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Electroreductive intramolecular coupling of aliphatic cyclic imides with ketones and *O*-methyloximes

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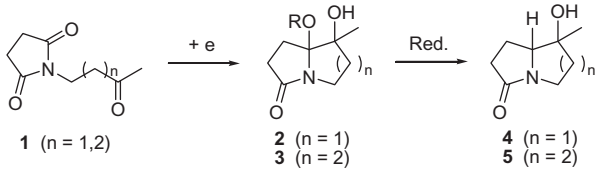
ABSTRACT

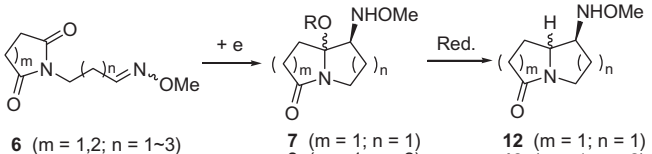
The electroreductive intramolecular coupling of aliphatic cyclic imides with ketones in isopropanol gave five- and six-membered cyclized products. Similarly, the electroreductive intramolecular coupling of aliphatic cyclic imides with *O*-methyloximes afforded five-, six-, and seven-membered cyclized products. These reactions provide a useful method to synthesize azabicyclo[n.m.0] compounds. The bicyclic products were stereoselectively transformed to the corresponding deoxylated compounds by reduction with $NaB(CN)H_3$ or $Et_3SiH/BF_3{\cdot}Et_2O$.

The reductive intramolecular coupling of cyclic imides with unsaturated functional groups provides a useful synthetic route to azabicyclo[n.m.0] skeletons, of which pyrrolizidine, indolizidine, isoindolinone, and related alkaloids are comprised. For this purpose, the reductive intramolecular coupling of aliphatic cyclic imides with alkenes using low-valent titanium reagents[1] and that of phthalimides with carbonyl compounds using samarium(II) iodide[2] have been reported. Recently, we disclosed that the electroreduction in the presence of chlorotrimethylsilane is also an effective tool for the reductive intramolecular coupling of phthalimides with α,β-unsaturated esters[3] and ketones.[4] Unfortunately, these electroreductive conditions could not be applicable to reductive coupling of aliphatic cyclic imides, such as succinimides and glutarimides, with carbonyl compounds. Therefore, we investigated the conditions to realize the electroreductive intramolecular coupling of aliphatic cyclic imides with ketones, since this type of reaction has scarcely been achieved.[5] We report herein that the electroreductive intramolecular coupling of *N*-(oxoalkyl)succinimides **1** ($n = 1, 2$) in isopropanol gave azabicyclic products, pyrrolizidines **2** ($n = 1$) and indolizidines **3** ($n = 2$) (Scheme 1). The obtained bicyclic *N*,*O*-acetals **2** and **3** could be deoxylated at the bridgehead carbon to give **4** and **5** stereoselectively. Furthermore, this electroreductive method was found to be more versatile for the intramolecular coupling of aliphatic cyclic imides with *O*-methyloximes (Scheme 2). From *N*-(*N*-methoxyiminoalkyl)-imides **6** ($m = 1, 2$; $n = 1–3$), pyrroloazepins **9** and quinolizidines **11** were also accessible in addition to pyrrolizidines **7** and indolizidines **8**, **10**. Similarly, the bicyclic *N*,*O*-acetals **7**–**11** could be reduced to deoxylated **12**–**16**.



1 (n = 1,2)
2 (n = 1)
3 (n = 2)
4 (n = 1)
5 (n = 2)

Scheme 1.



6 (m = 1,2; n = 1~3)
7 (m = 1; n = 1)
8 (m = 1; n = 2)
9 (m = 1; n = 3)
10 (m = 2; n = 1)
11 (m = 2; n = 2)
12 (m = 1; n = 1)
13 (m = 1; n = 2)
14 (m = 1; n = 3)
15 (m = 2; n = 1)
16 (m = 2; n = 2)

Scheme 2.

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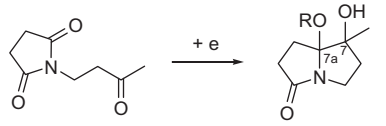
The electroreduction of 1-(3-oxobutyl)pyrrolidine-2,5-dione (**1a**) was carried out in isopropanol employing an undivided cell, according to our reported methods for the electroreductive cross-coupling of ketones[6] (Table 1). Five-membered cyclized product **2** was obtained as a mixture of 7,7a-diol **2a** and its 7a-isopropoxy analog **2b** (**2a**/**2b** = 20/80). The best combined yield of **2a** and **2b** (86%) was effected using Et_4NOTs/isopropanol as an electrolyte and a Pb cathode (run 1).[7] The use of a divided cell considerably decreased the yield of **2**, probably due to side reactions of **1a** caused by an electrogenetic base (run 2). On the other hand, when an undivided cell was employed, the pH value of the electrolyte was kept neutral. Since **2a** and **2b** are *N*,*O*-acetals, they were mutually convertible.[8] The use of ethanol and *t*-butanol in place of isopropanol decreased the yield of **2** to some extent (runs 7 and 8). While 7a-ethoxy analog **2c** was obtained as a major product (**2a**/**2c** = 15/85) in the case of ethanol solvent (run 7),[9] **2a** was the only product in the case of *t*-butanol solvent (run 8). The electroreduction of **1a** did not progressed in methanol, since hydrogen evolution exclusively proceeded. Next, the electroreduction of 1-(4-oxopentyl)pyrrolidine-2,5-dione (**1b**) under the same conditions as run 1 in Table 1 afforded six-membered cyclized product **3** as a 65/35 mixture of 8,8a-diol **3a** and its 8a-isopropoxy analog **3b** in 79% combined yield (Scheme 3). These azabicyclic products **2a**,**b** and **3a**,**b** were seemed to be obtained diastereospecifically (>99%) by ^1H and ^{13}C NMR analyses.[10] Although their stereostructures could not be determined absolutely, 2D-NMR (COSY and NOESY) analysis of **3a** suggests its 8,8a-cis configuration, which is supposed to be the thermodynamically more stable diastereomer.

The bicyclic *N*,*O*-acetals **2** and **3** were stereoselectively reduced to 7a- and 8a-deoxy analogs **4** and **5**, respectively (Table 2).[11] The reduction with $NaB(CN)H_3$ in TFA–methanol gave cis-isomers of **4** and **5** selectively (runs 1–4),[12] whereas that with $Et_3SiH/BF_3{\cdot}Et_2O$ in dichloromethane produced their trans-isomers predominantly (runs 5–8).[13] The stereostructure of each isomer of **4** and **5** was assumed by 2D-NMR (COSY and NOESY) analysis. The stereoselectivity in the reduction of **2** and **3** may be explained as shown in Scheme 4. In both cases, iminium ion **A** is the intermediate. In the reduction with $NaB(CN)H_3$, hydride ion attacks **A** selectively from the opposite side of the hydroxy group. On the other hand, Et_3SiH attacks **A** predominantly from the same side as the hydroxy group due to the chelation of Et_3SiH to the hydroxy oxygen atom.

The electroreduction of 3-(2,5-dioxopyrrolidin-1-yl)propanal *O*-methyl oxime **6a**, 4-(2,5-dioxopyrrolidin-1-yl)butanal *O*-methyl oxime **6b**, and 5-(2,5-dioxopyrrolidin-1-yl)pentanal *O*-methyl oxime **6c** under the same conditions as run 1 in Table 1 gave five-, six-, and seven-membered cyclized products **7**, **8**, and **9** as mixtures of diols (**7a**, **8a**, and **9a**) and their isopropoxy analogs (**7b**, **8b**, and **9b**): The combined yields of **7**, **8**, and **9** were 79%, 83%, and 85%, respectively (Scheme 5). This electroreductive method was also effective to the reductive cyclization of glutarimide derivatives, 3-(2,6-dioxopiperidin-1-yl)propanal *O*-methyl oxime **6d** and 4-(2,6-dioxopiperidin-1-yl)butanal *O*-methyl oxime **6e**. As

Table 1
Electroreductive intramolecular coupling of **1a**

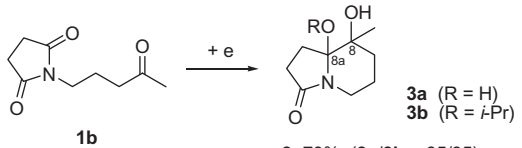


1a

2a (R = H)
2b (R = *i*-Pr)
2c (R = Et)

Run	Solvent	Electrolyte	Cathode	% Yield of **2**[a]
1	*i*-PrOH	Et_4NOTs	Pb	86[b]
2	*i*-PrOH	Et_4NOTs	Pb	21[b,c]
3	*i*-PrOH	Et_4NOTs	Sn	46[b]
4	*i*-PrOH	Et_4NOTs	Zn	26[b]
5	*i*-PrOH	Et_4NBF_4	Pb	57[b]
6	*i*-PrOH	Et_4NClO_4	Pb	45[b]
7	EtOH	Et_4NOTs	Pb	54[d]
8	*t*-BuOH	Et_4NOTs	Pb	40[e]

[a] Isolated yields.
[b] Combined yield of **2a** and **2b** (**2a**/**2b** = 20/80).
[c] Using a divided cell.
[d] Combined yield of **2a** and **2c** (**2a**/**2c** = 15/85).
[e] Yield of **2a**.



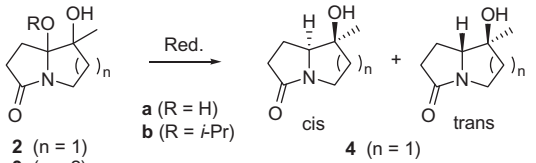
1b

3a (R = H)
3b (R = *i*-Pr)

3 79% (**3a**/**3b** = 65/35)

Scheme 3.

Table 2
Reduction of **2** and **3** to **4** and **5**



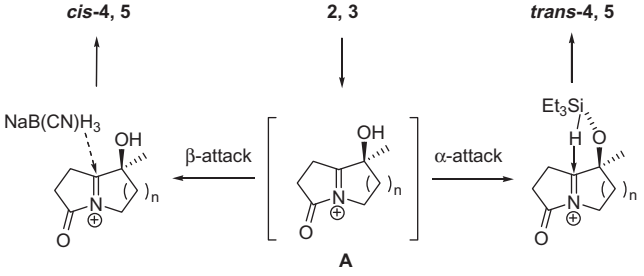
2 (n = 1)
3 (n = 2)

a (R = H)
b (R = *i*-Pr)

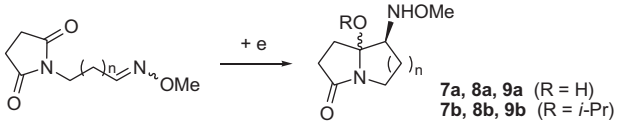
4 (n = 1)
5 (n = 2)

Run	Substrate	Reductant	Product	% Yield[a] (*cis*/*trans*)[b]
1	**2a**	$NaB(CN)H_3$	**4**	72 (87/13)
2	**2b**	$NaB(CN)H_3$	**4**	70 (88/12)
3	**3a**	$NaB(CN)H_3$	**5**	68 (95/5)
4	**3b**	$NaB(CN)H_3$	**5**	62 (95/5)
5	**2a**	Et_3SiH	**4**	87 (5/95)
6	**2b**	Et_3SiH	**4**	82 (5/95)
7	**2a**	Et_3SiH	**5**	93 (2/98)
8	**2b**	Et_3SiH	**5**	85 (1/99)

[a] Isolated yields.
[b] Determined by ^1H NMR.



Scheme 4.



6a (n = 1)
6b (n = 2)
6c (n = 3)

7a, 8a, 9a (R = H)
7b, 8b, 9b (R = *i*-Pr)

7 79% (**7a**/**7b** = 50/50)
8 83% (**8a**/**8b** = 20/80)
9 85% (**9a**/**9b** = 70/30)

Scheme 5.