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Electroreductive Intermolecular Coupling of Ketones with O-Methyl Oximes. A Convenient Route to Synthesis of 2-Amino Alcohols[1]

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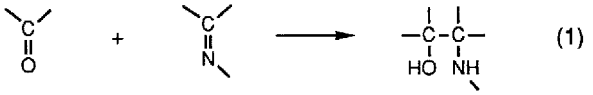
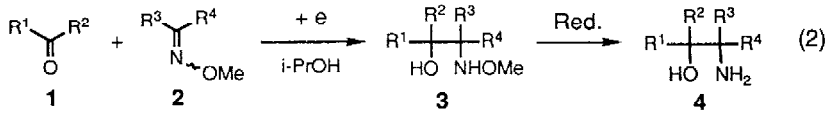
Summary: The electroreduction of ketones together with O-methyl oximes gave intermolecularly coupled products, 2-methoxyamino alcohols, which were easily reduced to 2-amino alcohols.

Reductive cross coupling of C=O group with C=N group will provide a convenient route to the synthesis of 2-amino alcohols (eq1). It has been reported that electroreductive coupling of N-methylbenzylideneamine with



(1)

benzaldehyde gave the corresponding 2-amino alcohol with low yield (22%).[2] Recently, reductive coupling of aromatic imines with aldehydes or ketones promoted by $NbCl_3$(DME) was also reported.[3] On the other hand, the electroreductive intra- or inter-molecular coupling of ketones with a variety of unsaturated compounds such as olefins,[4] acetylenes,[5] aromatic rings,[6] and nitriles[7] has been one of the main subjects in our continuing studies on electroorganic chemistry. Hence, the electroreductive coupling reaction depicted in eq1 is especially interesting since it is almost hitherto unknown and will provide a new route to the synthesis of 2-amino alcohols. Indeed, it was found in the present study that the electroreduction of ketones **1** together with O-methyl oximes **2** gave effectively the cross-coupling products **3** which were easily convertible to the corresponding 2-amino alcohols **4** (eq2).



(2)

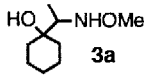
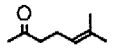
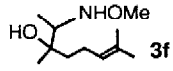
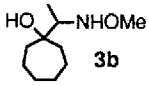
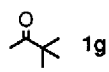
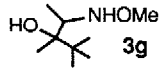
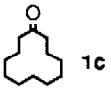
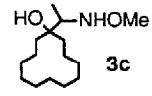
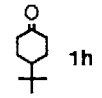
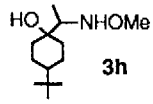
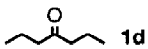
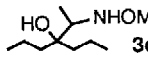
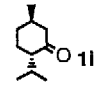
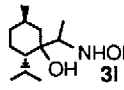
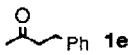
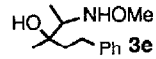
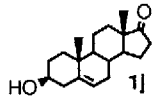
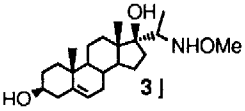
1 **2** **3** **4**

The electroreduction of a mixture of a ketone **1** (5 mmol) and an O-methyl oxime **2** (12.5 mmol) was carried out with a Sn cathode (5 X 10 cm^2) and a carbon anode in i-PrOH (40 mL) containing Et_4NOTs (10 g). The cathodic and anodic chambers were separated by a ceramic diaphragm. The electricity was passed at constant current of 0.2 A at 0~5 °C until almost all of **1** was consumed (3~6 *F*/mol based on **1**). After the catholyte was poured into water (200 mL) and extracted with CH_2Cl_2, the product **3** was isolated by column chromatography on silica gel (AcOEt-hexane).

The results of electroreductive coupling of ketones **1** with O-methyl acetoaldoxime **2a** are summarized in Table I. The electroreduction with Pb (**3a**, 94%), Cd (**3a**, 94%), or Ag (**3a**, 82%) cathode gave almost the same result as that with Sn cathode, whereas the yield decreased when the coupling was carried out in EtOH (**3a**, 62%) or DMF (**3a**, 52%). The other O-alkyl oximes **2b~f** also gave the cross-coupling products with ketones as shown in Table II.

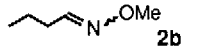
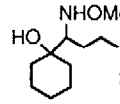
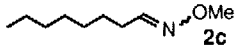
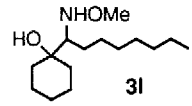
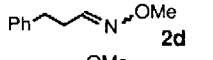
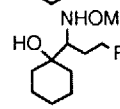
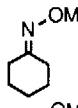
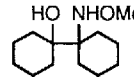
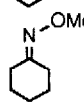
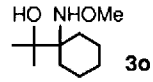
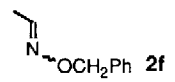
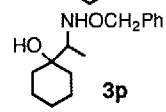
Although detail of the reaction mechanism is still not clear, it is reasonable that the reaction was initiated by reduction of not oximes but ketones **1**, since O-methyl oximes **2** were electrochemically inert under the

Table I. Electroreductive Intermolecular Coupling of Ketones **1** with O-Methyl Acetoaldoximes **2a**

Ketone **1**	Product **3**	% Yield of **3**[a] (ds)[b]	Ketone **1**	Product **3**	% Yield of **3**[a] (ds)[b]
 **1a**	 **3a**	98	 **1f**	 **3f**	93 (50:50)[c]
 **1b**	 **3b**	94	 **1g**	 **3g**	53 (75:25)[c]
 **1c**	 **3c**	72	 **1h**	 **3h**	85 (70:30)[d]
 **1d**	 **3d**	94	 **1i**	 **3i**	55 (85:15)[e]
 **1e**	 **3e**	96 (55:45)[c]	 **1j**	 **3j**	67 (50:50)[f]

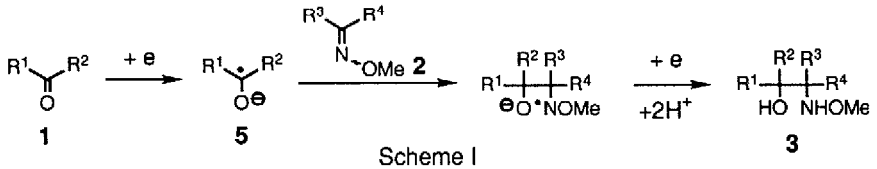
a. Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained for all of the products. b. Diastereomeric ratios determined by 200MHz ^{1}H NMR ($CDCl_3$). See ref. 8. c. The stereoconfiguration of each isomer could not be assigned. d. The ratio of *cis:trans*. See ref. 9. e. See ref. 12. f. See ref. 13.

Table II. Electroreductive Intermolecular Coupling of Ketones **1** with O-Alkyl Oximes **2**

Ketone **1**	O-Alkyl oxime **2**	Product **3**	% Yield of **3**[a]
 **1a**	 **2b**	 **3k**	88
 **1a**	 **2c**	 **3l**	90
 **1a**	 **2d**	 **3m**	94
 **1a**	 **2e**	 **3n**	65
 **1k**	 **2e**	 **3o**	43
 **1a**	 **2f**	 **3p**	72

a. Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained for all of the products.

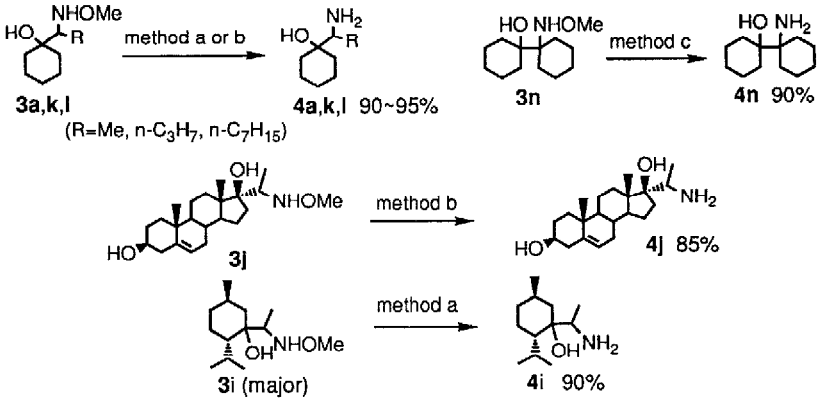
conditions which were just the same as those of the present reaction. As shown in Scheme I, the active species such as anion radical **5** formed from ketone **1** adds to the O-methyl oxime **2** to give the adduct **3**.



1 **5** **3**

Scheme I

The coupling products **3** were easily reduced to the corresponding 2-amino alcohols **4** with three types of method [a: H_2 (1 atm), cat. PtO_2/MeOH, r.t., 8h; b: LAH/THF, reflux, 6h; c[14]: $NaBH_4/ZrCl_4/CH_2Cl_2$, r.t., 2 h.] (Scheme II).



Scheme II

References and Notes

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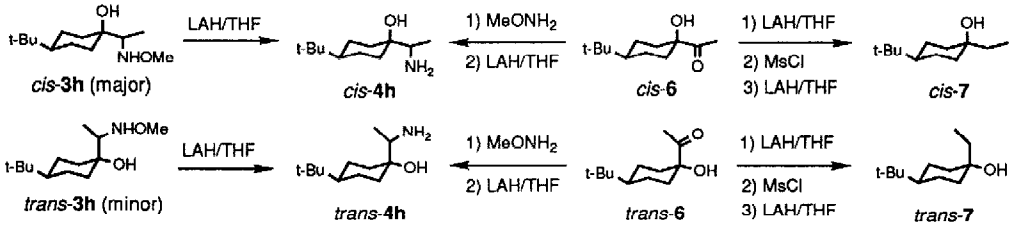
8. The chemical shifts (δ value, quartet) of methyn protons on the carbon atom having methoxyamino group were as follows: **3e** 3.05 (0.55H, J=6.8Hz), 3.09 (0.45H, J=6.8Hz); **3f** 2.99 (0.5H, J=6.9Hz), 3.02 (0.5H, J=6.9Hz); **3g** 3.24 (0.75H, J=6.5Hz), 3.31 (0.25H, J=6.5Hz); **3h** 2.85 (0.7H, J=6.7Hz), 3.23 (0.3H, J=6.8Hz); **3i** 3.16 (0.85H, J=6.6Hz), 3.28 (0.15H, J=6.9Hz); **3j** 3.02 (0.5H, J=6.7Hz), 3.12 (0.5H, J=6.2Hz); **3q** 2.98 (0.5H, J=6.8Hz), 3.03 (0.5H, J=6.8Hz); **3r** 2.98 (0.5H, J=6.6Hz), 3.02 (0.5H, J=6.6Hz).
9. The stereoisomers of **3h** could be separated by column chromatography on silica gel (AcOEt-hexane). The stereoconfiguration of each isomer was determined by transformation of it to 2-amino alcohol **4h** and the comparison of its ^{13}C NMR spectrum with that of the sample prepared from **6**. The compound **6** was formed by electroreduction of 4-*t*-butyl-cyclohexanone together with acetonitrile,[10] and the stereochemical structure of each isomer was assigned by conversion of it to the known compound **7**.[11] *cis*-**4h**: ^{13}C NMR (50 MHz, $CDCl_3$) 17.61

(q), 22.08 (t), 22.28 (t), 27.32 (q, 3C), 31.54 (t), 32.13 (s), 35.16 (t), 47.77 (d), 55.05 (d), 71.50 (s) ppm. *trans*-**4h**: ^{13}C NMR (50 MHz, $CDCl_3$) 16.29 (q), 23.02 (t), 23.64 (t), 27.36 (q, 3C), 32.01 (s), 35.10 (t), 36.20 (t), 45.94 (d), 47.15 (d), 71.69 (s) ppm.



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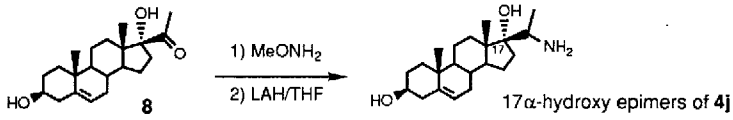
12. Two stereoisomers were formed and major isomer of them was isolated purely by column chromatography on silica gel (AcOEt-hexane, 1:5), though its stereochemical structure could not be assigned. **3i** (major): $[\alpha]_D^{25}$ -19.5 (c 4.3, $CHCl_3$); ^{13}C NMR (50 MHz, $CDCl_3$) 13.74 (q), 17.68 (q), 20.22 (t), 22.26 (q), 23.10 (q), 26.27 (d), 27.83 (d), 34.67 (t), 44.57 (t), 45.67 (d), 61.72 (q), 63.61 (d), 75.95 (s).

13. The products were obtained as a mixture of two stereoisomers and they could not be separated. **3j** (mixture): ^{13}C NMR (50 MIIz, $CDCl_3$) 14.78 (q,1C), 15.61 (q, 1C), 19.06 (q, 1C), 20.58 (t, 0.5C), 20.73 (t, 0.5C), 23.72 (t, 0.5C), 23.87 (t, 0.5C), 31.27 (t, 1C), 31.52 (t, 1C), 32.08 (t, 0.5C), 32.37 (d, 0.5C), 32.49 (d, 0.5C), 32.86 (t, 0.5C), 33.73 (t, 0.5C), 34.58 (t, 0.5C), 36.28 (s, 1C), 37.03 (t, 1C), 41.96 (t, 1C), 46.50 (s, 0.5C), 46.77 (s, 0.5C), 49.63 (d, 1C), 51.06 (d, 0.5C), 51.41 (d, 1C), 59.86 (d, 0.5C), 61.48 (q, 0.5C), 61.96 (q, 0.5C), 71.35 (d, 1C), 84.02 (s, 0.5C), 85.20 (s, 0.5C), 121.25 (d, 1C), 140.93 (s, 1C). Although the stereoconfiguration of obtained two stereoisomers of **3j** could not be determined, it seems reasonable that they have 17β-hydroxy configuration, since their reduced amines **4j** were not consistent with the 17α-hydroxy epimers derived from 17α-hydroxypregnenolone **8**.



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