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Cyclopropanation by Tandem Radical [2 + 1] Cycloaddition Conducted by Nickel Complexes Catalyzed Electroreduction

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Abstract: Bicyclo[3. 1. 0]-, 3-azabicyclo [3. 1. 0]- and 3-oxabicyclo[3. 1. 0]hexane derivatives were prepared by a nickel complex catalyzed elctroreduction of 2-bromo or 2-iodo-1, 6-diene derivatives.
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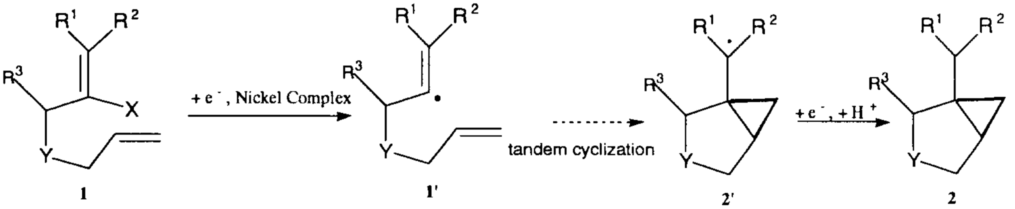
The development of new methods for the efficient and selective preparation of bicyclic and tricyclic cyclopropane derivatives is of great interest in organic chemistry due to frequent existence of these structures in biologically active compounds [1] and their role as valuable synthetic intermediates. [2] In the past ten years, palladium-catalyzed Heck reactions, [3] palladium-catalyzed cycloadditions other than Heck type reactions, [4] and intramolecular metal-carbene transformations [5] have been employed in the synthesis of these cyclopropane derivatives. However, the construction of (bicyclic) cyclopropane derivatives by means of radical reactions are known only in a few specially designed cases [6] or formed as an unexpected product. [7] The informative studies seem to suggest that the synthesis of these compounds by 3-*exo*-cyclization of 3-butenyl radicals [8] unlike those of cyclobutanes and β-lactams, which have been achieved successfully by stabilizing the corresponding cyclobutylcarbinyl or β-lactamidomethyl radicals, [9] could be accomplished when the rapid quenching of cyclopropylcarbinyl radicals besides the stabilization of these radicals are realized. This would be partly attributed to that cyclopropyl carbinyl radicals undergo much more rapid ring opening than the cyclobutylcarbinyl radicals.[10]

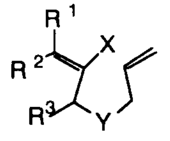
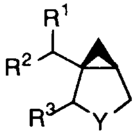
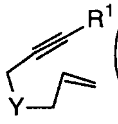
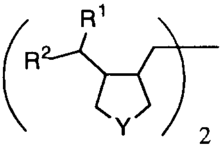
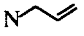
In connection with our continuing work toward development of the method which will efficiently form inter and intramolecular carbon-carbon bonds by use of nickel complexes catalyzed electroreduction,[11] we investigated tandem radical cyclization to afford bicyclic [3. 1. 0] skeletons from halides **1**[12], according to Scheme 1, where the lifetime of the cyclopropylcarbinyl radical **2'** should be selectively shortened by electroreduction to the corresponding carbanion. [11h, 13]



R^1 = COMe, Ph; R^2 = H, Me, Ph;
X = Br, I; Y = $C(CO_2Et)_2$, N-allyl, NBn, NTs

The electroreduction of **1b** using an usual amount,[11] 0.2 equiv. of Ni(II)(*tet* a)$(ClO_4)_2$[14] based on **1b** was found to provide a trace amount of a cyclopropyl derivative **2b** along with more than 60 % of the corresponding enyne **3b**. Then, the amount of the Ni(II) complex was increased to 0.3-0.5 equiv. In a typical electroreduction, [14] the substrate **1** (0.5 mmol) was dissolved in DMF or DMSO (10 ml) and elecrolyzed in the presence of Ni(II)(*tmc*)$(ClO_4)_2$ (**A**)[14] (0.17 mmol) or Ni(II)(*tet* a)$(ClO_4)_2$ (**B**)[14] (0.25 mmol) at room temperature under an inert gas. The crude product obtained by an usual work up was purified by a silica gel flash column chromatography to give products **2**, **3** and **4**.[15] The results were summarized in Table 1.

Table 1 Tandem Radical Cyclopropanation of Vinyl Halides by a Nickel Complexes Catalyzed Electroreduction[a]

	Substrate						**Product Yield (%)**[b]		
	 1								
Run		R^1	R^2	R^3	X	Y	2	3	4
1[c]	**1a**	COMe	H	H	I	$C(CO_2Et)_2$	**2a** (40)	**3a** (39)	**4a** (0)
2[c]	**1b**	COMe	H	H	I	NBn	**2b** (44)	**3b** (47)	**4b** (0)
3[d]	**1c**	COMe	H	H	I		**2c** (39)	**3c** (27)	**4c** (0)
4[d]	**1d**	COMe	H	H	I	NTs	**2d** (46)	**3d** (trace)	**4d** (0)
5[d]	**1e**	H	Ph	H	Br	O	**2e** (44)	**3e** (21)	**4e** (0)
6[d]	**1f**	Ph	Ph	H	Br	O	**2f** (46)	**3f** (0)	**4f** (0)
7[d]	**1g**	Me	Ph	H	Br	O	**2g** (18)	**3g** (0)	**4g** (18)
8[e]	**1g**						**2g** (41)	**3g** (0)	**4g** (10)
9[f]	**1g**						**2g** (10)	**3g** (0)	**4g** (31)
10[c]	**1h**	Ph	Ph	Ph	Br	O	**2h** (66)[g]	**3h** (0)	**4h** (0)
11[e]	**1h**						**2h** (43)[h]	**3h** (0)	**4h** (13)

a) Electrolyzed as described in the text. b) Isolated yield based on substrate. c) Electrolysis in DMF in a divided cell using (**B**) as a catalyst. d) Electrolysis in DMSO in an undivided cell using (**A**) as a catalyst.
e) Electrolysis at -20 °C in DMF in an undivided cell using (**A**) as a catalyst. f) Electrolysis at 80 °C in DMSO using (**A**) as a catalyst.
g) Mixture of stereoisomers,*cis/trans* ~ 1. h) Mixture of stereoisomers, *cis/trans*, ~ 1.5

As shown in Table 1, cyclopropane derivatives **2** were provided in comparable yield to those from other methods together with the 1,6-enynes **3**, and the dimer **4** formed by coupling of the homoallylic radical **1'**. The experiments of runs 8, 9 and 10, and runs 10 and 11 indicate that cooling to - 20 °C is not necessary favorable for formation of **2**. While the electrolysis of **1g** at the elevated temperature, 80 °C reduced the yield of **2g**. The electroreduction of **1h** at -20 °C (run 11) provided **2** as a mixture of stereoisomers where *cis*-isomer predominated, which would be the result of 3-*exo* cyclization of the homoallylic radical, *trans*-2,3-disubstituted cyclopentylmethyl radical, that was generated as a major isomer by 1,5-*exo* cyclization of the initial radical. [16] Electrolysis of the substrate where either R^1 or R^2 is hydrogen provided unexpected product 1,6-enynes **3** in similar yields as those of **2.** In the nickel complex catalyzed electroreductive radical addition or cyclizations [11a,b], we have observed formation of the simple reduction products of the halides or the coupling products like **4** as by-products. The attempted electrolysis of **1** without **A** or **B** at the potential of the reductive peak of complex **A**, -0.96 V vs. SCE, did not proceed. This suggests that a part of the electrogenerated Ni(I) complex plays a role for formation of **3** in a different manner observed in the previous electroreduction of halides[11] where the role of the Ni(I) complex could be explained according to the well recognized mechanistic studies[17,18] that the transient vinyl-Ni(III) complex formed by nucleophilic attack of the Ni(I) complex to C-X bond undergoes homolytic dissociation to give vinyl radicals and the Ni(II) complex. The formation of **3** is likely explained as a result of β-elimination of the transient vinyl-Ni(III) complex to afford **3** and Ni(III)H complex, of which cobalt analogue is well demonstrated in cobalt mediated-radical reactions. [19] The yields of **3a** (0.2 mmol), **3b** (0.24 mmol), **3c** (0.14 mmol) and **3d** (0.11 mmol) imply that more than 75 % of complex **B** and more than 60 % of **A** added were used to afford **3** and probably Ni(III)H complex which could not be reduced to Ni(I) species at the potential of redox couple Ni(I)/Ni(II) of complex **A.** This likely explains why more than two-fold of the Ni(II) complexes that were used in the previous electroreductiones of various halides [11] were required in the present electroreduction.

In this work, we have shown that the bicyclo[3. 1. 0]skeletons could be provided by the nickel complex catalyzed electroreduction from the vinyl halides bearing the substituents which would be able to stabilize the final radical and at the same time could shorten the lifetime of the final radicals by making them more susceptible to electroreduction. The simplicity of the method that temperature control and desiccation of the reaction system are not required could make the present elecroreductive method a convenient alternative to other methods for the formation of the bicyclo[3. 1. 0]skeletons.

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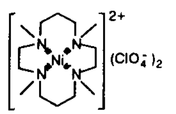
13 We have indicated that the radicals stabilized by elctron-withdrawing groups at α position are more reducible than smiple alkyl radicals and so they are reduced at the reductive potential of Ni(II) to the corresponding carbanions which would be react with water which is present in DMF or DMSO as a contaminant at the rate that is expected to be much greater than those of hydrogen abstraction from the solvents by the stabilized radicals

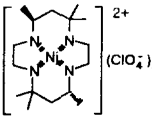
14. In electrolysis in a divided cell, a graphite plate and a platinum foil were used as a cathode and an anode, respectively. In electrolysis in an undivided cell a graphite plate and a zinc plate were used as a cathode and a sacrificial anode, respectively. Tetraethylammonium perchlorate (TEAP) (1 mmol) was used as a supporting electrolyte. Electricity of 2F/mol based on the halides was passed galvanostatically (3 mA). Complexes **A** and **B** are shown below.)

A



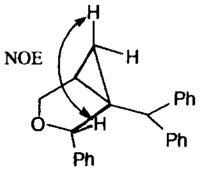
Ni (*tmc*)$(ClO_4)_2$
Ep; - 0.96 V *vs.* SCE

B

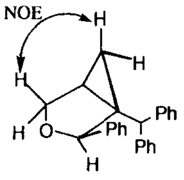


Ni (*tet a*)$(ClO_4)_2$
Ep; -1.38 V vs. SCE

15 All products **2**, **3** and **4** exhibited IR, ^{13}C NMR and ^{1}H NMR spectra which were consistent with the assigned structures. ^{1}H NMR spectra for *cis* and *trans*-**2h**. cis-**2h** (200 MHz, $CDCl_3$) σ 7.44-6.97 (15H, m, ArH), 4.89 (1H, s, CC*H*Ar), 4.42 (1H, s,CC*H*O), 4.15 (1H, dd, J 8.4, 2.7 Hz, CHC*H*HO), 4.05 (1H, d, J 8.4 Hz, CHCH*H*O), 1.69-1.63 (1H, m, CH_2C*H*CH_2), 0.74 (1H, dd, J 5.1, 4.6 Hz, C*H*H, cyclopropyl) and 0.08 (1H, dd, *J* 8.1, 5.1 Hz, CH*H*, cyclopropyl); trans-**2h** (200 MHz, $CDCl_3$) σ 7.31-6.90 (15H, m, ArH), 4.84 (1H, s, CC*H*Ar), 4.38 (1H, dd, J 8.2, 2.9 Hz, CHC*H*HO), 4.09 (1H, s,CC*H*O) 3.91 (1H, d, *J* 8.2 Hz, CHCH*H*O), 1.23 (1H, ddd, 7.7, 4.6, 2.9 Hz, CH_2C*H*CH_2), 0.98-0.88 (2H, m, CHCH_2CH, cyclopropyl). The stereochemical assignments of **2h** were based on the NOE experiments.



cis-**2h**



trans-**2h**

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18. The mechanism that the nickel complex works as the one-electron transfer catalyst, i. e., the scission of C-X bond to provide directly a radical and X$^-$ is caused by three-electron attack by the nickel-centered anion, the Ni(I)complex, and one that including homolytic dissociation of the R-Ni(III) complex to give a radical and the Ni(II) complex have been proposed.[17]

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