all reagents were purchased from commercial sources and were used without further purification. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are not corrected. IR spectra were recorded on a Mattson Genesis II FTIR spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker AMX-500. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants are given in Hz. MS spectra were recorded by EI method and HRMS spectra were measured on a Jeol JMX-DX 303 mass spectrometer. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

Diphenylacetohydroximoyl chloride: To a solution of diphenylacetaldehyde (10.0 g, 50.7 mmol) and hydroxylamine hydrochloride (4.07 g, 58.6 mmol) in 50% aq ethanol was added slowly NaOH (2.34 g, 58.6 mmol) dissolved in water (100 mL) at 25 °C, and the reaction mixture was stirred for 2 h at 25 °C. Ice-water was added slowly to the reaction mixture with good stirring and the resulting precipitates were filtered, washed with water, and dried to give diphenylacetaldoxime (10.6 g, 98%). The aldoxime (10.6 g, 49.9 mmol) was dissolved in DMF (100 mL) and NCS (7.33 g, 54.9 mmol) was added slowly at near 25 °C. After being stirred for 1 h, the reaction mixture was poured into ice-water to form precipitates. The precipitates were filtered, washed with water, and dried. The dried solids were washed again with hexane-dichloromethane (v/v, 1/1) and dried to give diphenylacetolhydroximoyl chloride (12.1 g, 98%) as a white powder.

mp 155.0-156.1 °C; ^{1}H NMR ($CDCl_3$) δ 5.26 (s, 1H), 7.23-7.39 (m, 10H), 7.67 (s, 1H); IR (NaCl) 3289, 2360, 1090, 988, 723, 698 cm^{-1}.

3-Diphenylmethyl-*syn*-5-(1-hydroxy-3-butenyl)isoxazoline (*syn*-**1**, R_1=diphenylmethyl) : Diphenylacetonitrile oxide (3.00 g, 11.6 mmol) was prepared as a solution in benzene from diphenylacetohydroximoyl chloride by being treated with triethylamine, extracted, and dried over anhydrous $MgSO_4$. To a solution of 1,5-hexadien-3-ol (1.55 g, 15.7 mmol) in benzene (50 mL) was slowly added EtMgBr (8.0 mL, 3.0 M in THF) at 0 °C, and the reaction mixture was stirred for 30 min at that temperature. The solution of diphenylacetonitrile oxide was added slowly to the reaction mixture at 0 °C. After being stirred for 3 h, the reaction mixture was poured into ice-water, extracted with ethyl acetate (80 mL × 2), washed with aqueous 5% HCl solution (100 mL) and brine, dried over $MgSO_4$, and then concentrated to give an oil. The oily residue was purified by flash column chromatography (*n*-hex/EtOAc, 5/1) to afford ***syn*-1** (R_1=diphenylmethyl) as white solids (3.66 g, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (d, 1H, J = 7.1 Hz), 2.32 (t, 2H, J = 6.6 Hz), 2.89 (dd, 1H, J = 7.8, 17.2 Hz), 2.97 (dd, 1H, J = 10.8, 17.2 Hz), 3.54-3.59 (m, 1H), 4.55 (ddd, 1H, J = 4.1, 7.8, 11.6 Hz), 5.11-5.15 (m, 2H), 5.17 (s, 1H),

5.79-5.87 (m, 1H), 7.24-7.34 (m, 1H); MS m/z (relative intensity) 307 (M^+, 2), 236 (5), 206 (4), 167 (100); IR (NaCl) 3451, 3027, 2923, 1494, 1452, 928, 749 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_2$ 307.15722, found 307.15708.

***syn*-5-[1-(*tert*-Butyldimethylsilyloxy)-3-butenyl]-3-diphenylmethyl isoxazole**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.83 (s, 9H), 2.01-2.04 (m, 1H), 2.29-2.34 (m, 1H), 2.80 (dd, 1H, *J* = 8.9, 17.3 Hz), 2.87 (dd, 1H, *J* = 10.8, 17.3 Hz), 3.77-3.80 (m, 1H), 4.59 (ddd, 1H, *J* = 5.5, 9.0, 10.8 Hz), 5.03 (d, 2H, *J* = 7.7 Hz), 5.16 (s, 1H), 5.76-5.85 (m, 1H), 7.26-7.35 (m, 10H); MS m/z (relative intensity) 422 (M^+, 47), 195 (7), 167 (100); IR (NaCl) 3062, 3028, 1494, 1453, 1255, 1111, 913, 835 cm^{-1}; HRMS calcd for $C_{26}H_{35}NO_2Si$, 421.24370 found 421.24225.

3-Diphenylmethyl-*syn*-5-[1-(4-methoxybenzyloxy)-3-butenyl]-isoxazole: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16-2.30 (m, 1H), 2.32-2.37 (m, 1H), 2.77 (dd, 1H, *J* = 10.0, 20.0 Hz), 2.86 (dd, 1H, *J* = 15.0, 20.0 Hz), 3.44-3.48 (m, 1H), 3.80 (s, 3H), 4.53 (d, 1H, *J* = 15.0 Hz), 4.58 (d, 1H, *J* = 15.0 Hz), 4.67 (ddd, 1H, *J* = 5.0, 10.0, 15.0 Hz), 5.04-5.07 (m, 2H), 5.16 (s, 1H), 5.77-5.84 (m, 1H), 6.83 (d, 2H, *J* = 8.6 Hz), 7.18 (d, 2H, *J* = 8.6 Hz), 7.24-7.31 (m, 10H): MS m/z (relative intensity) 428 (M^+, 53), 350 (7), 236 (6), 210 (7), 167 (71), 121 (100); IR (NaCl) 3062, 3044, 2932, 1612, 1513, 1248, 1080, 1033 cm^{-1}; HRMS calcd for $C_{28}H_{29}NO_3$ 427.21474 found 427.21399.

3-(4-Methoxybenzyl)-*syn*-5-(1-hydroxy-3-butenyl)isoxazoline (*syn*-**1**, R_1=4-methoxybenzyl): To a solution of 1,5-hexadien-3-ol (1.55 g, 15.7 mmol) in benzene (50 mL) was slowly added EtMgBr (16.0 mL, 3 M in THF) at 0 °C, and the reaction mixture was stirred for 30 min. The solution of crude 4-methoxyphenylacetohydroximoyl chloride (4.71 g, 23.6 mmol) in benzene was added slowly to the reaction mixture at 0 °C. After being stirred for 3 h, the reaction mixture was poured into ice-water, extracted with ethyl acetate (80 mL × 2), washed with aqueous 5% HCl solution (100 mL) and brine, dried over $MgSO_4$, and then concentrated to give an oil. The oily residue was purified by flash column chromatography (*n*-hex/EtOAc, 5/1) to afford ***syn*-1** (R_1=4-methoxybenzyl) as pale yellow oil (1.80 g, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (t, 2H, *J* = 6.4 Hz), 2.72 (dd, 1H, *J* = 8.0, 17.3 Hz), 2.85 (dd, 1H, *J* = 10.5, 17.3 Hz), 3.51-3.54 (m, 1H), 3.61 (dd, 2H, *J* = 15.0, 19.5 Hz), 3.79 (s, 3H), 4.45-4.50 (m, 1H), 5.10-5.14 (m, 2H), 5.78-5.86 (m, 1H), 6.85 (d, 2H, *J* = 8.5 Hz), 7.13 (d, 2H, *J* = 8.5 Hz); MS m/z (relative intensity) 261 (M^+, 9), 190 (2), 147 (5), 132 (3), 121 (100), 107 (15), 91 (11); IR (NaCl) 3435, 2933, 2360, 2341, 1513, 1248 cm^{-1}; HRMS calcd for $C_{15}H_{19}NO_3$ 261.13649, found 261.13716.

***syn*-5-[1-(*tert*-Butyldimethylsilanyloxy)-3-butenyl]-3-(4-methoxybenzyl)isoxazole**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.84 (s, 9H), 1.97-1.99 (m, 1H), 2.25-2.27 (m, 1H), 2.68 (ddd, 2H, *J* = 8.5, 11.2, 16.8 Hz), 3.50 (d, 1H, *J* = 14.9 Hz), 3.60 (d, 1H, *J* = 14.9 Hz), 3.69-3.73 (m, 1H), 4.49 (ddd, 1H, *J* = 5.4, 8.5, 11.2 Hz), 3.78 (s, 3H), 4.99-5.03 (m, 1H), 5.74-5.80 (m, 1H), 6.83-6.85 (d, 2H, *J* = 8.7 Hz), 7.11-7.13 (d, 2H, *J* = 8.7 Hz); MS m/z (relative intensity) 318 (M^+, 0.1), 261 (0.2), 185 (2), 160 (0.4), 121 (100), 101 (4), 91 (3); IR (NaCl) 2953, 2856, 1513, 1249, 1108, 836 cm^{-1}; HRMS calcd for $C_{21}H_{33}NO_3Si$ 375.22297, found 375.22577.

3-(4-Methoxybenzyl)-*syn*-5-[1-(4-methoxybenzyloxy)-3-butenyl]-isoxazole: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17-2.23 (m, 1H), 2.29-2.34 (m, 1H), 2.63 (dd, 1H, *J* = 8.4, 17.1 Hz), 2.73 (dd, 1H, *J* = 10.8, 17.1 Hz), 3.42-3.45 (m, 1H), 3.55 (d, 1H, *J* = 14.9 Hz), 3.62 (d, 1H, *J* = 14.9 Hz), 3.80 (s, 6H), 4.53 (dd, 2H, *J* = 11.4, 19.4 Hz), 4.61 (ddd, 1H, *J* = 5.0, 8.4, 10.8 Hz), 5.04-5.11 (m, 2H), 5.77-5.85 (m, 1H), 6.84 (d, 4H, *J* = 8.6 Hz), 7.13 (d, 2H, *J* = 8.5 Hz), 7.18 (d, 2H, *J* = 8.5 Hz); MS m/z (relative intensity) 381 (M^+, 0.2), 311 (1), 190 (6), 137 (4), 121 (100), 91 (5), 77(8); IR (NaCl) 2933, 2837, 2360, 2341, 1512, 1248 cm^{-1}; HRMS calcd for $C_{23}H_{27}NO_4$ 381.19400, found 381.19392.

Typical procedure of iodoetheration[2] (Entry 3 in Table 2): To a solution of 5-(1-*t*-butyldimethylsilyloxy-3-butenyl)-3-diphenylmethyl-4,5-dihydroisoxazole (**2**, 0.68 g, 1.60 mmol) in dichloromethane (5 mL) was slowly added iodine monochloride (2.0 mL, 1.0 M in dichloromethane) at 0 and stirred for 3 h at that temperature. The reaction mixture was washed with aqueous 20% sodium bisulfite solution (10 mL × 2), dried over $MgSO_4$, and concentrated to give an oil. The oily residue was purified by flash column chromatography (*n*-hex/EtOAc, 20/1) to afford ***trans*-3** (0.340 g) and ***cis*-3** (0.112 g) as pale yellow oils. The ratios (***trans*-3**/***cis*-3**) of the diastereomers were determined by GC/MS.

References

1. Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1995**, *60*, 4196; Beebe, X.; Chiappari, C. L.; Kruth, M. J.; Schore, N. E. *J. Org. Chem.* **1993**, *58*, 7320; Kurth, M. J.; Rodriguez, M. J.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 283; Kurth, M. J.; Rodriguez, M. J. *Tetrahedron* **1998**, *45*, 6963.
2. Kim, H. C.; Woo, S. W.; Seo, M. J.; Jeon, D. J.; No, Z.; Kim, H. R. *Synlett* **2002**, 1691.
3. Gibbs, L. W.; Wedegaertner, D. K. *J. Org. Chem*. **1991**, *56*, 7320; Wieland, H.; Rodenfeld, B. *Justus Ann. Chem*. **1930**, *484*, 236.
4. Hurd, C. D.; Nilson, M. E.; Wikholm, D. M. *J. Am. Chem. Soc.* **1950**, *72*, 4697.
5. Kumaran, G.; Kulkarni, G. H. *J. Org. Chem.* **1997**, *62*, 1516.
6. Kim, J. N.; Kim, H. R.; Ryu, E. K. *Synth. Commun*. **1993**, *23*, 1673; Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324; Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett*. **1991**, *32*, 6367; Kanemasa, S.; Nishiuchi, M.; Wada, E. *Tetrahedron Lett*. **1992**, *33*, 1357.