Stereoselectivity in Intramolecular Cyclization of Non-conjugated Unsaturated Ketones by Electroreduction

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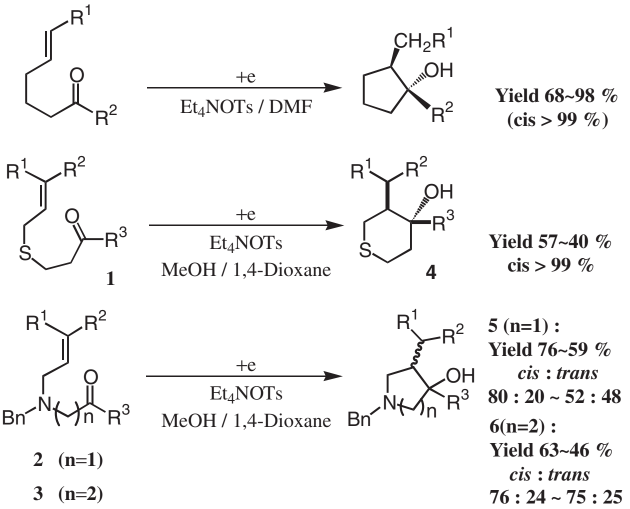
This study showed some decrease in stereoselectivity in electroreductive intramolecular cyclization of nitrogen-containing non-conjugated enones in comparison with high stereoselectivity for the corresponding enones possessing an all-carbon-chain or a sulfur-containing chain. This phenomenon may provide some actual experimental supports for the remarkable stereochemical features of the electroreductive cyclization.

It was reported that electroreductive intramolecular coupling of non-conjugated enones brought about stereoselective 5-*exo*- or 6-*exo*-cyclization to give *cis*-1,2-dialkylcycloalkanols exclusively in good to excellent yields (Scheme 1).[1] Although this electrochemical intramolecular cyclization may be quite interesting and useful in organic synthesis because of excellent yield, high regio- and stereoselectivity, and mild conditions, and many applications have been accomplished,[2–4] high *cis*-dialkyl stereochemistry has been elucidated only by a speculated hypothesis without any experimental supports.[1b]



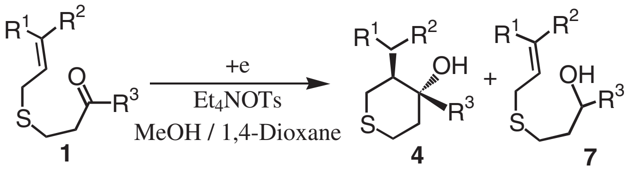
Scheme 1.

In this study, we wish to report the effects of a heteroatom such as a nitrogen or a sulfur atom on the stereoselectivity in electroreductive cyclization of non-conjugated enones containing the heteroatom between an olefinic moiety and a carbonyl group, providing some actual experimental supports for the high stereoselectivity. Thus, electroreduction of 3-(allylthio) ketones (**1**), 2-(*N*-allylamino) ketones (**2**), and 3-(*N*-allylamino) ketones (**3**) led to selective intramolecular cyclization to give the corresponding heteroatom-containing cyclic alcohols, 4-hydroxytetrahydrothiopyrans (**4**), 3-hydroxypyrrolidines (**5**), 4-hydroxypiperidine (**6**), as the main products, respectively, in moderate to excellent yields, which may be expected to be useful as synthetic intermediates of a variety of biologically active compounds,[5] as shown in Scheme 1.

Electroreduction of a series of heteroatom-containing non-conjugated unsaturated ketones (**1**)–(**3**) was generally carried out in a mixed solvent of methanol and 1,4-dioxane (or tetrahydrofuran) containing tetraethylammonium *p*-toluenesulfonate (Et_4NOTs) as a supporting electrolyte at ambient temperature (15–30 °C) under constant-current conditions (current density: 10 mA/cm^2) using an undivided cell equipped with aluminum plates[6] as the anode and the cathode after 10 F/mole of electricity passed through the system.

Electroreduction of sulfur-containing non-conjugated enones, 3-allylthio ketones (**1**), brought about intramolecular cyclization to give the corresponding *cis*-3,4-dialkylthiacycloalkan-4-ols (**4**)[7] exclusively in 57–40% yields (Table 1).

Table 1. Electroreduction of Sulfur-Containing Non-conjugated Enones



Entry	R^1	R^2	R^3	Yield 4/%[a]	Yield 7/%[a]
1	H	H	Me	57	1
2	H	H	Et	40	8

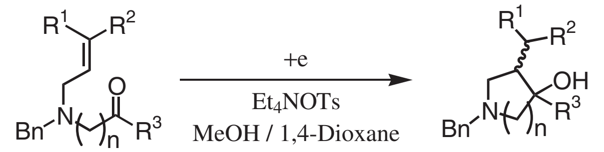
[a] GC yield.

This electroreductive intramolecular cyclization is also applicable to non-conjugated enones, 2-(*N*-allylamino) ketones (**2**) and 3-(*N*-allylamino) ketones (**3**), that contain an amino nitrogen atom in the main chain between the carbonyl group and the olefinic moiety, giving the corresponding pyrrolidine (**5**)[7] and piperidine derivatives (**6**)[7] as the main products in moderate yields. However, the stereoselectivity of this intramolecular cyclization decreased to some extent in comparison with the case of carbon and sulfur analogues (Table 2).

Introduction of a variety of substituents on the nitrogen atom of N-containing non-conjugated enones provided interesting information for some decrease in stereoselectivity in the electroreduction of **2** and **3**. As shown in Table 3, sterically bulky groups did not give any difference in stereoselectivity while introduction of electron-withdrawing groups such as acetyl and benzyloxycarboxy groups brought about distinctive effect in stereoselectivity of the electroreductive cyclization (Table 3).

In the previously proposed mechanism,[1b] the first electron transfer from cathode to the carbonyl group of the substrates generated the corresponding anion radical species, which subsequently interacted with the olefinic moiety. In the cyclized intermediate, which was formed by the interaction of the anion radical with the inner carbon atom of the C–C double bond

Table 2. Electroreductive Cyclization of N-Containing Non-conjugated Enones

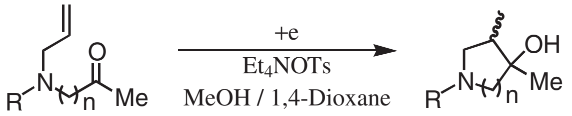


2(n=1) ,**3**(n=2) **5**(n=1), **6**(n=2)

Entry	R^1	R^2	R^3	n	Yield/%^{a}	cis : trans
1	H	H	Me	1	76	70 : 30
2	H	Me	Me	1	69	74 : 26
3	Me	Me	Me	1	69	80 : 20
4	H	H	^{t}Bu	1	59	52 : 48
5	H	H	Me	2	63	76 : 24
6	H	H	Et	2	46	75 : 25

^{a}GC yield.

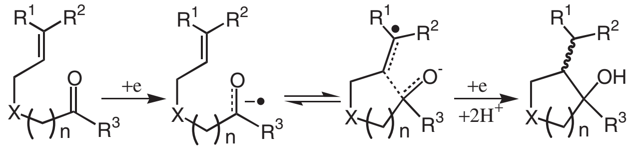
Table 3. Effect of Substituents on the Nitrogen Atom of N-Containng Enones



Entry	R	n	Conv./%	Yield/%^{a}	cis/trans
1	PhCH$_2$	1	83	76	70/30
2	n-Bu	1	87	67	73/27
3	1-Ethylpropyl	1	89	69	73/27
4	H	2		Complex Mixture	
5	Ac	2	88	53	80/20
6	Cbz	2	90	55	81/19

^{a}GC yield.

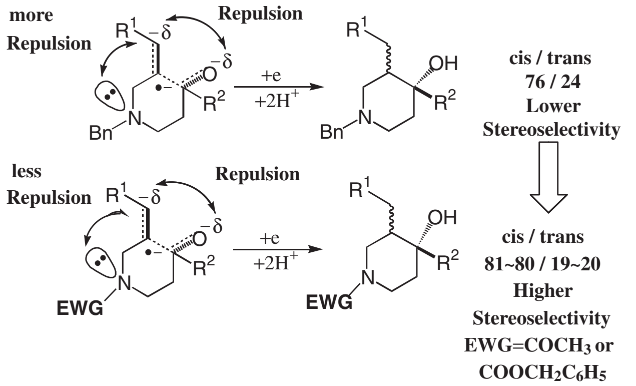
through a radical-type of cyclization, both the oxygen atom and the terminal carbon atom of the C–C double bond possessed some negative charges, which kept both moieties away from each other. As the result, the stereochemistry of two alkyl groups on the ring was formed with *cis* configuration selectively. However, the stereoselectivity of the present electroreductive cyclization leading to the pyrrolidine and piperidine derivatives decreased to 52–80% vs 48–20% for *cis* vs *trans* configuration (Scheme 2).



X=CH$_2$, S, N-Y Y= Bn, Ac, Boc n=1 or 2 R^1,R^2,R^3 = Alkyl Group

Scheme 2.

The following explanation may figure out why nitrogen-containing non-conjugated enones give the less stereoselectivity. We propose that the lone pair electron of the nitrogen atom of the nitrogen-containing non-conjugated enones may make some disturbance of the electronic repulsion between the oxygen atom and the terminal carbon atom of the C–C double bond to result in some decrease in the stereoselectivity. As the strong support of this hypothesis, the introduction of an electron-withdrawing group on the nitrogen atom such as an acetyl group or a benzyloxycarbonyl group brings about some increase in stereoselectivity because it may decrease the electron density of a lone pair of the nitrogen atom to provide some decrease in the electronic disturbance (Scheme 3).



Scheme 3.

Electroreductive cyclization of the sulfur-containing non-conjugated enones gives the higher stereoselectivity in contrast with the lower stereoselectivity in that of the nitrogen analogues. This difference may be explained by bond length between the carbon atom and the heteroatom. That is, the bond length between the carbon atom and sulfur atom is 1.81–1.83 Å and that between the carbon atom and nitrogen atom is 1.45–1.46 Å.[8] This means that a lone pair electron of sulfur is much more remote to the cyclized center than that of nitrogen, giving little electronic disturbance.

As a conclusion, the decrease in stereoselectivity caused by the presence of a nitrogen atom in a main chain of non-conjugated enones may be also a strong support for our initial proposal concerning high stereoselectivity in their electroreductive cyclization.

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References and Notes

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6 The similar electroreduction of nitrogen-containing non-conjugated enone (**2**) using various metals other than Al as the electrodes was found to give the product (**5**) in the following yields: Carbon (8%), Zn (7%), Sus (0%), and Pt (0%).
7 All of the products in this study were identified by a variety of spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MASS) and elemental analysis.
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