OXIDATION OF 1,2,3,4-TETRAHYDROISOQUINOLINES TO 3,4-DIHYDROISOQUINOLINES WITH MOLECULAR OXYGEN CATALYZED BY COPPER(II) CHLORIDE

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Abstract - A catalytic oxidation system, a $CuCl_2$-O_2 system, was efficient for dehydrogenation of 1,2,3,4-tetrahydroisoquinolines to 3,4-dihydroisoquinolines. Oxidation of 1,2,3,4-tetrahydroquinoline was also carried out.

The oxidation of amines to imines can be only carried out under severe reaction conditions generally.[1] 1,2,3,4-Tetrahydroisoquinolines are one of the cyclic amines and only a few oxidation methods to the 3,4-dihydroisoquinolines have been reported.[2] The 3,4-dihydroisoquinoline derivatives become useful intermediates for the synthesis of isoquinoline alkaloids.[3] However, the oxidation of 1,2,3,4-tetrahydroisoquinolines sometimes proceeds until undesirable overoxidized imine *N*-oxides.[4] Especially, there has been no report for dehydrogenation of the tetrahydroisoquinolines with molecular oxygen. As dehydrogenation of heterocyclic compounds, oxidation of indolines to indoles was reported with a CuCl-pyridine-O_2 system.[5] We have investigated a $CuCl_2$-amine-O_2 catalytic oxidation system, and effective synthetic methods of *p*-benzoquinones[6] and *p*-hydroxybenzaldehyde[7] from phenols were reported in the previous papers. We report herein the catalytic

dehydrogenation of 1,2,3,4-tetrahydroisoquinolines to 3,4-dihydroisoquinolines with this oxidation system.

When 1,2,3,4-tetrahydroisoquinoline (**1a**) was treated with molecular oxygen in the presence of a catalytic amount of copper(II) chloride, 3,4-dihydroisoquinoline (**2a**) which was dehydrogenated on the C-1 and N-1 positions of **1a** was isolated. The results of the oxidation under various reaction conditions are summarized in Table 1. The aspects of the tetrahydroisoquinoline oxidation were different from those of methyl-substituted phenol oxidations. In the oxidation of the phenols, the oxidations extremely accelerated with amines or oximes as additives.[5,6] However, in the oxidation of **1a**, the effect of additives such as amines or amine hydrochlorides was not strongly observed (Entries 1-3). Acetone oxime as an additive only caused some increase in the yield of **2a** (Entry 4). It is possible that the oximino group might be converted into a NO_2 ligand of copper as reported in olefin oxidation

Table 1. Oxidation of Tetrahydroisoquinoline (**1a**)[a]

Entry	Catalyst	Additive	Solvent	Conv.(%)	Yield (%) of **2**
1	$CuCl_2 \cdot 2H_2O$	Et_2NH	MeCN	57	32
2	"	$Et_2NH \cdot HCl$	"	68	34
3	"	$NH_2OH \cdot HCl$	"	54	25
4	"	$Me_2C{=}NOH$	"	100	61
5	"	-	"	85	55
6	"	$Me_2C{=}NOH$	MeOH	94	52
7	"	"	EtOH	94	46
8	CuCl	$Me_2C{=}NOH$	MeOH	94	51
9	$Cu(OAc)_2 \cdot H_2O$	"	"	74	35
10	$Cu(acac)_2$[b]	"	"	24	4
11	$FeCl_3 \cdot 6H_2O$	"	"	22	3
12	$CoCl_2 \cdot 6H_2O$	"	"	34	3
13	$MnCl_2 \cdot 4H_2O$	"	"	27	6

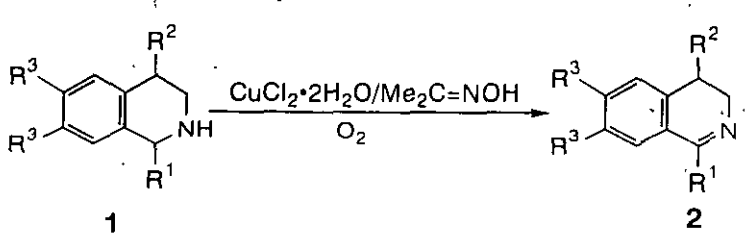
[a] Reaction conditions: **1a**, 2 mmol; catalyst, 0.2 mmol; additive, 0.2 mmol; solvent, 2 ml; pO_2, 114.7 kPa; 40°C, 6 h.

[b] acac = acetylacetonato.

with a CuCl-acetone oxime-$PdCl_2$-O_2 system.[8] Alcohols were essential as solvent in the oxidation of the phenols, while better yields of 3,4-dihydroisoquinolines were obtained in acetonitrile than in alcohols (Entries 4, 6, and 7).

Copper salts were the only active metals for the dehydrogenation of tetrahydroisoquinolines. Other metal salts tested this time such as Fe, Co, Mn gave low conversions of **1a** and very low yields of **2a** (Entries 11-13). A copper complex coordinated by a strong bidented ligand also did not show activity to the oxidation (Entry 10). The bidented ligands would exclude the coordination of the other molecules such as molecular oxygen or substrates.

Oxidations with the $CuCl_2$-acetone oxime-O_2 system were carried out for substituted 1,2,3,4-tetrahydroisoquinolines(**1**)in acetonitrile (Table 2). Large substituents retarded the oxidation and the yields of **2** were decreased. Especially, substituents on the C-1 prevented the dehydrogenation of **1** and the yields of **2** were very low (Entries 15 and 16). The steric hindrance around nitrogen atom would also prevent from coordination to a copper atom.

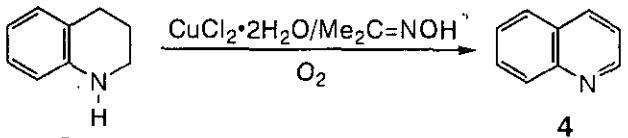


1 **2**

Table 2. Oxidation of Tetrahydroisoquinolines (**1**)[a]

Entry	Compound	R^1	R^2	R^3	Yield of **2** (%)
14	**a**	H	H	H	61
15	**b**	Me	H	H	1
16	**c**	Ph	H	H	5
17	**d**	H	Me	H	45
18	**e**	H	Ph	H	9
19	**f**	H	H	MeO	31

[a]Reaction conditions: **1**, 2mmol; $CuCl_2$•$2H_2O$, 0.2 mmol; acetone oxime, 0.2 mmol; MeCN, 2 ml; pO_2, 114.7 kPa, 40°C, 6 h.



3 4

The copper(II) chloride-O_2 oxidation system was applied for another heterocyclic compound. When 1,2,3,4-tetrahydroquinoline (**3**) was oxidized with the catalytic oxidation, quinoline (**4**) was obtained in 41 % yield but dihydroquinolines were not detected in this oxidation. Similar direct dehydrogenations of tetrahydroquinoline to quionoline using other oxidation systems were also reported.[2d]

It is concluded that 1,2,3,4-tetrahydroisoquinolines were oxidized to 3,4-dihydroisoquinolines with the copper(II) chloride-acetone oxime-O_2 system. The oxidation was greatly influenced with sterical effect.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus. ^{1}H-Nmr spectra were obtained with a Hitachi R-40 High-Resolution (90 MHz) with tetramethylsilane as an internal standard. Ir spectra were recorded on a JASCO FT IR-7000 Fourier Transfer Infrared Spectrophotometer. Gas chromatographic analyses were performed on a Shimadzu GC-14A gas chromatograph fitted with a HiCap-CBP1 column.

*General Procedure for the Oxidation of 1,2,3,4-Tetrahydroisoquinoline (**1a**).* The oxidations were carried out using a gas-sealed system. 1,2,3,4-Tetrahydroisoquinoline (**1a**, 2 mmol), copper(II) chloride dihydrate (0.2 mmol), and an additive (0.2 mmol) were put into a 10 ml glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. A solvent (2 ml) was added to the reaction mixture and the reaction was started with vigorous stirring under an oxygen atmosphere (114.7 kPa) at 40 °C for 6 h. The amount of consumed oxygen was measured by a gas burette. The yields of the products were determined by a glc method with naphthalene as a standard.

*General Procedure for the Oxidation of 1,2,3,4-Tetrahydroisoquinolines (**1b-f**).* The oxidations were carried out as described above in acetonitrile (2 ml). After the reaction, water was added to the reaction mixture and the product was extracted with CH_2Cl_2 (10 ml x 3). The organic layer was washed with water (50 ml), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude product was chromatographed on silica gel with a dichloromethane-acetone-methanol (100:10:2) mixture as an eluent. The yields of the products were determined by isolation.

3,4-Dihydroisoquinoline (**2a**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 2.73 (t, 2H, *J*=7.5 Hz), 3.76 (dt, 2H, *J*=2.5, 7.5 Hz), 7.1-7.4 (m, 4H), 8.34 (m, 1H). Ir (liquid film): ν 1630, 1580, 1210, 880, 750 cm^{-1}. Picrate: mp 176-177 °C (from EtOH) (lit.,[9] 174-176°C).

3,4-Dihydro-1-methylisoquinoline (**2b**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 2.36 (t, 3H, *J*=1.3 Hz), 2.69 (t, 2H, *J*=6.4 Hz), 3.67 (br t, 2H, *J*=6.4 Hz), 7.1-7.6 (m, 4H). Ir (liquid film): ν 1630, 1570, 1450, 1440, 1380, 1290, 760 cm^{-1}. Picrate: mp 188-189 °C (from EtOH) (lit.,[10] 193-194 °C).

3,4-Dihydro-1-phenylisoquinoline (**2c**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 2.67 (t, 2H, *J*=6.2 Hz), 3.68-3.85 (m, 2H), 7.1-7.4 (m, 7H), 7.5-7.7 (m, 2H). Ir (liquid film): ν 1610, 1570, 1450, 1320, 1020, 750, 700 cm^{-1}. Picrate: mp 169-170 °C (from EtOH) (lit.,[11] 174-175 °C).

3,4-Dihydro-4-methylisoquinoline (**2d**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 1.20 (d, 3H, *J*=7.3 Hz), 2.85 (hex, 1H, *J*=7.3 Hz), 3.3-3.9 (m, 2H), 7.1-7.5 (m, 4H), 8.32 (br s, 1H). Picrate: mp 133 °C (from EtOH) (lit.,[12] 134-136 °C).

3,4-Dihydro-4-phenylisoquinoline (**2e**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 3.8-4.2 (m, 2H), 6.8-7.5 (m, 9H), 8.39 (br s, 1H). Ir (KBr): ν 1670, 1630, 1490, 1450, 1330, 1140, 1060, 750, 700 cm^{-1}. Picrate: mp 223 °C (decomp.) (from EtOH). Anal. Calcd for $C_{12}H_{16}N_4O_7$: C, 57.80. H, 3.67; N, 12.84. Found C, 57.76; H, 3.79; N, 12.86.

3,4-Dihydro-6,7-dimethoxyisoquinoline (**2f**): Oil. ^{1}H-Nmr ($CDCl_3$): δ 2.63 (t, 2H, *J*=8.0 Hz), 3.5-3.9 (m, 2H), 3.86 (s, 6H), 6.66 (s, 1H), 6.80 (s, 1H), 8.22 (*br* s, 1H). *Ir (liquid film)*: ν 1630, 1605, 1576, 1518, 1280, 1120 cm^{-1}. Picrate: mp 206-207 °C (from EtOH) (lit.,[13] 206-208 °C).

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