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NEW SYNTHESIS OF 4-ACETOXY-2-AZETIDINONES BY USE OF ELECTROCHEMICAL OXIDATION

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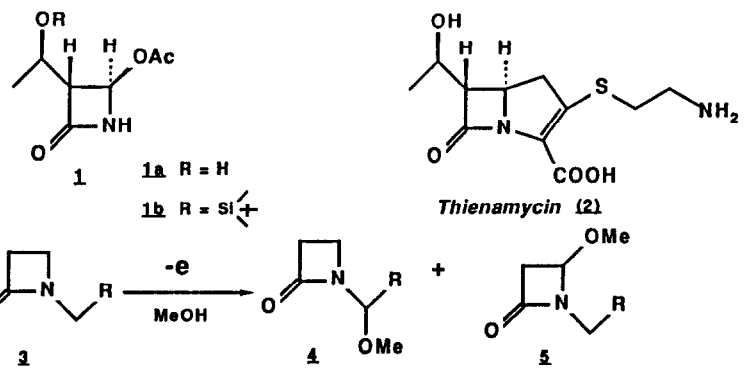
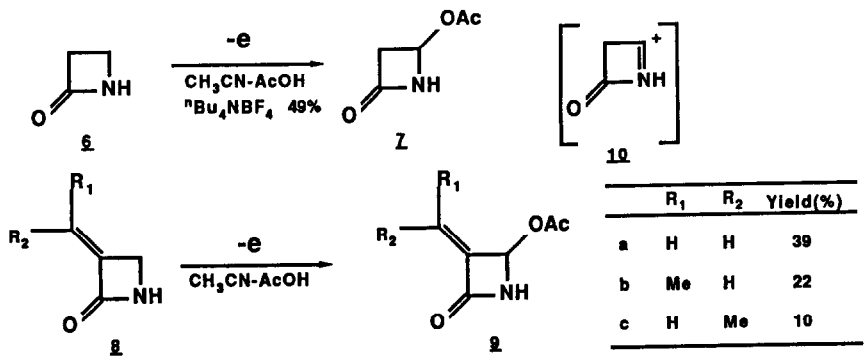
Abstract----Optically pure 4-acetoxy-3-[1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone(1b), which is a highly versatile intermediate for the synthesis of thienamycin(2) and other biologically active β-lactam analogs, was synthesized from 4-carboxy-3-[1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone(18) by Kolbe-type electrolysis.

In order to synthesize the new β-lactam derivatives with more efficacious activities, a variety of methods for the syntheses of 4-acetoxy-2-azetidinones has been reported because the acetoxy moiety is readily displaced by a wide range of nucleophiles under mild conditions.[1,2] Especially, the synthetic approach to thienamycine(2) was based on the highly versatile intermediate, 4-acetoxy-2-azetidinone(1) having hydroxyethyl group at C-3 position.[1b,c] In this communication we wish to describe a new method for the synthesis of 4-acetoxy-2-azetidinones through electrochemical process.

We first tried to introduce the acetoxy group at the C-4 position of 2-azetidinones directly. Since the electrochemical oxidation of the 2-azetidinone 3 in MeOH provided non-regioselectively the exo- and the endo-methoxylated compounds 4 and 5,[3] N-unsubstituted β-lactams[4] seemed to be more appropriate for the introduction of the acetoxy group into C-4 position by use of electro-

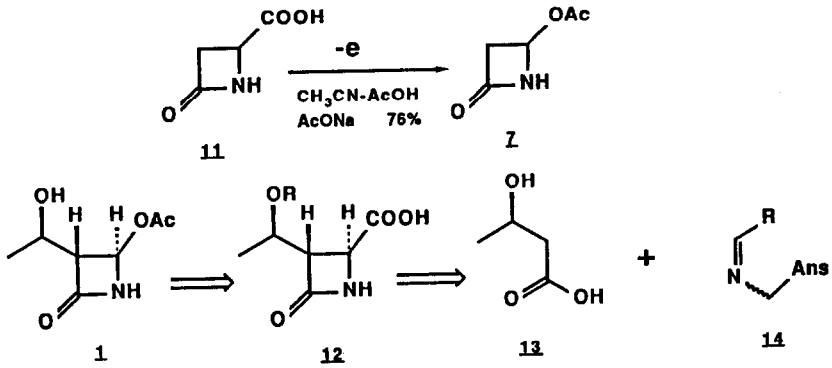


chemical oxidation. The β-lactam (6) was electrolyzed in an undivided cell using platinum plates as electrodes in the presence of n-Bu_4NBF_4 as electrolyte in AcOH-CH_3CN(1:9). After 3.0 F/mol of electricity was passed through the solution under a constant current with external cooling, the desired 4-acetoxy-2-azetidinone(7) was obtained in the yield of 49 %. In a similar manner, 3-methylene-2-azetidinone(8a)[4] gave 4-acetoxy-3-methylene-2-azetidinone(9a) in 39 % yield. E- and Z-3-Ethylidene-4-acetoxy-β-lactams 9b and 9c were obtained from the corresponding 2-azetidinones 8b and 8c in the yield of 22 % and 10 %, respectively. Since the β-lactams showes no oxidation peak below 2.2 V from the cyclic voltammogram in CH_3CN,[4] direct electrolysis of β-lactams may not be applied to β-lactams having oxidation-labile functions. Recent studies of Kolbe-type electrolysis suggested that the decarboxylation of carboxylic acid having heteroatoms at the α-position easily occurred under the lower oxidation potential to generate the cations, which could smoothly react with nucleophiles because they were stabilized by adjacent nitrogen[5] or oxygen.[6] Therefore, the acyl-iminium cation 10 generated by the direct electrolysis of β-lactams 6 should be provided by the Kolbe-type electrolysis of β-lactam 11 having carboxy group at C-4 position.



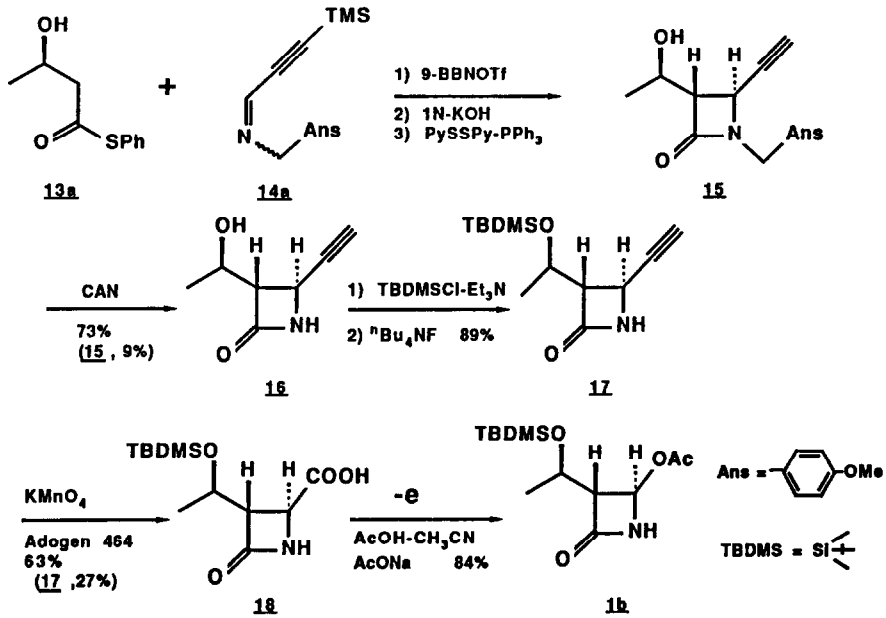
	R_1	R_2	Yield(%)
a	H	H	39
b	Me	H	22
c	H	Me	10

Thus, 4-carboxy-2-azetidinone(11) was electrolyzed using platinum plates as anode and cathode in the presence of NaOAc as electrolyte in an undivided cell in AcOH-CH_3CN(1:3). After 5.0 F/mol of electricity was passed through the solution under a constant current, 4-acetoxy-2-azetidinone 7 was obtained in 76 % yield. Subsequently, this method was applied to the synthesis of optically pure 4-acetoxy-3-hydroxyethyl-2-azetidinone(1). The key carboxylic acid 12 was prepared from readily available 3(R)-hydroxybutyric acid(13) by use of our method.[7] Condensation of the borone enolate generated from the thiol ester 13a with the imine 14a followed by cyclization afforded the β-lactam 15 in high stereoselectivity.[7] Deprotection of p-methoxybenzyl group with ceric ammonium nitrate(CAN) afforded compound 16, which was treated with TBDMSCl and NEt_3 followed by exposure to n-Bu_4NF to lead to the O-protected β-lactam 17.



To convert the ethynyl group to the carboxyl group, compound 17 was treated with $KMnO_4$ in the presence of Adogen 464 and AcOH in CH_2Cl_2-H_2O [8] to give the desired carboxylic acid 18 in 63 % yield along with the starting material(17, 27 % yield). The β-lactam 18 was electrolyzed in an undivided cell in the presence of AcONa in AcOH-CH_3CN(1:4).[9] After 11 F/mol of electricity was passed through the solution, 4-acetoxy-β-lactam 1b was obtained in 84 % yield as optically pure form {$[\alpha]_D^{17.5}$ +51.0°(c, 1.00, $CHCl_3$), mp 107.0-108.0°C.}.[10]

Further studies are in progress in our laboratory.



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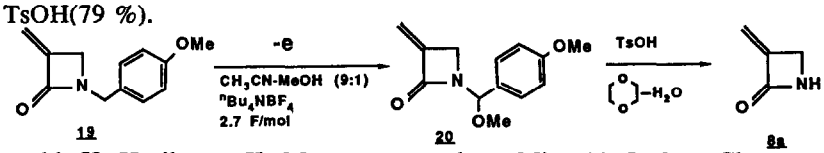

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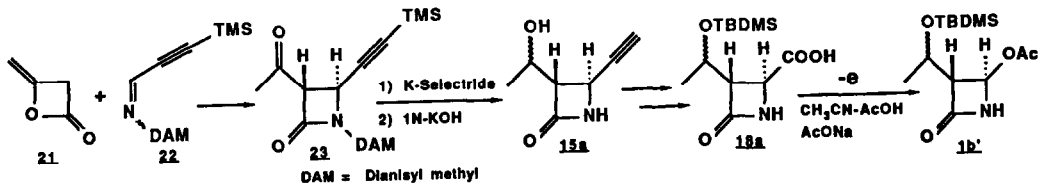
9. To examine the Kolbe-type electrolysis of β-lactam having hydroxyethyl group at C-3 position, the racemic β-lactam 18a derived from diketene 21 and the imine 22(Y. Ishida, T. Iimori, and M. Shibasaki, unpublished result) was electrolyzed in an undivided cell. After passage of 7 F/mol of electricity, the desired racemic 4-acetoxy-β-lactam 1b' was obtained in 62 % yield. When 11 F/mol of electricity was used in this reaction, the β-lactam 1b' was obtained in higher yield(85 %).



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