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ANODIC OXIDATION OF N-ALKYL-β-LACTAMS

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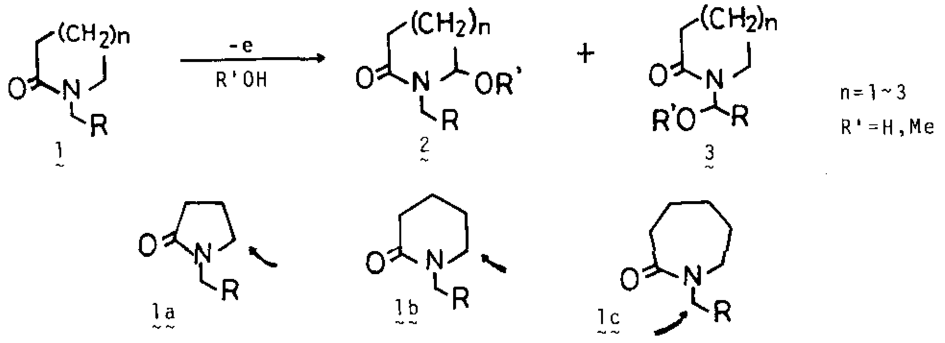
Abstract—— β-Lactams were electrolyzed in an undivided cell with platinum plate as anode in methanol under constant current. The oxidation of β-lactams 5 and α-methylene-β-lactams 10 proceeded both at the exo- and endo-cyclic carbons α to nitrogen, though five, six and seven membered lactams were regioselectively electrolyzed under the same conditions.

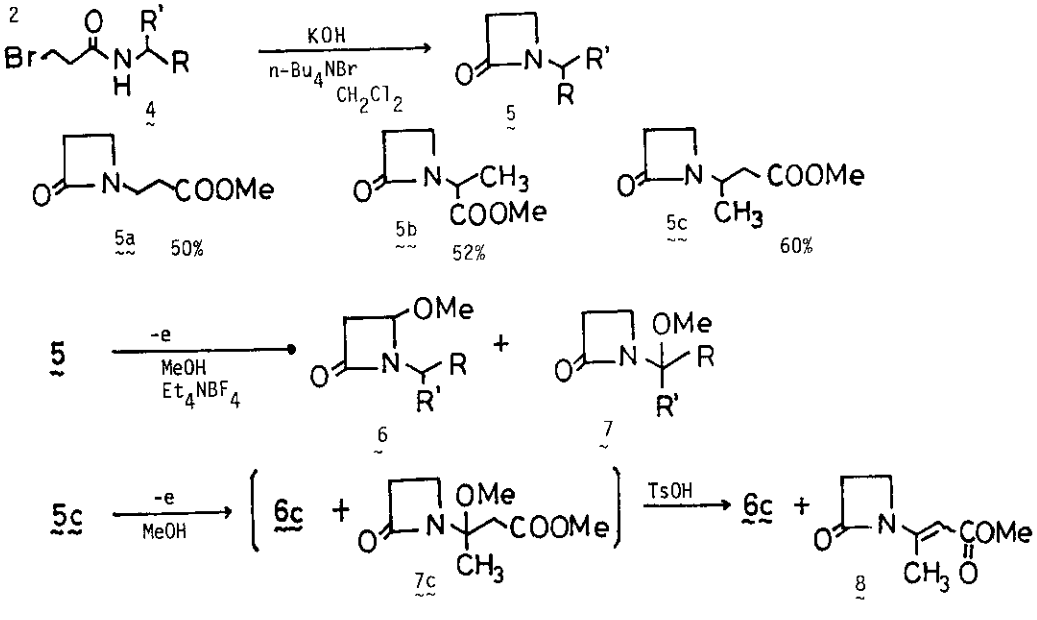
The electrochemical oxidation of lactams in alcohol is very fascinating because oxidation occurs at the carbon atom located at α to nitrogen atom under very mild conditions[1] and the oxidation products are useful as the synthetic intermediates.[2] It is particularly noteworthy that the regioselectivity of the oxidation is dependent upon the size of the rings.[1a] Namely, with five- and six-membered rings, oxidation occurs preferentially at the endo-cyclic carbon atom α to nitrogen, whereas with seven membered rings, oxidation proceeds at the exo-cyclic carbon atom. Now our attention is focussed to a problem which of carbon atoms next to nitrogen is electrolyzed with the four membered lactams,[3] particularly because these β-lactams are very important in view of search for biologically active substances.

Scheme 1



Monocyclic β-lactams were readily synthesized from 2-bromopropionamide derivatives 4 in the presence of phase transfer reagent.[4] The general procedure of the electrochemical oxidation of monocyclic β-lactams was carried out as follows. A solution of β-lactams(2 mmol) containing Et_4NBF_4(0.5 mmol) as supporting electrolyte in MeOH(5 mL) was electrolyzed in an undivided cell with platinum plates(10 x 25 mm^2) as anode and cathode under constant current(30 mA). After about 3 F/mol was passed under ice-cooling, solvent was removed under reduced pressure and ethyl acetate was added to the residue. Undissolved material was filtered off and the solvent was removed to leave a residue which was chromatographed on silica gel to afford the products. These results were shown in Scheme 2 and Table 1. Oxidation of compound 5 smoothly proceeded to afford compounds 6 and 7, which could not be separated on thin layer chromatography. Thus, the ratio of the compounds 6 and 7 was estimated by integration of the nmr spectrum. The exo-cyclic carbon α to nitrogen was more easily oxidized than the endo-cyclic carbon(Run 1). However, with the compounds 5b and 5c carrying the tertiary carbon atom for the substituent on nitrogen, the formation of the endo-oxidation products 6b and 6c was remarkably increased compared with the case of 5a(Run 2 and 3). These results suggest that the alkoxy group can be introduced to the 4-position of β-lactams possessing carboxyl group at the α-position for the substituent on nitrogen by use of electrochemical oxidation. The nmr spectrum of oxidation products of 5c in CCl_4 shows three

Scheme 2



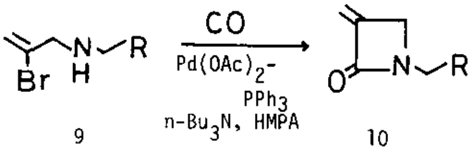
peaks of methyl protons [δ 1.31(d, J=7 Hz), 1.35(d, J=7 Hz), and 1.64(s)]. The former two peaks were assigned to the methyl signals of diastereomers of 6c and the latter to the methyl signal of 7c. When the same sample was measured in $CDCl_3$, a new allylic methyl peak appeared at δ 2.61(d, J=1 Hz) and the methyl peak at δ 1.64(s) in CCl_4 disappeared. These results showed that compound 7c should convert to compound 8 with a trace of acid in $CDCl_3$. Therefore, the crude anodic oxidation products of 5c was treated with TsOH in MeOH to afford 6c and 8.

Subsequently, it was surveyed to examine the influence of the α-methylene group of β-lactam for the electrochemical oxidation. α-Methylene-β-lactams were easily synthesized from 2-bromoallylamine derivatives 9 and carbon monoxide in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3.[5] Electrochemical oxidations of α-methylene-β-lactams 10 also smoothly proceeded to afford

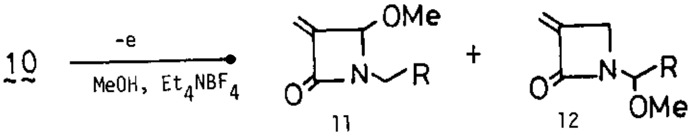
Table 1 Electrochemical oxidation of 5 and 10

Run	Compound	F/mol	Total Yield	ring CH_2 (6 or 11)	:	substituent CH_2 (7 or 12)
1	5a	3.0	86 %	1	:	2.5
2	5b	4.2	91	1	:	0.75
3	5c	2.8	83	1	:	0.67
4	10a	2.6	66	1	:	1.3
5	10b	2.8	74	1	:	3.3
6	10d	4.4	66	1	:	4.6

Scheme 3



9 10



11 12

Table 2 Carbonylation of compound 10 from 9

Substrate	R	Yield of 10
10a	CH_2COOMe	38 %
10b	CH_2OTHP	63
10c	CH_2Ph	62
10d	Ph	67

compounds **11** and **12** except compound **10c**. These results were summarized in Scheme 3 and Table 1. With α-methylene-β-lactams **10**, an increase of the oxidation product at the endo-cyclic position was observed(Run 1 and 4). When compound **10c** was oxidized under the same conditions, the reaction mixture was colored to brown and the tarry matter adhered on the electrode surface. It was very interesting that the major product of the electrolysis of **10d** was compound **12d** oxidized at the benzylic position(Run 6).[6] In these reactions, the first step of the anodic oxidation of lactams should proceed from the amide nitrogen, but the first electron abstraction of **10d** might occur from the aromatic ring of N-benzyl group or both of them. These results suggest that N-benzyl group of β-lactams might be easily removed by use of the electrochemical oxidation followed by hydrolysis.

Although the anodic oxidation of N-alkyl-lactams occurred regioselectively at the endo-cyclic carbon atom α to nitrogen in five and six-membered rings and at the exo-cyclic α-carbon atom in seven membered ring, the anodic oxidation of β-lactams proceeded at the exo- and endo-cyclic carbons α to nitrogen. Further studies are in progress in our laboratory.

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