NEW SHORT STEP SYNTHESIS OF 3-HYDROXYETHYL-4-CYANOAZETIDIN-2-ONE DERIVATIVE: A POTENTIAL PRECURSOR OF THE PENEMS AND THE CARBAPENEMS

Masao Shiozaki*, Hiroshi Maruyama and Noboru Ishida
Chemical Research Laboratories, Sankyo Co., Ltd.
Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan

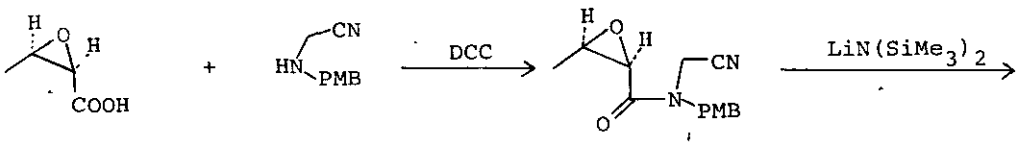
Abstract - 3-Hydroxyethyl-4-cyanoazetidin-2-one derivative was synthesized from (2R,3R)-2,3-epoxybutyric acid in two steps.

For the past few years, we have been investigating the synthetic opportunities for analogues of thienamycin.[1] 3-tert-Butyldimethylsilyloxyethyl-4-cyanoazetidin-2-one (6) is a potential precursor of the penems and the carbapenems. The synthesis of this compound from penicillin and its further conversion to isopenam derivative had already been reported.[2] Since the synthesis of this compound from penicillin needed numerous steps, we attempted a short step synthesis of this compound, and here we wish to report our successful results.

Condensation of (2R,3R)-2,3-epoxybutyric acid (1)[3] and p-methoxybenzylaminoacetonitrile (2)[4] by use of dicyclohexylcarbodiimide as a condensing reagent gave an epoxyamide (3) in 51% yield in addition to the starting amine (34%). Treatment of 3 with 1.1 equivalents of lithium hexamethyldisilazide in tetrahydrofuran at 10-20°C for 1 min after dropwise addition during a period of 10 min gave the trans azetidin-2-one[5] (4, 51% yield) as a crystalline solid: mp 80-82°C: $[\alpha]_D^{24}$ -29.5° (c=1.93, EtOH), and cis-isomer[6] (4', 22% yield) as a crystalline solid: mp 86-88°C. Protection of the hydroxy group of 4 with the $^tBuMe_2Si$ group gave 5 in 69% yield as an oil. Deprotection of the methoxybenzyl group of 5 by $K_2S_2O_8$-K_2HPO_4 (2:1) in acetonitrile-water (1:1) under argon[7] gave a corresponding azetidin-2-one (6, 53% yield) as a crystalline solid: mp 140-142°C: $[\alpha]_D^{24}$ -26.4° (c= 2.04, $CHCl_3$).

Thus, we could obtain 3-hydroxyethyl-4-cyanoazetidin-2-one derivative with the desired stereochemistry in few steps.

Scheme 1.



1 2 3

4. R^1=H, R^2=PMB

5. R^1=$SiMe_2Bu^t$, R^2=PMB

6. R^1=$SiMe_2Bu^t$, R^2=H

4'

PMB = p-methoxybenzyl

REFERENCES

1. M. Shiozaki, N. Ishida, T. Hiraoka and H. Maruyama, Tetrahedron, in press.
2. K. Hirai, Y. Iwano and K. Fujimoto, Tetrahedron Letters, 1982, 23, 4025.
3. H. Shimazaki, Nippon-Kagaku Zasshi, 1966, 87, 459.
4. This amine (2) is easily prepared from bromoacetonitrile and p-methoxybenzylamine in THF by use of Et_3N as a base.
5. ^1H NMR (60 MHz, $CDCl_3$, δ) of 4: 1.25 (3H, d, J=6 Hz), 2.29 (1H, d, J=4.5 Hz, OH), 3.54 (1H, dd, J=2.5, 4 Hz), 3.88 (3H, s), 4.05, 4.69 (2H, AB-q, J=15 Hz), 4.07 (1H, d, J=2.5 Hz), 4.20 (1H, m), 6.87 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.5 Hz).
6. ^1H NMR (60 MHz, $CDCl_3$, δ) of 4': 1.40 (3H, d, J=6 Hz), 2.94 (1H, bs, OH), 3.38 (1H, dd, J=5.5, 9 Hz), 3.77 (3H, s), 4.06, 4.66 (2H, AB-q, J=15 Hz), 4.09 (1H, d, J=5.5 Hz), 4.22 (1H, m), 6.86 (2H, d, J=9 Hz), 7.19 (2H, d, J=9 Hz).
7. cf. W.F. Huffman, K.G. Holden, T.F. Buckley, III, J.G. Gleason and L. Wu, J. Am. Chem. Soc., 1977, 99, 2352.

Received, 1st May, 1984