Tetrahedron Letters,Vol.25,No.10,pp 1063-1066,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

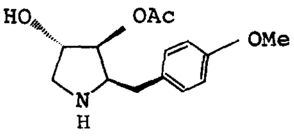
HALOAMIDATION OF 3-HYDROXY-4-PENTENYLAMIDES: STEREOSELECTIVE SYNTHESIS OF cis-1-HALOMETHYL-2-HYDROXYPYRROLIDINES

Y. Tamaru, S. Kawamura, K. Tanaka, and Z. Yoshida*

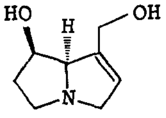
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida,
Kyoto 606, Japan

Summary: Haloamidation of N-p-toluenesulfonyl 3-hydroxy-4-pentenamides, irrespectively of substitution pattern, provides N-p-toluenesulfonyl cis-1-halomethyl-2-hydroxypyrrolidines with high selectivity ($\geqslant$ 95 %) and in high yield.

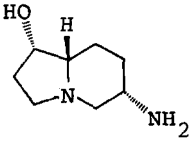
Recently we[1] and others[2] have reported that halolactonization of 3-hydroxy-4-alkenoic amides and acids provides cis-3-hydroxy-4-halomethyl-γ-butyrolactones in high stereochemical purity. As an extension of this synthetically useful reaction, we examined an intramolecular haloamidation of 3-hydroxy-4-pentenylamines in the expectation of the stereoselective formation of cis-1-halomethyl-2-hydroxypyrrolidines (equation 1). The product not only shares the partial structure with many types of interesting alkaloid (e.g., anisomycin 1,[3] etronecine 2,[4] and slaframine 3,[5] etc.), but also is assembled with halomethyl functionality, desirable for the further manipulation to the total synthesis of these alkaloids.



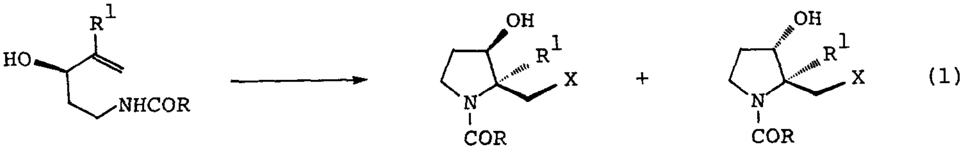
1



2



3



4 **5** **6**

Carbamate 4 (R = OMe, R^1 = H), prepared by a sequential standard method,[6] was exposed to I_2 (2 equiv) and $NaHCO_3$ (2 equiv) in 1,2-dimethoxyethane-H_2O (5 : 2 v/v) at ambient temperature for 4 days. TLC monitoring indicates that the reaction is slow and would not reach a completion even after prolonged reaction times, however, the reaction is clean only providing a single spot except for the one corresponding to the starting material. A mixture of 5 and 6 (R = OMe, R^1 = H, in a ratio of 93 : 7) was isolated in 83% yield (based on 66% conversion). The cis structure of the predominant product was established by the higher field resonance of the iodomethyl group in 5 (as a benzoate derivative: δ 1.32 ppm) compared with that in 6 (as a benzoate derivative: δ 5.53 ppm) in the ^{13}C NMR spectra.[7] The authentic sample of the latter was prepared from 5 by a specific inversion (Mitsunobu reaction).[8]

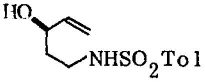
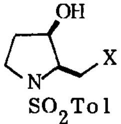
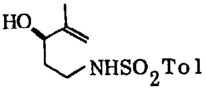
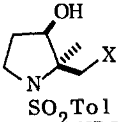
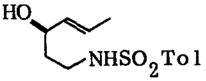
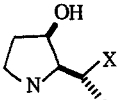
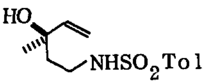
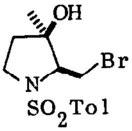
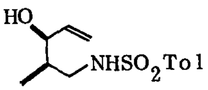
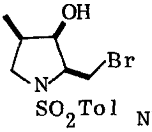
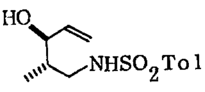
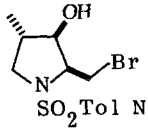
Although being successful with unsubstituted carbamate, the iodoamidation with substituted carbamate 4 (R = OMe, R^1 = Me) was troubled with instability of the product. As judged from ^1H NMR spectrum and TLC monitoring of the crude extract, the clean intramolecular iodoamidation is apparent, but the product decomposed gradually at ambient temperature to provide some polar material (TLC).[9]

Despite our extensive examinations, the intramolecular haloamidatoin of the amide derivatives 4 (R = Me or Ph, R^1 = Me) was totally unsuccessful. Under the above and somewhat modified conditions, no cyclization took place, instead iodohydrines were obtained in quantitative yield. Under anhydrous conditions, these amides were unreactive and recovered completely (I_2 in CH_3CN, N-iodosuccinimide in THF in the presence or absence of ^tBuOK).

It has been frequently pointed out that the course of the reaction and the yields of this type of olefin amidation is a subject of the basicity of amines.[10] And hence next we examined the haloamidation with p-toluenesulfonamide derivatives. All the sulfonamides, irrespectively of the substitution pattern, were cyclized to give rise to the expected N-toluenesulfonyl cis-1-halomethyl-2-hydroxypyrrolidines in high selectivity and in high yield. Results, together with the reaction conditions, were summarized in Table I. All the products were stable and could be purified by means of preparative TLC. Compared with the carbamate derivatives 4 (R = OMe), the reaction with sulfonamides was much faster and attained completion in short periods of reaction time even at the temperatures lower than ambient temperature. The reaction can be successfully undertaken both in aqueous media (dimethoxyethane-H_2O or Et_2O-H_2O (two phase)) and in anhydrous media (dichloromethane), while in acetonitrile considerable amount of by-product(s) was detected on TLC.

We are now under extensive study on a clarification of scope of the present reaction and

Table I. Halosulfoamidation of N-p-Toluenesulfonyl 3-Hydroxy-4-pentenamides

substrate	main product	reaction conditions[a] (equiv)	product ratio[b] cis/trans	yield of[c] products
		NBS (1.1), DME-H_2O, - 5 °C, 1 h	95 : 5	88
		I_2 (1.5), $NaHCO_3$ (1.5), Et_2O-H_2O, - 5°C, 4 h	96 : 4	86
		I_2 (1.1), CH_3CN, 0 °C, 2 h	94 : 6	53[d]
		NBS (1.1), DME-H_2O, r.t., 5 min	90 : 10	56
		NBS (1.1), DME-H_2O, - 50 °C, 1 h	95 : 5	95
		NBS (1.1), CH_2Cl_2, - 78 °C, 2 h	93 : 7	100
		NIS (1.1), CH_2Cl_2, - 50 °C, 4 h	89 : 11	100
		NBS (1.1), DME-H_2O, - 5 °C, 15 min	94 : 6	82
		I_2 (1.5), $NaHCO_3$ (1.5), Et_2O-H_2O, - 5 °C, 4 h	95 : 5	91
		NBS (1.1), DME-H_2O, 0 °C, 1 h	97 : 3	77[d]
		NBS (1.1), DME-H_2O, 0 °C, 1 h	97 : 3	80
		NBS (1.1), DME-H_2O, 0 °C, 1 h,	97 : 3	82

a) Reaction conditions are given in the following order: reagents (equiv to substrate in parenthesis), solvent, bath temperature, and reaction time. NBS = N-Bromosuccinimide, NIS = N-Iodosuccinimide, DME = 1,2-Dimethoxyethane. DME-H_2O = DME (5 mL) and H_2O (2 mL) to 1 mmol of substrate. Et_2O-H_2O = ether (5 mL) and H_2O (2 mL) to 1 mmol of substrate. Acetonitrile and dichloromethane were dried over P_2O_5 and CaH_2, respectively. h = hour, min = minute. b) Product ratio was determined based on the area intensity in carbon-13 NMR spectra. c) Yield (%) refers to the isolated and chromatographically pure materials. d) Single spot was detected at the larger rf value than those of the listed compounds. The structure of this product is under investigation.

its mechanism. Short total syntheses of 1, 2, and the related alkaloids are also our strong concern.[11]

References and Notes

1) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z. J. Am. Chem. Soc., 1983, 105, in press.

2) (a) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. J. Am. Chem. Soc., 1981, 103, 4114. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P. Tetrahedron Lett., 1981, 22, 4611. (c) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. J. Am. Chem. Soc., 1983, 105, 5819.

3) Schumacher, D. P.; Hall, S. S. J. Am. Chem. Soc., 1982, 104, 6076.

4) (a) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. J. Am. Chem. Soc., 1983, 105, 4096. (b) Chamberlin, A. R.; Chung, J. Y. L.; Ibid., 1983, 105, 3635. (c)Stevens, R. V. in "The Total Synthesis of Natural Products", Vol. 3, ApSimon, J., Ed.; John Wiley & Sons, Inc., New York, 1977.

5) Gobao, R. A.; Bremmer, M. L.; Weinreb, S, M. J. Am. Chem. Soc., 1982, 104, 7065.

6) All the amino alcohols appeared in this paper were prepared by an cross aldol of lithium salt of nitriles with unsaturated aldehydes or ketone (THF, - 78 °C), followed by a reduction with excess $LiAlH_4$ in ether.

7) Levy, G. C.; Lichter, R. L.; Nelson, G. N. "Carbon-13 NMR Spectroscopy", 2nd Ed.; John Wiley & Sons, New York, 1980.

8) Mitsunobu, O. Synthesis, 1981, 1.

9) Quite recently we have found that O-acetyl derivative of 4 (R = OMe, R^1 = Me) was iodoamidated to provide O-acetyl derivatives of 5 and 6 in a ratio of ca. 7 : 1 (ca. 50% conversion at ambient temperature for 4 days). These products were stable enough for preparative TLC and storable at room temperature without noticeable decomposition.

10) (a) Biloski, A. J.; Wood, R. D.; Ganem, B. J. Am. Chem. Soc., 1982, 104, 3233. (b) Hegedus, L. S.; McKearin, J. M. Ibid., 1982, 104, 2444. (c) Danishefsky, S.; Taniyama, E.; Webb, R. R., II, Tetrahedron Lett., 1983, 24, 11. (d) Kozikowski, A. P.; Scripko, J. Ibid., 1983, 24, 2051.

11) We acknowledge partial supprot for this work provided by the Ministry of Education, Science and Culture, the Japanese Government (Grant-in-Aid for Special Project Research No. 57118006 and Scientific Research B No. 58470066).

(Received in Japan 26 November 1983)