

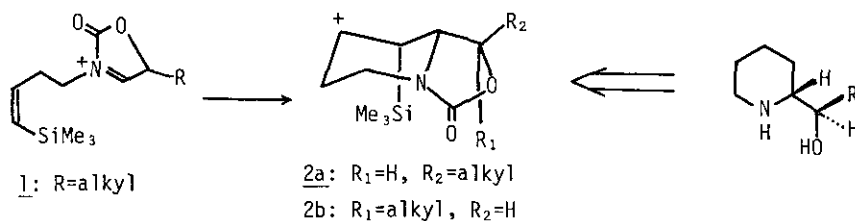
A DIASTERESELECTIVE SYNTHESIS OF THREO 2-(α -HYDROXYALKYL)PIPERIDINES
VIA OXACARBAMOYLIMINIUM ION-(Z)-VINYLSILANE CYCLIZATION

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Abstract — Reduction of 5-alkyl-N-(Z-4-silyl-3-butenyl)oxazolidine-2,4-diones (5a,b) with NaBH₄, followed by cyclization with TiCl₄ afforded the corresponding 1,8a-trans-1-alkyl-1,5,6,8a-tetrahydro-3H-oxazolo[3,4-a]pyridines (9a,b), respectively, with high diastereoselectivity. Catalytic hydrogenation of 9a, followed by alkaline hydrolysis gave threo 2-(α -hydroxyethyl)piperidine (12a). In a similar fashion, threo 2-(α -hydroxypropyl)piperidine (12b), ($\pm$)- β -conhydrine, was obtained from 9b.

π Cyclization of N-acyliminium ions has been documented as an important method for a synthesis of a wide variety of heterocyclic systems.¹ Such cyclizations have been found to achieve remarkable stereocontrol.^{1,2} The use of vinylsilanes as terminators for cationic cyclizations has been applied to a regiocontrolled synthesis of unsaturated azaheterocycles.³ In connection with our interest in a diastereoselective synthesis of α -(α' -hydroxyalkyl)-N-heterocycles,⁴ we have examined the cationic cyclizations of oxacarbamoyliminium ion-(Z)-vinylsilane systems (1), in the expectation that cyclization proceeds with high diastereoselectivity through the intermediate (2a) rather than 2b which have significant steric repulsion between trimethylsilyl and R₁ group. (See Scheme 1). The method would also provide a promising route to threo 2-(α -hydroxyalkyl)-piperidines. The results of our studies are described in this paper.

Scheme 1

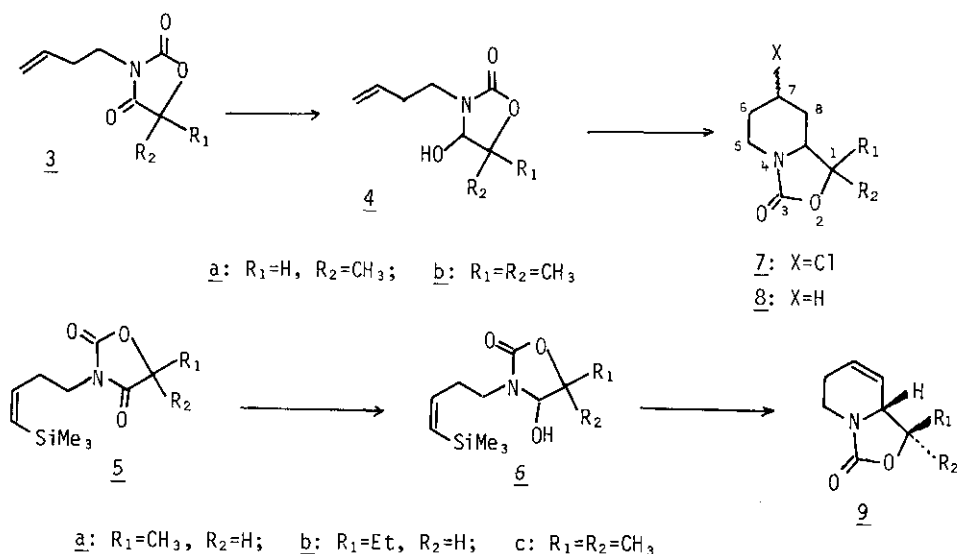


The N-butenyl- (4a,b) and N-(Z-4-trimethylsilyl-3-butenyl)-4-hydroxyoxazolidin-2-ones (6a-c) required for the formation of oxacarbamoyliminium ions were prepared as follows. Condensation of 3-buten-1-ol with 5-substituted oxazolidine-2,4-diones⁵ by an application of Mitsunobu's method⁶ afforded 3a,b. In a similar way, 5a-c were prepared by using (Z)-4-trimethylsilyl-3-buten-1-ol^{3b} and 5-substituted oxazolidine-2,4-diones.⁵ Reduction of 3a,b and 5a-c with NaBH₄ (methanol, 0°C) afforded the corresponding 4-hydroxy derivatives (4a,b) and (6a-c), respectively.

First, we examined the cyclization of 6a whether the reaction proceeded with diastereoselectivity with regard to the stereochemistry of 1-alkyl and 8a-H. Treatment of 4a with TiCl₄ (2 equiv., CH₂Cl₂, reflux, 2 h) gave 7a in 58 % yield. Dechlorination of 7a (n-Bu₃SnH, AIBN, benzene, reflux, 3 h) yielded 8a as a mixture of diastereomers in a ratio of ca 1:1.⁷ Cyclization of 4b under the same conditions yielded 7b, in 65 % yield, mp 55-59°C, dechlorination of which afforded 8b,⁸ mp 64-66°C.

Next, we explored the diastereoselective synthesis of 1,8a-trans-1-alkyl-1,5,6,8a-tetrahydro-3H-oxazolo[3,4-a]pyridines. Treatment of 6a with TiCl₄ yielded the desired cyclization product (9a)⁸ in 65 % yield, bp 122-124°C (3 torr), as a single diastereomer. Under the same conditions, 1-ethyl analogue (9b)⁸ was obtained from 6b in 70 % yield, bp 125-128°C (3 torr). In the case of 6c, the desired cyclization product (9c) was not obtained but 7b was obtained in 22 % yield. Formation of 7b from 6c can be accounted for by predominant protonation-desilylation prior to cyclization because of steric repulsion between trimethylsilyl and methyl group in the intermediate (2: R₁=R₂=CH₃).

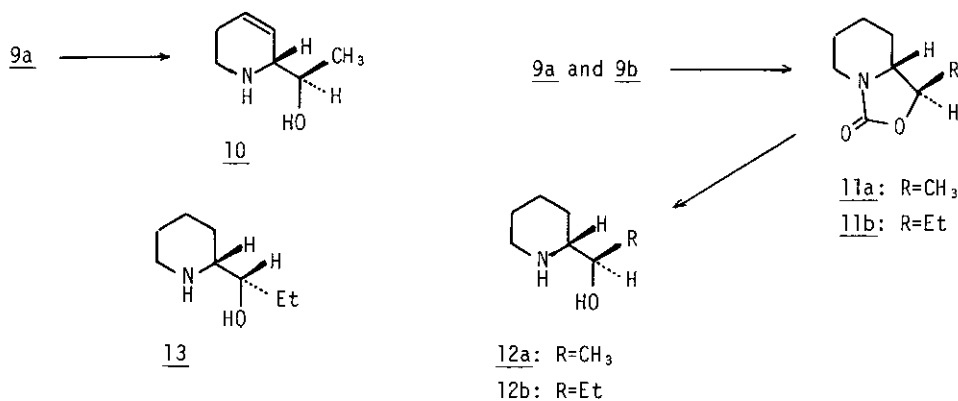
Scheme 2



Cleavage of oxazolidinone ring of 9a was carried out by heating with 10 % NaOH-EtOH (reflux, 2 h) to give 10⁸ in 88 % yield. Catalytic hydrogenation of 9a and 9b over Pt catalyst afforded 11a,⁸ mp 54-56°C, and 11b,⁸ mp 56-58°C, in nearly quantitative yield, respectively. Hydrolysis of 11a (10 % NaOH-EtOH, reflux, 2 h) afforded 88 % yield of 12a. In a similar fashion, threo 2-(α -hydroxypropyl)piperidine (12b) was obtained by hydrolysis of 11b, in 85 % yield, mp 87-88°C (lit.⁹ 87-88°C), which was identical with ($\pm$)- β -conhydrine [threo 2-(α -hydroxypropyl)piperidine], provided from professor Michael Vaultier. The product was not identical with ($\pm$)- α -conhydrine (13),⁹ erythro isomer, also donated from Professor Michael Vaultier.

As mentioned above, a facile diastereoselective synthesis of threo 2-(α -hydroxyalkyl)piperidine derivatives was achieved. The method would also be applicable to a synthesis of a variety of 2-substituted 1,2,5,6-tetrahydropyridine derivatives.

Scheme 3



ACKNOWLEDGMENT

The authors are deeply grateful to Professor Michael Vaultier, Université de Rennes, France, for the gifts of samples, ¹H NMR and ¹³C NMR spectra of ($\pm$)- α -conhydrine and ($\pm$)- β -conhydrine.

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7. The ratio was determined based on the signals due to 1-CH₃ (δ 1.30 and 1.37, each d, $J=6.5$ Hz) and 1-H (δ 3.98-4.28 and 4.48-4.78, each m) in its ¹H NMR (CDCl₃) spectrum.
8. All new compounds gave satisfactory microanalysis and spectral data. Selected spectral data are as follows. Only characteristic signals are given for ¹H NMR spectra.
8b: ¹H NMR (CDCl₃) δ 1.32 (3H, s), 1.43 (3H, s), 2.60-2.92 (1H, m), 3.22 (1H, dd, $J=3$ and 9 Hz), 3.86 (1H, dd, $J=4$ and 12 Hz), IR (CHCl₃) 1740 cm⁻¹.
9a: ¹H NMR (CDCl₃) δ 1.43 (3H, d, $J=6$ Hz), 2.80-3.12 (1H, m), 3.70-4.31 (3H, m), 5.57 (1H, broad d, $J=10$ Hz), 5.82-6.00 (1H, m), IR (CHCl₃) 1738 cm⁻¹.
10: ¹H NMR (CDCl₃) δ 1.37 (3H, d, $J=6$ Hz), 1.92-2.19 (2H, m), 2.72-3.13 (3H, m), 3.42-3.72 (1H, m), 5.65 (1H, dd, $J=2$ and 11 Hz), 5.79-6.02 (1H, m), CI Mass m/z 128 (M⁺).
11a: ¹H NMR (CDCl₃) δ 1.37 (3H, d, $J=6$ Hz), 2.57-2.88 (1H, m), 3.00-3.22 (1H, m), 3.77 (1H, dd, $J=4$ and 12 Hz), 3.92-4.20 (1H, m), IR (CHCl₃) 1735 cm⁻¹, CI Mass m/z 156 (M⁺+1).
11b: ¹H NMR (CDCl₃) δ 1.00 (3H, t, $J=7$ Hz), 2.63-2.93 (1H, m), 3.10-3.32 (1H, m), 3.73-4.08 (2H, m), IR (CHCl₃) 1740 cm⁻¹, CI Mass m/z 170 (M⁺+1).
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