

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

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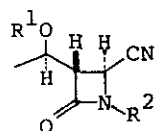
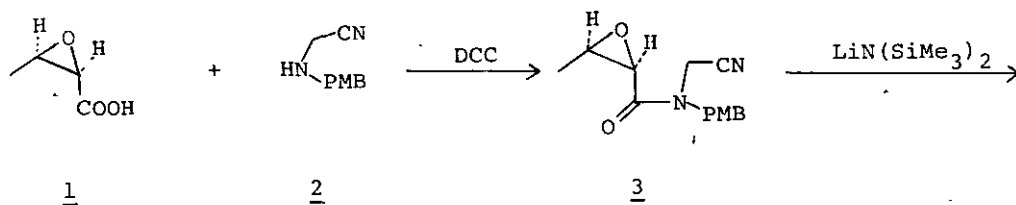
Abstract - 3-Hydroxyethyl-4-cyanoazetidin-2-one derivative was synthesized from (2R,3R)-2,3-epoxybutyric acid in two steps.

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-one⁵ (4, 51% yield) as a crystalline solid: mp 80-82°C: $[\alpha]_D^{24}$ -29.5° (c=1.93, EtOH), and cis-isomer⁶ (4', 22% yield) as a crystalline solid: mp 86-88°C. Protection of the hydroxy group of 4 with the ^tBuMe₂Si group gave 5 in 69% yield as an oil. Deprotection of the methoxybenzyl group of 5 by K₂S₂O₈-K₂HPO₄ (2:1) in acetonitrile-water (1:1) under argon⁷ 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, CHCl₃).

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

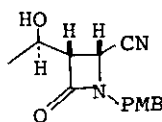
Scheme 1.



4. $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{PMB}$

5. $\text{R}^1 = \text{SiMe}_2\text{Bu}^t$, $\text{R}^2 = \text{PMB}$

6. $\text{R}^1 = \text{SiMe}_2\text{Bu}^t$, $\text{R}^2 = \text{H}$



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.

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