A DIASTEREOSELECTIVE SYNTHESIS OF *threo* 2-(α-HYDROXYALKYL)PIPERIDINES VIA OXACARBAMOYLIMINIUM ION-(*Z*)-VINYLSILANE CYCLIZATION

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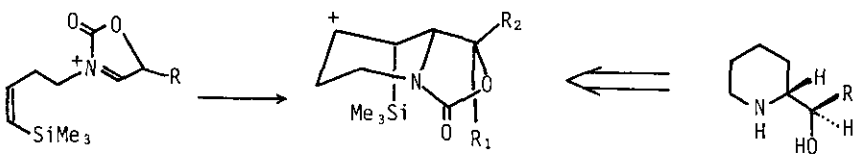
Abstract —— Reduction of 5-alkyl-N-(*Z*-4-silyl-3-butenyl)oxazolidine-2,4-diones (5a,b) with $NaBH_4$, followed by cyclization with $TiCl_4$ afforded the corresponding 1,8a-*trans*-1-alkyl-1,5,6,8a-tetrahydro-3*H*-oxazolo[3,4-a]pyridines (9a,b), respectively, with high diastereoselectivity. Catalytic hydrogenation of 9a, followed by alkaline hydrolysis gave *threo* 2-(α-hydroxyethyl)piperidine (12a). In a similar fashion, *threo* 2-(α-hydroxypropyl)piperidine (12b), (±)-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 R_1 group. (See Scheme 1). The method would also provide a promissing route to *threo* 2-(α-hydroxyalkyl)-piperidines. The results of our studies are described in this paper.

Scheme 1



1: R=alkyl

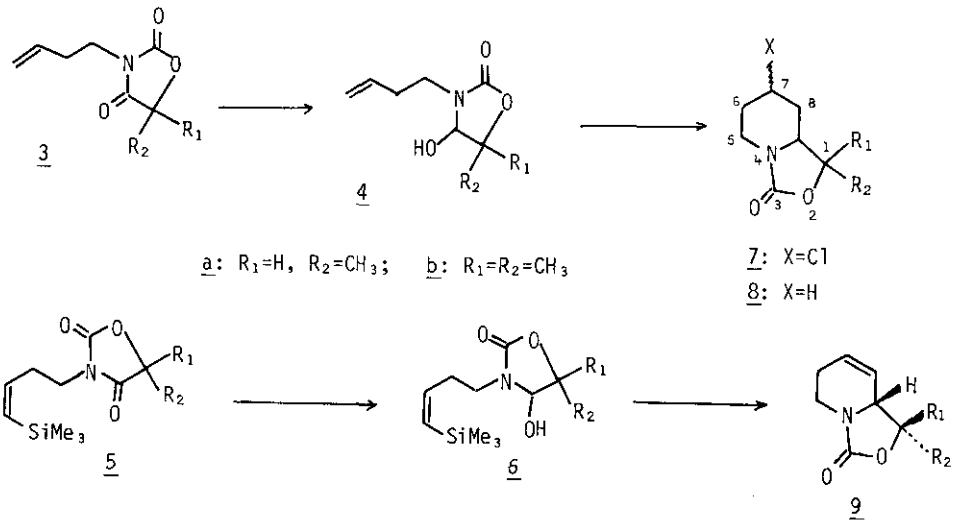
2a: R_1=H, R_2=alkyl
2b: R_1=alkyl, R_2=H

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-diones[5] by an application of Mitsunobu's method[6] 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 $NaBH_4$ (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 $TiCl_4$ (2 equiv., CH_2Cl_2, reflux, 2 h) gave 7a in 58 % yield. Dechlorination of 7a (n-Bu_3SnH, 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 $TiCl_4$ 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: R_1=R_2=CH_3).

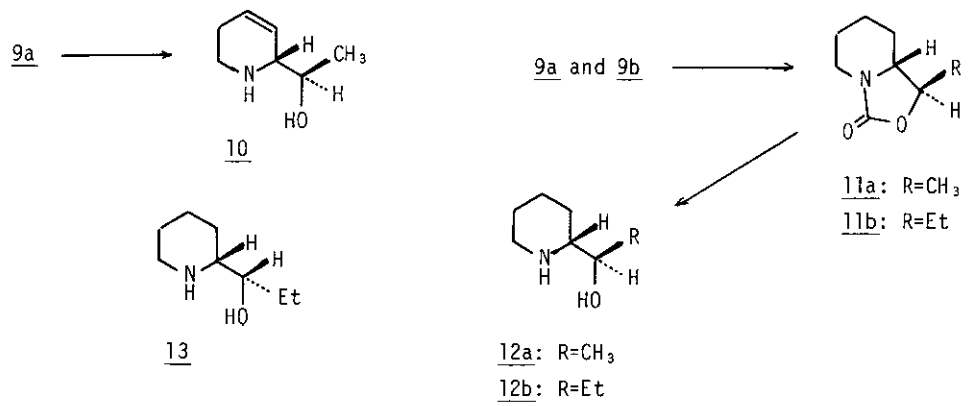
Scheme 2



Cleavage of oxazolidinone ring of 9a was carried out by heating with 10 % NaOH-EtOH (reflux, 2 h) to give 10[8] 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 (±)-β-conhydrine [threo 2-(α-hydroxypropyl)piperidine], provided from professor Michael Vaultier. The product was not identical with (±)-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



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7. The ratio was determined based on the signals due to 1-CH_3 (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 ^{1}H NMR ($CDCl_3$) spectrum.
8. All new compounds gave satisfactory microanalysis and spectral data. Selected spectral data are as follows. Only characteristic signals are given for ^{1}H NMR spectra.

   8b: ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 1740 cm^{-1}.

   9a: ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 1738 cm^{-1}.

   10: ^{1}H NMR ($CDCl_3$) 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: ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 1735 cm^{-1}, CI Mass m/z 156 (M^++1).

   11b: ^{1}H NMR ($CDCl_3$) 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 ($CHCl_3$) 1740 cm^{-1}, CI Mass m/z 170 (M^++1).
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