Cobaloxime-Mediated Intramolecular Radical Addition onto Oxime Functions in the Electrolysis Media: Formation of Mannich Base Analogues

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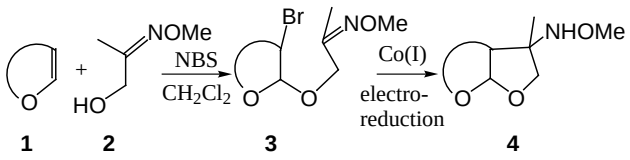
Abstract: Addition of the carbon radical generated from α-bromoacetals onto the *O*-alkyloximes, affording Mannich base analogues, was achieved by the electrolysis in MeOH containing cobaloxime (catalytic) as a mediator at a Zn sacrificial electrode in an undivided cell. Cyclization proceeded stereoselectively in some cases to afford the 2-alkoxy-3-alkyl-4-aminotetrahydrofurans.

Key words: acetals, amines, cyclization, ring closure, radical reactions

The carbon-nitrogen double bond of *O*-alkyloximes has been used as a good radical acceptor in the intramolecular[1-4] and intermolecular[5] radical couplings, which may be accounted for by the stability of the resulting alkoxy aminyl radical by conjugation with a lone pair on the adjacent oxygen atom. Furthermore, the method is of value for assembly of amine function in the complex natural products syntheses.[1d] Besides to *O*-alkyloximes, hydrazones are also utilized in radical couplings.[6] Although radical cyclization of *O*-alkyloximes has mainly been examined for five- and six-membered carbocyclic systems,[2,3] few is known about radical cyclization for heterocyclic systems.[4,5b] Especially, addition of the radical from α-halo acetals onto the oxime double bonds would provide a potential entry to synthetically valuable β-amino carbonyl derivatives, known as "Mannich base." However, to the best of our knowledge, the synthesis of Mannich bases by radical reaction has little been attempted.[7]

Prior to the present study, we have developed a convenient procedure for generation of radicals from haloalkanes by using a combination of (chloropyridine)cobaloxime(III) and zinc foils as a sacrificial anode in an undivided electrolysis cell. The reaction can be achieved with less than 5 mol% of the cobalt catalyst, which is recycled by regenerating active low valence cobalt(I) species on the cathode during the electrolysis.[8] Since the catalyst is recycled, the cobalt-induced radical reaction is considered to be ecologically friendly, compared with tributyltin hydride- and Sm(II)-based protocols.[1] Recently, triethylborane was employed for radical reactions of imine derivatives.[5b] In continuation of our research on indirect electrochemical reduction with cobaloxime as a mediator,[9] we examined the radical cyclization of *O*-alkyloximes **3**, giving functionalized 3-aminoacetals **4**[10] (Scheme 1).



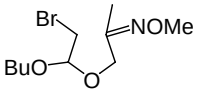
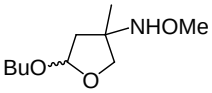
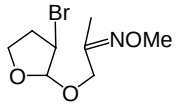
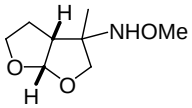
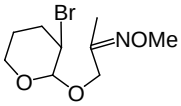
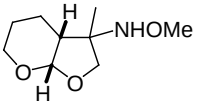
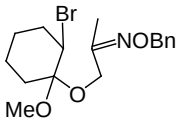
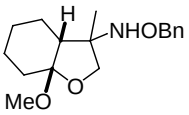
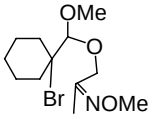
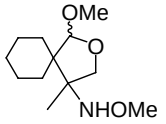
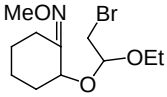
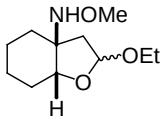
Scheme 1

As shown in general strategy in Scheme 1, the substrates **3** for radical cyclizations were easily prepared by bromoalkoxylation of readily available enol ethers **1** and hydroxyacetone *O*-alkyloximes **2**.[11] 2-Hydroxycyclohexanone, accessible by acyloin condensation, was also employed for the synthesis of a counterpart of the substrate, e.g. **3f** (Table). The electrochemical reactions were carried out in the presence of cobaloxime (5-22 mol%) and a small amount of 40% NaOH with two zinc foil electrodes, one of which is used as a dissolving electrode, and performed in a simple undivided cell. Thus, the passage of 4.3 F/mol of electricity for the electrolysis of compound **3b** afforded the desired cyclization product **4b** in 66% yield as a single stereoisomer.[12] In this case, trace of 1,2-elimination, leaving **2**, was found. On the other hand, the reaction of the bromohydrin derivative from 2,3-dihydropyran and β-hydroxy ketone *O*-alkyloxime resulted in the 1,2-elimination of the starting bromoacetal, predominantly.[13]

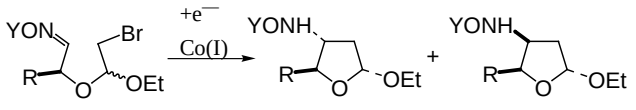
Ring formation via radical cyclization is known to be stereoselective in many cases.[1c] As shown in Table 1, the *O*-alkyloximes of various structure were examined for the radical cyclization. The radicals generated from primary, secondary, and tertiary alkyl bromides added to the carbon-nitrogen double bonds without any difficulty and difference in their reactivity. The reaction of **3b**, **3c**, and **3d** afforded **4b**, **4c**, and **4d** as a single isomer, respectively, though relative stereochemistry of the methoxyamino group is not determined at present. The configuration of bicyclic systems in the products **4b**, **4c**, **4d**, and **4f** were assigned *cis* on the basis of precedent literature.[2j]

In order to obtain the 5-substituted acetals **6**, we examined the cyclization of **5**, bearing an alkyl or a phenyl group at the position α to the oxime group. However, the reactions, unfortunately, were not stereoselective and a mixture of *trans*- and *cis*-**6** was obtained as separable isomers[14] (Scheme 2).

Table Cobaloxime-Mediated Radical Cyclization onto *O*-Alkyloximes **3** in the Electrolysis Media[a]

	Bromo Acetals **3**	Electricity, F/mol (Cobaloxime, mol%)	Products **4**	Yield[b] (Ratio)
a		5.2 (15)		61 (5.6/1)
b		4.3 (10)		66[c]
c		5.8 (10)		65[c]
d		7.8 (5)		76[c,d]
e		7.8 (13)		73 (3/1)
f		10.4 (22)		47[e] (1/1)

[a] Electrochemical reactions were carried out by using **3** (0.8-2.0 mmol), cobaloxime (5-22 mol%) in an MeOH (7 mL)-NaOH (40%, 3 drops)-Et_4NOTs (400 mg)-(Zn)-(Zn) system under an applied voltage of 3 V at room temperature for passage of 4.3-10.4 F/mol of electricity. [b] Isolated yields by column chromatography (SiO_2) and isomers are ascribed to the stereoisomers at the acetal carbon whose ratios are based on isolated products. [c] One stereoisomer was formed, exclusively. [d] Yield was improved to 82% using 25 mol% of cobaloxime (from 76% with 5 mol% of cobaloxime). [e] Carried out without adding 40% NaOH.



5 **a**, R = Me, Y = Bn
b, R = Ph, Y = Me

6, *trans* (**a**: 22%, **b**: 38%)

6, *cis* (**a**: 27%, **b**: 20%)

Scheme 2

In conclusion, radical addition onto *O*-alkyloximes, providing a new entry to synthetically useful β-aminocarbonyl derivatives, was achieved by electrochemical reduction with cobaloxime as a recyclable catalyst. Stereoselective ring formation, giving 3-aminoacetals, is also achieved.

Acknowledgement

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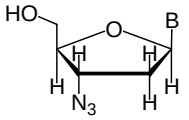

AZT (B: thymine)

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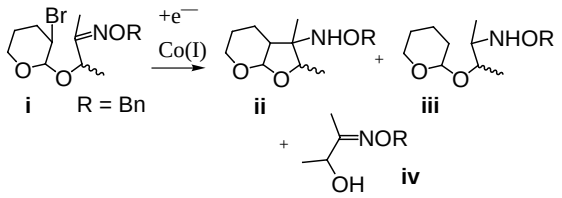
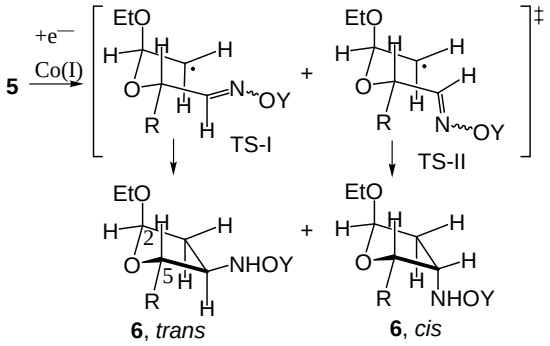
(12) The typical electrochemical procedure: A solution of the bromide **3b** (504 mg, 2.00 mmol) and (chloropyridine)cobaloxime(III) (80 mg, 0.20 mmol) in MeOH (7 mL) containing 40% NaOH (3 drops) and Et_4NOTs (400 mg) as an electrolyte was electrolyzed with two zinc foils ($1.0 \times 2.0 \times 0.5$ cm^3) as a cathode and an anode under a constant applied voltage of 3 V (current: 35-70 mA). The reaction was monitored by TLC and the electrolysis was continued until almost all of the starting material had been consumed (340 min). The mixture was filtered on a celite pad and the resulting solution was concentrated and the residue was worked up in the usual manner to yield **4b** (229 mg, 66%) as a single stereoisomer after column chromatography (SiO_2, hexane-AcOEt = 3:1). Spectroscopic data of the electrolysis products **4** in Table 1 are as follows: **4a**: IR (film) 3255, 2809, 1457, 1155, 1095, 1031, 918 cm^{-1}; ^1H NMR (300 MHz) δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.33-1.42 (m, 2H), 1.33 (s, 3H), 1.50-1.58 (m, 2H), 1.81 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.02 (d, *J* = 13.6 Hz, 1H), 3.31-3.39 (m, 1H), 3.54 (s, 3H), 3.60 (d, *J* = 9.3 Hz, 1H), 3.62-3.70 (m, 1H), 3.98 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 5.2 Hz, 1H), 6.13 (brs, 1H); ^{13}C NMR (75.5 MHz) δ 13.8, 19.3, 22.5, 31.7, 42.7, 62.9, 64.9, 67.2, 75.3, 104.1. **4b**: IR (film) 3248, 2810, 1373, 1099 cm^{-1}; ^1H NMR (400 MHz) δ 1.34 (s, 3H), 1.76-1.86 (m, 1H), 2.03-2.10 (m, 1H), 2.46-2.51 (m, 1H), 3.46 (s, 3H), 3.53 (d, *J* = 8.4 Hz, 1H), 3.59 (d, *J* = 8.4 Hz, 1H), 3.82-3.87 (m, 2H), 5.50 (brs, 1H), 5.67 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 24.8, 25.6, 51.8, 62.7, 65.8, 69.1, 75.2, 109.6. **4c**: IR (film) 3261, 2809, 1448, 1216, 1043 cm^{-1}; ^1H NMR (300 MHz) δ 1.28 (s, 3H), 1.32-1.44 (m, 1H), 1.63-1.94 (m, 4H), 3.37-3.45 (m, 1H), 3.49 (s, 3H), 3.52 (d, *J* = 8.9 Hz, 1H), 3.81-3.89 (m, 1H), 4.23 (d, *J* = 8.9 Hz, 1H), 5.03 (d, *J* = 3.6 Hz, 1H), 6.20 (brs, 1H); ^{13}C NMR (75.5 MHz) δ 19.6, 20.4, 22.6, 45.2, 62.9, 63.4, 66.1, 75.7, 102.5. **4d**: IR (film) 3274, 1454, 1361, 1085, 1025, 887, 698 cm^{-1}; ^1H NMR (300 MHz) δ 1.20-1.42 (m, 3H), 1.52 (s, 3H), 1.55-1.73 (m, 3H), 1.75-2.00 (m, 3H), 3.21 (s, 3H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.77 (d, *J* = 9.5 Hz, 1H), 4.69 (ABq, *J* = 11.5 Hz, 2H), 5.59 (br, 1H), 7.33 (m, 5H); ^{13}C NMR (75.5 MHz) δ 21.1, 22.87, 22.91, 24.1, 29.9, 47.5, 52.7, 67.7, 74.3, 76.9, 108.5, 127.6, 128.0 (2C), 128.2 (2C), 137.8. **4e**: (less polar component and major product) IR (KBr) 3266, 2850, 2804, 1380, 1220, 1020, 962, 927 cm^{-1}; ^1H NMR (300 MHz) δ 1.10 (s, 3H), 1.12-1.20 (m, 3H), 1.30-1.45 (m, 3H), 1.60-1.72 (m, 3H), 1.77-1.83 (m, 1H), 3.40 (s, 3H), 3.48 (s, 3H), 3.54 (d, *J* = 9.2 Hz, 1H), 4.28 (d, *J* = 9.2 Hz, 1H), 4.86 (s, 1H), 6.61 (brs, 1H); ^{13}C NMR (75.5 MHz) δ 15.2, 23.1, 23.2, 25.3, 25.9, 30.3, 50.5, 55.3, 63.0, 68.2, 73.6, 107.7. (polar component and minor product): IR (film) 3274, 2861, 1456, 1373, 1106, 1031, 929 cm^{-1}; ^1H NMR (500 MHz) δ 1.16-1.20 (m, 2H), 1.26-1.34 (m, 1H), 1.36-1.48 (m, 1H), 1.38 (s, 3H), 1.48-1.56 (m, 2H), 1.58-1.67 (m, 2H), 1.68-1.73 (m, 1H), 1.90-1.95 (m, 1H), 3.34 (s, 3H), 3.47 (s, 3H), 3.62 (d, *J* = 9.0 Hz, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 4.83 (s, 1H), 5.76 (brs, 1H); ^{13}C NMR (75.5 MHz) δ 21.0, 23.4, 23.9, 25.7, 28.1, 28.9, 50.4, 55.1, 62.9, 67.6, 76.1, 109.2. **4f**: (less polar component) IR (film) 3247, 2807, 1446, 1375, 1334, 1110, 1049, 1000 cm^{-1}; ^1H NMR (300 MHz) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.32-1.79 (m, 8H), 1.93 (dd, *J* = 13.6, 3.0 Hz, 1H), 2.08 (dd, *J* = 13.6, 5.8 Hz, 1H), 3.39-3.49 (m, 1H), 3.53 (s, 3H), 3.72-3.82 (m, 1H), 3.99 (t, *J* = 5.0 Hz, 1H), 5.09 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.82 (br, 1H); ^{13}C NMR (75.5 MHz) δ 15.3, 20.4, 21.0, 27.6, 29.8, 41.9, 63.0, 63.3, 65.0, 76.5, 102.3. (polar component): IR (film) 3243, 2807, 1375, 1112, 993, 941 cm^{-1}; ^1H NMR (300 MHz) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.30-1.45 (m, 1H), 1.55-1.75 (m, 5H), 1.83-1.95 (m, 2H), 1.92 (dd, *J* = 14.1, 4.4 Hz, 1H), 2.13 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.38-3.50 (m, 1H), 3.53 (s, 3H), 3.74-3.86 (m, 1H), 3.87 (dd, *J* = 9.1, 6.0 Hz, 1H), 5.18 (dd, *J* = 6.3, 4.4 Hz, 1H), 5.42 (br, 1H); ^{13}C NMR (75.5 MHz) δ 15.3, 21.9, 22.5, 29.8, 30.0, 39.3, 63.1, 63.6, 67.2, 78.6, 103.6.

(13) This reaction seems to be influenced by some steric factor in the cyclization process. For example, the compound **i** bearing an additional methyl group, compared with **3c**, produced the radical cyclized **ii** (24%), along with uncyclized **iii** (15%) and the 1,2-elimination product **iv** (53%).



(14) The formations of *trans*- and *cis*-isomers **6** are explained by the transition states TS-I and TS-II, in both of which the ethoxy group prefers axial orientation due to anomeric effect and the alkyl or aryl group will take equatorial direction due to steric reasons. In this case, orientation of the C=NOY terminuses is considered to be crucial to the stereochemical outcome of the products. Stereochemistry of **6b** is assigned based on ^1H NMR data of a proton on the C-5 carbon: *trans* isomer showed coupling constant of 6.4 Hz and *cis* isomer 2.8 Hz. Stereochemistry of **6a** was decided by analogy with **6b**. ^1H NMR (500 MHz) of **6b**, *trans*-isomer (less polar component): δ 1.26 (t, *J* = 7.0 Hz, 3H), 2.17-2.20 (m, 2H), 3.52-3.58 (m, 1H), 3.55 (s, 3H), 3.75-3.79 (m, 1H), 3.88-3.95 (m, 1H), 4.94 (d, *J* = 6.4 Hz, 1H), 5.26 (dd, *J* = 4.6, 3.1 Hz, 1H), 5.30-5.70 (br, 1H), 7.30-7.45 (m, 5H). *cis*-isomer (polar component): δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.93 (dd, *J* = 13.7, 1.2 Hz, 1H), 2.17-2.23 (m, 1H), 3.49-3.52 (m, 1H), 3.54-3.59 (m, 1H), 3.56 (s, 3H), 3.80-3.87 (m, 1H), 5.18 (d, *J* = 2.8 Hz, 1H), 5.36 (d, *J* = 4.9 Hz, 1H), 6.05 (brs, 1H), 7.24-7.47 (m, 5H).



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