A NEW SYNTHESIS OF BICYCLO-[1,3]OXAZINE DERIVATIVES

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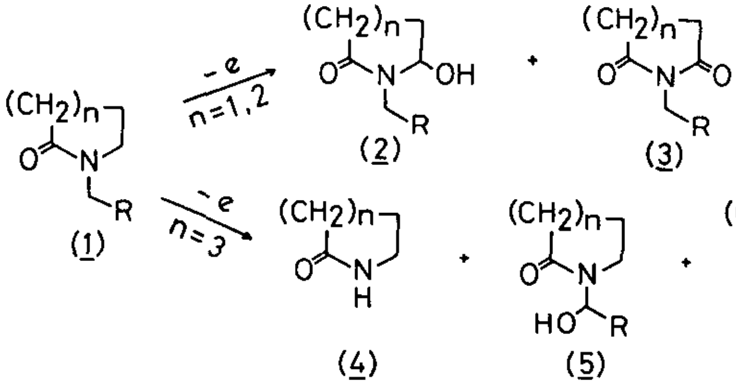
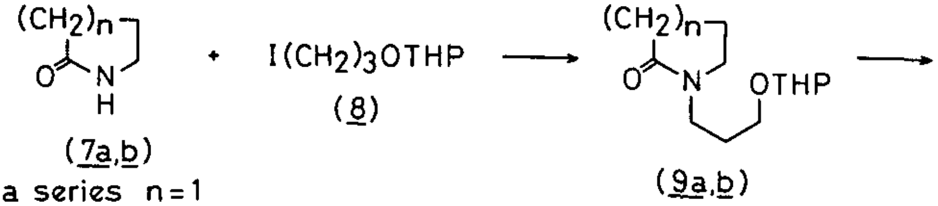
Abstract —— There has been described a new synthesis of bicyclo-tetrahydro-[1,3]-oxazine derivatives from five- and six-membered lactams by anodic oxidation, followed by simultaneous cyclization.

It was reported in the previous communication[1] that the anodic oxidation of N-(primary alkyl)lactams(1) in acetonitrile containing a small amount of water regioselectively occurred at the endocyclic methylene-α-carbon of nitrogen in five-(1, n=1) and six-membered(1, n=2) rings to furnish the hydroxylated lactams(2) and the corresponding imides(3). With the seven-membered lactams(1, n=3), however, oxidation proceeded at the exocyclic methylene-α-carbon of N-alkyl group to afford 4, 5, and 6.[1] These results are at variance with those provided by M. Mitzlaff et al.,[2] who state that the anodic oxidation of N-alkyllactams(1) carried out in a R'OH solution furnishes the exocyclic alkoxylated lactams(5, n=1,2, etc., R'O instead of OH), but does not give the endocyclic oxidized material(2, R'O in place of OH), unless the substituent at the nitrogen is either of H, secondary or tertiary alkyls.

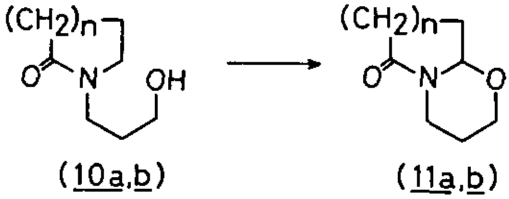
In the present communication, we describe a new synthesis of bicyclo-tetrahydro-[1,3]oxazines(11a,b), followed by simultaneous cyclization, which demonstrates our previous observations about oxidation sites to be valid even in this series and useful for the synthesis of important heterocycles.[3]

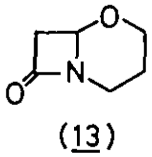
For preparation of the substrates(10a,b), trimethylene iodohydrine[4] was reacted with 3,4-dihydro-α-pyran in the presence of TsOH to give the protected iodide(8), which was refluxed with 2-pyrrolidinone(7a) in tetrahydrofuran with the aid of sodium hydride for 2 days to afford N-alkyllactams(9a). The compound(9a) was treated with TsOH in methanol at room temperature to remove the protecting group, furnishing the compound(10a), which was submitted to the anodic oxidation by

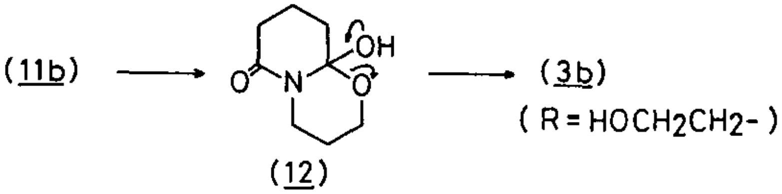




a series n = 1
b series n = 2







constant current method. A typical procedure for electrolysis of lactams, followed by cyclization is shown as follows: A mixture of the lactam(2 mmol), Et_4NBF_4(0.5 mmol), acetonitrile(5 ml) and water(0.25 ml) was placed in a 10 ml size of undivided cell equipped with two platinum electrodes. The constant current(30 mA) was passed through the cell until 2 F/mol of electricity was consumed. The solvent was distilled off, and the supporting electrolyte was removed by crystallization, and the residue was purified by chromatography on alumina to afford the cyclization product. According to this procedure, the tetrahydro-[1,3]oxazino derivatives, [11a, $bp_{0.1}$73-74°, IR(neat) ν 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.4-2.6(m, 6H), 2.99(m, 1H), 3.71(m, 1H), 4.0-4.3(m, 2H), 4.94(m, 1H); m/e 141(M^+), 140(base peak), 112, 111] and [11b, $bp_{0.05}$74-75°, IR(neat) ν 1640 cm^{-1}; NMR($CDCl_3$) δ 1.4-2.2(m, 6H), 2.38(m, 2H), 2.73(m, 1H), 3.74(m, 1H), 4.11(m, 1H), 4.7-4.9(m, 2H); m/e 155(M^+, base peak), 154, 99], were obtained in 74% yield from 10a and in 63% yield from 10b, respectively.

On the occasion when the excess of electricity(50 mA, 3.2 F/mol) was passed, the yield of 11b decreased to 46% and the glutarimide[3b, $R=HO(CH_2)_2-$] was generated in 18% yield, which might be assumed to be formed from 11b through a possible intermediate(12). Thus, the present work provides a new efficient synthesis of bicyclo-tetrahydro-[1,3]oxazine derivatives, which are the close relatvies of the biologically active "oxacepham" skeleton(13).[6] Studies in line with this direction are in progress. We thank the Ministry of Education, Science and Culture for a Grant-in-Aid for Special Project Research "Nitrogen Organic Resources".

REFERENCES AND NOTES

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4. G. L. Hodgson, D. F. MacSweeney, and T. Money, J. C. S. Perkin I, 1973, 2113.
5. The compound(**10b**) was prepared from **7b** and **8** via **9b** in a similar manner.
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