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A STEREOSELECTIVE INTRODUCTION OF AN AMINO GROUP TO THE 3-*POSITION OF* A *READILY* AVAILABLE 3-HYDROXYETHYL-AZETIDINONE DERIVATIVE

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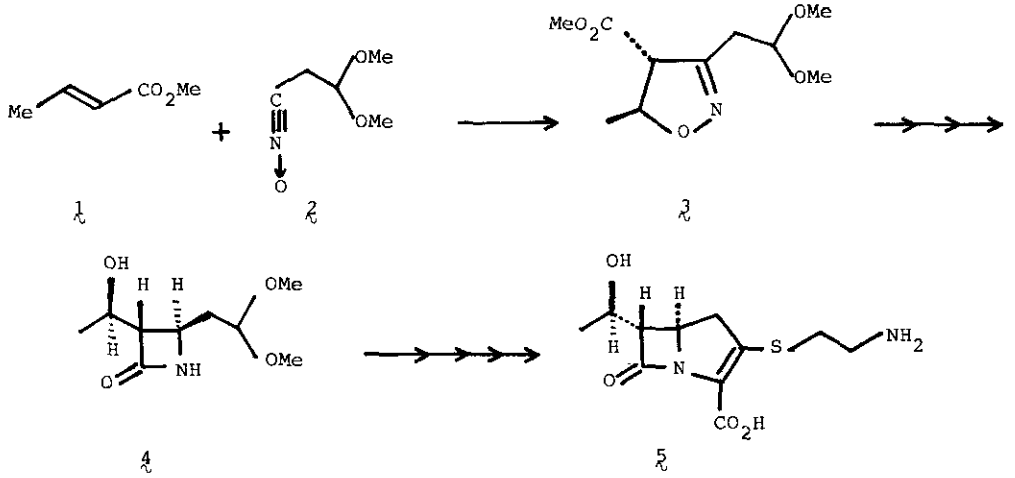
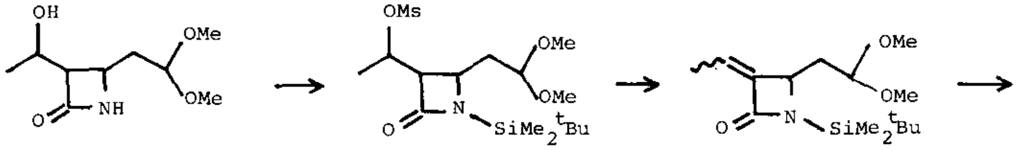
Abstract —— A stereoselective introduction of an amino group at the 3-position of an azetidinone from a readily available 3-hydroxyethylazetidinone was described.

Recently we have postulated the synthesis of a 3-hydroxyethylazetidin-2-one derivative (4) in an efficiently large scale via the izoxazoline (3) by employing 1,3-dipolar cycloaddition reaction of the nitrile *oxide (2) with methyl crotonate (1)* as a key reaction.[1]



Scheme 1

Since the azetidinone (4) had been successfully transformed[1] into the carbapenem antibiotic, thienamycin (5), we have further investigated the introduction of an amino group at the 3-position of the azetidinone (4), because such replacement of a functional group at that position would be of biological interest, and the product would be a potential intermediate for the synthesis of 6-aminocarbapenem antibiotics and monobactam derivatives. In the amino-substituted β-lactam, such as penicillins and cephalosporins, the relative stereochemistry between the C-3 and C-4 positions on azetidinone ring would be desirable to be *cis* to display the antibacterial activity.[2] With that precedent in mind, we prepared the keto-lactam (7) from the azetidinone (4) by adopting the procedure developed by us.[3] Silylation of 4 with *tert*-butyldimethylchlorosilane, followed by mesylation with mesyl chloride gave the mesylate, whose elimination on treatment with sodium hydride gave the olefin (6) as a mixture of *E* and *Z* isomers. Ozonolysis of the olefin (6) and subsequent treatment with methyl sulfide furnished the desired keto-lactam (7) in 63 % overall yield from 4. In order to introduce an amino function, the keto-lactam (7) was treated with hydroxylamine hydrochloride in methylene chloride and pyridine to give the oximes (8 and 9) in 65 % yield in the ratio of ca. 1 : 3.5. The stereochemistry of the oximes was determined on the basis of their spectral data. Catalytic hydrogenation of both oximes over rhodium-alumina in methanol under 5 atm of hydrogen afforded the desired amino compounds (10 and 11) in 51 % yield in the ratio of 5 : 1. The stereochemistry between C-3 and C-4 positions of the major compound (10) was deduced to be *cis* based on its nmr spectrum, and this results indicated that the hydrogenation occurred from the less hindered side of the azetidinone to furnish the desired 3,4-*cis*-amine. Thus, the stereoselective introduction of an amino group at the 3-position of the azetidinone (4) was achieved successfully. The amino compounds (10 and 11) were then converted into the corresponding amide derivatives (12 and 13) respectively. Finally, the compound (13) was desilylated on treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran to give the monobactam derivative (14). Antibacterial activity of the compounds prepared is now under investigation.



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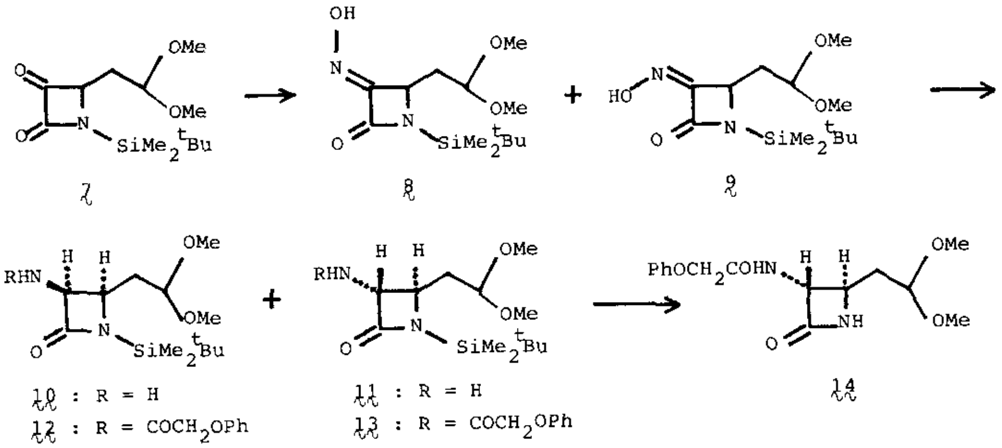

Scheme 2

EXPERIMENTAL

Ir spectra were obtained with a Hitachi 260-10 spectrophotometer, nmr spectra with a JEOL PMX-60 instrument (tetramethylsilane as internal reference), and mass spectra with a JEOL JMS-D 300 spectrometer. Mps were determined with a Yanaco micro apparatus. All products described were homogeneous on t.l.c.

(E)- and (Z)-[N-(tert- Butyldimethylsilyl)-(R*)-4-(2',2'-dimethoxyethyl)-2-azetidinone]-3-oxime (8 and 9).

A solution of the keto-lactam (7)(2.28 g), hydroxylamine hydrochloride (0.72 g) and pyridine (1.26 g) in methylene chloride (30 ml) was stirred at ambient temperature for 18 h. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with benzene-acetone (97:3 v/v) gave the E-oxime (8)(0.346 g) as a pale yellowish powder, mp 85 °C, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1725; nmr($CDCl_3$)δ: 0.24 (3H, s, Me), 0.27 (3H, s, Me), 0.93 (9H, s, ^{t}Bu), 2.07 (2H, m, $C\underline{H}_2CH(OMe)_2$), 3.34 (3H, s, OMe), 3.38 (3H, s, OMe), 4.07 (1H, dd, J = 2.8 and 9 Hz, C_4-H), 4.72 (1H, dd, J = 3 and 10 Hz, $CH(OMe)_2$), 8.20 (1H, bs, OH). Anal. calcd for $C_{13}H_{26}N_2O_4Si$: C, 51.63; H, 8.67; N, 9.26. Found: C, 51.77; H, 8.89; N, 8.82. Further elution with the same solvent afforded the (Z)-oxime (9)(1.213 g) as a colorless oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 1750; nmr ($CDCl_3$) δ: 0.28 (3H, s, Me), 0.32 (3H, s, Me), 0.98 (9H, s, ^{t}Bu), 2.14 (2H, m, $C\underline{H}_2CH(OMe)_2$), 3.35 (3H, s, OMe), 3.38 (3H, s, OMe), 4.45 (1H, dd, J = 4 and 9 Hz, C_4-H), 4.77 (1H, dd, J = 4 and 9 Hz, C$\underline{H}$(OMe)$_2$), 8.32 (1H, s, OH); ms m/z 302 (M^+).

cis- and trans-N-(tert-Butyldimethylsilyl)-3-amino-(R*)-4-(2',2'-dimethoxyethyl)-2-azetidinone (10 and 11).

A solution of the oximes (**8** and **9**) (1.56 g) in methanol (30 ml) in the presence of 5% rhodium on alumina (1 g) was shaken at ambient temperature under 5 atm of hydrogen for 30 h. After the insoluble material was filtered off, the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with benzene-acetone (92:8 v/v) gave the cis-amine (**10**) (623 mg) as a yellowish oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1725; nmr($CDCl_3$)δ: 0.22 (3H, s, Me), 0.24 (3H, s, Me), 0.95 (9H, s, ^{t}Bu), 1.62 (2H, br s, NH_2), 2.01 (2H, m, C$\underline{H}_2$CH(OMe)$_2$), 3.35 (6H, s, 2 × OMe), 3.75 (1H, m, C_4-H), 4.27 (1H, d, J = 5.7 Hz, C_3-H), 4.54 (1H, m, C$\underline{H}$(OMe)$_2$). Further elution with the same solvent afforded the trans-amine (**11**)(126 mg) as a yellowish oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 3455, 1730; nmr($CDCl_3$)δ: 0.22 (3H, s, Me), 0.24 (3H, s, Me), 0.95 (9H, s, ^{t}Bu), 1.62 (2H, br s, NH_2), 2.01 (2H, m, C$\underline{H}_2$CH(OMe)$_2$), 3.35 (6H, s, 2 × OMe), 3.56 (1H, m, C_4-H), 4.00 (1H, m, C_3-H), 4.45 (1H, m, C$\underline{H}$(OMe)$_2$).

cis-N-(tert-Butyldimethylsilyl)-3-phenoxyacetamido-(R*)-4-(2',2'-dimethoxyethyl)-2-azetidinone (12).

To a stirred solution of the amine (**10**)(335 mg) in methylene chloride (30 ml) containing triethylamine (236 mg) was added phenoxyacetyl chloride (238 mg) at 0 °C and the resulting mixture was further stirred for 1 h at the same temperature. The organic layer was washed with aqueous sodium hydrogen carbonate and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded the residue which was subjected to column chromatography on silica gel. Elution with benzene-acetone (98: 2 v/v) afforded the amide (**12**)(221 mg , 45%) as a colorless oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 3415, 1745, 1685; nmr($CDCl_3$)δ: 0.21 (3H, s, Me), 0.32 (3H, s, Me), 0.97 (9H, s, ^{t}Bu), 1.80-2.03 (2H, m, C$\underline{H}_2$CH(OMe)$_2$), 3.19 (3H, s, OMe), 3.33 (3H, s, OMe), 3.91 (1H, m, C_4-H), 4.40 (1H, m, C$\underline{H}$(OMe)$_2$), 4.53 (2H, s, CH_2O). 5.50 (1H, dd, J = 7 and 10 Hz, C_3-H), 6.95-7.35 (5H, m, Ar H), 7.85 (1H, d, J = 10 Hz, NH).

trans-N-(tert-Butyldimethylsilyl)-3-phenoxyacetamido-(R*)-4-(2',2'-dimethoxyethyl)-

2-azetidinone (13).

The amide (13) was prepared from the trans-amine (11) by the same procedure as described above, in 46% yield, as an oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 3415, 1745, 1690; nmr(CDCl$_3$)δ: 0.27 (6H, s, 2 × Me), 0.98 (9H, s, ^{t}Bu), 1.85-2.15 (2H, m, C$\underline{H}_2$CH(OMe)$_2$), 3.30 (3H, s, OMe), 3.34 (3H, s, OMe), 3.70 (1H, m, C$_4$-H), 4.51 (2H, s, CH$_2$O), 4.57 (1H, m, C$\underline{H}$(OMe)$_2$), 4.64 (1H, m, C$_3$-H), 6.95-7.35 (6H, m, Ar H and NH).

trans-3-Phenoxyacetamido-(R*)-4-(2',2'-dimethoxyethyl)-2-azetidinone (14).

To a stirred solution of the amide (13)(73.5 mg) in tetrahydrofuran (10 ml) was added tetra-n- butylammonium fluoride (0.5 ml of 1M solution in tetrahydrofuran) at ambient temperature, and the resulting mixture was further stirred for 5 min. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using benzene-acetone (85:15 v/v) as eluent to give 14 (43.5 mg, 81%) as a yellowish oil, ir$\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1760, 1685; nmr(CDCl$_3$)δ: 2.17 (2H, m, C$\underline{H}_2$CH(OMe)$_2$), 3.35 (6H, s, 2 × OMe), 3.74 (1H, m, C$_4$-H), 4.51 (2H, s, CH$_2$O), 4.51 (1H, m, C$\underline{H}$(OMe)$_2$), 4.67 (1H, dd, J = 1.7 and 7 Hz, C$_3$-H), 6.10 (1H, br s, NH), 6.95-7.35 (6H, m, Ar H and NH).

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