Doctoral Thesis

A New Electrooxidative Synthesis of Novel Pharmaceutical Intermediates

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Contents

Chapter III

Title : Electrooxidative Cyclization of Hydroxyamino Compounds Possessing a Benzyl Group

Chapter IV

Title : Unexpected Formation of Novel Oxazolidine and Tetrahydrooxazine Derivatives by Condensation of 2-(Hydroxymethy) or 2-(2-Hydroxyethyl) Piperidine, and Ketones

Chapter V

Chapter I

Introduction

The earliest examination of successful electrochemical reaction from the view point of organic synthesis can be found in literature in 1849, which is known as the Kolbe reaction where dimerized aliphatic carboxylic acids were obtained by electrochemical oxidation of aliphatic carboxylic acid. [1] To date, electroorganic chemistry is generally unfamiliar to the field of organic synthesis yet. The one of the purpose of this study is to show the usefulness of the electrochemical method for synthesizing organic compounds especially for novel pharmaceutical intermediates. [2] In the field of preparation of organic compounds, environmentally friendly synthetic methods are strongly desired. For examples, solvent-free condition, without use of poisonous and/or expensive reagents and

near at room temperature under atmospheric pressure. Generally, electrooxidation can be carried out without use of any special reagent and/or hazardous oxidant. Moreover, usually control of the electrolytic reaction is extremely easy by making an adjustment of current intensity from the outside of the electrolytic reaction cell. Nowadays, highly developed power-supply equipment and none noble metal electrodes are easily available. Figure 1 shows electrooxidation and reduction, Figure 2 shows direct and indirect electrooxidation.

In our laboratory, variety of electrooxidations of nitrogenous organic compounds such as amine, imine, enamine, hydrazone and their derivatives have been carried out. When hydrazones were used as the starting substrate, [3] not only academically interest but also useful products that difficult to obtain by usual chemical method could be often obtained.

In continuation of our interest, in this study,

Figure 1. Electrooxidation and Electroreduction

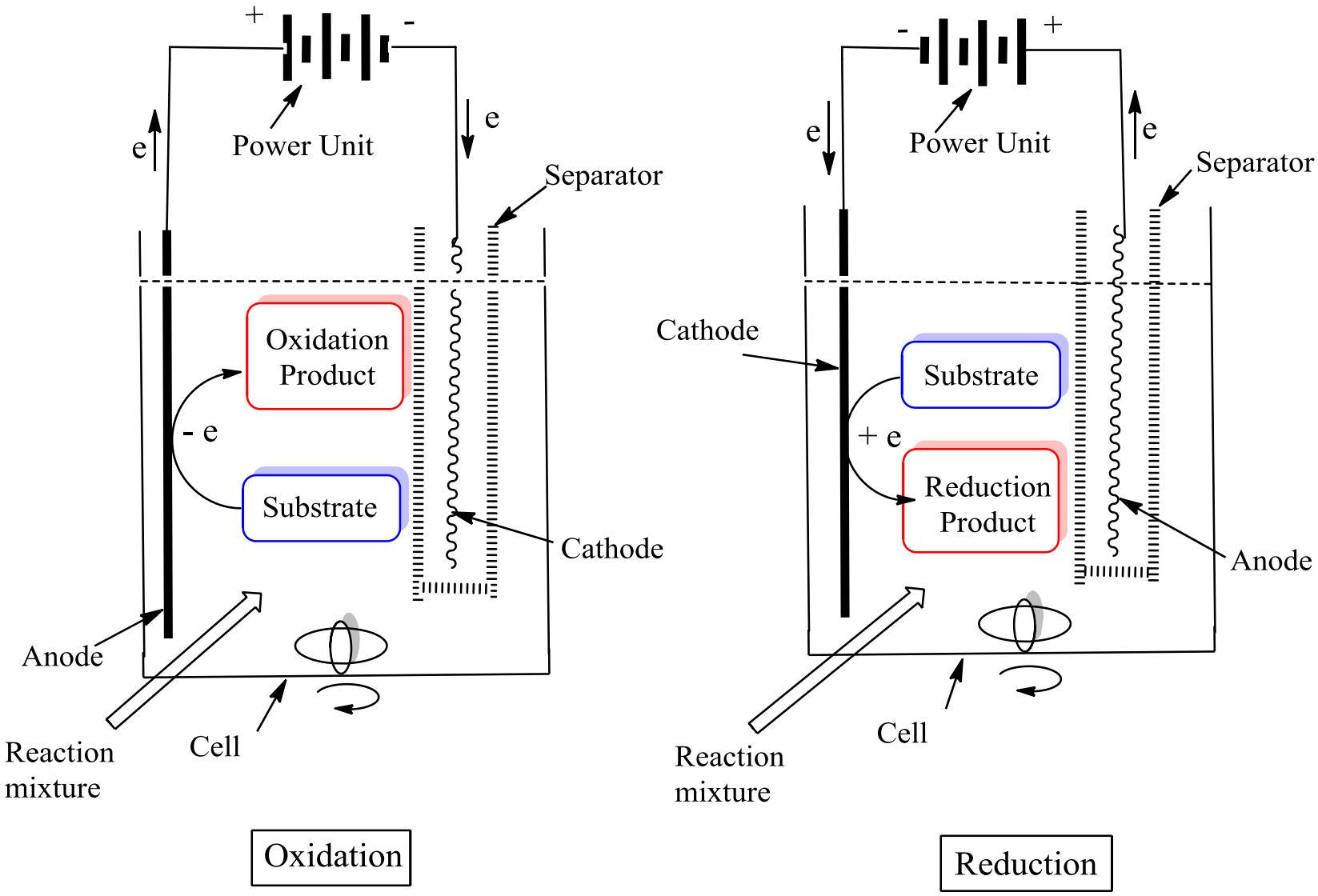
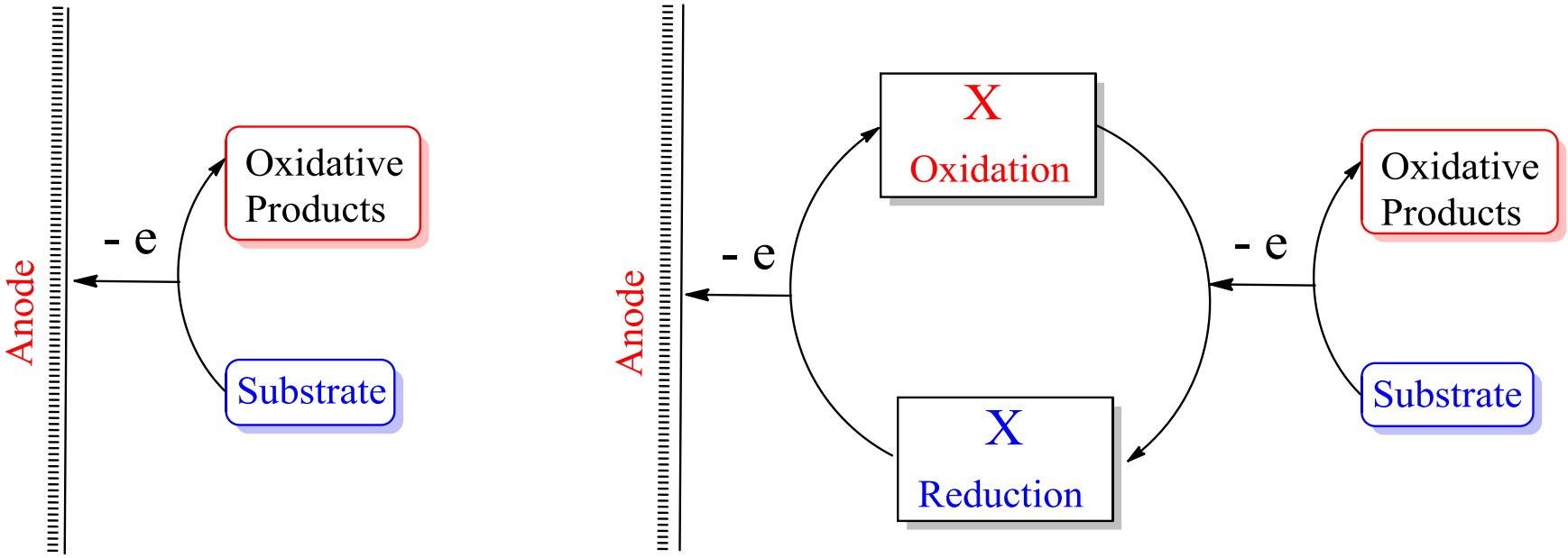


Figure 2. Direct and Indirect Electrooxidation



Direct Electrooxidation

Indirect Electrooxidaton

X = catalytic amount of metal ion, halogen ion and/or organic compounds.

electrooxidation of *N*-phenylsemicarbazones that were very easily available by condensation of an equivalent amount of *N*-phenylsemicarbazide and ketones was examined as described in Chapter II. As the results, interestingly it was found that *N*-phenylsemicalbazones were cleaved into three comportments, that is, methylphenyl carbamate and parent ketones involving evolution of gaseous nitrogen by the electrooxidation. To the best of our knowledge, there are no reports regarding the oxidation of ketone *N*-phenylsemicalbazones by neither chemical oxidant nor electrooxidative method.

In Chapter III, several novel 2-aryl-1,3-oxazinane and 2-aryl-1,3-oxazolidine derivatives were synthesized from *N*-benzyl-2-piperidineethanols and *N*-benzyl-2-piperidinemethanols, respectively, by using electrooxidative methods in MeOH. In contrast, 3-dialkylamino-1-phenylpropanols afforded the expected cyclic 6-phenyl-1,3-oxazinane derivatives using only a

small excess amount of the base.

In Chapter IV, formation of three rings oxazine and oxazolizine derivatives was found unexpectedly during preparation of hydroxyl enamines as a starting material for electrooxidation. Although desired starting hydroxyl enamines were not obtained here, instead some novel heterogeneous three rings compounds that possess spiro-carbon could be newly obtained.

1. For example see:

(a) Tilford, C. H.; Van Campen Jr., M. G. *J. Am. Chem. Soc.*, **1954**, *76*, issue 9, 2431-2441.

(b) McCary, F. J.; Tilford, C. H.; Van Campen Jr., M. G. *J. Am. Chem. Soc.*, **1957**, *79*, issue 2, 472-480.

2. Kolbe, H. *Ann.*, **1849**, *69*, issue 3, 257-294.

3. For example see:

(a) Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem.*, **1983**, *48*, issue 18, 2968-2972.

(b) Okimoto, M.; Chiba, T. *J. Org. Chem.*, **1990**, *55*, issue 3, 1070-1076.

(c) Okimoto, M.; Takahashi. Y. *Bull. Chem. Soc. Jpn.*, **2002**, *75*, issue 9, 2059-2060.

Chapter II

Anodic Cleavage of Several Ketone *N*-Phenylsemicarbazones into Methyl *N*-Phenylcarbamate and the Corresponding Dimethyl Acetals [1]

Abstract

Several ketone *N*-phenylsemicarbazones were electrooxidized in the presence of potassium iodide and a base using methanol as the solvent, to give nearly commensurate amounts of methyl *N*-phenylcarbamate and the corresponding dimethyl acetals. Continuous evolution of gaseous nitrogen was observed from the anolyte during the electrooxidation. The reactions were

carried out under very mild reaction conditions, and are presumed to proceed through a four-electron oxidation process, in which the iodide ion plays an important role as an electron carrier.

II-1. INTRODUCTION

Aldehydes and ketones can be readily converted to the corresponding *N*-phenylsemicarbazones via condensation reactions using equivalent amounts of *N*-phenyl-semicarbazide. The resulting semicarbazone derivatives are often used for identification of carbonyl compounds based on their known melting points. [2] The *N*-phenylsemicarbazone is the oxidized form of parent *N*-phenylsemicarbazide. Although a few reports are found regarding oxidation of ketone semicarbazones via typical

chemical methods using oxidizing reagents, [3-10] to the best of our knowledge, there are no reports on the oxidation of ketone *N*-phenylsemicarbazones via electrooxidative methods in MeOH. [11-13] Our studies focused on the electrooxidation of nitrogenous organic compounds, such as amines, enamines, and hydrazones, not only from the viewpoint of synthesis, but also of studying the reactivities of the substrates. [14-22] During our investigation, we observed a novel and interesting behavior of ketone *N*-phenylsemicarbazone (**1**) under anodic conditions.

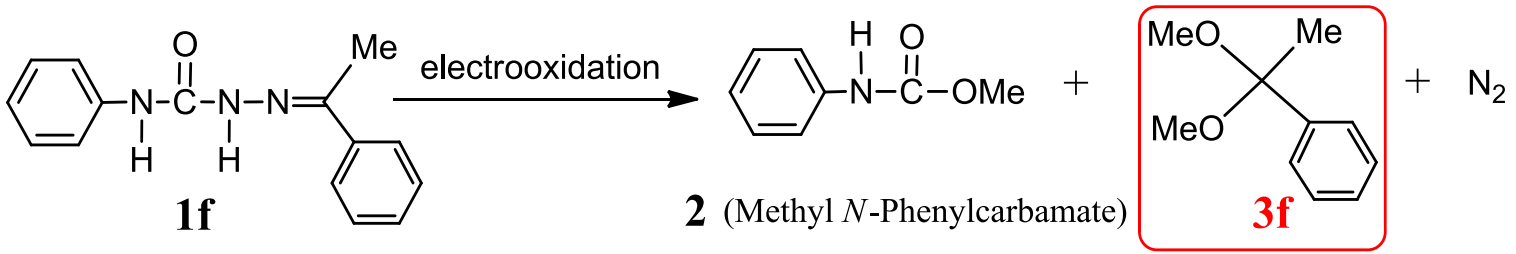
II-2. RESULTS AND DISCUSSION

At the beginning of the electrooxidation, almost all of substrate **1** existed as an insoluble fine powder in the

anolyte due to its poor solubility in MeOH. Upon passage of electric current and under vigorous stirring, substrate **1** gradually dissolved into the anolyte. Interestingly, during the electrooxidation, continuous evolution of nitrogen gas from the anolyte was observed, which clearly indicates the decomposition of **1**. At the same time, gas-liquid chromatography (GC) analysis of the anolyte indicated the immediate formation of methyl *N*-phenyl-semicarbamate (**2**) and the corresponding dimethyl acetal (**3**). After the electric current passage of nearly 4 $Fmol^{-1}$ of electrical current, most of **1** was dissolved, and the evolution of gaseous nitrogen ceased.

First, the optimal reaction conditions for the electrooxidative decomposition of **1** were determined using acetophenone semicarbazone (**1f**) as a model substrate. The types of the supporting electrolytes, along with the corresponding yields of **2** and acetophenone dimethylacetal (**3f**) are listed in Table 1.

Table 1. Optimal reaction conditions for the anodic cleavage of acetophenone phenyl-semicarbazone into *N*-phenyl-methylcarbamate, acetophenone dimethylacetal and nitrogen[a)]



1f **2** (Methyl *N*-Phenylcarbamate) **3f**

Entry	Supporting electrolytes (mmol)				Yield of **2** and **3f** [b)] (%)	
	Electrolyte		Mediator		**2**	**3f**
1	NaOMe	(5.0)	None		11	26
2	None		KI	(7.5)	95	94
3	NaOMe	(2.5)	KI	(7.5)	78	94
4	NaOMe	(2.5)	NaI	(7.5)	91	88
5	NaOMe	(2.5)	KBr	(7.5)	13	30
6	NaOMe	(2.5)	KCl	(7.5)	15	25
7	NaOAc	(2.5)	KI	(7.5)	90	83
8	NaOH	(2.5)	KI	(7.5)	91	94
9	KO(*t* -Bt)	(2.5)	KI	(7.5)	69	95
10	$NaClO_4$	(5.0)	None		12	20
11	$LiClO_4$	(5.0)	None		10	16

[a)] **1f** : 2.03g (8 mmol); MeOH : 40 mL; constant current : 0.3 A; current passed : 4.2 $Fmol^{-1}$; reaction temperature : *ca.* 20 ˚C.

[b)] Yield was determined by GC analysis.

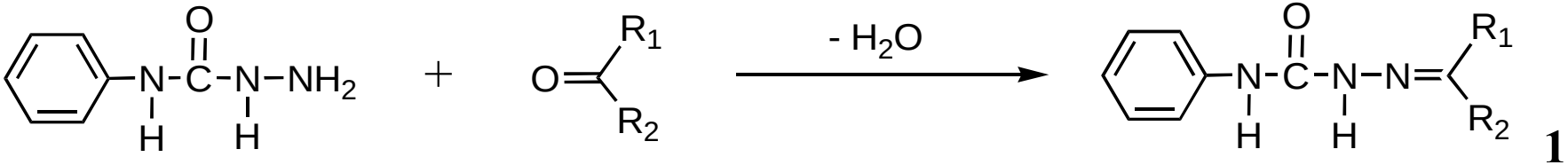
Remarkably, the use of merely one equivalent of KI (relative to **1f**) was the most effective in the formation of **2** and **3f** (95% and 94% yields, respectively, Entry 2). One drawback, however, was that the terminal voltage tended to surpass 20 V during the first half step; this was easily resolved by the addition of NaOMe (*ca.* 0.3 equivalents relative to **1f**) without affecting the yield of **3f** (Entry 3). However, the yield of **2** decreased from 95% to 78%. Substitution of KI with KBr (Entry 5) or KCl (Entry 6) resulted in poor yields of **2** and **3f** with unreacted **1** remaining within the electrolytic cell.

Although the use of a stronger base such as KO(*t*-Bu) (Entry 9) resulted in a yield of **3f** (94%) that was comparable as that of NaOMe. The use of a weaker base such as NaOAc (Entry 7) gave a somewhat lower yield of **3f** (83%). In regards to the mediator, the yields of **3f** were less than 30% for electrooxidation reactions that lacked KI (Entries 1, 4, 5, 6, 10 and 11), illustrating the critical

role of KI (source of iodide ions) in the decomposition reactions of **1f** (Entries 2-3 and 7-9). Significant differences in the yields of **3f** were observed by varying the amounts of KI (5 mmol, 91%; 2 mmol, 70%; 1 mmol, 49%) and NaOMe (2.5 mmol, 94%; 10 mmol, 70%; 20 mmol, 49%). Immediately upon the start of the electrooxidation reactions, the yields of **2** and **3f** were proportional to the amount of current passed; 34% and 35% after the electric current passage of 1.5 $Fmol^{-1}$, respectively and then 65% and 69% after 3.0 $Fmol^{-1}$, respectively. In other words, these reactions are highly efficient (over 86%) during the early stages. Theoretically, most of **1f** was consumed after a small excess amount of electric current (4.2 $Fmol^{-1}$) was passed. Based on the above results, the optimal reaction conditions were applied towards the electrooxidative cleavage of various ketone *N*-phenylsemicarbazones **1a-s**, as listed in Table 2-6. For alkyl ketone *N*-phenylsemicarbazones **1a-c**, **e**, the

yields of the decomposed products varied between 68 to 85% of **2** and 58 to 67% of **3b**, **c**, **e**, respectively. However, in the case of **1d**, the yields of **2** and **3d** unexpectedly decreased after the current passage of 3.0 $Fmol^{-1}$. **3a** could not be detected clearly by GC because of the low boiling point. For **1a-e**, the electrooxidations were carried out in the absence of NaOMe, which was found to decrease the yields of the products. Alkyl aryl ketones **1f-o** gave decomposed products in moderate to good yields (**2**, 64-95%, and **3**, 63-94%), except in the case of **1o**. For the benzophenone substrates, although good yields were obtained for **1p** (98% of **2** and 74% of **3p**), lower yields were observed for the substituted benzophenone *N*-phenylsemicarbazones **1q-s**, in which the parent substituted benzophenones were formed as the by-product in the yields of 20% to 36%. As a note, the solubilities of **1p-s** which contain three aromatic rings were improved using *t*-BuOH as a co-solvent to MeOH.

Table 2. Preparation of *N*-phenyl-semicarbazone by condensation reaction of *N*-phenyl-semicarbazid and alkyl ketone[a)]

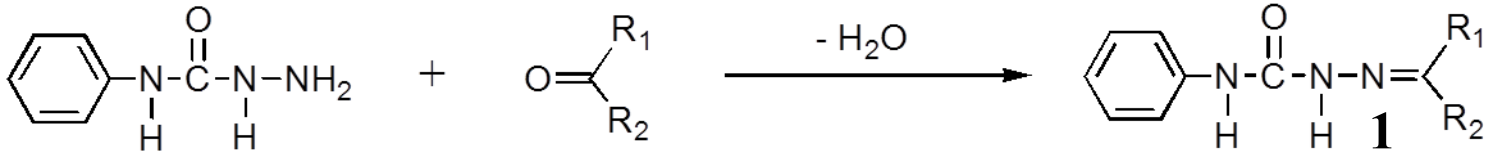


1

Product	Alkyl ketones		Reaction time	Yield	Melting point
	R_1	R_2	(hr)	(%)	(˚C)
1a	Me	Me	8.0	6 9	156 - 157
1b	-$(CH_2)_5$-		2.5	9 8	194 - 195
1c	-$(CH_2)_2$	-CH(*t*-C_4H_9)-$(CH_2)_2$-	5.5	9 6	191 - 192
1d	*n*-C_3H_7	*n*-C_3H_7	7.0	7 6	88 - 89
1e	Me	*n*-C_6H_{13}	5.5	7 5	86 - 87

[a)]Refluxed in EtOH solution in the presence of catalytic amount of *p*-toluene sulfonic acid

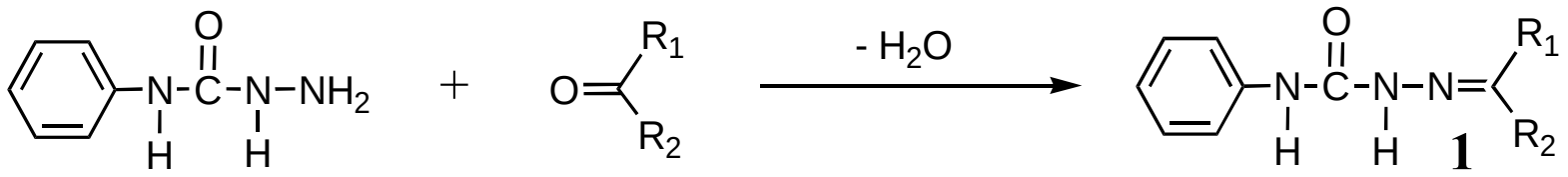
Table 3. Preparation of *N*-phenyl-semicarbazone by condensation reaction of *N*-phenyl-semicarbazid and alkyl aryl ketone[a)]



Product	Alkyl Aryl ketone		Reaction time	Yield	Melting point
	R_1	R_2	(hr)	(%)	(˚C)
1f	Me	Ph	3.0	9 6	181 - 182
1g	Me	*p*-Me-C_6H_4	5.0	8 3	192 - 193
1h	Me	*p*-MeO-C_6H_4	1.0	9 2	161 - 162
1i	Me	*p*-Cl-C_6H_4	1.5	9 6	192
1j	Et	*p*-Me-C_6H_4	8.0	6 9	156 - 157
1k	*i*-Pr	Ph	2.5	9 8	194 - 195
1l	*i*-Pr	*p*-MeO-C_6H_4	5.5	9 6	191 - 192
1m	*n*-Bu	Ph	9.5	6 6	131 - 133
1n	Me	3-Pyridyl	1.5	9 8	180 - 182
1o	Me	2-Furyl	1.0	9 0	176 - 177

[a)] Refluxed in EtOH solution in the presence of catalytic amount of *p*-toluene sulfonic acid.

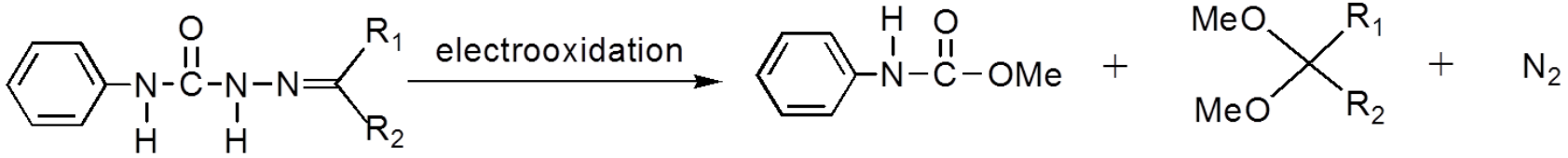
Table 4. Preparation of *N*-phenyl-semicarbazone by condensation reaction of *N*-phenyl-semicarbazid and diaryl ketone and benzaldehyde[a)]



Product	Diaryl ketone and benzaldehyde		Reaction time	Yield	Melting point
	R_1	R_2	(hr)	(%)	(˚C)
1p	Ph	Ph	5.0	8 3	192 - 193
1q	*p*-Me-C_6H_4	*p*-Me-C_6H_4	1.0	9 2	161 - 162
1r	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	21.0	9 0	167 - 171
1s	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	2.0	7 8	216 - 219
1t	Ph	H	0.1	8 2	174 - 176
1u	*p*-Me-C_6H_4	H	0.1	9 2	176 - 177
1v	*p*-MeO-C_6H_4	H	0.1	9 3	173 - 174
1w	*p*-Cl-C_6H_4	H	0.1	9 4	194 - 195

[a)] Refluxed in EtOH solution in the presence of catalytic amount of *p*-toluene sulfonic acid.

Table 5. Anodic cleavage of ketone phenyl-semicarbazone into *N*-phenyl-methylcarbamate and corresponding dimethylacetal[a)]



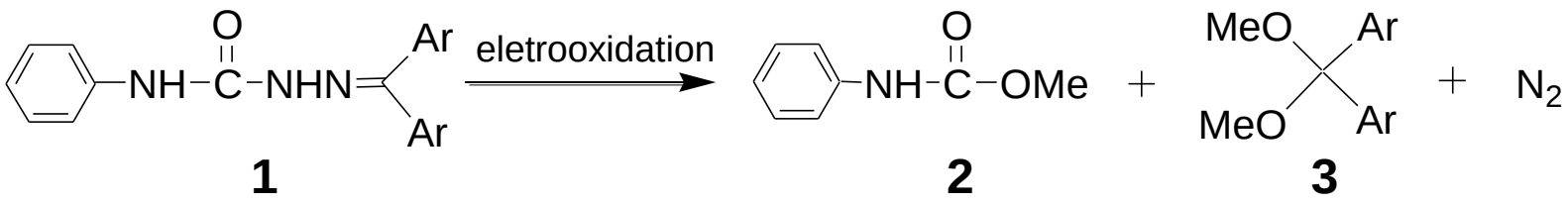
1 **2** (Methyl *N*-Phenylcarbamate) **3**

Substrate	**1**		Yield of **2** and **3** (%)[b)]	
	R_1	R_2	**2**	**3**
1a[c)]	Me	Me	85	-
1b[c)]	$-(CH_2)_5-$		82	66
1c[c)]	$-(CH_2)_2$	$-CH(t\text{-}C_4H_9)-(CH_2)_2-$	84	57
1d	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	52	52
1e[c)]	Me	$n\text{-}C_6H_{13}$	93	64
1f	Me	Ph	95	94
1g	Me	$p\text{-Me-}C_6H_4$	88	86
1h	Me	$p\text{-MeO-}C_6H_4$	80	77
1i	Me	$p\text{-Cl-}C_6H_4$	64	91
1j	Et	$p\text{-Me-}C_6H_4$	85	85
1k	*i*-Pr	Ph	78	79
1l	*i*-Pr	$p\text{-MeO-}C_6H_4$	68	63
1m	*n*-Bu	Ph	64	84
1n	Me	3-Pyridyl	83	75
1o[c)]	Me	2-Furyl	45	38

[a)] **1** : 8 mmol; KI : 7.5 mmol; NaOMe : 2.5 mmol; MeOH : 40 mL; constant current : 0.3 A; current passed : 4.2Fmol^{-1}; reaction temperature : *ca,* 20 ° C.

[b)] Determined by GC analysis. [c)] Electorolysis was carried out without base.

Table 6. Anodic cleavage of benzophenone phenylsemicarbazone into *N*-phenylmethylcarbamate and corresponding dimethylacetal[a)]



1 **2** **3**

Substrate	Benzophenone	Yield of **2** and **3**[b), c)]	
	Ar	**2**	**3**
1p	Ph	98	74
1q	*p*-Me-C_6H_4	93	55
1r	*p*-MeO-C_6H_4	62	45
1s	*p*-Cl-C_6H_4	73	51

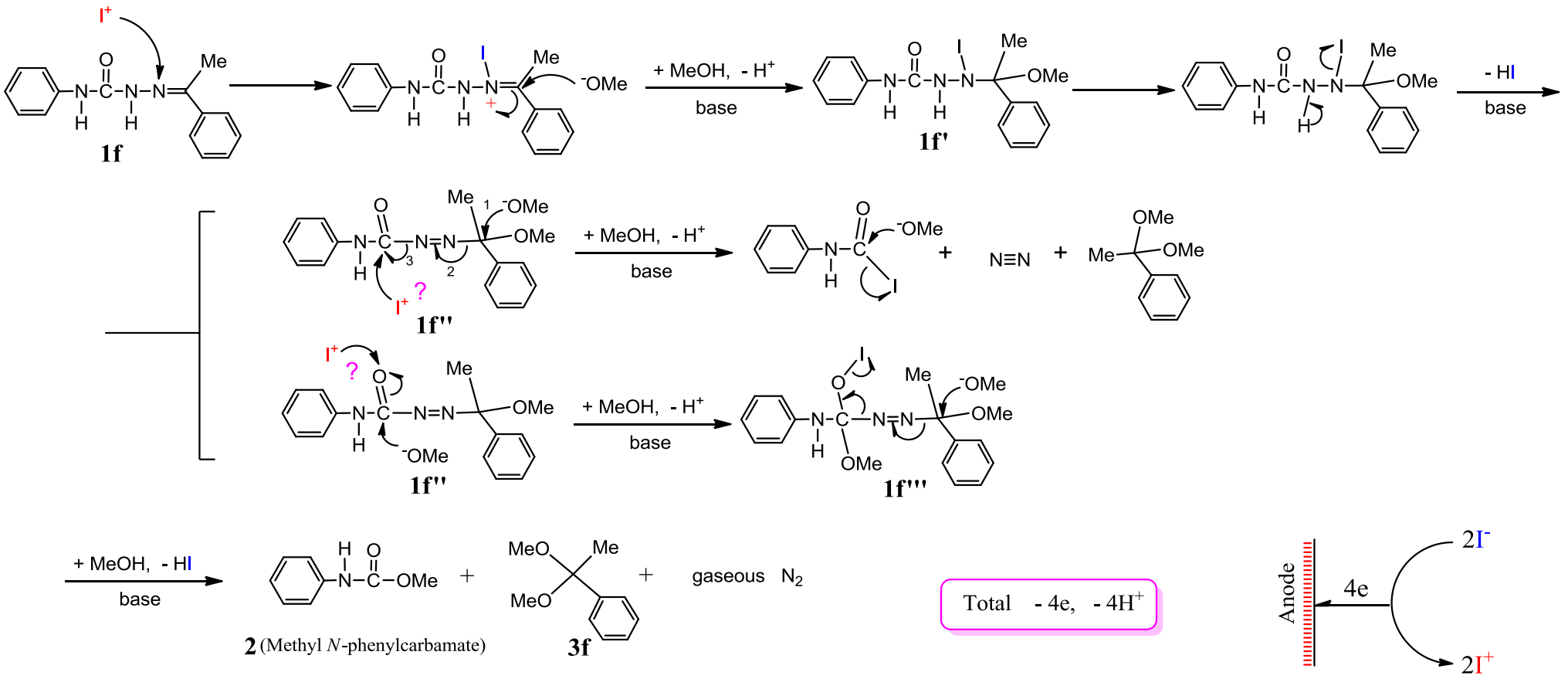
a) **1** : 8 mmol; KI : 7.5 mmol; MeOH : 20 mL; *t*-BuOH : 20mL; constant current : 0.3 A; current passed : 4.2 $Fmol^{-1}$; reaction temperature : *ca* 20 ˚C.

b) Yields of **2** and **3p~s** were determined by GC analysis.

c) Formation of parent ketones was observed in the anolyte (In the case of **1p** =17 %, **1q** =17 %, **1r** =49 % and **1s** =13 %).

Following the electrooxidations, decomposed products **2** and **3** were readily isolated using silica-gel column chromatography. As a note, the phenyl-amido group (PhNHCO-) of **1** can be used repeatedly as a component of parent *N*-phenylsemicarbazide by refluxing isolated **2** with a small excess of hydrazinehydrate in EtOH.

Although the reaction pathway of these electrooxidiations still needs to be fully investigated, it is clear that iodide ions play an important role as electron carriers. As illustrated in Scheme 1, the anodic cleavage may involve the consumption of 3 equivalents of MeOH and elimination of four protons through a four-electron oxidation process.



Scheme 1. One of the probable reaction path way for the four electron electrooxidative cleavage

In conclusion, the electrooxidation of ketone *N*-phenylsemicarbazone resulted in cleavage to methyl *N*-phenylsemicarbamate and the corresponding dimethyl acetal with generation of gaseous nitrogen. In addition to this interesting behavior of **1** under anodic conditions in MeOH, the reaction may be applicable for the preparation of various organic compounds. Moreover, the advantages of our method include: 1) very mild reaction conditions (*ca.* 20°C), 2) absence of harsh toxic reagents, such as metal oxidants or special reagents, and 3) a simple one-pot reaction.

II-3. EXPERIMENTAL

Ketone *N*-phenylsemicarbazones were prepared in high yields (83-95%) via typical condensation reactions

between *N*-phenylsemicarbazide and a small excess of the ketone by refluxing in EtOH for 1-5 h. Preparative-scale electrooxidations were carried out in a tall 50-mL beaker equipped with a fine frit cup as the cathode compartment with a nickel coil cathode, along with a cylindrical platinum net anode (50 mesh).

Typical procedures :

A solution of acetophenone *N*-phenylsemicarbazone **1f** (8 mmol) in MeOH (40 mL) containing KI (7.5 mmol) and NaOMe (2.5 mmol) was electrooxidized under a constant current (0.3 A). During the course of the electrooxidation, the anolyte was magnetically stirred at *ca.* 20 °C, and the composition of the reaction mixture was monitored by GC (FFAP-1.5 m) analysis. Passage of the electric current was continued until almost all of the substrate was dissolved. Upon electric current passage of 4.2 F mol^{-1}, the reaction mixture was concentrated *in vacuo* (*ca.* 10 mL) at approximately 50 °C. The resulting oily residue

was treated with water (*ca.* 30 mL), then extracted with ethyl ether (3×40 mL), and dried over sodium sulfate overnight. After removal of the solvent *in vacuo*, the crude mixture of **2** and **3f** were purified by silica-gel column chromatography using ether/hexane (3:5) as the eluent. The electrooxidation products were identified by comparing against authentic samples using GC analysis, high resolution mass and/or IR spectroscopy.

II-4. REFERNCES

1. Nishikawa, S.; Yamamori, H.; Ohashi, K.; Okimoto, M.; Hoshi, M.; Yoshida, T. *Synth. Commun.* **2013**, in press.

2. Shriner, R. L.; Buson, R. C. *The Systematic*

Identification of Organic Compounds, *3 ed*; Wiley: New York, **1948**, 231, 262-266.

3. Braun, J. V.; Steindorff, A. *Chem. Ber.* **1905**, *38*, issue 3, 3094-3107.

4. Barton, D. H. R.; Lester, D. J.; Ley, S. V. *Chem. Commun.* **1977**, 445-446.

5. Bird, J. W.; Diaper, D. G. M. *Can. J. Chem.* **1969**, *47*, issue 1, 145-150.

6. Pilgram, K.; Skiles, R. D.; Pollard, G. E. *J. Heterocycl. Chem.* **1976**, *13*, issue 6, 1257-1263.

7. Yang, R. Y.; Dai. L. X. *J. Org. Chem.* **1993**, *58*, issue 12, 3381-3383.

8. Cameron, A. M.; West, P. R.; Warkentin, J. *J. Org. Chem.* **1969**, *34*, issue 11, 3230-3233.

9. Prakash, O.; Gujral, H. K.; Rani, N.; Singh, S. P. *Synth. Commun.* **2000**, *30*, issue 3, 417-425.

10. Zhang, G. S.; Chai, B. *Synth. Commun.* **2000**, *30*, issue 10, 1849-1855.

11. Lund, H. *Acta Chem. Scand.* **1959**, *13*, 249-267.

12. Refaey, S. A. M.; Hassan, A. A.; Shehata, H. S. *Int. J. Electrochem. Sci.* **2008**, *3*, issue 3, 325-337.

13. Lotfi, B.; Mustafa, B.; Leila, B.; Salima, M. *Int. J. Electrochem. Sci.* **2011**, *6*, issue 6, 1991-2000.

14. Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org.*

Chem. **1979**, *44*, issue 20, 3519-3523.

15. Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org*. *Chem*. **1983**, *48*, issue 18, 2968-2972.

16. Okimoto, M.; Chiba, T. *J. Org*. *Chem*. **1990**, *55*, issue 3, 1070-1076.

17. Chiba, T.; Okimoto, M. *J. Org*. *Chem*. **1992**, *57*, issue 5, 1375-1379.

18. Okimoto, M.; Nagata, Y.; Takahashi, Y. *Bull*. *Chem*. *Soc*. *Jpn*. **2003**, *76*, issue 7, 1447-1448.

19. Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Tomozawa, K.; Chiba, T. *Heterocycles*, **2008**, *75*, issue 1, 35-42.

20. Okimoto, M.; Numata, K.; Tomozawa, K.; Shigemoto, T.; Hoshi, M.; Takahashi, Y. *Aust. J. Chem.* **2005**, *58*, issue 7, 560-563.

21. Okimoto, M.; Takahashi, Y.; Nagata, Y.; Numata, K.; Sasaki, G. *Synth. Commun.* **2005**, *35*, issue 15, 1989-1995.

22. Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Tomozawa, K.; Chiba, T. *Synth. Commun.* **2008**, *38*, issue 19, 3320-3328.

Chapter III

Electrooxidative Cyclization of Hydroxyamino Compounds Possessing a Benzyl Group [1]

Abstract

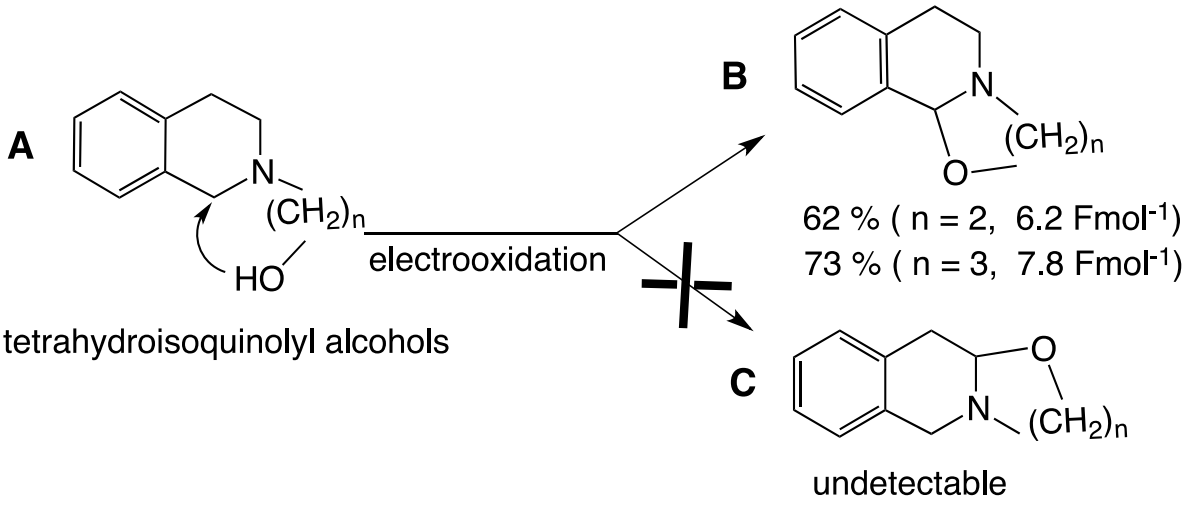
Several novel 2-aryl-1,3-oxazinane and 2-aryl-1,3-oxazolidine derivatives were synthesized from *N*-benzyl-2-piperidineethanols and *N*-benzyl-2-piperidine-methanols, respectively, by using electrooxidative methods in MeOH. For these reactions, the yields of the corresponding cyclized compounds were significantly increased by using catalytic amounts of iodide ions. In contrast, 3-dialkylamino-1-phenylpropanols afforded the expected cyclic 6-phenyl-1,3-oxazinane derivatives using

only a small excess amount of the base.

III-1. RESULTS AND DISCUSSION

Electrooxidation is well known as an extremely useful and attractive method for the oxidation of various organic compounds. [2] Electrooxidation often provides specific and/or unique reaction products that are difficult to obtain using typical chemical reagents. [3] Our studies focused on the electrooxidation of nitrogenous organic compounds, such as amines, enamines, and hydrazones, not only from the viewpoint of synthesis, but also to study the reactivities of the substrates. [4] We have previously reported on the indirect electrooxidation of tetrahydroisoquinolyl alcohols **A** in the presence of KI and a base in MeOH [5] in which the oxygen atom of the

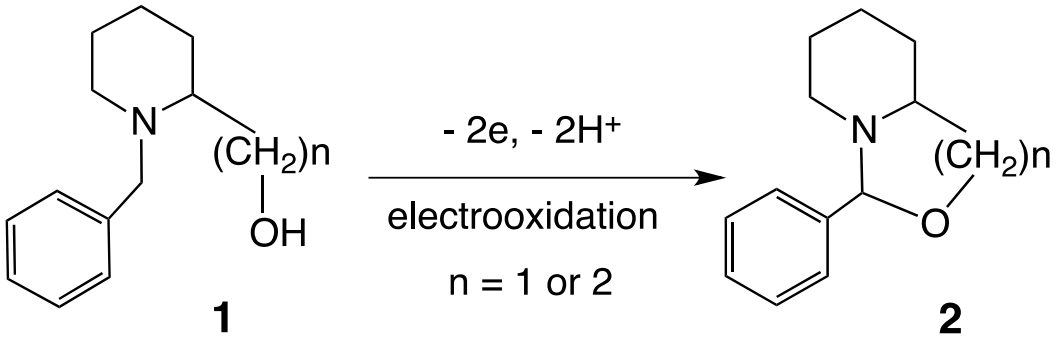
hydroxy group selectively attacked the benzylic carbon to yield the corresponding cyclic compound **B** without any cyclic compound **C**, as illustrated in Scheme 1.



Scheme 1. Electrooxidative cyclization of tetrahydroisoquinolyl alcohols **A**

Based upon the selectivity of the above reaction, we reasoned that *N*-benzylpiperidine (**1**), possessing a hydroxy group (n=1 or 2), should cyclize under electrooxidative conditions to give 2-aryl-1,3-oxazolidine (**2**; n=1) and 2-aryl-1,3-oxazinane (**2**; n=2) derivatives,

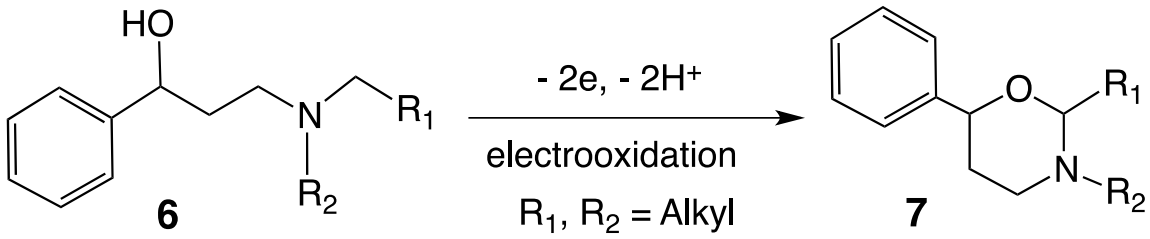
respectively (Scheme 2).



Scheme 2. Electrooxidative cyclization of *N*-benzylpiperidine alcohols **1**

Accordingly, as described in the present study, electrooxidative cyclizations of *N*-benzylpiperidine alcohols **1** (n=1 and 2) were carried out in the presence of catalytic amount of KI and a base in MeOH to afford the expected cyclic compound **2**. Similarly, the electrooxidation of 3-dialkylamino-1-phenylpropanols (**6**) under similar reaction conditions (in the presence of a strong base in MeOH) gave the corresponding cyclic compounds such as 6-phenyl-1,3-oxazinane derivatives

(**7**), as shown in Scheme 3.



Scheme 3. Electrooxidative cyclization of 3-dialkylamino-1-phenylpropanols **6**

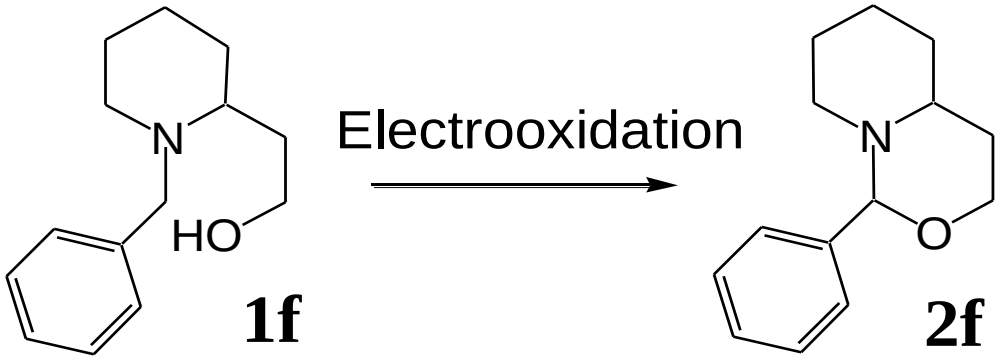
Although there are a few reports that describe the synthesis and/or conformational analysis of these compounds, to the best of our knowledge, the application of electrooxidation for the preparation of these compounds has yet to be reported. [6]

Initially, the optimal reaction conditions for the electrooxidation of **1** were determined using *N*-benzyl-2-piperidineethanol (**1f**) as the model substrate. Various combinations of the supporting electrolytes (mediators and bases) along with the corresponding yields of the

resulting cyclized product (**2f**) are listed in Table 1. When either NaOMe or KI was used alone, the yield of **2f** was merely 35 % and 40%, respectively (Entries 1 and 2). Remarkably, the presence of both KI (0.25 equivalents to substrate) and NaOMe (0.63 equivalents) was effective in increasing the yield of **2f** to 57% (Entry 3). The yield was further increased to nearly 70% using a small excess of NaOMe (1.25 equivalents, Entry 4). Although the use of a strong base such as *t*-BuOK was similarly effective (yield of 69%, Entry 7), the use of a weak base such as NaOAc decreased the yield of **2f** (Entry 8). In contrast, substitution of KI (Entry 4) with KBr (Entry 9) or KCl (Entry 10) resulted in lower yields of **2f** (37% and 31%, respectively). These results indicate that the yield of **2f** is strongly affected by the presence of KI.

Immediately upon the start of the electrooxidation reaction, the yield of **2f** was proportional to the amount of current passed – specifically, 34% after 3.0 $Fmol^{-1}$, and

Table 1. Effects of supporting electrolyte on the product yield [a)]



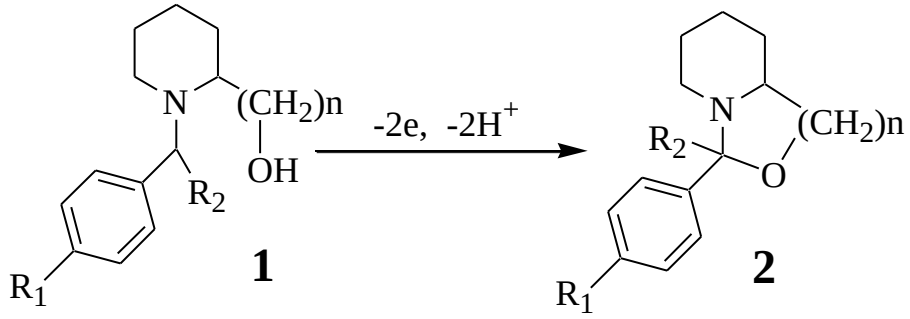
1f **2f**

Entry	Mediator kind (2 mmol)	Base kind (mmol)		Yield of **2f** (%)
1	None	NaOMe	5	35
2	KI	None	-	40
3	KI	NaOMe	5	57
4	KI	NaOMe	10	69
5	KI	NaOMe	40	55
6	KI	NaOH	10	63
7	KI	*t*-BuOK	10	69
8	KI	NaOAc	5	37
9	KBr	NaOMe	10	37
10	KCl	NaOMe	10	31

[a)] **1f** : 8 mmol; MeOH : 40 mL; Constant current : 0.3A; Current passed : 6.2 $Fmol^{-1}$; Anode : Pt; Cathode : Ni; reaction temperature : *ca.* 15℃.

then 67% after 6.0 $Fmol^{-1}$. However, as the reaction proceeded, the current efficiency gradually decreased to 66% after 8.0 $Fmol^{-1}$, and therefore, the amount of current passed was deemed to be sufficient to consume most of **1f**. Subsequently, these optimal reaction conditions were used to carry out the electrooxidations of *N*-benzyl-2-piperidinemethanols (**1a-1e**) and substituted *N*-benzyl-2-piperidineethanols (**1f-1j**) to form 1,3-oxazolidines (**2a-2e**) and 1,3-oxazinanes (**2f-2j**), respectively as listed in Table 2. The composition of the anolyte was monitored by GC analysis. Although the consumptions of *N*-benzyl-2-piperidinemethanols **1a-1e** were faster than those of *N*-benzyl-2-piperidineethanols **1f-1j**, the yields of products **2a-2e** were lower than those of **2f-2j**. The lower yields can be attributed to the differences in the structural strain between the five- and six-membered rings of the cyclic products. In both cases of **1** (n=1 and 2), the substituent effects at the *para*-position

Table 2. Electrooxidative cyclization of *N*-benzyl-2-(hydroxymethyl)- and *N*-benzyl-2-(2-hydroxyethyl)piperidines[a)]



Substrate	1		n	Current passed ($Fmol^{-1}$)	Yield of **2a-j** (%)[b)]
	R_1	R_2			
1a	H	H	1	3.8	60
1b	Me	H	1	3.9	62
1c	MeO	H	1	3.7	61
1d	Cl	H	1	3.7	60
1e	H	Me	1	4.0	trace
1f	H	H	2	6.2	65
1g	Me	H	2	5.3	66
1h	MeO	H	2	4.9	63
1i	Cl	H	2	5.4	67
1j	H	Me	2	5.0	trace

[a)] **1**: 8 mmol; KI: 2 mmol; NaOMe: 10 mmol; MeOH: 40 mL; Constant current: 0.3A; Anode: Pt; Cathode: Ni; Reaction temperature: *ca.* 5˚C.

[b)] Isolated yields based on **1**.

of the benzene ring did not affect the yields of **2**.

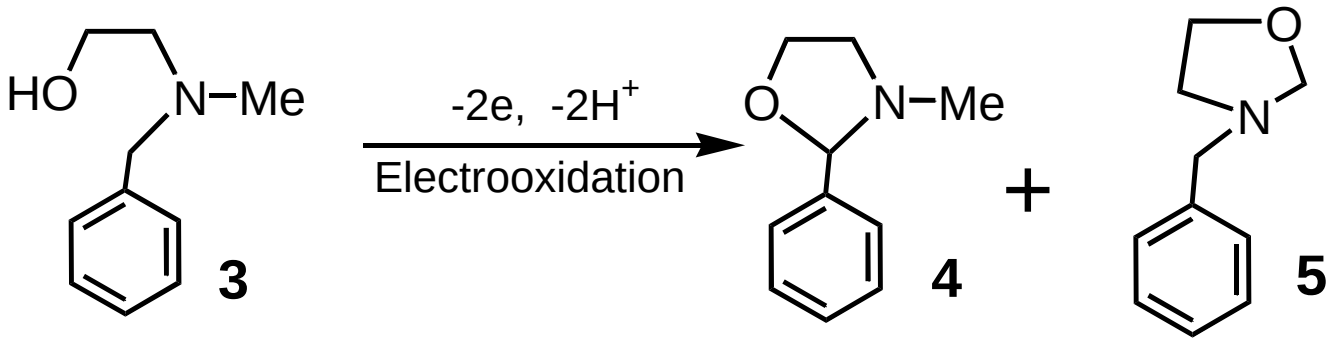
In contrast, the electrooxidations of *N*-ethylphenyl- and *N*-propylphenyl-2-piperidineethanols, which do not possess a benzylic carbon that is directly connected to the nitrogen atom to form the conjugate system, did not selectively form the corresponding cyclic compounds. GC analysis revealed multiple peaks indicating unselective electrooxidation.

It is noteworthy that a chemical reaction of **1d** with excess amount of iodine (1.5 equivalent) as the oxidant gave only below 10% yield of **2d** in spite of long reaction period (6 h) and elevated temperature (50°C) in separate examination.

On the other hand, interestingly, our investigations indicated that the amino alcohols do not necessarily require a benzyl group for intramolecular cyclization as shown in Table 3.

The electrooxidations of 2-benzyl(methyl)aminoethanol

Table 3. Optimal reaction conditions for the intramolecular cyclization[a)]



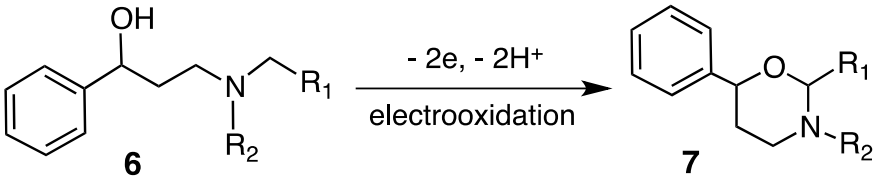
Entry	Supporting electolyte and mediator (mmol)			Current passed ($Fmol^{-1}$)	Yield of **4** + **5**[b)] (%)	Proportion of products[b)] (%) **4** : **5**
1	NaOMe (10)	KI	(5)	5.1	79	58 : 42
2	NaOMe (20)	KI	(5)	5.1	76	59 : 41
3	NaOMe (20)	KI	(10)	5.1	80	59 : 41
4	KO(*t* - Bt) (10)	KI	(5)	5.1	66	59 : 41
5	NaOMe (10)	KBr	(5)	2.3	73	49 : 51
6	NaOMe (20)	KCl	(5)	2.1	60	50 : 50
7	NaOMe (10)	KCl	(5)	5.1	trace	— : —

[a)] Substrate **3** : 1.32g (8 mmol); MeOH : 40 mL; Constant current : 0.3 A; reaction temperature : *ca.* 15 ℃; Anode : Pt net; Cathode : Ni coil.

[b)] Determined by GC analysis.

(**3**) under similar conditions afforded mixture (58:42) of 2-pheny-3-methyl-1,3-oxazolidine (**4**) and 3-benzyl-1,3-oxazolidine (**5**) in a total yield of 79% (as determined by GC analysis). However, the separation of **4** and **5** by either column chromatography or distillation was not successful due to the similarities in their properties. Nonetheless, the IR spectra of the mixture of **4** and **5** confirmed the disappearance of the hydroxyl group of **3** with the presence of the corresponding ether bond, and the HR-MS analysis indicated that both compounds possess the same formula composition, but with distinct fragment peaks. The findings demonstrated that not only a benzyl, but an alkyl carbon can also undergo the intramolecular attack by the hydroxy group. The unexpected results indicated that a benzylic carbon is not necessary for the cyclization. As a consequence, we had to revise our understanding on these reactions, and reasoned that 3-dialkylamino-1-phenylpropanols that

possess a hydroxy group at their benzylic position carbon, such as **6**, can be cyclized to yield 6-phenyl-1,3-oxazinane derivatives **7**, as illustrated in Scheme 4.

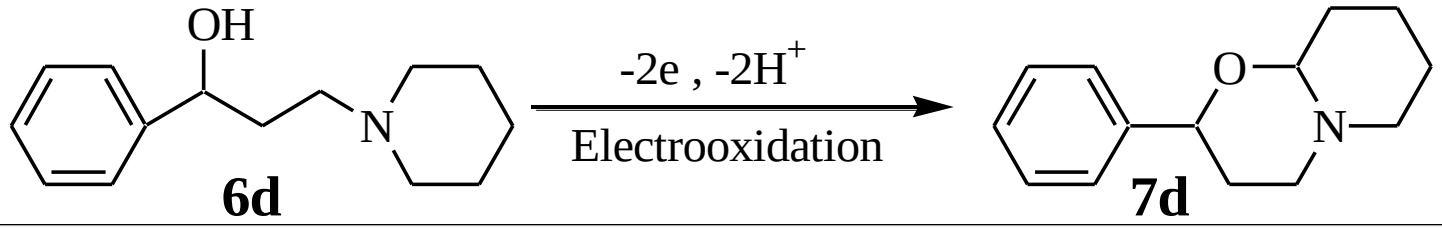


Scheme 4. Electrooxidative cyclization of 3-dialkyl-amino-1-phenylpropanols **6**

As expected, the carbon at the α-position of the nitrogen atom of **6** underwent nucleophilic attack by the hydroxyl group to form the corresponding cyclized compound 6-phenyl-1,3-oxazinane derivatives **7**. Initially, the most effective supporting electrolyte for the electrooxidation of **6** was determined using 1-phenyl-3-piperidinopropanol (**6d**) as the model substrate. The corresponding yields of the resulting cyclized product (**7d**) are listed in Table 4.

Surprisingly, the combination of KI and NaOMe (entry 1), which was effective in the formation of cyclized compound **2e** (Table 1, entry 4), gave the cyclized product **7d** in 52% yield, with 41% of the starting substrate **6d** remaining even after the passage of sufficient current. When an excess amount of only NaOMe was used, without KI, the yield of **2e** increased from 59% (entry 2) to 61% (entry 4). Likewise, the use of strong base such as *t*-BuOK afforded the product with a yield of 57 % (Entry 5). In contrast, the use of a weak base such as NaOAc (entry 6) resulted in a tar-like material with a combined yield of 33% of the starting substrate **6d** and product **7d**. The use of neutral salts such as *p*-TsON(Et)$_4$ (entry 7) or $NaClO_4$ (entry 8) suppressed the formation of **7d** in which a large portion of substrate **6d** remained unreacted. These results indicate that the cyclization process of **6** to **7** is significantly different than that of **1** to **2**. Subsequently, our electrooxidation process was applied

Table 4. Influence of supporting electrolyte on the yield of cyclic compound **7d**[a)]



Entry	Supporting electrolyte (mmol)		Recovery of **6d** (%)[b)]	Yield of cyclic compound **7d** (%)[b)]
1	KI - NaOMe	(5 - 10)	41	52
2	NaOMe	(10)	trace	59
3	NaOMe	(5)	1	60
4	NaOMe	(20)	trace	61
5	KO (*t* - Bt)	(10)	2	57
6	NaOAc	(10)	12	21
7	*p*-TsON(Et)$_4$	(10)	59	12
8	$NaClO_4$	(10)	52	10

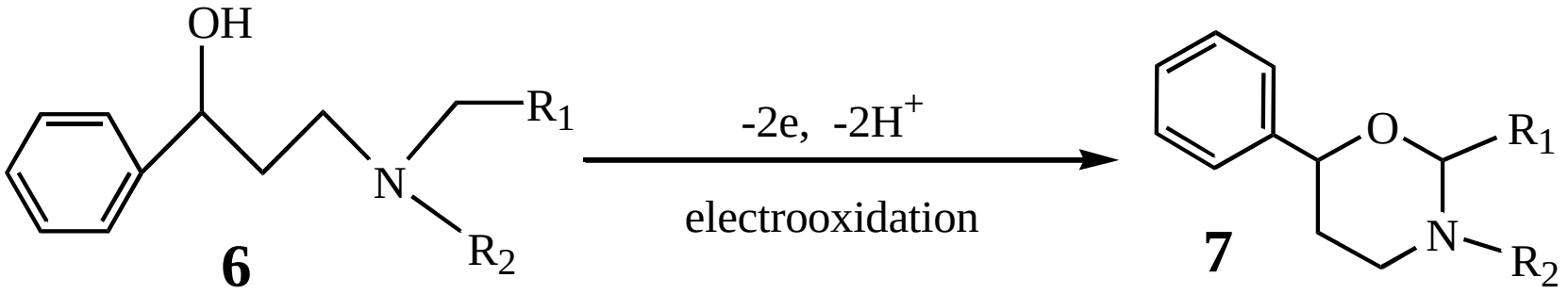
a) Substrate **6d** : 1.76 g (8 mmol); MeOH : 40 mL; Constant current : 0.3 A; Current passed : 3.73 $Fmol^{-1}$; reaction temperature : *ca.* 15 ℃; Anode : Pt net; Cathode : Ni coil .

b) Determined by GC analysis.

for the formation of 6-phenyl-1,3-oxazinane derivatives (**7a-c**) and (**7e-h**) starting from 3-dialkylamino-1-phenylpropanols (**6a-c**) and (**6e-h**), respectively. For these reactions, symmetrical amino moieties ($R_1CH_2 = R_2$) were employed to avoid the formation of structural isomers. As listed in Table 5, the corresponding cyclized products were obtained in moderate to good yields using only NaOMe as the supporting electrolyte.

Cyclized products **7a** and **7f** were obtained in somewhat low yields from **6a** and **6f**, respectively. In contrast, despite the passage of a small amount of current (2.8 $Fmol^{-1}$), the highest yield was obtained for the formation of **7g** (82%) starting with a substrate that possesses a hexamethyleneimino moiety **6g**. In the case of **6e**, the corresponding cyclized product **7e** was obtained as an equal mixture of the *cis-trans* isomers with a yield of 74%. The passage of electrical current was continued until almost all the starting substrate was consumed. For the

Table 5. Electrooxidative cyclization of aminoethylbenzyl alcohols[a)]

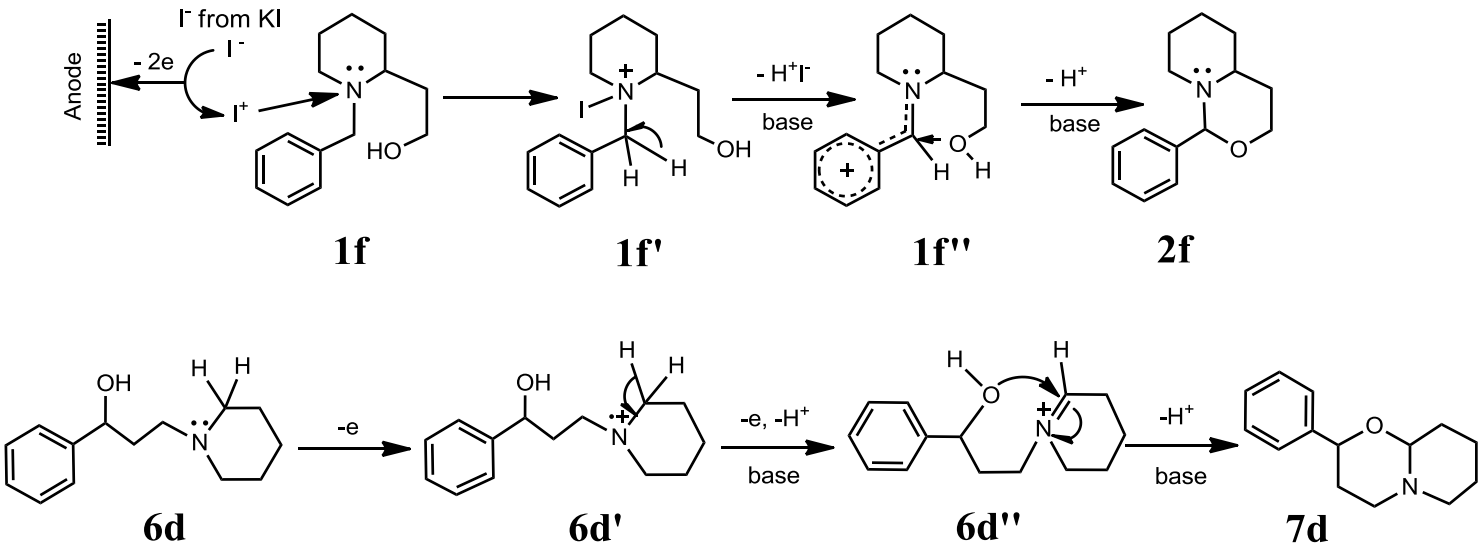


	6a-h		Current passed	Isolated yield of 7 a-h
	R_1	R_2	(F mol^{-1})	(%)
a	*n*-C_2H_5	*n*-C_3H_7	3.0	5 6
b	*iso*-C_3H_7	*iso*-C_4H_9	3.3	7 4
c	-$(CH_2)_3$-		3.4	7 0
d	-$(CH_2)_4$-		3.7	6 2
e	-$CH_2CH(CH_3)$ CH_2CH_2-		3.0	7 4
f	-$CH(CH_3)CH_2CH$ (CH_3) CH_2 -		3.8	5 5
g	-$(CH_2)_5$-		2.8	8 2
h	-$CH_2OCH_2CH_2$-		3.6	6 7

[a)] Substrate **6** : 8 mmol; NaOMe : 10mmol; MeOH : 40 mL; Constant current : 0.3 A; reaction temperature : *ca.* 15 ℃; Anode : Pt net; Cathode : Ni coil.

reactions with low yields, considerable amounts of tar-like material remained in the distillation flask and/or on the top of the column used for chromatographic cleanup. Although the detailed reaction mechanisms for the two cyclization processes remain unclear, their reaction pathway can be proposed as illustrated in Scheme 5. Based on the optimal reaction conditions as listed in Table 1 and 4, the processes for **1f** and **6d** are significantly different; the former reaction proceeds predominately via indirect electrooxidation and the latter reaction principally involves direct electrooxidation. Specifically, in the case of **1f**, the iodide ion from KI would lose two electrons on the anode to form an iodonium ion at the beginning of the reaction. The resulting cationic species would attack substrate **1f** at the lone pair of the nitrogen atom to form iminium cation (**1f'**), followed by elimination of HI to give conjugated cation (**1f"**), which would undergo an intramolecular nucleophillic attack by

the oxygen atom of the hydroxy group to give cyclic product **2f**. On the other hand, in the case of **6d**, the formation of cation radical (**6d'**) would involve the drawing of one electron from the lone pair of the nitrogen atom. The cation radical would then lose another electron via deprotonation to form iminium cation (**6d"**), which would then undergo a nucleophillic attack by the hydroxy group's oxygen atom to give cyclized product **7d**. In both cases, the presence of a strong base such as NaOMe or *t*-BtOK would promote deprotonation during the course of the reaction.



Scheme 5. Proposed reaction pathway for the cyclization of **1f** and **6d**

In conclusion, our electrooxidation methodology was successfully applied for the cyclization reactions of *N*-benzyl-2-piperidine alcohols and 3-dialkyl amino-1-phenylpropanol. Although the yields were moderate, the preparation of such cyclized compounds via electrooxidation is novel and allowed us to gain insight into their peculiar behavior. Furthermore, it is important to note that such electrooxidation reactions could be carried out in a one-pot reaction, under very mild reaction

conditions, and without the use of any hazardous oxidants.

III-3. EXPERIMENTAL

N-Benzyl-2-piperidinemethanol and *N*-Benzyl-2-piperidineethanol were prepared from 2-piperidine-methanol and 2-piperidineethanol, respectively, via typical benzylation reaction using benzyl chloride and refluxing in EtOH for 3-4 h (83-93%). [7] The 3-dialkyl amino-1-phenylpropanols were prepared via reduction of the corresponding 3-dialkyl amino-1-phenylpropanones using $NaBH_4$ and refluxing in EtOH for 1-2 h (65-92%). [8] The 3-dialkyl amino-1-phenylpropanones were synthesized from 3-chloropropiophenone via alkylation of symmetrical amines and refluxing in EtOH for 3-8 h

(54-87%). [7] Preparative-scale electrooxidations were carried out in a tall 50-mL beaker equipped with a fine frit cup as the cathode compartment with a nickel coil cathode, along with a cylindrical platinum net anode (45-mm height, 25-mm diameter, 50 mesh).

Typical procedures (**1f** in Table 2): A solution of *N*-benzyl-2-piperidineethanol 1.76g (8 mmol) in MeOH (40 mL) containing KI (0.33g, 2 mmol) and NaOMe (10 mmol) was subjected to electrooxidation under a constant current (0.3 A) with magnetic stirring at *ca.* 5 °C. The course of the electrooxidation was monitored by GC analysis (FFAP 10%-Chromosorb W AW, 1.5 m). The passage of electric current was continued until almost all the substrate has been consumed. Upon passage of the electrolytic current (6.2 $Fmol^{-1}$), the reaction mixture was concentrated (*ca.* 10 mL) *in vacuo* at approximately 50 °C, then extracted using diethyl ether (3×40 mL) without use of water. The resulting, slightly muddy ether solution was

dried over sodium sulfate overnight and then filtered. After removal of the solvent *in vacuo*, the cyclized products were isolated by reduced pressure distillation and/or silica gel column chlomatography (350-mm height, 28-mm diameter) using diethyl ether/hexane (1:1) as the eluent.

Typical procedures (**6d** in Table 5): A solution of 3-piperidino-1-phenylpropanol (1.76g, 8 mmol) in MeOH (40 mL) containing NaOMe (10 mmol) was subjected to electrooxidation under a constant current (0.3 A) at *ca.* 15 °C with magnetic stirring. Upon passage of the electrolytic current (3.7 $Fmol^{-1}$), the reaction mixture was concentrated (*ca.* 10 mL) *in vacuo* at approximately 50 °C. The resulting residue was treated with water (20 mL), and then extracted using diethyl ether (3×40 mL). The combined ether layers were dried over sodium sulfate overnight. After removal of the solvent *in vacuo*, the cyclized products were isolated by reduced pressure

distillation (in the case of **7a** and **7b**) or silica-gel column chromatography (350-mm height, 28-mm diameter) using AcOEt:EtOH (3:1) as the eluent. Physical properties, IR, NMR, and Mass spectra of all products are shown below:

3-phenylhexahydro-1*H*-oxazolo[3,4-*a*]pyridine (2a)

Colorless viscous oily liquid; yield: 0.98g (60%); Bp 151-153 ℃/2.0 mbar; R_f = 0.68(diethyl ether- *n*-hexane, =1:1). IR (neat) : 2937(s), 2871, 1456, 1377, 1099, 1078, 1024(s), 755, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) :δ= 1.18-1.44(m, 1H), 1.46-1.66(m, 3H), 1.72-1.86(m, 2H), 1.98-2.06(m, 1H), 2.44-2.54(m, 1H), 2.64-2.74(m, 1H), 3.60-3.74(m, 1H), 4.04-4.16(m, 1H), 4.59(s, 1H), 7.18-7.38(m, 3H, Ph), 7.39-7.48(m, 2H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$) :δ= 23.52(CH_2), 24.75(CH_2), 26.59(CH_2), 47.14(CH_2), 62.77(CH), 71.23(CH_2), 96.62(CH), 128.00(CH), 128.18(CH), 128.84(CH), 139.18(C). MS (EI, 70 eV): m/z (relative intensity %) = 203(36)[M^+], 202(73), 173(34), 172(60), 126(100)[M^+-Ph], 105(39), 98(24), 91(51), 77(29), 65(13). HRMS : m/z calcd for $C_{13}H_{17}NO$: 203.1310 ; found : 203.1318 [M^+].

3-*p*-tolylhexahydro-1*H*-oxazolo[3,4-*a*]pyridine (2b)

White powder (from EtOH); yield: 1.08g (62%); Mp 48-49 ℃; R_f = 0.67(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2944(s), 1326, 1196, 1149, 1124, 1090(s), 1017, 935, 821, 804 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) :δ= 1.18-1.42(m, 2H), 1.45-1.46(m, 1H), 1.57-1.65(m, 1H), 1.78-1.86(m, 2H), 1.96-2.06(m, 1H), 2.34(s, 3H, CH_3), 2.43-2.52(m, 1H), 2.66-2.73(m, 1H), 3.62-6.68(m, 1H), 4.01-4.07(m, 1H), 4.56(s, 1H), 7.15(d, J= 8Hz, 2H, Arom), 7.34(d, J= 8Hz, 2H, Arom). ^{13}C NMR (400 MHz, $CDCl_3$) :δ= 21.26(CH_3), 23.56(CH_2), 24.78(CH_2), 26.99(CH_2), 41.18(CH_2), 62.79(CH), 71.17(CH_2), 96.54(CH), 127.94(CH), 128.91(CH), 136.23(C), 138.58(C). MS (EI, 70 eV): m/z (relative intensity %) = 217(49)[M^+], 216(99), 187(34), 186(63), 127(26), 126(100)[M^+-$C_6H_4CH_3$], 119(34), 98(25), 91(37), 41(28).

HRMS : m/z calcd. for $C_{14}H_{19}NO$: 217.1467 ; found : 217.1417 [M^+].

3-(4-methoxyphenyl)hexahydro-1*H*-oxazolo[3,4-*a*]pyridine (2c)

White fine needle-like crystal (from EtOH); yield: 1.14g (61%); Mp

30-31 ℃; R_f = 0.54(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2943(s), 1613, 1515, 1300, 1248(s), 1169, 1092, 1026(s), 825, 807 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) :δ= 1.22-1.42(m, 2H), 1.44-1.56(m, 1H), 1.58-1.65(m, 1H), 1.78-1.87(m, 2H), 1.95-2.05(m, 1H), 2.43-2.51(m, 1H), 2.64-2.72(m, 1H), 3.61-3.67(m, 1H), 3.79(s, 3H, CH_3O), 4.00-4.06(m, 1H), 4.55(s, 1H), 6.88(d, J = 8Hz, 2H, Arom), 7.38(d, J = 8Hz, 2H, Arom). ^{13}C NMR (400 MHz, $CDCl_3$) :δ= 23.57(CH_2), 24.80(CH_2), 27.03(CH_2), 47.17(CH_2), 55.23(CH_3O), 67.75(CH), 71.08(CH_2), 96.34(CH), 113.61(CH), 129.25(CH), 131.30(C), 160.12(C). MS (EI, 70 eV): m/z (relative intensity %) = 233(26)[M^+], 232(100), 203(14), 202(32), 135(28), 126(56) [M^+-$C_6H_4OCH_3$], 121(15), 119(5), 96(5), 79(9), 41(7), HRMS : m/z calcd for $C_{14}H_{19}NO_2$: 233.1416 ; found : 233.1471 [M^+].

3-(4-chlorophenyl)hexahydro-1*H*-oxazolo[3,4-*a*]pyridine (2d)

White powder (from EtOH); yield: 1.14g (60%); Mp 36-37 ℃; R_f = 0.66(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2939(s), 2804, 1492, 1363, 1089(s), 1023, 1015, 841, 823, 807 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) :δ= 1.18-1.40(m, 2H), 1.42-1.55(m, 1H),

1.58-1.72(m, 1H), 1.75-1.91(m, 2H), 1.97-2.08(m, 1H), 2.42-2.54(m, 1H), 2.62-2.70(m, 1H), 3.62-3.70(m, 1H), 4.02-4.08(m, 1H), 4.56(s, 1H), 7.32(d, J= 8Hz, 2H, Arom), 7.39(d, J= 8Hz, 2H, Arom).

^{13}C NMR (400 MHz, $CDCl_3$) :δ= 23.49(CH_2), 24.74(CH_2), 26.96(CH_2), 47.09(CH_2), 62.74(CH), 71.33(CH_2), 95.82(CH), 128.43(CH), 129.44(CH), 134.59(C), 137.87(C).

MS (EI, 70 eV): m/z (relative intensity %) = 239(17)[M^+, ^{37}Cl], 238(46), 237(53) [M^+, ^{35}Cl], 236(85), 208(43), 207(46), 206(61), 139(43), 127(43), 126(100)[M^+-C_6H_4Cl], 41(38).

HRMS : m/z calcd for $C_{13}H_{16}NOCl$: 237.0920 ; found : 237.0952 [M^+].

1-phenyloctahydropyrido[1,2-*c*][1,3]oxazine (2f)

White fine rod-like crystal (from EtOH); yield: 1.13g (65%); Bp 113-115 ℃/2.7 mbar; Mp 53-55 ˚C; R_f = 0.53(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2934(s), 2844, 1453, 1369, 1130, 1118, 1083(s), 755, 670 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) :δ= 1.22-1.34(m, 1H), 1.38-1.52(m, 4H), 1.58-1.76(m, 3H), 1.82-1.96(m, 1H), 2.20-2.30(m, 1H), 2.34-2.44(m, 1H), 3.60-3.74(m, 1H), 4.06-4.16(m, 1H), 4.34(s, 1H), 7.22-7.38(m, 3H,

Ph), 7.38-7.52(m, 2H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$) :δ= 24.10(CH_2), 25.53(CH_2), 32.42(CH_2), 32.74(CH_2), 49.03(CH_2), 61.41(CH), 67.82(CH_2), 97.39(CH), 127.88(CH), 128.25(CH), 128.52(CH), 139.86(C). MS (EI, 70 eV): m/z (relative intensity %) = 217(4) [M^+], 173(83), 172(43), 140(42) [M^+-Ph], 105(15), 96(20), 92(28), 91(100), 82(18), 77(13), 65(20). HRMS : m/z calcd for $C_{14}H_{19}NO$: 217.1467 ; found : 217.1436 [M^+].

1-*p*-tolyloctahydropyrido[1,2-*c*][1,3]oxazine (2g)

White powder (from EtOH); yield: 1.22g (66%); Mp 66-67 ℃; R_f = 0.49(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2934(s), 2922, 1368, 1255, 1118(s), 1096, 1081(s), 1043, 817 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) :δ= 1.21-1.34(m, 1H), 1.35-1.54(m, 4H), 1.56-1.75(m, 3H), 1.82-1.95(m, 1H), 2.18-2.28(m, 1H), 2.33(s, 3H, CH_3), 2.80-3.45(m, 1H), 3.65-3.74(m, 1H), 4.07-4.12(m, 1H), 4.30(s, 1H), 7.14(d, J= 8Hz, 2H, Arom), 7.34(d, J= 8Hz, 2H, Arom).

^{13}C NMR (400 MHz, $CDCl_3$) :δ= 21.23(CH_3), 24.14(CH_2), 25.55(CH_2), 32.48(CH_2), 32.76(CH_2), 49.12(CH_2), 61.54(CH), 67.83(CH_2), 97.33(CH),

127.77(CH), 128.96(CH), 136.94(C), 138.22(C). MS (EI, 70 eV): m/z (relative intensity %) = 231(23)[M^+], 230(32), 187(64), 140(79) [M^+-$C_6H_4CH_3$], 120(42), 112(35), 105(100), 91(31), 83(34), 55(35).

HRMS : m/z calcd for $C_{15}H_{21}NO$: 231.1623 ; found : 231.1601 [M^+].

1-(4-methoxyphenyl)octahydropyrido[1,2-*c*][1,3]oxazine (2h)

White fine needle-like crystal (from EtOH); yield: 1.24g (63%); Mp 88-89 ℃; R_f = 0.30(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2921(s), 1615, 1517, 1245(s), 1175, 1115, 1079(s), 1030, 831, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) :δ= 1.18-1.33(m, 1H), 1.37-1.52(m, 4H), 1.58-1.76(m, 4H), 1.80-1.95(m, 1H), 2.17-2.27(m, 1H), 2.37-2.44(m, 1H), 3.65-3.74(m, 1H), 3.78(s, 3H, CH_3O), 4.28(s, 1H), 6.86(d, J= 8Hz, 2H, Arom), 7.37(d, J= 8Hz, 2H, Arom).

^{13}C NMR (400 MHz, $CDCl_3$) :δ= 24.18(CH_2), 25.59(CH_2), 32.57(CH_2), 32.80(CH_2), 49.18(CH_2), 55.23(CH_3O), 61.58(CH), 67.80(CH_2), 97.02(CH), 113.63(CH), 129.00(CH), 132.25(C), 159.74(C). MS (EI, 70 eV): m/z (relative intensity %) = 247(2) [M^+], 246(3), 203(18), 140(7) [M^+-$C_6H_4OCH_3$], 136(9), 135(6), 122(10), 121(100), 92(4), 77(5), 76(6).

HRMS : m/z calcd for $C_{15}H_{21}NO_2$: 247.1572; found : 247.1580 [M^+].

1-(4-chlorophenyl)octahydropyrido[1,2-*c*][1,3]oxazine (2i)

White fine rod-like crystal (from EtOH); yield: 1.35g (67%); Mp 70-71 ℃; R_f = 0.54(diethyl ether- *n*-hexane, =1:1). IR (KBr) : 2924(s), 2847, 2788, 1367, 1226, 1119, 1083(s), 1043, 1011, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) :δ= 1.18-1.32(m, 1H), 1.33-1.53(m, 4H), 1.56-1.76(m, 3H), 1.80-1.94(m, 1H), 2.20-2.30(m, 1H), 2.31-2.40(m, 1H), 3.64-3.74(m, 1H), 4.06-4.13(m, 1H), 4.32(s, 1H), 7.31(d, J= 8Hz, 2H, Arom), 7.40(d, J = 8Hz, 2H, Arom).

^{13}C NMR (400 MHz, $CDCl_3$) :δ= 24.00(CH_2), 25.49(CH_2), 32.23(CH_2), 32.69(CH_2), 48.89(CH_2), 61.26(CH), 67.81(CH_2), 96.42(CH), 128.45(CH), 129.30(CH), 134.17(C), 138.49(C). MS (EI, 70 eV): m/z (relative intensity %) = 253(7) [M^+, ^{37}Cl], 251(19) [M^+, ^{35}Cl], 250(25), 207(44), 141(42), 140(100) [M^+-C_6H_4Cl], 127(36), 125(66), 112(38), 83(36), 55(37).

HRMS : m/z calcd for $C_{14}H_{18}NOCl$: 251.1077 ; found : 251.0990 [M^+].

Mixture of **4** and **5**

Colorless viscous oily liquid; yield: 0.87g (67%, GC yield 78%); Bp 185-192 ℃/21 mbar; R_f = 0.59(diethyl ether- *n*-hexane, =1:1). IR (neat): 2946, 2884, 2798, 1455, 1055(s), 1026, 758, 699(s) cm^{-1}.

3-methyl-2-phenyloxazolidine (4)

MS (EI, 70 eV): m/z (relative intensity %) = 163(22)[M^+], 162(67), 132(40), 105(43), 91(29), 86(100)[M^+-C_6H_5], 77(32)[C_6H_5], 58(22), 51(13), 42(15).

HRMS : m/z calcd. for $C_{10}H_{13}NO$: 163.0997 ; found : 163.0991 [M^+].

HRMS (fragment) : m/z calcd. for $C_4H_8NO^-$: 86.0606 ; found : 86.0772 [M^+- C_6H_5].

HRMS (fragment) : m/z calcd. for $C_6H_5^-$: 77.0391 ; found : 77.0398 [M^+-3-methyloxazolidine ring (C_4H_8NO)].

3-benzyloxazolidine (5)

MS (EI, 70 eV): m/z (relative intensity %) = 163(13)[M^+], 162(36), 118(12), 105(11), 92(33), 91(100)[$C_6H_5CH_2$], 86(18),

72(49)[M^{+}-$C_6H_5CH_2$], 65(24), 42(35).

HRMS : m/z calcd. for $C_{10}H_{13}NO$: 163.0997 ; found : 163.0993 [M^{+}].

HRMS (fragment) : m/z calcd. for $C_3H_6NO^{-}$: 72.0449 ; found : 72.0541 [M^{+}- $C_6H_5CH_2$].

HRMS (fragment) : m/z calcd. for $C_7H_7^{-}$: 91.0548 ; found : 91.0593 [M^{+}-oxazolidine ring (C_3H_6NO)].

2-ethyl-6-phenyl-3-propyl-1,3-oxazinane (7a)

Colorless viscous oily liquid; yield: 1.04g (56%); Bp 115-117 ℃/2.7 mbar; R_f = 0.87 (EtOH-EtOAc, 1:3). IR (neat) : 2963(s), 2935, 2872, 1452, 1189, 1091(s), 1071(s), 962, 752, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) : δ=0.92(t, J=7.4Hz, 3H, CH_3), 0.98(t, J=7.4Hz, 3H, CH_3), 1.36-1.61(m, 3H), 1.64-1.76(m, 2H), 1.88-1.98(m, 1H), 2.53-2.70(m, 2H), 2.90-3.01(m, 1H), 3.17-3.28(m, 1H), 4.20(t, J=5.8Hz, 1H), 4.52-4.58(m, 1H), 7.18-7.41(m, 5H, Ph).

^{13}C NMR (400 MHz, $CDCl_3$): δ=9.91(CH_3), 12.00(CH_3), 21.52 (CH_2), 26.34(CH_2), 28.74(CH_2), 47.74(CH_2), 50.02(CH_2), 79.48(CH), 94.67(CH), 125.75(CH), 127.29(CH), 128.31(CH), 143.09(C). MS (EI, 70 eV): m/z

(relative intensity %) = 233(4) [M^+], 204(90), 132(43), 117(49), 105(100), 100(74), 77(84), 72(71), 51(42), 43(47).

HRMS: m/z calcd for $C_{15}H_{23}NO$: 233.1780; found : 233.1761[M^+].

3-isobutyl-2-isopropyl-6-phenyl-1,3-oxazinane (7b)

Colorless viscous oily liquid; yield: 1.55g (74%); Bp 126-128 ℃/ 2.7 mbar; R_f = 0.83 (EtOH-EtOAc, 1:3). IR (neat) : 2956(s), 2927, 2869, 1468, 1453, 1094(s), 1074, 986, 749, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) : δ= 0.85-1.03(m, 12H), 1.42-1.48(m, 1H), 1.60-2.06(m, 3H), 2.22-2.30(m, 1H), 2.40-2.57(m, 1H), 3.18-3.27(m, 1H), 3.83-3.90(m, 2H), 4.50-4.58(m, 1H), 7.19-7.40(m, 5H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$) : δ=18.75(CH_3), 18.96(CH_3), 19.27(CH_3), 19.83(CH_3), 20.55(CH), 20.67(CH), 21.16(CH), 26.21(CH), 27.54(CH_2), 27.64(CH_2), 29.63(CH_2), 44.57(CH_2), 49.90(CH_2), 52.78(CH_2), 61.68(CH_2), 79.24(CH), 96.51(CH), 98.96(CH), 125.52(CH), 125.94(CH), 127.07(CH), 127.31(CH), 128.20(CH), 128.36, (CH), 143.41(C), 143.49(C), MS (EI, 70 eV): m/z (relative intensity %) = 261(2) [M^+], 216(76), 187(15), 117(38), 112(21), 105(100), 84(50), 83(44), 82(37), 77(53).

HRMS: m/z calcd for $C_{17}H_{27}NO$: 261.2093; found 261.2051 [M^+].

2-phenylhexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazine (7c)

Slightly yellow viscous oily liquid; yield: 1.14g (70%); R_f = 0.41 (EtOH-EtOAc, 1:3).

IR(neat) : 2943(s), 2859, 1451, 1348(s), 1147, 1053(s), 990, 969, 751, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) : δ=1.19-1.47(m, 1H), 1.57-2.18(m, 5H), 2.70-2.86(m, 1H), 3.05-3.45(m, 3H), 4.44-4.59(m, 1H), 4.60-4.70(m, 1H), 7.09-7.48(m, 5H, Ph).

^{13}C NMR (400 MHz, $CDCl_3$) : δ=21.55(CH_2), 27.32(CH_2), 31.92(CH_2), 46.10(CH_2), 47.66(CH_2), 78.61(CH), 92.01(CH), 125.85(CH), 127.43(CH), 128.36(CH), 142.78(C).

MS (EI, 70 eV): m/z (relative intensity %) = 203(16) [M^+], 132(47), 105(100), 97(71), 84(79), 83(46), 77(90), 51(52), 43(47), 42(46). HRMS: m/z calcd for $C_{13}H_{17}NO$: 203.1310; found : 203.1313 [M^+].

2-phenyloctahydropyrido[2,1-*b*][1,3]oxazine (7d)

Slightly yellow viscous oily liquid; yield: 1.08g (62%); R_f = 0.60 (EtOH-EtOAc, 1:3).

IR(neat) : 2941(s), 2857, 1451, 1349, 1281, 1145, 1136, 1079(s), 754, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.33-1.47(m, 1H), 1.55-1.90(m, 6H), 2.00-2.21(m, 2H), 2.48-2.58(m, 1H), 2.86-2.96(m, 1H), 3.00-3.08(m, 1H), 3.64-3.72(m, 1H), 4.43-4.50(m, 1H), 7.20-7.42(m, 5H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 22.51(CH_2), 25.12(CH_2), 31.54(CH_2), 32.75(CH_2), 52.56(CH_2), 53.86(CH_2), 79.57(CH), 92.75(CH), 126.03(CH), 127.53(CH), 128.37(CH), 142.30(C). MS (EI, 70 eV): m/z (relative intensity %) = 217(7)[M^+], 132(45), 131(23), 111(24), 105(100), 104(25), 98(32), 84(31), 77 (75), 51(26). HRMS: m/z calcd for $C_{14}H_{19}NO$: 217.1467; found 217.1463 [M^+].

8-methyl-2-phenyloctahydropyrido[2,1-*b*][1,3]oxazine (7e)

Colorless viscous oily liquid; yield: 1.37g (74%); R_f = 0.69 (EtOH-EtOAc, 1:3).

IR(neat) : 2948(s), 2923, 2867, 1452, 1135, 1120, 1089(s), 1078, 753, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ=0.93(d, J=6.4Hz, 1.5H, CH_3×1/2), 0.97(d, J=6.4Hz, 1.5H, CH_3×1/2), 1.21-1.28(m, 1H), 1.30-1.47(m, 2H), 1.52-1.64(m, 1H), 1.75-2.18(m, 4H), 2.35-2.54(m, 1H), 2.98-3.10(m, 1H), 3.17-3.27(m, 1H), 4.41-4.64(m, 2H), 7.18-7.45(m, 5H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ=21.37(CH_3), 21.85(CH_3), 25.08(CH), 27.92(CH_2), 30.02(CH), 33.43(CH_2), 33.69(CH_2), 33.80(CH_2), 38.98(CH_2), 40.06(CH_2), 45.66(CH_2), 52.36(CH_2), 53.24(CH_2), 53.84(CH_2), 79.44(CH), 79.90(CH), 87.76(CH), 93.16(CH), 125.77(CH), 126.07(CH), 127.47(CH), 127.53(CH), 128.36(CH), 128.42(CH), 142.18(C), 143.04(C). MS (EI, 70 eV): m/z (relative intensity %) = 231(7) [M^+], 132(47), 112(49), 105(100), 98(48), 97(37), 77(86), 56(39), 55(62), 51(52). HRMS: m/z calcd for $C_{15}H_{21}NO$: 231.1623; found 231.1616 [M^+].

7,9-dimethyl-2-phenyloctahydropyrido[2,1-*b*][1,3]oxazine (7f)

Colorless viscous oily liquid; yield: 1.08g (55%); R_f = 0.73

(EtOH-EtOAc, 1:3).

IR (neat): 2951, 2921, 1454, 1219, 1154, 1142, 1099, 1089(s), 749, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ=0.87(d, J=6.4Hz, 3H, CH_3), 0.97(d, J=6.4Hz, 3H, CH_3), 1.10-1.28(m, 1H), 1.69-2.10(m, 5H), 2.30-2.42(m, 1H), 2.72-2.82(m, 1H), 3.01-3.17(m, 2H), 3.19-3.75(m, 1H), 4.35-4.48(m, 1H), 7.19-7.42(m, 5H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ=17.49(CH_3), 19.19(CH_3), 30.08(CH), 33.41(CH_2), 35.98(CH), 41.04(CH_2), 54.04(CH_2), 61.65(CH_2), 79.04(CH), 98.83(CH), 125.78(CH), 127.27(CH), 128.21(CH), 142.417(C).

MS (EI, 70 eV): m/z (relative intensity %) = 245(6) [M^+], 174(13), 139(21), 132(31), 126(29), 112(23), 105(100), 104(19), 77(76), 51(23).

HRMS: m/z calcd for $C_{16}H_{23}NO$: 245.1780; found 245.1780 [M^+].

2-phenyloctahydro-2*H*-[1,3]oxazino[3,2-*a*]azepine (7g)

Slightly yellow viscous oily liquid; yield: 1.52g (82%); R_f = 0.72 (EtOH-EtOAc, 1:3).

IR(neat) : 2934(s), 2853, 1452, 1354, 1118, 1095(s), 995, 955, 752, 699

cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 1.31-1.88(m, 9H), 2.08-2.18(m, 1H), 2.38-2.50(m, 1H), 3.08-3.24(m, 3H), 4.45(t, J=7Hz, 1H), 4.55(dd, =10Hz, 2.5Hz, 1H), 7.15-7.47(m, 5H, Ph).

^{13}C NMR (400 MHz, $CDCl_3$): δ=21.90(CH_2), 29.80(CH_2), 29.90(CH_2), 30.21(CH_2), 34.87(CH_2), 48.90(CH_2), 55.20(CH_2), 79.39(CH), 92.32(CH), 112.88(CH), 127.38(CH), 128.36(CH), 143.03(C). MS (EI, 70 eV): m/z (relative intensity %) = 231(3)[M^+], 174(12), 132(28), 131(18), 115(17), 112(16), 105(100), 104(15), 77(71), 51(59).

HRMS: m/z calcd for $C_{15}H_{21}NO$: 231.1623; found 231.1612 [M^+].

2-phenylhexahydro-2*H*-[1,3]oxazino[2,3-*c*][1,4]oxazine (7h)

Colorless viscous oily liquid; yield: 1.17g (67%); R_f = 0.70 (EtOH-EtOAc, 1:3).

IR (neat): 2921, 2857(s), 1453, 1343, 1279, 1152, 1131(s), 1090(s), 755, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ=1.70-1.82(m, 1H), 2.10-2.17(m, 1H), 2.39-2.51(m, 1H), 2.61-2.74(m, 1H), 2.84-2.96(m, 1H), 3.00-3.12(m, 1H),

3.46-3.58(m, 1H), 3.73-3.92(m, 4H), 4.49-4.58(m, 1H), 7.21-7.41(m, 5H, Ph). ^{13}C NMR (400 MHz, $CDCl_3$): δ=32.11(CH_2), 50.80(CH_2), 52.91(CH_2), 66.75(CH_2), 69.11(CH_2), 79.60(CH), 88.93(CH), 125.92(CH), 127.74(CH), 128.43(CH), 141.69(C). MS (EI, 70 eV): m/z (relative intensity %) = 219(15)[M^+], 189(23), 132(45), 131(26), 105(100), 104(80), 103(36), 78(35), 77(92), 51(35).

HRMS: m/z calcd for $C_{13}H_{17}NO_2$: 219.1259 ; found 219.1199 [M^+].

III-4. REFERENCES

1. Okimoto, M.; Ohashi, K.; Yamamori, H.; Nishikawa, S.; Hoshi, M.; Yoshida, T. *Synthesis* **2012**, *44*, issue 9, 1315-1322.

2. (a) Nelson, R. F. *Techniques of Electroorganic Synthesis*; Wiley: New York, **1974** ;

(b) Torii, S. *Electroorganic Synthesis*; Kodansha: Tokyo, **1985**;

(c) Okimoto, M.; Takahashi, Y. *Curr. Org. Synth.* **2004**, *1*, issue3, 233-251.

3. (a) Andreades, S.; Zahnow, E. W. *J. Am. Chem. Soc.* **1969**, *91*, issue 15, 4181-4190.

(b) Torii, S.; Inokuchi, T.; Takahashi, N. *J. Org. Chem.* **1978**, *43*, issue 26, 5020-5022.

(c) Miller, L. L.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1967**, *89*, issue 3, 593-597.

(d) Johnson, D. K.; Jansson, R. E. W. *J. Electrochem. Soc.* **1981**, *128*, issue 9, 1885-1889.

(e) Okimoto, M.; Numata, K.; Takahashi, Y.; Hoshi, M.; Tomozawa, K.; Shigemoto, T. *Synlett* **2005**, issue 16, 2507-2509.

(f) Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Numata, K.; Tomozawa, K. *Synlett*

2006, issue 11, 1753-1755.

4. (a) Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem.* **1979**, *44*, issue 20, 3519-3523.

(b) Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem.* **1983**, *48*, issue 18, 2968-2972.

(c) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1990**, *55*, issue 3, 1070-1076.

(d) Chiba, T.; Okimoto, M. *J. Org. Chem.* **1992**, *57*, issue 5, 1375-1379.

(e) Okimoto, M.; Takahashi, Y.; Kakuchi, T. *Synthesis* **2003**, issue 13, 2057-2063.

(f) Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Tomozawa, K.; Chiba, T. *Heterocycles* **2008**, *75*, issue 1, 35-42.

(g) Okimoto, M.; Numata, K.; Tomozawa, K.; Shigemoto, T.; Hoshi, M.; Takahashi, Y. *Aust. J. Chem.* **2005**, *58*, issue 7, 560-563.

(h) Okimoto, M.; Takahashi, Y.; Nagata, Y.; Numata, K.; Sasaki, G. *Synth. Commun.* **2005**, *35*, issue 15, 1989-1995.

(i) Okimoto, M.; Chiba, T. *J. Org. Chem.* **1988**, *53*, issue 1, 218-219.

5. Okimoto, M.; Yoshida, T.; Hoshi, M.; Hattori, K.; Komata, M.; Numata, K.; Tomozawa, K. *Heterocycles* **2006**, *68*, issue 12, 2563-2570.

6. (a) Fernández, B.; Carballeira, L.; Ríos, M. A. *J. Mol. Struct.* **1991**, *245*, issues 1-2, 53-67.

(b) Crabb, T. A.; Newton, R. F. *Tetrahedron* **1968**, *24*, issue 12, 4423-4436.

(c) Taguchi, T.; Kasuga, S. *Chem. Pharm. Bull.* **1965**, *13*, issue 3, 241-247.

(d) Tilford, C. H.; Campen, M. G. V. *J. Am. Chem. Soc.* **1954**, *76*, issue 9, 2431-2441.

(e) Goodson, L. H.; Christopher, H. *J. Am. Chem. Soc.*

1950, *72*, issue 1, 358-362.

(f) Azzena, U.; Pilo, L.; Piras, E. *Tetrahedron Lett.* **2001**, *42*, issue 1, 129-131.

(g) Azzena, U. *J. Chem. Soc., Perkin Trans. 1* **2002**, issue 3, 360-365.

(h) Cook, A. G.; Schering, C. A.; Campbell.; P. A. Hayes, S. S. *Tetrahedron Lett.* **2005**, *46*, issue 33, 5451-5454.

(i) Bentley, N.; Singh, G.; Howarth, O. W. *Tetrahedron* **1993**, *49*, issue 20, 4315-4320.

(j) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1960**, *82*, issue 19, 5148-5155.

(k) Winterfeld, K.; Michael, H. *Arch. Pharm.* **1961**, *294*, issue 2, 65-76.

(l) Trávníček. M.; Potáček. M. A. *Arkivoc.* **2001**, issue 5, 156-163.

7. Wilson, F. G.; Wheeler, T. S. *Org. Synth. Coll. Vol. I*;

John Wiley & Sons: New York, **1941**, 102.

8. Gaylord, N. G. *Reduction with Complex Metal Hydride*; Wiley: New York, **1956**.

Chapter IV

Unexpected Formation of Novel Oxazolidine and Tetrahydrooxazine Derivatives by Condensation of 2-(Hydroxymethyl) or 2-(2-Hydroxy-ethyl) Piperidine, and Ketones [1]

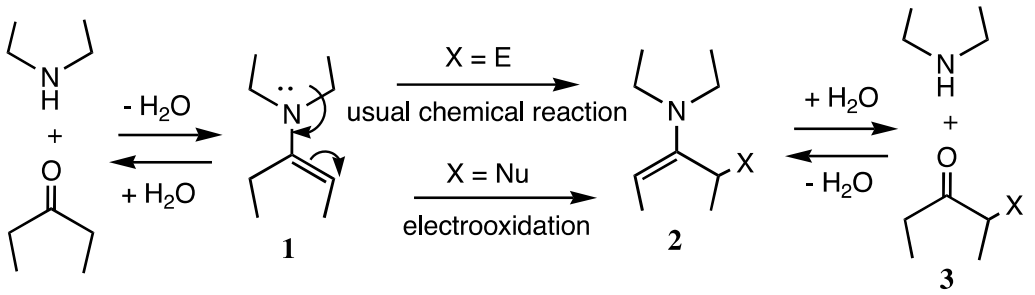
Abstract

Several novel oxazolidine and tetrahydrooxazine derivatives, which possess a spiro carbon, were unexpectedly obtained during our attempts to prepare enamines that possess a hydroxy group by condensation between a piperidine alcohol and a ketone in the presence of an acidic catalyst. The reaction times under reflux

conditions were significantly influenced by the structure of the starting substrates.

IV-1. INTRODUCTION

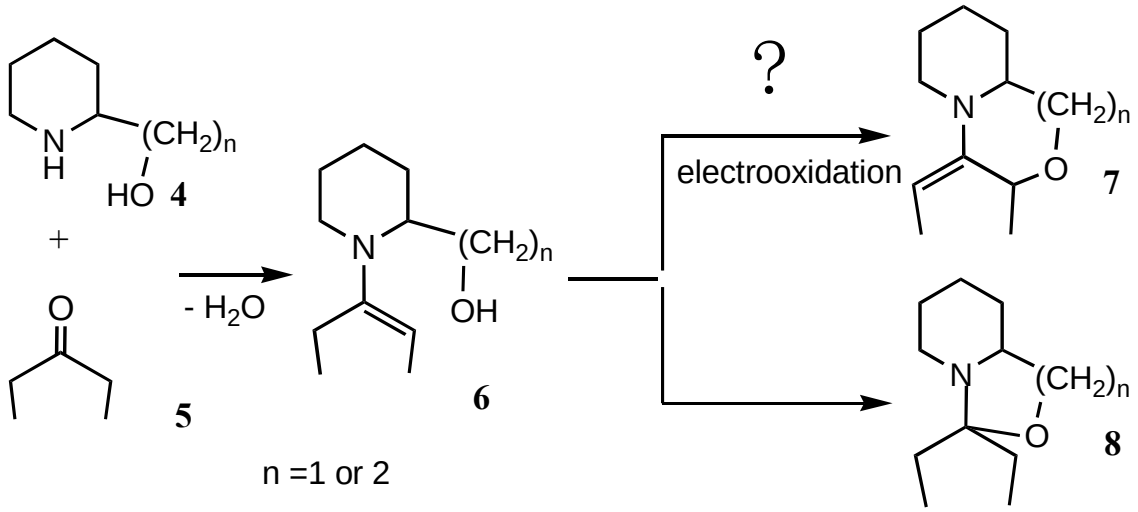
As shown in Scheme 1, enamine **1** is often utilized as a precursor for the preparation of α-substituted ketone **3**. In such reactions, electrophiles (E) such as alkyl or acyl halides attacks **1** at the β-position of the nitrogen atom to give substituted enamine **2** (X=E), which readily undergoes hydrolytic cleavage to yield **3** (X=E). [2, 3]



Scheme 1. Preparation of α-substituted ketone via enamine

In contrast, Shono et al. [4] and Chiba et al. [5] have previously reported that **1** can instead be attacked by a nucleophile (Nu), such as a methoxide ion or organic anions derived from β-dicarbonyl compounds, via electrooxidation to give **2** (X=Nu), which then hydrolyzes to **3** (X=Nu). Consequently, we were naturally interest in the electrooxidative behavior of enamines, such as compound **6** that possess a hydroxyl group. We attempt to prepare **6** by refluxing a mixture of **4** and **5** in toluene in the presence of catalytic amount of an acidic catalyst. However the reaction resulted in unexpected formation of

three ring compounds, probably via autoxidation by ambient oxygen in the open dehydration apparatus. [6]



Scheme 2. Unexpected formation of three rings compound **8**

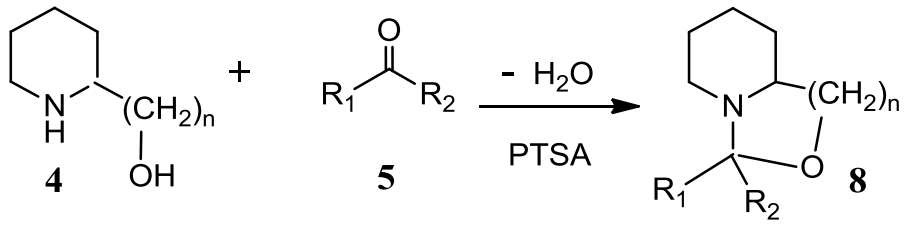
IV-2. RESULTS AND DISCUSSION

Beginning of the study, we examined preparation of **6** by refluxing 2-(hydroxymethy) piperidine (**4d**, n=1)

(Entry 4 in Table 1) or 2-(2-hydroxyethyl) piperidine (**4e**, n=2) (Entry 5), and several symmetrical ketones (**5a-h**). Although after theoretical amount of water could be removed from the reaction mixture, unexpected oxazolidine (**8d**, n=1) and tetrahydrooxazine (**8e**, n=2) derivatives were formed dominantly via a probable formation of the corresponding **6** (n=1 or 2) as the intermediates in good yield.

Interestingly, to the best of our knowledge, there are only very few reports regarding the preparation of compound type **8**, and most of the unique products consisting of three condensed rings obtained here are novel compounds. [7-12]

Table 1. Formation of Oxazolidine and Tetrahydrooxazine derivatives [a)]



Entry	**4**, **5**, **8**	n	R_1	R_2	r. time (h)	Yield of **8** (%) [b)]
1	**a**	1	Et	Et	70	75
2	**b**	1	$-(CH_2)_4-$		2	93
3	**c**	2	$-(CH_2)_4-$		3	95
4	**d**	1	$-(CH_2)_5-$		2	88
5	**e**	2	$-(CH_2)_5-$		26	87
6	**f**	1	$-(CH_2)_2CH(t\text{-Bu})(CH_2)_2-$		7	95
7	**g**	1	$-(CH_2)_6-$		7	85
8	**h**	1	$-(CH_2)_7-$		9	64

[a)] **4**: 50 mmol, **5** : 55 mmol, PTSA : 0.1 g. Refluxing in toluene : 50 mL.

[b)] Isolated yields.

Table 1 shows relationship among the type of piperidine **4**, ketone **5**, reaction time, and the yields of the corresponding cyclic compound **8**. Refluxing times (see

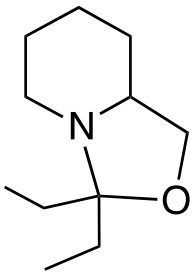
experimental section) required to complete the reaction were significantly depended on the structure of not only **4** but also **5** moiety. For example cyclopentanone **5b** (Entry 2), **5c** (Entry 3) and cyclohexanone **5d** (Entry 4) react readily with **4** (n=1 and 2) to give the corresponding cyclic compounds **8b**, **8c** and **8d** in high yields (88~95%), however much more long reaction times were needed in the cases of 3-pentanone **5a** (Entry 1, 70h) and cyclohexanone **5e** (Entry 5, 26h). Long refluxing time decreased the yield of **8h** (r. time 20hr, 55%) in the case of Entry 8. Further investigations of reactivity between **4** and **5**, and into the stereo-specificity of the products are currently underway in our laboratories.

IV-3. EXPERIMENTAL

The oxazolidine (**8**, n=1) and tetrahydrooxazine (**8**, n=2) derivatives were prepared as follow: in a 200-mL round bottomed flask equipped with a water trap condenser was added hydroxy piperidine **4** (50 mmol), symmetrical ketone **5** (55 mmol), and *p*-toluenesulfonic acid (PTSA 0.1 g) in toluene (50 mL). The reaction mixture was refluxed until water was completely removed using the water trap (Table 1). After removal of the toluene under vacuum, the resulting residue was purified by distillation under reduced pressure. Structures of the isolated products were confirmed by IR and NMR and High resolution mass spectra. Infrared spectra (IR) were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. NMR spectra were obtained on a JEOL JNM-ECX 400 spectrometer. High resolution mass spectra were measured on a JEOL JMS-100GCV gas

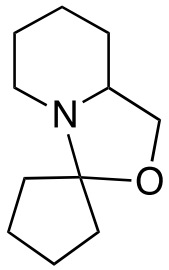
chromatography time-of-flight mass spectrometer.

3,3-Diethylhexahydro-1*H*-oxazolo[3,4-*a*]pyridine (8a).



Colorless viscous oily liquid, bp：108-110˚C/19 mmHg. R_f：0.90(Silica gel TLC, Et_2O). IR (neat)：2934, 2861, 2805, 1463, 1441, 1347, 1153, 1144, 1079, 1032 cm^{-1}. ^1H NMR ($CDCl_3$)：δ= 0.84(t, J= 12Hz, 3H), 0.90(t, J=12Hz, 3H), 1.1-1.2(m, 2H), 1.3-1.8(m, 8H), 2.4-2.5(m, 1H), 2.7-2.8(m, 2H), 3.3-3.4(m, 1H), 3.9-4.0(m, 1H). ^{13}C NMR ($CDCl_3$)：δ= 7.30(CH_3), 8.85(CH_3), 23.89(CH_2), 25.88(CH_2), 27.15(CH_2), 27.89(CH_2), 28.45(CH_2), 44.67(CH_2), 58.57(CH), 71.62(CH_2), 96.86(C). MS m/z (relative intensity, %)：183(2) [M^+], 156(14), 155(33), 154(100), 98(48), 70(10), 57(17), 56(14), 41(18), 29(15). HRMS：m/z calcd. for $C_{11}H_{21}NO$：183.1623 ;found：183.1614[M^+].

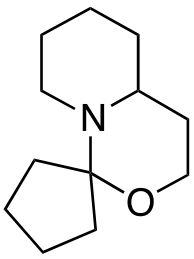
Hexahydrospiro[cyclopentane-1,3'-oxazolo[3,4-*a*]pyridine] (8b).



Colorless viscous oily liquid, bp：143-145˚C/45 mmHg. R_f：0.56(Silica gel TLC, Et_2O). IR (neat)：2935, 2867, 2798,

1440, 1323, 1280, 1226, 1141, 1057, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.2-1.4(m, 2H), 1.5-1.9(m, 11H), 2.2-2.3 (m, 1H), 2.5-2.7(m, 1H), 2.8-2.9(m, 1H), 3.4-3.5(m, 2H), 3.8-4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 23.01(CH_2), 23.25(CH_2), 24.48(CH_2), 25.29(CH_2), 27.78(CH_2), 29.55(CH_2), 35.35(CH_2), 45.35(CH_2), 59.87(CH), 69.31(CH_2), 105.58(C). MS m/z (relative intensity, %) : 181(20) [M^+], 153(36), 152(100), 139(21), 98(33), 97(36), 82(28), 57(25), 55(28), 41(25). HRMS : m/z calcd. for $C_{11}H_{19}NO$: 181.1467 ;found : 181.1470[M^+].

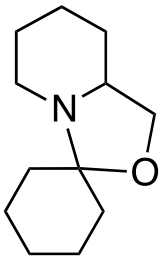
Hexahydro-3'*H*-spiro[cyclopentane-1,1'-pyrido[1,2-*c*][1,3]oxazine] (8c). [7, 8]



Slightly yellowish viscous oily liquid, bp : 143-145˚C/19 mmHg. R_f : 0.23(Silica gel TLC, Et_2O). IR (neat) : 2933, 2858, 2796, 1442, 1373, 1244, 1229, 1200, 1123, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.1-1.2(m, 1H), 1.3-1.4(m, 2H), 1.5-1.8(m, 10H), 1.9-2.3(m, 4H), 2.7-3.0(m, 2H), 3.7-3.8(m, 2H). ^{13}C NMR ($CDCl_3$) :δ=22.39(CH_2), 23.59(CH_2), 24.83(CH_2), 26.26(CH_2), 26.68(CH_2), 28.70(CH_2), 32.88(CH_2), 38.73(CH_2), 45.16(CH_2),

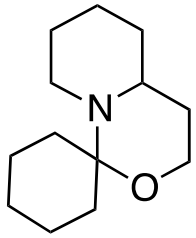
53.55(CH_2), 60.65(CH), 100.10(C). MS m/z (relative intensity, %) : 195(41) [M^+], 166(100), 151(55), 150(72), 138(64), 122(86), 84(54), 83(57), 55(51), 41(52). HRMS : m/z calcd. for $C_{12}H_{21}NO$: 195.1623 ; found : 195.1648[M^+].

Hexahydrospiro[cyclohexane-1,3'-oxazolo[3,4-*a*]pyridine] (8d).



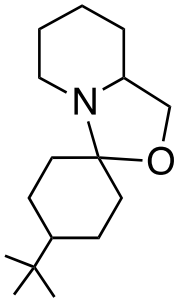
Colorless viscous oily liquid, bp : 132-134˚C/16 mmHg. R_f: 0.85(Silica gel TLC, Et_2O). IR (neat) : 2933, 2860, 2804, 1448, 1365, 1291, 1203, 1155, 1130, 1037 cm^{-1}. ^1H NMR ($CDCl_3$) :δ= 1.0-1.3(m, 4H), 1.4-1.9(m, 12H), 2.2-2.4(m, 1H), 2.6-2.9(m, 2H), 3.3-3.5(m, 1H), 3.8-4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ=22.86(CH_2), 23.77(CH_2), 23.83(CH_2), 25.73(CH_2), 25.81(CH_2), 28.14(CH_2), 29.93(CH_2), 35.78(CH_2), 45.43(CH_2), 58.72(CH), 70.08(CH_2), 94.93(C). MS m/z (relative intensity, %) : 195(26) [M^+], 166(17), 153(35), 152(100), 139(25), 98(26), 96(23), 82(18), 55(21), 41(23). HRMS : m/z calcd. for $C_{12}H_{21}NO$:195.1623 ;found : 195.1638[M^+].

Hexahydro-3'*H*-spiro[cyclohexane-1,1'-pyrido[1,2-*c*][1,3]oxazine] (8e). [7, 8]



Slightly yellowish viscous oily liquid, bp : 153-155°C/19 mmHg. R_f : 0.47(Silica gel TLC, Et_2O). IR (neat) : 2932, 2857, 2796, 1445, 1375, 1289, 1258, 1227, 1117, 1084 cm^{-1}. ^1H NMR ($CDCl_3$) : δ= 1.0-1.2(m, 1H), 1.2-1.4(m, 4H), 1.4-1.8(m, 12H), 2.1-2.2(m, 1H), 2.2-2.3(m, 1H), 2.6-2.8(m, 1H), 2.9-3.0(m, 1H), 3.6-3.8(m, 2H). ^{13}C NMR ($CDCl_3$) : δ= 21.84(CH_2), 22.41(CH_2), 22.66(CH_2), 23.72(CH_2), 26.10(CH_2), 26.74(CH_2), 31.85(CH_2), 34.24(CH_2), 36.10(CH_2), 45.84(CH_2), 52.04(CH_2), 58.80(CH), 87.39(C). MS m/z (relative intensity, %) : 209(20) [M^+], 166(70), 165(49), 164(34), 138(29), 123(34), 122(100), 82(36), 55(36), 41(35). HRMS : m/z calcd. for $C_{13}H_{23}NO$: 209.1780 ;found : 209.1764[M^+].

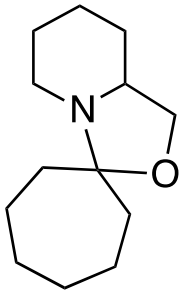
4-*tert*-Butylhexahydrospiro[cyclohexane-1,3'-oxazolo[3,4-*a*]pyridine] (8f).



Colorless viscous oily liquid, bp : 125-127°C/2 mmHg. R_f : 0.87(Silica gel TLC, Et_2O), IR (neat) : 2938, 2865, 2804,

1442, 1365, 1289, 1203, 1154, 1130, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 0.86(s, 9H, 3×CH_3), 0.8-1.0(m, 2H), 1.1-1.8(m, 13H), 2.2-2.3(m, 1H), 2.7-2.8(m, 1H), 2.8-2.9(m, 1H), 3.3-3.4(m, 1H), 3.9-4.0(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 23.64(CH_2), 23.82(CH_2), 24.58(CH_2), 25.70(CH_2), 27.71(CH_3), 28.13(CH_2), 29.82(CH_2), 32.39(C), 35.93(CH_2), 45.45(CH_2), 47.82(CH), 58.87(CH), 70.12(CH_2), 94.23(C). MS m/z (relative intensity, %) : 251 (14) [M^+], 236(18), 194(38), 153(40), 152(100), 139(29), 98(28), 97(28), 55(25), 41(25). HRMS : m/z calcd. for $C_{16}H_{29}NO$: 251.2249 ;found : 251.2260[M^+].

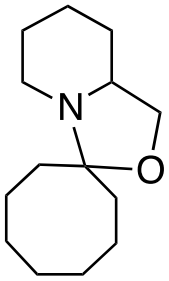
Hexahydrospiro[cycloheptane-1,3'-oxazolo[3,4-*a*]pyridine] (8g).



Colorless viscous oily liquid, bp : 150-152°C/19 mmHg. R_f: 0.96(Silica gel TLC, Et_2O), IR (neat): 2931, 2857, 2799, 1455, 1441, 1275, 1221, 1126, 1074, 1032 cm^{-1}. ^{1}H NMR ($CDCl_3$) :δ= 1.1-1.3(m, 2H), 1.3-1.9(m, 16H), 2.2-2.3(m, 1H), 2.5-2.6(m, 1H), 2.9-3.0(m, 1H), 3.3-3.4(m, 1H), 3.8-3.9(m, 1H). ^{13}C NMR ($CDCl_3$) :δ= 22.86(CH_2), 23.29(CH_2), 23.72(CH_2), 25.71(CH_2), 27.88(CH_2), 30.08(CH_2), 30.75(CH_2), 32.82(CH_2), 40.55(CH_2),

45.14(CH_2), 58.54(CH), 69.91(CH_2), 98.21(C). MS m/z (relative intensity, %) : 209(24) [M^+], 166(37), 153(36), 152(100), 139(30), 98(27), 97(28), 82(21), 55(27), 41(25). HRMS : m/z calcd. for $C_{13}H_{23}NO$:209.1780 ;found : 209.1792[M^+].

Hexahydrospiro[cyclooctane-1,3'-oxazolo[3,4-*a*]pyridine] (8h).



Colorless viscous oily liquid, bp : 162-164°C/17 mmHg. R_f : 0.72(Silica gel TLC, Ethyl ether), IR (neat) :2930, 2854, 2800, 1443, 1278, 1195, 1142, 1124, 1075, 1037 cm^{-1}. ^1H NMR ($CDCl_3$)*δ*= 1.1-1.3(m, 2H), 1.4-1.9(m, 18H), 2.2-2.3(m, 1H), 2.6-2.7(m, 1H), 2.9-3.1(m, 1H), 3.3-3.4(m, 1H), 3.8-3.9(m, 1H). ^{13}C NMR ($CDCl_3$) :*δ*= 22.15(CH_2), 22.64(CH_2), 23.78(CH_2), 24.80(CH_2), 25.92(CH_2), 27.65(CH_2), 28.16(CH_2), 28.70(CH_2), 29.47(CH_2), 36.83(CH_2), 45.91(CH_2), 59.15(CH), 70.11(CH_2), 97.08(C). MS m/z (relative intensity, %) : 223(23) [M^+], 194(26), 192(26), 166(32), 153(45), 152(100), 139(87), 98(44), 97(59), 55(34). HRMS : m/z calcd. for $C_{14}H_{25}NO$:223.1936 ;found : 223.1933[M^+].

IV-4. REFERENCES

1. Nishikawa, S.; Okimoto, M.; Yoshida, T.; Hoshi, M.; Ohashi, K. *Bulg. Chem. Commun.* **2012**, *44*, issue 4, 314-317.

2. Cook, A. G. *Enamine*; Marcel Dekker: New York, **1969**.

3. Stork, G.; Brizzolara, A.; Landesman, H.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, issue 2, 207-222.

4. Shono, T.; Matsumura, Y.; Hamaguchi, H.; Imanishi, T.; Yoshida, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, issue 7, 2179-2180.

5. Chiba, T.; Okimoto, M.; Nagai, H.; Takata, Y. *J. Org. Chem.* **1979**, *44*, issue 20, 3519-3523.

6. Angelova, V. T.; Vassilev, N. G.; Chauvin, A-S.; Koedjikov, A. H.; Ivanov, P. M.; Pojarlieff, I. G. *ARKIVOC* **2008**, issue 11, 11-23.

7. Cook, A. G.; Schering, C. A.; Campbell, P. A.; Hayes, S. S. *Tetrahedron Lett.* **2005**, *46*, issue 33, 5451-5454.

8. Ohki, S.; Shimada, H.; Sugimoto, K. *Yakugaku Zasshi* **1967**, *87*, issue 11, 1359-1363.

9. Tilford, C. H.; Campen, Jr. M.G. V. *J. Am. Chem. Soc.* **1954**, *76*, issue 9, 2431-2441.

10. McCary, F. J.; Tilford, C. H.; Van Campen Jr., M. G. *J. Am. Chem. Soc.* **1957**, *79*, issue 2, 472-480.

11. Goodson, L. H.; Christopher, H. *J. Am. Chem. Soc.* **1950**, *72*, issue 1, 358-362.

12. Beyeman, H. C.; Maat, L.; Veen, A. V.; Zweistra, A.; Philipsborn, W. V. *Rec. Trav. Chim.* **1965**, *84*, issue 10, 1367-1379.

Chapter V

Conclusion

In this study, we have successfully discovered a novel cleavage reaction of ketone *N*-phenylsemicalbazones into methylphenyl carbamate, parent ketones and gaseous nitrogen by use of electrooxidative method.

Furthermore, we have successfully applied for the cyclization reactions of *N*-benzyl-2-piperidine alcohols and 3-dialkyl amino-1-phenylpropanol.

Moreover, during preparation of hydroxyl enamines as starting material for electrooxidation, fortunately I found convenient method for preparation of three rings oxazine and oxazolizine derivatives having a spiro carbon. Although majority of the compounds obtained here are novel, it will be applied as one of reaction steps for preparation of pharmaceutical intermediates in which

possess oxazine and oxazolizine ring moiety.

In this study we have shown that the electrooxidation of heterogeneous compound such as hydrazones, piperidinealcohols, aminoalcohols, and enamine derivatives can serve as a useful method toward the synthesis of various organic compounds.

Most of the yield of the products are good and this method is advantageous because: 1) the reaction does not require any oxidant and /or special reagent, 2) the reaction conditions are very mild, (reaction temperature ca.15˚C) and 3) the substrate are readily available, 4) the reaction involves a simple procedure.

Further investigations toward the electorooxidative formation of carbon-carbon and carbon-heteroatom bonds for pharmaceutical intermediate are in progress in our laboratory.

Acknowledgement

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