Tetrahedron Letters,Vol.25,No.15,pp 1591-1594,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

THREE-STEP SYNTHESIS OF 4-(2'-HYDROXYETHYL)AZETIDIN-2-ONE AND ITS SUBSTITUTED DERIVATIVES FROM 4-ACETOXY-2-PYRIDONES[1]

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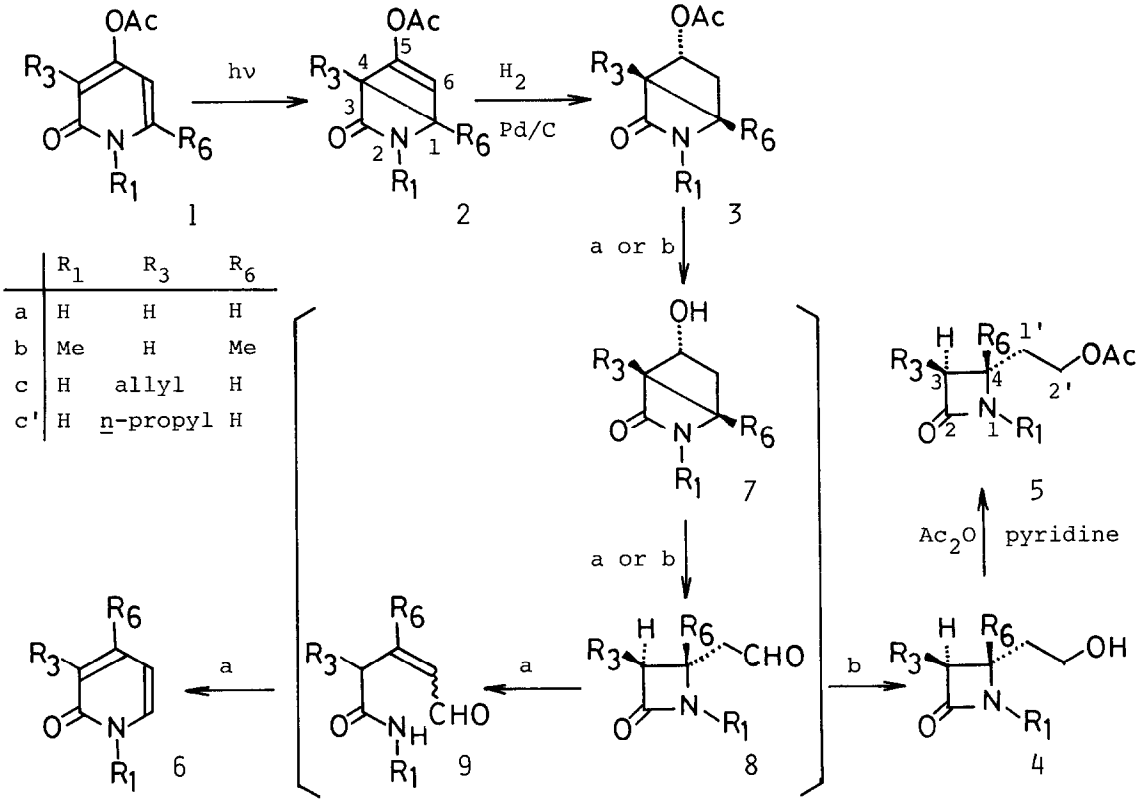
Abstract: 4-(2'-Hydroxyethyl)azetidin-2-one, an important synthetic intermediate for carbapenem, and its substituted derivatives have been synthesized from 4-acetoxy-2-pyridones by photolysis, catalytic hydrogenation, followed by basic hydrolysis in the presence of sodium borohydride.

3-Oxo-2-azabicyclo[2.2.0]hex-5-enes[2] (e.g., 2), photoisomers of 2-pyridones, are fused β-lactams. Using these photopyridones, successful syntheses of azetidin-2-ones, which may serve as starting materials for the synthesis of carbapenem antibiotics, have been achieved by two groups.[2,3] However, these azetidinones are restricted for 3,4-disubstituted ones, since ozonolysis of the photoisomers to cleave the C_5-C_6 double bond is the common way to access the azetidinone system.

Here, we report an another way to use these photoisomers for the synthesis of azetidin-2-ones having a terminally oxygenated ethyl side-chain at the 4-position by the regioselective cleavage of the C_4-C_5 bond in these photoisomers.

Thus, a solution of 4-acetoxy-1,6-dimethyl-2-pyridone[5] (1b) in ether was irradiated[6] by high-pressure mercury lamp (Ushio 450W, Pyrex filter) to give the photopyridone[7] (2b, mp 65.5-66.5°C) in 82% yield as a sole isolable product. Hydrogenation of the olefinic bond of 2b over palladium on charcoal gave a single stereoisomer [mp 70.5-71.5°C, δ_H ($CDCl_3$): 1.47 (s, 3H), 2.00 (s, 3H), 2.10 (dd, J=5.2, 13.5 Hz, 1H), 2.43 (dd, J=8.0, 13.5 Hz, 1H), 2.73 (s, 3H), 3.68 (d, J=8.0 Hz), 5.15 (td, J=8.0, 5.2 Hz, 1H)] which was assigned the endo-configuration (3b), since the coupling constant between the protons of C_4 and C_5 is 8.0 Hz. Thus, as expected, hydrogenation occurs from the least-hindered face of the molecule (2b).

An attempted hydrolysis of 3b under basic conditions (1% K_2CO_3/MeOH, room temp.) did not give the corresponding hydroxy derivative (7b), but afforded 1,4-dimethyl-2-pyridone[8] (6b) in 64% yield as a sole detectable product. The formation of 6b is best explained by assuming the intermediacy of 1,4-dimethyl-4-formylmethylazetidin-2-one (8b) formed by retro-aldol ring opening of the simple hydrolysis product (7b). Retro-Michael ring cleavage[9] at the N-C_4 bond in 8b by



	R_1	R_3	R_6
a	H	H	H
b	Me	H	Me
c	H	allyl	H
c'	H	n-propyl	H

a) 1% K_2CO_3/MeOH.

b) 1% K_2CO_3/MeOH in the presence of $NaBH_4$.

abstraction of a proton in the active methylene function would then gives 9b, which cyclizes to the final product (6b)

Therefore, in order to obtain the azetidinone derivative from 3b, the formyl function in 8b should be reduced, before the above N-C_4 bond cleavage occurs. Actually, treatment of 3b by 1% K_2CO_3 in methanol in the presence of an excess of sodium borohydride, followed by acetylation (Ac_2O-pyridine) gave 4-(2'-acetoxyethyl)-1,4-dimethylazetidin-2-one [5b, oil, δ_H ($CDCl_3$): 1.37 (s, 3H), 1.96 (t, J=6.5 Hz, 2H), 2.00 (s, 3H), 2.60 (d, J=14.5 Hz, 1H), 2.68 (s, 3H), 2.90 (d, J=14.5 Hz, 1H), 4.09 (t, J=6.5 Hz, ν(film): 1753 sh, 1735 cm^{-1}] in 95% yield.

The same three-step procedure has also been applied successfully to the synthesis of 4-(2'-acetoxyethyl)azetidin-2-one (5a). Thus, irradiation of 4-acetoxy-2-pyridone (1a) in ether-acetonitrile (3:1 v/v) gave the corresponding

photopyridone (2a, mp 103-105°C) in 93% yield, which by hydrogenation (H_2/Pd-C/MeOH) gave 3a (mp 61.5-63°C) in 89% yield. Finally, treatment of 3a under the same conditions as above gave 4-(2'-acetoxyethyl)azetidin-2-one[10] [5a, mp 44-47°C, $\nu(CHCl_3)$: 1755, 1735 cm^{-1}] in 75% yield.

Added to high overall yield[11] and easy handling, this three-step synthetic method of azetidinone derivatives has wide applicability for a variety of substituted derivatives of 4-(2'-hydroxyethyl)azetidin-2-one. Namely, if the C-3, C-5, or C-6 substituted 4-acetoxy-2-pyridone will be used as respective starting materials, 4-(2'-acetoxyethyl)azetidin-2-ones having either C-3, C-1', or C-4 substituent should be obtained. For example, from 4-acetoxy-3-allyl-2-pyridone[2c] (1c), 4-(2'-acetoxyethyl)-3-n-propylazetidin-2-one [5c', oil, δ_H ($CDCl_3$): 0.95 (t, J=6.7 Hz, 3H), 1.25-2.1 (m, 6H), 2.07 (s, 3H), 2.7-2.95 (m, 1H, C_3-H), 3.38 (ddd, J=2.5, 6.0, and 6.8 Hz, 1H, C_4-H), 3.95-4.4 (m, 2H), 6.41 (bs, NH)] was obtained in high overall yield (77%). As expected from epimerization of cis-3,4-disubstituted azetidin-2-one to trans isomer under strongly basic conditions (e.g., potassium tert-amylate),[12] thermodynamically stable trans-configuration between C_3-H and C_4-H is assigned for 5c', since retro-aldol reaction of 7c' should initially afford the azetidinone enolate of 8c'. Small coupling constant (2.5 Hz) between these two protons in the nmr spectrum of 5c' also supports this view.

The short, efficient sequence described herein allow the preparation of analogues of 4-(2'-hydroxyethyl)azetidin-2-one[13] having a variety of substituents either on azetidinone ring or on the side chain from 4-acetoxy-2-pyridones. Further application of this method to a variety of substituted 4-oxygenated-2-pyridones and further manupilation of the resultant azetidinones to new analogues of carbapenem antibiotics are in progress.

REFERENCES AND NOTES

1. Part XVIII of "Cycloadditions in Syntheses." For Part XVII, see: C. Kaneko, Y. Momose, T. Maeda, T. Naito, and M. Somei, Heterocycles, 20, 2169 (1983).
2. a) H. Furrer, Chem. Ber., 105, 2780 (1972); b) R.C. De Selms and W.R. Schleigh, Tetrahedron Lett., 1972, 3563; c) C. Kaneko, K. Shiba, H. Fujii, and Y. Momose, J. Chem. Soc. Chem. Comm., 1980, 1177; d) W.J. Begley, G. Lowe, A.K. Cheetham, and J.M. Newsam, J. Chem. Soc. Perkin I, 1981, 2620.
3. J. Brennan, J. Chem. Soc. Chem. Comm., 1981, 880.
4. T. Kametani, T. Mochizuki, and T. Honda, Heterocycles, 20, 2169 (1983).
5. This compound was prepared by acetylation (Ac_2O-pyridine) of 4-hydroxy-6-methyl-2-pyridone: C. Wang, J. Heterocyclic Chem., 7, 389 (1970).
6. All irradiations were continued until almost all of the starting 2-pyridone (1) was consumed. The reactions were monitored UV spectroscopically and continued until the absorption maxima of 1 (around 300 nm) became almost nil.

7. Satisfactory accurate mass data were obtained for all new compounds.
8. R. Adams and A.W. Schrecker, J. Chem. Soc., 1948, 1186.
9. This type of retro-Michael ring opening under comparable conditions is common in the 2-azetidinones having an active methylene group at the 1'-position: M.A. Morrison and M.J. Millar, J. Org. Chem., 48, 4421 (1983).
10. F.A. Bouffard, D.B.R. Johnston, and B.G. Christensen, J. Org. Chem., 45, 1130 (1980).
11. Since 2-pyridones having 4-alkoxy or 4-acetoxy function never photodimerize under any condition, corresponding photopyridones are obtained in very high yield. See reference 2c.
12. D. Favara, A. Omodei-Sale, P. Consonni, and A. Depaoli, Tetrahedron Lett., 23, 3105 (1982).
13. Syntheses of 5a and its derivatives (e.g., 4-carboxymethyl-2-azetidinone) and their utility in the syntheses of carbapenem antibiotics have been reported by several groups added to those quoted already in references 9, 10, and 12: a) S.M. Schmitt, D.B.R. Johnston, and B.G. Christensen, J. Org. Chem., 45, 1135, 1142 (1980); b) M. Shiozaki, N. Ishida, T. Hiraoka, and H. Yanagisawa, Tetrahedron Lett., 22, 5205 (1981); c) D.G. Melillo, I. Shinkai, T. Liu, K. Ryan, M. Sletzinger, Tetrahedron Lett., 21, 2783 (1980); d) M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, J. Am. Chem. Soc., 103, 2405 (1981); e) S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, J. Am. Chem. Soc., 103, 2406 (1981); f) K. Okano, Y. Kiyotani, H. Ishihama, S. Kobayashi, and M. Ohno, J. Am. Chem. Soc., 105, 7186 (1983); g) K. Okano, T. Izawa, and M. Ohno, Tetrahedron Lett., 24, 217 (1983); h) T. Kametani, T. Honda, J. Sasaki, H. Terasawa, Y. Nakayama, and K. Fukumoto, Heterocycles, 14, 575 (1980); i) S. Oida, A. Yoshida, and E. Ohki, Chem. Pharm. Bull., 28, 3494 (1980); j) C.W. Greengrass and D.W.T. Hoople, Tetrahedron Lett., 22, 1161 (1981); k) T. Kobayashi, N. Ishida, I. Shinkai, T. Liu, R.A. Reamer, and M. Sletzinger, Tetrahedron Lett., 23, 4899 (1982).

(Received in Japan 17 January 1984)