DIASTEREOSELECTIVE SYNTHESIS OF 2,6-DISUBSTITUTED 3-HYDROXYPIPERIDINE, 2-(α-HYDROXYALKYL)-3-HYDROXYPIPERIDINE AND 2-(α-HYDROXYALKYL)-3-HYDROXYPYRROLIDINE DERIVATIVES

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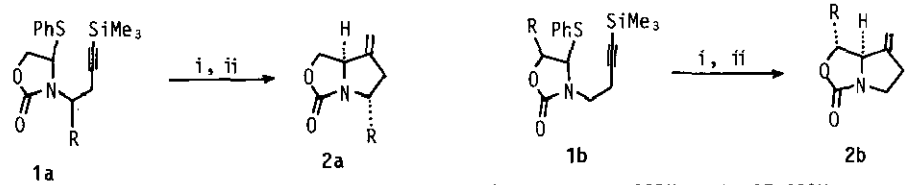
Abstract —— Reduction of 5-substituted 5,8a-trans-oxazolo[3,4-a]pyridin-8-ones (**7a,b**), obtained by an application of α-acylamino radical cyclization at the initial stage, with $NaBH_4$ and K-Selectride was found to proceed with complete stereocontrol in all cases. Reduction of 1-substituted 1,8a-trans-oxazolo[3,4-a]pyridin-8-one (**7c**) and pyrrolidine analogue (**10**) with $NaBH_4$ and K-Selectride was also found to proceed with high diastereoselectivity.

In the previous paper,[1] we reported the diastereoselective synthesis of 1- and 5-substituted tetrahydropyrrolo[1,2-c]oxazoloes (**2a,b**) from **1a,b** by an application of α-acylamino radical cyclization.[2]

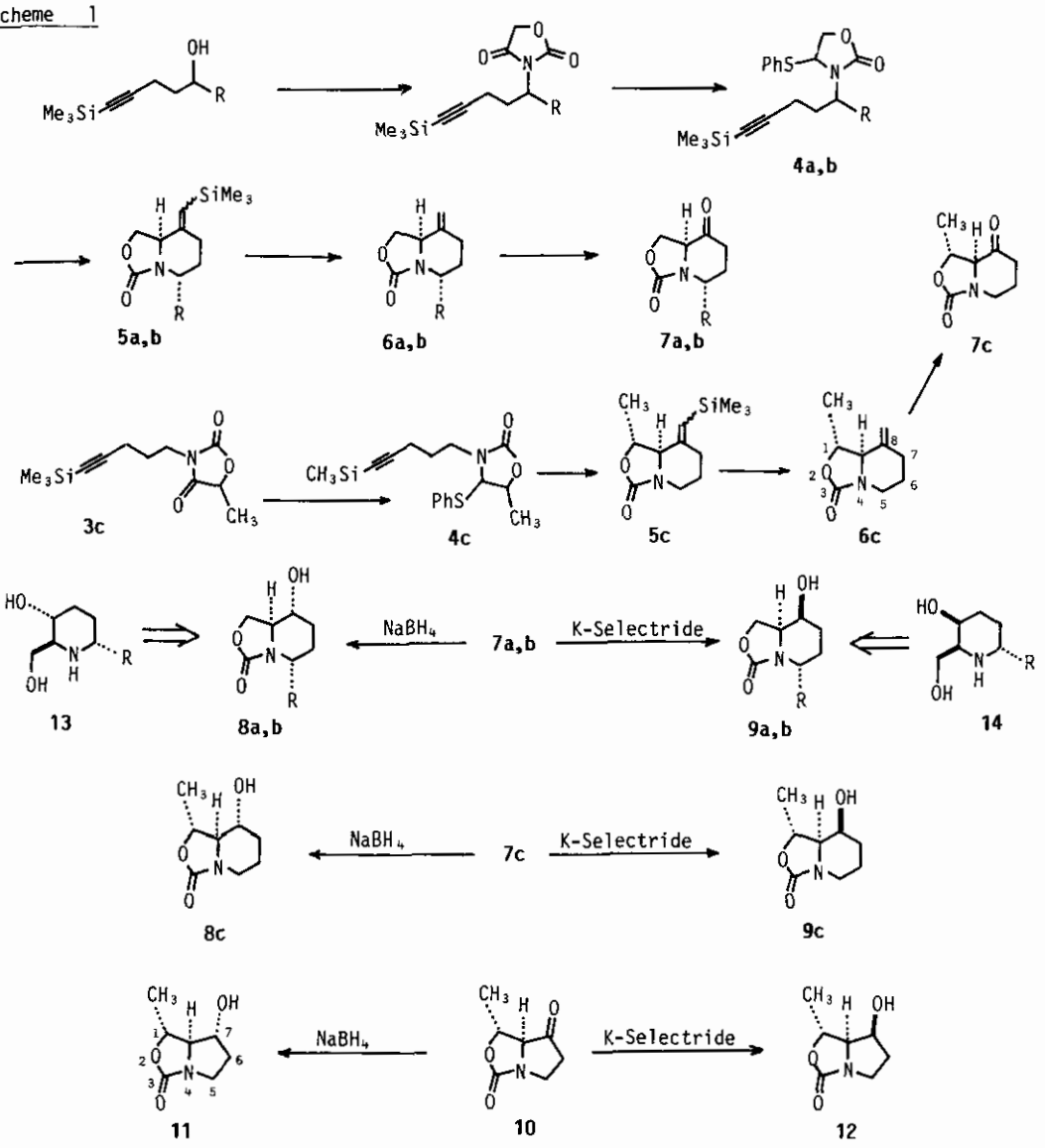


i. n-Bu_3SnH, AIBN ii. CF_3COOH

The method was extensively applied to a diastereoselective synthesis of 1- and 5-substituted 8-methyleneoxazolo[3,4-a]pyridine derivatives (**6a-c**),[3] which were easily converted to the corresponding 8-oxo derivatives (**7a-c**), respectively. As part of our study on a diastereoselective synthesis of 2,3,6-trisubstituted piperidine derivatives (**13, 14**), which would be interesting from both synthesis and biological evaluation as exemplified by prosopis piperidine alkaloids,[4] we examined the reduction of **7a,b** with $NaBH_4$ and K-Selectride. These reactions were found to proceed with complete stereocontrol to give **8,9**. Reduction of **7c**, and **10** gave the corresponding alcohols, potentially useful intermediates for a preparation of the corresponding 3-hydroxy-2-(α- hydroxyalkyl)piperidine and pyrrolidine analogues. The results are herein described. (See Scheme 1)

At the first stage, 4-phenylthiooxazolidin-2-ones (**4a-c**),[5] used for generation of the radical species, were prepared by an application of the method reported previously[1] as outlined in the Scheme 1. Condensation of oxazolidine-2,4-dione with corresponding silylated alcohols by the

Scheme 1



For **3-9** **a:** R=CH_3; **b:** R=n-Pr

Mitsunobu's method[6] (Ph_3P, i-PrOCON=NCOO-i-Pr, THF) afforded **3a,b**. Reduction of **9a,b** with $NaBH_4$, followed by treatment with diphenyl disulfide in benzene in the presence of tri-n-butylphosphine yielded **4a,b**. In a similar way, **3c**, obtained by condensation of 5-methyloxazolidine-2,4-dione and 5-trimethylsilylpentyn-1-ol, was converted to **4c** through reduction with $NaBH_4$ and subsequent replacement of the hydroxy group with phenylthio group.

Benzene solution of **4a-c** (0.01-0.02 M solution) was heated in the presence of tri-n-butyltin hydride (1.3 equiv.) and AIBN by the usual way[1,2] to give the corresponding oxazolo[3,4-a]pyridine derivatives (**5a-c**) as a mixture of E- and Z-isomers (**5a**, 72 %; **5b**, 70 %; **5c**, 68 % yield). Desilylation of **5a-c** with CF_3COOH-CH_2Cl_2 (1:2, room temperature, 14 h) gave nearly quantitative yields of **6a-c**, respectivley, as an oil in all cases. The relative configuration at 5-H/8a-H of **6a,b** was assigned as trans based on the observation of the signals due to 5-H around at δ 4.0 in their ^{1}H-nmr ($CDCl_3$) spectra though they were partially overlapped with signals due to 8a-H and one of 1-H_2. The presence of this lower signals due to 5-H indicates strongly that the substituent at the 5-position takes cis-relationship with 8a-H.[1] The ^{1}H-nmr spectrum of **6c** showed only one CH_3 signal at δ 1.52 (d, J=6 Hz), which is characteristic of signals due to cis-oriented CH_3 to 8a-H.[1] The magnitude of $J_{1,8a}$(=6.5 Hz) also supports the relative configuration at 1-H/8a-H to be trans. Conversion of **6a-c** to the 8-oxo derivatives (**7a-c**), an oil, was successfully achieved by ozonolysis procedure (CH_2Cl_2, -78°C, then MeSMe) in nearly quantitative yield in all cases.

Reduction of **7a-c** with $NaBH_4$ (1.5 equiv.) in methanol (0°C, 4 h and then quenched with $NaHCO_3$ aqueous solution, extract with $CHCl_3$) yielded **8a**[5] (mp 88-89°C, 87 % yield), **8b**[5] (oil, 85 % yield), and **8c**[5] (oil, 88 % yield), respectively, as a single diastereomer in all cases. The stereochemical course of the reduction is consistent with the propensity of $NaBH_4$ to reduce unhindered cyclohexanones with axial delivery of hydride to give the thermodynamically more stable products. The relative configuration at 8-H/8a-H of **8a-c** was assigned as trans on the basis of the magnitude of $J_{8,8a}$ (for **8a,b**, 9.6 Hz; for **8c**, 9.0 Hz) observed in their ^{1}H-nmr ($CDCl_3$, 400 MHz) spectra and the Dreiding model. On the other hand, reduction of **7a-c** with K-Selectride (1.5 equiv. of 1 M solution in tetrahydrofuran) in tetrahydrofuran (-78°C, 2 h and then quenched with 10 % NH_4OH, extract with $CHCl_3$) afforded **9a**[5] (mp 141-142°C, 82 % yield), **9b**[5] (mp 113-114°C, 80 % yield), and **9c**[5] (oil, 75 % yield), respectively. The relative configuration at 8-H/8a-H of **9a-c** was also determined as cis again based on the magnitude of $J_{8,8a}$ (for **9a,b**, 2.2 Hz; for **9c**, 2.1 Hz) and the Dreiding model. Upon reduction of **7a-c** with K-Selectride, hydride attacked from the less hindered side to give the thermodynamically less stable isomers. Thus, reduction of 1- and 5-substituted oxazolo[3,4-a]-pyridin-8-one with $NaBH_4$ and K-selectride was found to proceed with complete stereocontrol in both cases. Reduction of the ketone (**10**), obtained by ozonolysis of **2b** (R=CH_3)[1] in 70 % yield as an oil, with $NaBH_4$ and K-Selectride was also examined. Reduction with $NaBH_4$ afforded **11**[5] (oil, 80 % yield) whose relative configuraiotn at 7-H/7a-H was determined as trans on the basis of the magnitude of $J_{7,7a}$ (=6.2 Hz) and the Dreiding model. Reduction with K-Selectride gave **12**[5] (mp 109-110°C, 75 % yield). The magnitude of $J_{7,7a}$ (=3.2 Hz) observed in its ^{1}H-nmr ($CDCl_3$, 400 MHz) indicates the relative configuration at 7-H/7a-H to be cis. Thus reduction of **10** was found to show the similar

behaviour to that of **7c**. The routes to 1- and 5-substituted oxazolo[3,4-a]pyridin-8-ols and related compounds described here would be apparently useful for a diastereoselective synthesis of 6-substituted 3-hydroxy-2-hydroxymethylpiperidines, 2-(α-hydroxyalkyl)-3-hydroxypiperidine and pyrrolidine derivatives.

REFERENCES AND NOTES

1. S. Kano, Y. Yuasa, Y, Asami, and S. Shibuya, Chem. Lett., 1986, 735.
2. For reviws of radical chemistry including recent publications: B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds'; Pergamon: Oxford, 1986; D. P. Curran, Synthesis, 1988, 417, 489; M. Ramaiah, Tetrahedron, 1987, **43**, 3541.
3. Trimethylsilylalkynyl-α-acylamino radical cyclization: J.-K. Choi and D. J. Hart, Tetrahedron, 1985, **41**, 3959; J. M. Dener, D. J. Hart, and S. Ramesh, J. Org. Chem., 1988, **53**, 6022.
4. Recent publications on a synthesis of prosopinine and related compounds: A. B. Holmes, J. Thompson, A. J. B. Baxter, and J. Dioxon, J. Chem. Soc., Chem. Commun., 1985, 37; T. N. Birkinshaw and A. B. Holmes, Tetrahedron Lett., 1987, **28**, 813; M. A. Ciufolini, C. W. Hermann, K. H. Whitmire, and N. E. Byrne, J. Am. Chem. Soc., 1989, **111**, 3473.
5. All new compounds described in this paper gave satisfactory microanalyses (some of them were characterized by high resolution mass spectra) and ir, ^{1}H-nmr (90 and 400MHz), and mass spectra. Selected spectral data are as follows. **8a**: δ ($CDCl_3$) 1.23 (5-CH_3, d, J=7 Hz), 3.45 (8-H, ddd, J=4.2, 6.2, 9.6 Hz), 3.56 (8a-H, ddd, J=5.1, 8.0, 9.6 Hz), 4.12 (5-H, dq, J=5.9, 7.0 Hz), 4.22 (1-H, dd, J=5.1, 8.9 Hz), 4.43 (1-H, dd, J=8.0, 8.9 Hz); **8b**: δ ($CDCl_3$) 3.45 (8-H, ddd, J=4.1, 6.2, 9.6 Hz), 3.49 (8a-H, ddd, J=4.0, 7.8, 9.6 Hz), 3.93-3.87 (5-H, m), 4.25 (1-H, dd, J=4.0. 9.0 Hz), 4.42 (1-H, J=7.8, 9.0 Hz), **8c**: δ ($CDCl_3$) 1.48 (1-CH_3, d, J=6.3 Hz), 2.74 (5-H, dt, J=3.4, 12.9 Hz), 2.97 (5-H, dd, J=5.5, 9.0 Hz), 3.47 (8a-H, br s), 3.80 (5-H, dd, J=5.0, 12.9 Hz), 4.50 (1-H, dq, J=6.1, 6.3 Hz); **9a**: δ ($CDCl_3$) 1.22 (5-CH_3, d, J=7 Hz). 3.79 (8-H, br s), 3.87 (8a-H, ddd, J=2.2, 6.6, 8.8 Hz), 4.18 (5-H dq, J=6.0, 7.0 Hz), 4.30 (1-H, dd, J=8.5, 8.7 Hz), 4.36 (1-H, dd, J=6.6, 8.5 Hz); **9b**: δ ($CDCl_3$) 3.77 (5-H, br s), 3.83 (8a-H, ddd, J=2.2, 5.7, 9.5 Hz), 3.96-4.01 (5-H, m), 4.30 (1-H, dd, J=8.5, 9.5 Hz), 4.38 (1-H, dd, J=5.7, 8.5 Hz); **9c**: δ ($CDCl_3$) 1.43 (1-CH_3, d, J=6.3 Hz), 2.82 (5-H, dt, J=12.8, 3.4 Hz), 3.20 (8a-H, dd, J=2.1, 6.6 Hz), 3.86 (1H, br s), 3.89 (5H, dd, J=5.2, 12.8 Hz), 4.64 (1-H, dq, J=6.4, 6.3 Hz); **11**: δ ($CDCl_3$) 1.51 (1-CH_3, d, J=6.4 Hz), 3.38 (8-H, dd, J=4.0, 6.2 Hz), 4.56 (1-H, dq, J=4.0, 6.4 Hz); **12**: δ ($CDCl_3$) 1.49 (1-CH_3, d, J=6.5 Hz), 3.24 (5-H, ddd, J=4.5, 8.0, 10.9 Hz), 3.44 (8-H, dd, J=3.2, 3.2 Hz), 3.71 (5-H, ddd, J=8.5, 8.8, 10.9 Hz), 4.21 (7-H, br s), 4.81 (1-H, dq, J=3.2, 6.5 Hz).
6. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., 1972, **94**, 679.

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