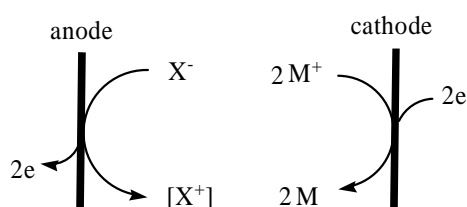


# Efficient Synthesis of $\beta$ -Lactams by Electrochemical Coupling between Active Methylene and Methyne Groups under Mild Conditions

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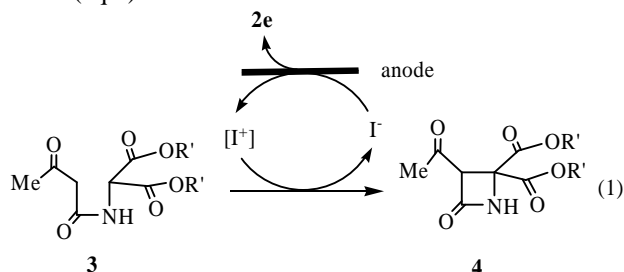
Electrochemical oxidation using halogen mediator is characterized by its mild conditions. For example, electrochemical Hofmann rearrangement can be achieved under almost neutral conditions, while conventional Hofmann rearrangement must be carried out under strongly basic conditions, where starting materials or products labile to basic conditions can not survive.<sup>1)</sup> On the other hand, the conditions in an electrochemical mediator system are neutral in the bulk phase because halogen active species  $[X^+]$  is gradually generated at the surface of anode and  $M$  working as an electrochemically generated base (EGB) is also gradually generated at the surface of cathode as shown in Fig. 1. We report herein an efficient electrochemical mediator system for the formation of  $\beta$ -lactams.



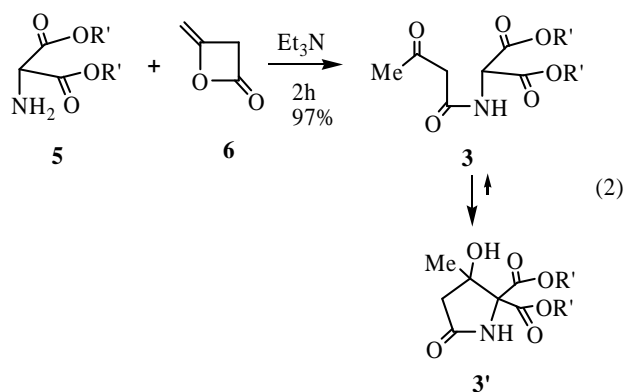
$X^-$ : halide ion  
 $M^+$ : metal ion

Figure 1. Electrochemical Mediator System

Our method consists of electrochemical intramolecular coupling between active methylene and methyne groups bound by a nitrogen-atom containing tether (eq 1).



The starting compounds **3** were easily prepared according to the procedure shown in eq 2.



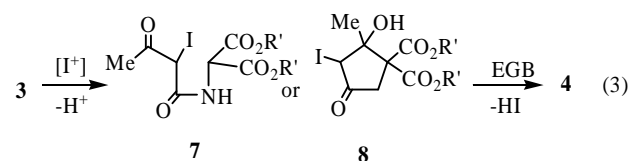
The isolated products in the reaction were not **3** but they were pyrrolidine derivatives **3'**. Subsequent electrochemical oxidation of **3'** gave  $\beta$ -lactams **4**, suggesting that there might be an equilibrium between a chain form **3** and its cyclized form **3'**.

Electrochemical oxidation of **3'** was carried out as follows: Into a cell equipped with two platinum plate electrodes was added a solution of **3'** ( $R'=Et$ , 1mmol) and NaI (1.5mmol) in acetonitrile (10mL), and a direct electric current was passed through the solution. After 2F/mol of electricity was passed at 0°C, a usual working up gave **4** ( $R'=Et$ ) in 95% yield. The result obtained under several reaction conditions are summarized in Table 1, which shows that iodide ion is essential for the formation of  $\beta$ -lactams **4** from **3**.

Table 1. Electrochemical Intramolecular Coupling of **3** ( $R'=Et$ )

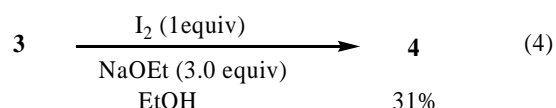
entry	Supporting electrolyte	equiv	Solvent	F/mol	Yield (%) of <b>4</b> ( $R'=Et$ )
1	NaI	1.5	MeCN	2	95
2	NaI	1.5	EtOH	2	87
3	NaI	0.2	EtOH	3	70
4	KI	0.2	EtOH	2	60
5	Et <sub>4</sub> NI	0.2	EtOH	5	41
6	Et <sub>4</sub> NBF <sub>4</sub>	0.2	EtOH	2	0
7	NaBr	1.5	MeCN	2	0
8	NaBr	1.5	EtOH	2	0

The reaction may proceed through an intermediate **7** or its cyclized intermediate **8** (eq 3).



EGB: electrochemically generated base

In contrast with an electrochemical method, a conventional chemical method ( $I_2$  and NaOEt) was not so satisfactory (eq 4).<sup>2)</sup>



It was found that the product **4** was labile under basic conditions.

Enantioselective formation of  $\beta$ -lactams was also achieved by using chiral *N*-protecting group in respect with **3**. Those results will be presented.

## References

- 1) a) Matsumura, Y.; Maki, T.; Satoh, Y. *Tetrahedron Lett.* **1997**, 38, 8879-8882. b) Matsumura, Y.; Satoh, Y.; Shirai, K.; Onomura, O.; Maki, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2057-2060. c) Matsumura, Y.; Satoh, Y.; Maki, T.; Onomura, O. *Electrochim. Acta* **2000**, 45, 3011-3020.
- 2) Coupling of *N*-benzyl derivative by  $I_2$ /NaOEt: Simig, G.; Doleschall, G.; Hornyák, G. *Tetrahedron* **1985**, 41, 479-484.