Diastereoselective Reduction and Grignard Reaction of 3-Aryltetrahydropenta[d]isoxazol-4-ones

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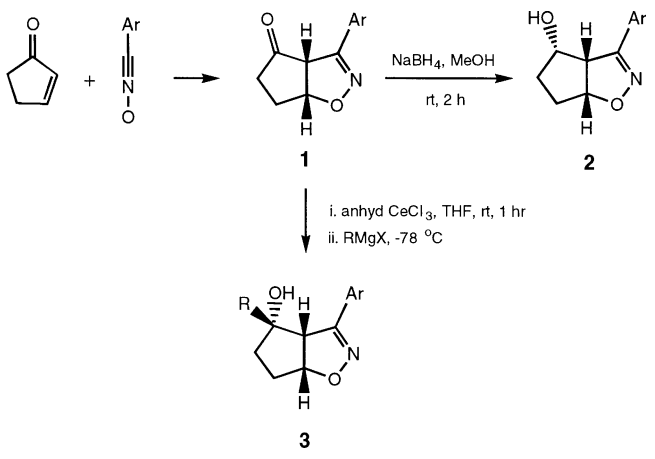
1,3-Dipolar cycloaddition reactions of nitrile oxides with olefins are very interesting reactions in organic synthesis due to their facile induction of stereocenters[1] and easy conversion[2] of the resulting isoxazolines to synthetically useful functional groups, such as β-hydroxyketones,[1f,3] β-hydroxyamines,[4] α,β-unsaturated ketones,[5] substituted tetrahydrofurans.[6] Although the 1,3-dipolar cycloaddition reactions of nitrile oxides with α,β-unsaturated ketones generally afforded a mixture of two regioisomers, the cycloadditions of aryl nitrile oxides with 2-cyclopenten-1-one could afford predominantly the corresponding 3-aryltetrahydrocyclopent[d]isoxazol-4-ones (**1**).[7]

The reductions of 3-alkyl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d]isoxazol-4-ones by $NaBH_4$ were reported[8] to afford only 3a,4-*cis* isomers in quantitative yields. We have also found that the reduction of 3-methyl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d]isoxazol-4-one showed a similar diastereoselectivity and gave a 9:1 mixture of 3a,4-*cis* and 3a,4-*trans* isomer. However, there have been few studies on the reduction and Grignard reaction of carbonyl group in **1**.[1f,8] Herein we wish to report the diastereoselective reduction and Grignard reaction of 3-aryltetrahydrocyclopent-1,2-isoxazol-4-ones (**1**).

When the carbonyl group of 3-aryltetrahydrocyclopent[d] isoxazol-4-ones (**1**) were reduced to the corresponding 3-aryltetrahydrocyclopent-1,2-isoxazol-4-ols (**2**) by sodium bo-rohydride in methanol, we isolated only 3a,4-*cis*-3a,6a-*cis*-isomers in excellent yields without any trace of 3a,4-*trans*-3a,6a-*cis*-isomers. This excellent diastereoselectivity may result from the attack of reducing agent to the convex side of the *cis*-fused structure. Interestingly, the reduction of 3a,7a-*cis*-3-phenyl-3a,4,5,6,7,7a-hexahydro-1,2-benzisoxol-7-one, a 6-membered ring-fused isoxazolinone by $NaBH_4$ showed less diastereoselectivity and afforded a 2:1 mixture of 3a,4-*cis* and 3a,4-*trans* isomers.[9]

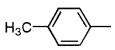
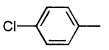
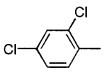
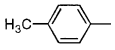
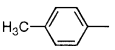
The relative stereochemistry of three stereocenters of **2a** (Ar =phenyl) were confirmed by NOE experiments in ^1H NMR. Irradiation of H-3a at 4.07 ppm showed 2.36% and 2.12% enhencement of signals for H-4 at 4.55 ppm and H-6a at 5.21 ppm, respectively.

Grignard reactions of methylmagnesium chloride or ethylmagnesium bromide with **1** were examined in THF at 0 °C, and we observed the reactions proceeded very slow and afforded **3** in low yields with the complicated by-products probably due to the abstraction of acidic protons at C-3a or C-5 position. When Imamoto's method[10] was applied in this Grignard reaction, we found that the reaction was completed within 3 h at -78 °C in excellent yield. All of the products obtained from the Grignard reactions of 1 were only 3a,4-*cis*-3a,6a-*cis*-isomers as expected, which were confirmed by

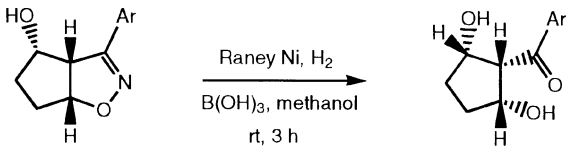


Scheme 1

Table 1. Reduction and Grignard Reaction of 3-aryltetrahydrocyclopent-1,2-isoxazol-4-ones (**1**)

Entry	Ar	Reagent	Product (Yield)[a]
1		$NaBH_4$	**2a** (97%)
2		$NaBH_4$	**2b** (89%)
3		$NaBH_4$	**2c** (87%)
4		$NaBH_4$	**2d** (88%)
5		$NaBH_4$	**2e** (89%)
6		CH_3MgCl	**3a** (96%)
7		CH_3MgCl	**3b** (93%)
8		CH_3CH_2MgBr	**3c** (96%)
9		CH_3CH_2MgBr	**3d** (91%)

[a]Isolated yields.



2 **4**

Scheme 2

NOE experiments in ^{1}H NMR. In case of **3a** (Ar=phenyl), irradiation of H-3a at 3.77 ppm showed 4.81% and 4.63% of enhencement of signals for CH_3-4 at 1.48 ppm and H-6a at 5.22 ppm, respectively. The results are summarized in Scheme 1 and Table 1.

The catalytic hydrogenation[3] with Raney Ni of 3a,4-*cis*-3a,6a-*cis*-3-phenyl-3a,5,6,6a-tetrahydro-4H-cycenta[d]isoxazol-4-ol (**2a**) provided the corresponding 2-benzoyl-1,3-cyclopentanediol **4** in good yields as shown in Scheme 2. For the structure of 1,3-diol **4** has a symmetic plane, proton peaks of H-1 and H-3 appeared at same position (4.72-4.69 ppm) in ^{1}H NMR spectrum and only eight carbon peaks were found in ^{13}C NMR spectrum. The irradiation of H-2 at 3.41 ppm showed 8.25% enhencement of signals for H-1 and H-2 at 4.71 ppm in ^{1}H NMR of 4 (Ar=Ph). We could confirm the relative stereochemistry of three stereocenters of **4** by theses NMR experiments.

In conclusion, we could prepare the highly functionalized cyclopentanes *via* diastereoselective reductions or Grignard reactions of 3-aryl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d] iso-xazol-4-ones prepared from the 1,3-dipolar cycloadditions of nitrile oxides with 2-cyclopenten-1-one, followed by the re- ductive cleavage of the isoxazoline ring.

Experimental Section

^{1}H NMR spectra, ^{13}C NMR spectra, and spectra of NOE experiments were recorded on Bruker AM-300MHz using TMS as a internal standard. FTIR spectra were taken with Digilab FTs-80 or Digilab FTs-165 spectrometer. HRMS spectra were obtained by Jeol JMX-DX 303 mass spectrometer. Flash column chromatography was carried out on silica gel Merck (230-400 mesh). All chemicals and solvents except THF were directly used from commercial sources. THF was dried over potassium metal before use.

General procedure for the reduction of 1 with $NaBH_4$. To a solution of 3-aryl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d] isoxazol-4-one (3 mmol) in 95% methanol (20 mL) was added $NaBH_4$ (6 mmol, 2 equiv) at 0 °C in small portions. After stirred for 30 min, the reaction mixture was poured into cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated by a rotary evaporator to afford pure 3a,4-*cis*-3a,6a-*cis*-3-aryl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d]isoxazol-4-ol (**2**). The yields and spectroscopic data are as follows.

2a: Yield: 97.4%. ^{1}H NMR ($CDCl_3$) δ 7.79-7.69 (m, 2H), 7.44-7.32 (m, 3H), 5.26-5.17 (m, 1H), 4.59-4.52 (m, 1H), 4.07 (dd, *J*=6.96, 2.40 Hz, 1H), 2.24-2.10 (m, 1H), 2.07-1.93 (m, 2H), 1.90-1.80 (m, 1H); ^{13}C NMR ($CDCl_3$), 156.80, 130.02, 129.74, 128.61, 126.88, 88.08, 75.38, 56.71, 33.80, 30.66; FTIR (cm^{-1}) 3364.42, 2935.33, 1444.61, 1361.87, 892.05, 759.19; MS (20eV) *m/z* (rel intensity) 204 (M^++1, 8.3), 203 (M^+, 13.3), 175 (8.7), 159 (5.7), 146 (100.0), 118 (7.2); HRMS calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0946.

2b: Yield: 88.7%. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J*=8.12 Hz, 2H), 7.18 (d, *J*=8.12 Hz, 2H), 5.22-5.17 (m, 1H), 4.59-4.45 (m, 1H), 4.06 (dd, *J*=7.12, 2.72 Hz, 1H), 2.35 (s, 3H), 2.23-2.12 (m, 1H), 2.06-1.91 (m, 2H), 1.83-1.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 153.22, 129.34, 127.62, 126.81, 125.17, 85.72, 75.44, 60.24, 35.46, 27.75, 21.42; FTIR (cm^{-1}) 3396.95, 2958.32, 1359.42, 1043.4, 904.89, 816.28; MS (20 eV) *m/z* (rel intensity) 218 (M^++1, 2.2), 217 (M^+, 13.7), 216 (2.2), 161 (13.3), 160 (100.0), 159 (87.1); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1102, found 217.1101.

2c: Yield: 86.8%. ^{1}H NMR ($CDCl_3$) δ 7.70 (d, *J*=8.72 Hz, 2H), 7.35 (d, *J*=8.72 Hz, 2H), 5.20-5.17 (m, 1H), 4.61-4.50 (m, 1H), 4.13 (dd, *J*=7.35, 2.22 Hz, 1H), 2.19-2.12 (m, 1H), 2.09-1.90 (m, 2H), 1.83-1.69 (m, 1H); ^{13}C NMR ($CDCl_3$), 155.41, 129.10, 128.87, 128.71, 128.26, 88.39, 75.61, 56.41, 33.88, 30.63; FTIR (cm^{-1}) 3400.89, 2893.34, 1360.51, 1225.68, 1086.42, 1043.91, 908.64, 827.33; MS (20eV) *m/z* (rel intensity) 237 (M^+, 14.4), 182 (36.9), 181 (37.3), 180 (100.0), 179 (70.1); HRMS calcd for $C_{12}H_{12}NO_2Cl$ 237.0556, found 237.0562.

2d: Yield: 87.0%. ^{1}H NMR ($CDCl_3$) δ 7.96-7.80 (m, 1H), 7.40-7.28 (m, 1H), 7.20-7.03 (m, 2H), 5.23-5.13 (m, 1H), 4.59-4.48 (m, 1H), 4.18-4.16 (m, 1H), 2.25-2.11 (m, 1H), 2.04-1.86 (m, 2H), 1.80-1.68 (m, 1H); ^{13}C NMR ($CDCl_3$), 152.79, 131.28, 131.21, 129.80, 128.97, 128.95, 124.56, 87.96, 75.86, 57.59, 32.89, 30.74; FTIR (cm^{-1}) 3443.96, 2958.27, 1591.97, 1495.37, 1348.67, 1229.48, 1098.22, 928.55; MS (20eV) *m/z* (rel intensity) 222 (M^++1, 3.2), 221 (M^+, 16.9), 220 (3.0), 165 (10.8), 164 (91.4), 164 (100.0); HRMS calcd for $C_{12}H_{12}NO_2F$ 221.0852, found 221.0854.

2e: Yield: 84.4%. ^{1}H NMR ($CDCl_3$) δ 7.57 (d, *J*=8.38 Hz, 1H), 7.40 (d, *J*=2.62 Hz, 1H), 7.25 (dd, *J*=2.62, 8.38 Hz, 1H), 5.23-5.16 (m, 1H), 4.47-4.41 (m, 2H), 2.19-1.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 155.20, 135.50, 132.85, 131.76, 129.76, 129.99, 128.99, 127.24, 87.71, 57.28, 32.53, 30.73; FTIR (cm^{-1}) 3420.63, 2928.79, 1580.57, 1479.99, 1345.06, 887.25; MS (20eV) *m/z* (rel intensity) 272 (M^++1, 2.4), 271 (M^+, 4.4), 214 (100.0), 213 (46.8), 159 (10.6); HRMS calcd for $C_{12}H_{11}NO_2$-Cl_2 271.0166, found 271.0158.

General procedure for the reaction of 1 with Grignard reagents. To a solution of 3-aryl-3a,5,6,6a-tetrahydro-4H-cyclopenta[d]isoxazol-4-one (3 mmol) in anhydrous THF (20 ml) was added anhydrous $CeCl_3$ (3.3 mmol) at rt. After stirred for 1 h at rt, the reaction mixture was cooled to -78 °C and alkyl Grignard reagent (3.3 mmol) was added to the reaction mixture. It was stirred for 3 h at -78 °C and then poured into the saturated NH_4Cl solution. The organic layer was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated by a rotary evaporator to

afford pure 3a,4-cis-3a,6a-cis-4-alkyl-3-aryl-3a,5,6,6a-tetrahydro-4H-cyclenta[d]is-oxazol-4-ol (**3**). The yields and spectroscopic data are as follows.

3a: Yield: 95.4%. ^{1}H NMR ($CDCl_3$) δ 7.75-7.70 (m, 2H), 7.39-7.38 (m, 3H), 5.28-5.17 (m, 1H), 3.77 (d, *J*=8.90 Hz, 1H), 2.35-1.85 (m, 4H), 1.48 (s, 1H); ^{13}C NMR ($CDCl_3$), 157.32, 130.21, 129.72, 128.60, 127.25, 88.72, 81.87, 61.62, 39.78, 30.68, 28.88; FTIR (cm^{-1}) 3497.01, 2965.69, 1445.74, 1353.16, 1189.53, 916.01; HRMS calcd for $C_{13}H_{15}NO_2$ 217.1102, found 217.1103.

3b: Yield: 93.1%. ^{1}H NMR ($CDCl_3$) δ 7.60 (d, *J*=8.00 Hz, 2H), 7.19 (d, *J*=8.02 Hz, 2H), 5.22-5.15 (m, 1H), 3.74 (d, *J*=8.91 Hz, 1H), 2.37 (s, 3H), 2.37-1.56 (m, 4H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.22, 129.29, 129.06, 127.29, 127.16, 88.52, 81.78, 61.69, 39.77, 30.62, 28.85, 21.35; FTIR (cm^{-1}) 3498.51, 2964.63, 1444.24, 1350.76, 1185.16, 915.44; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1261, found 231.1263.

3c: Yield: 96.8%. ^{1}H NMR ($CDCl_3$) δ 7.70-7.67 (m, 2H), 7.37-7.35 (m, 3H), 5.20-5.15 (m, 1H), 3.78 (d, *J*=9.32 Hz, 1H), 2.18-2.13 (m, 1H), 1.98-1.72 (m, 4H), 1.67-1.59 (m, 1H), 1.22 (s, 1H), 1.04 (t, *J*=7.38 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.32, 130.41, 129.66, 128.60, 127.16, 88.48, 84.51, 60.26, 36.27, 33.60, 30.52, 8.24; FTIR (cm^{-1}) 3510.57, 2972.47, 1442.53, 1351.36, 1183.84, 909.08; HRMS calcd for $C_{14}H_{17}$-NO_2 231.1259, found 231.1269.

3d: Yield: 90.2%. ^{1}H NMR ($CDCl_3$) δ 7.58 (d, *J*=8.11 Hz, 2H), 7.18 (d, *J*=8.11 Hz, 2H), 5.19-5.12 (m, 1H), 3.76 (d, *J*=8.90 Hz, 1H), 2.35 (s, 3H), 2.16-1.57 (m, 6H), 1.02 (t, *J*=7.43 Hz,, 3H); ^{13}C NMR ($CDCl_3$) δ 157.22, 129.26, 128.97, 127.47, 127.04, 88.24, 84.39, 60.31, 36.19, 33.55, 30.43, 21.31, 8.20; FTIR (cm^{-1}) 3517.36, 2970.39, 1448.73, 1349.18, 1182.52, 908.81; HRMS calcd for $C_{15}H_{19}NO_2$ 245.1438, found 245.1440.

1,2-*cis*-2,3-*cis*-2-Benzoyl-1,3-cyclopentanediol (4a). To a solution of **2a** (0.406 g, 2 mmol) in 5/1 methanol/water (15 ml) was added boric acid (0.245 g, 4 mmol) and a spatula tip (estimated 10-20 mg) of W-2 Raney Ni. The reaction proceeded under H_2 atmosphere by means of a balloon attached to three-way stopcock. The mixture was stirred vigorously for 3 h at rt and filtered through Celite into a separatory funnel containing water and CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 2 more times and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated by a rotary evaporator to give an oily residue. It was purified by silica gel column chromatography (EtOAc/n-hexane, 4/1) to afford 2-benzoyl-1,3-cyclopentanediol (0.300 g, 72.9%).

^{1}H NMR ($CDCl_3$) δ 7.99-7.95 (m, 2H), 7.64-7.45 (m, 3H), 4.72-4.69 (m, 2H), 3.44-3.39 (m, 1H), 2.07 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 202.58, 136.67, 133.81, 128.82, 128.21, 75.34, 56.61, 33.97; FTIR (cm^{-1}) 3467.97, 2957.46, 1664.70, 1449.20, 1350.35, 1221.26, 1044.74; HRMS calcd for $C_{12}H_{14}O_3$ 206.0951, found 206.0951.

1,2-*cis*-2,3-*cis*-2-Toluyl-1,3-cyclopentanediol (4b). 4b was made by the reductive cleavage from **2b** according to the method described above.

Yield: 74.0%. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J*=7.12 Hz, 2H), 7.25 (d, *J*=7.12 Hz, 2H), 4.54-4.46 (m, 2H), 3.81-3.77 (m, 1H), 2.39 (s, 3H), 2.13-1.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 199.69, 129.45, 129.38, 128.93, 128.76, 75.63, 64.09, 33.05, 21.66; FTIR (cm^{-1}) 3417.24, 2961.26, 1667.12, 1446.03, 1349.31, 1184.38, 1014.08; HRMS calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1101.

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