RING CONSTRUCTION OF BICYCLIC γ-LACTAMS BY USE OF ELECTROCHEMICAL OXIDATION

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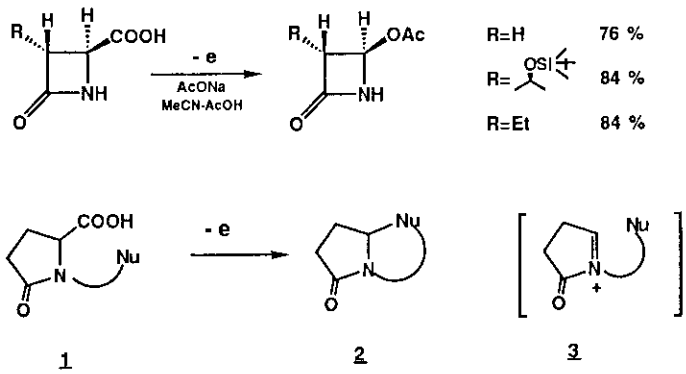
Abstract— α-Acetoxy lactam derivatives generated from α-carboxy lactams by the use of electrochemical oxidation in the presence of AcONa in MeCN-AcOH were useful intermediates for the synthesis of bicyclic lactams.

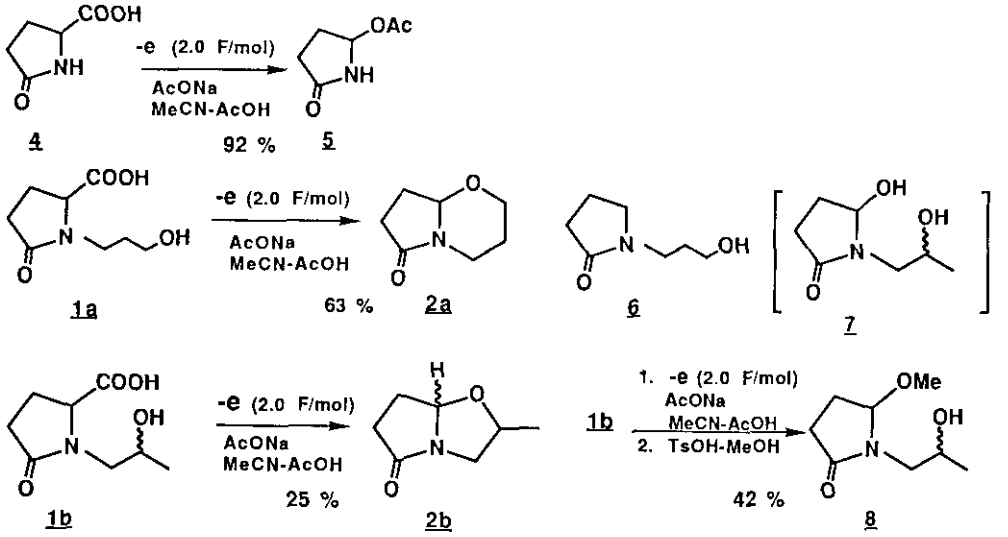
We have already reported on the synthetic procedure of 4-acetoxy-2-azetidinones from 4-carboxy-2-azetidinones by the use of electrochemical oxidation. [1] Using this method, a new synthetic method of optically active 3-hydroxyethyl-4-acetoxy-2-azetidinone which was an intermediate for the synthesis of thienamycin and its analogues, was developed[1a] and a formal total synthesis of (+)-PS-5 was reported.[1b] As part of the continuing interest in the introduction of acetoxy group to the α-position of lactams, we have studied the electrochemical oxidation of γ-lactams. We now wish to report that a variety of γ-lactams 1 having carboxylic acid at the α-position were oxidized to give bicyclic lactams 2 via acyl imminium cation 3.



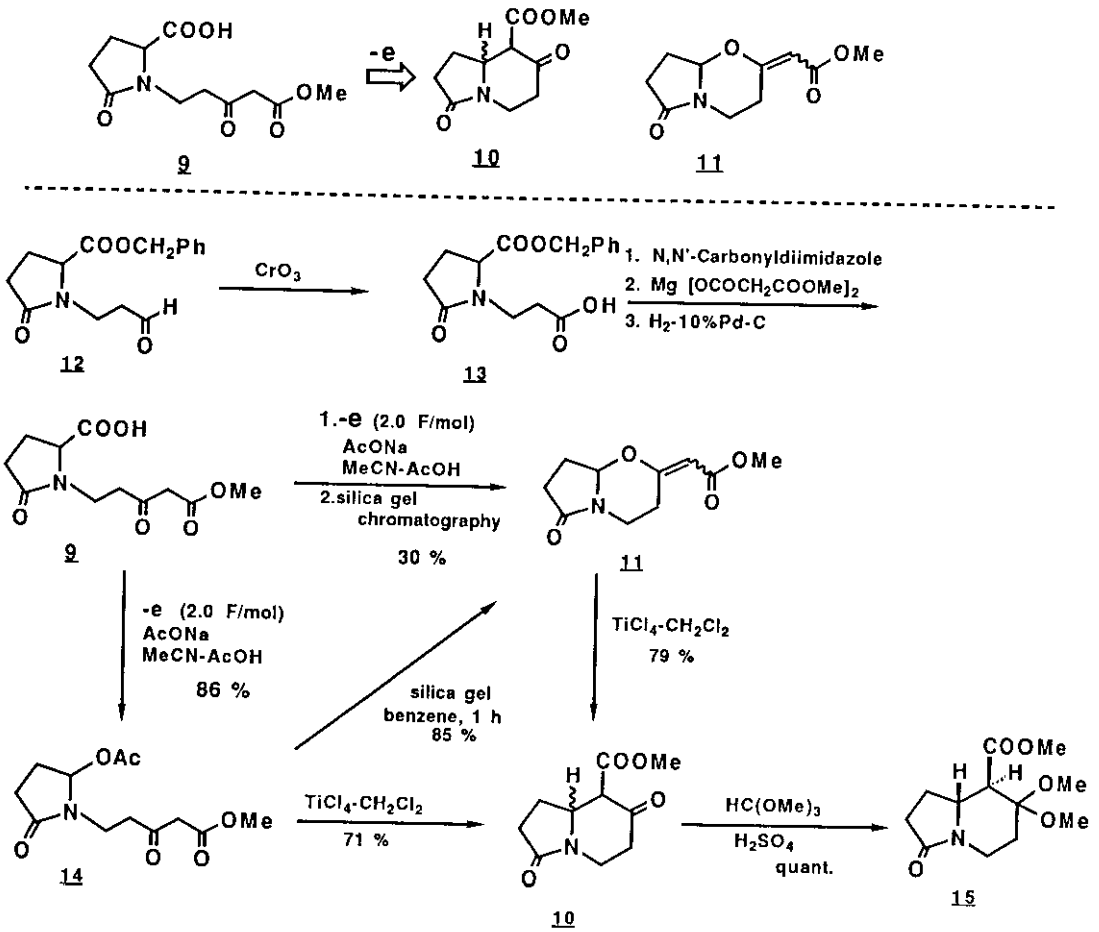
1 2 3

The initial work for this study was the electrolysis of pyroglutamic acid 4 in an undivided cell using platinum plates as an electrode in the presence of AcONa(0.25 eq) in MeCN-AcOH(9:1). After 2.0 F/mol of electricity was passed through the solution, 5-acetoxypyrrolidone 5 was obtained in 92 % yield. Compound 5 was a versatile intermediate for the synthesis of bicyclic lactams.[2]

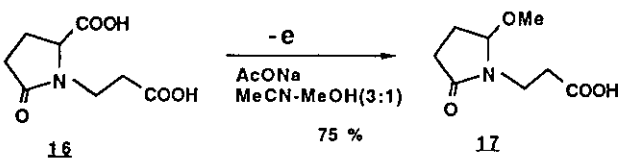
Subsequently, the electrolysis of compound 1a[3] was carried out to provide the desired 1,3-oxazine derivative 2a in 63 % yield. The spectral data of 2a was in complete agreement with that of an authentic sample obtained by electrolysis of compound 6.[4] Compound 1b was electrolyzed in a similar manner to give an acid sensitive product 2b in a low yield because C-O bond fission of compound 2b easily occurred to give compound 7. When the crude product was treated with p-TsOH in MeOH, methoxylated compound 8 was obtained in 42 % yield.



It was assumed that if the acyl imminium cation generated by electrolysis of compound 9 was attacked by a carbon or oxygen nucleophile on the nitrogen substituent, bicyclic lactam 10 or 11 would be formed In order to prepare compound 9, aldehyde 12 was oxidized to carboxylic acid 13, which was converted to keto ester 9 by Masamune's procedure[5] followed by deprotection of benzyl group. Electrolysis of compound 9 was carried out in a similar manner to provide 1,3-oxazine derivative 11 in 30 % yield after purification of thin layer chromatography on silica gel. However,the nmr spectrum of the crude electrolyzed product was that of 5-acetoxy derivative 14, not cyclized product 11. The cyclization appeared to occur during the preparative thin layer chromatography on silica gel. Thus, a benzene solution of compound 14 was stirred with silica gel for 1 h to afford 1,3-oxazine derivative 11 in good yield. On the other hand, treatment of compound 14 with $TiCl_4$ in CH_2Cl_2 at room temperature for 3 h afforded bicyclic lactam 10 in good yield. Moreover, compound 11 was treated with $TiCl_4$ in CH_2Cl_2 at room temperature to produce bicyclic lactam 10 in good yield which was converted to dimethyl ketal 15 as a single product.[6]



It was already known that this electrochemical oxidation proceeds from one electron abstraction of carboxylate anion followed by decarboxylation even in the presence of AcONa as a supporting electrolyte.[7] When compound 16 was electrolyzed in the presence of AcONa in MeCN-MeOH(3:1), methoxylated compound 17 was obtained in 75 % yield after 2.0 F/mol of electricity was passed through the solution. The result was very interesting because primary carboxylic acid and acetic acid could not be oxidized under the reaction conditions. Presumably, the reaction would be affected by the concentration of the conjugate bases of the respective acids since one electron abstraction occurred from the carboxylate anion.



The acyl imminium cation generated by electrolysis was a useful intermediate for the synthesis of various bicyclic lactams. Further studies are in progress.

REFERENCES AND NOTES

1. a) M. Mori, K. Kagechika, K. Tohjima, and M. Shibasaki, *Tetrahedron Lett.*, 1989, **29**, 1409. b) M. Mori, K. Kagechika, H. Sasai, and M. Shibasaki. *Chem. Express*, 1989, **4**, 89 .
2. Y. Nagao, W. -M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Am. Chem. Soc.*, 1989, **110**, 289.
3. For the synthesis of bicyclic lactam 2, the starting material was prepared by Wacker oxidation of benzyl N-allylpyroglutamate 18. Oxidation of compound 18 by $PdCl_2$ in the presence of $CuCl_2$ under oxygen afforded expected ketone 19. On the other hand, aldehyde 12 was obtained as a main product when CuCl was used as reducing agent.[Oxidation of 3-vinyl-2-azetidinone by $PdCl_2$-CuCl-O_2 afforded aldehyde as a main product. A. K. Bose, L. Krishnan, D. R. Wagle, and M. S. Mnhas, *Tetrahedron Lett.*, 1986, **27**, 5955.] The results were very interesting though the reason was not clear why the ratios of the products were affected by the difference of the employed copper ion. Treatment of compounds 12 and 19 with $NaBH_4$ followed by deprotection gave carboxylic acids 1a and 1b in good yields, respectively.

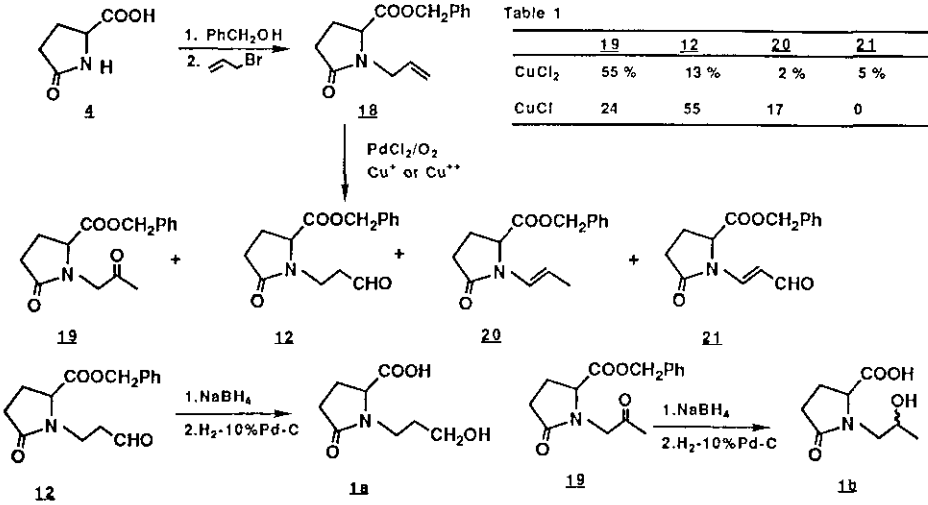


Table 1

	19	12	20	21
$CuCl_2$	55 %	13 %	2 %	5 %
CuCl	24	55	17	0

4. M. Okita, T. Wakamatsu, M. Mori, and Y. Ban, *Heterocycles*, 1980, **14**, 1089.
5. D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 72.
6. The nmr spectrum of compound 10 suggested that it was an equilibrium mixture of keto and enol forms. The stereochemistry of compound 15 was decided by its nmr spectrum. 14: Ir ν(neat) 1740, 1690 cm.-1. Nmr (C_6D_6) δ 0.9-1.2(m, 2 H) 1.51(ddd, J=2.2, 3.7, 13.6 Hz, 1 H), 1.7-1.9(m, 1 H), 2.22(d, J=11.0 Hz, 1 H), 2.58(dt, J=3.7, 13.2 Hz, 1 H), 3.01(s, 6 H), 3.36(s, 3 H), 3.89(ddd, J=7.0, 7.3, 13.2 Hz, 1 H), 4.09(ddd, J=2.2, 5.5, 13.2 Hz, 1 H). Ms m/z 211(M^+), 196, 152, 123.
7. a) T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, 1977, **42**, 2419. b) idem, *ibid.*, 1979, **44**, 1552. c)H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, *Tetrahedron Lett.*, 1976, 191.

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