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Synthesis of 2,2-Disubstituted 2,5-Dihydro-4-methyloxazoles.

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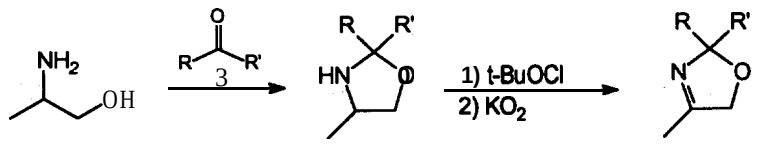
Abstract: *2,2-Disubstituted 2,5-dihydro-4-methyloxazoles (1) were synthesizedfrom 2-aminopropanol in three steps. 3-Oxazolines I can be converted into various a-sulfinyl ketimines such as (SS)-{[(4-methylphenyl)sulfinyl]methyl}-2,2-diethyl-2,5-dihydrooxazole (5) which was stereoselectively reduced with Dibal-H to give 3-hydroxy-2-aminopropyl sulfoxide 7.*

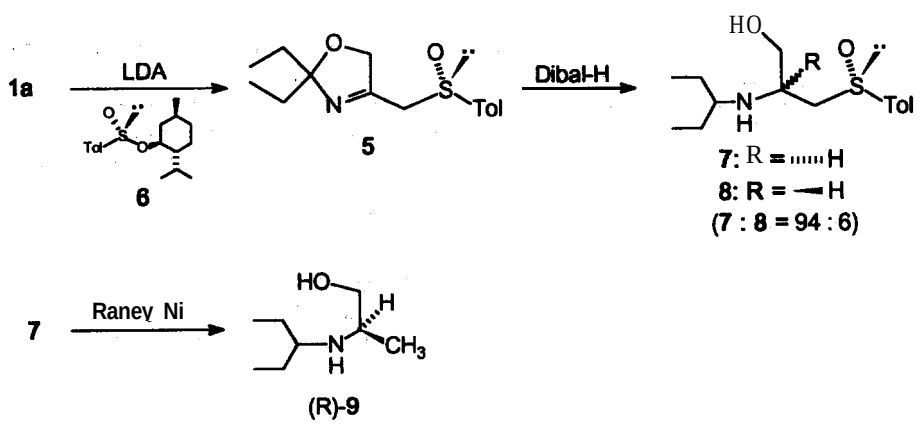
In our studies of the asymmetric total synthesis of nojirimycin' via α-sulfinyl ketimines (such as **5**),[2] we have investigated the preparation of the required precursor, 4-methyl-2,5-dihydrooxazoles (1) (or 4-methyl-3-oxazolines). Several methods have been reported for the synthesis of 2,5-dihydrooxazoles: (1) condensation of a-hydroxy ketones with ammonia and aromatic aldehydes[3] or ketones,[4] (2) thermal

Scheme 1



4a: R = R' = Et
4b: R = R' = $(CH_2)_5$
4c: R = CH_3CO, R' = cyclohexyl
4d: R = CH_3CO, R' = Ph
4e: R = CH_3CO, R' = p-NO_2-Ph

Scheme 2



decomposition of 2-diazo-1,2-diphenylethanone in the presence of diarylmethanimines,[5] (3) photocyclixation of 3-aryl-2*H*-azirines with carbonyl compounds,[6] (4) coupling of axomethine ylides with a-chloroacyl chlorides,' and (5) condensation of a-halo aldehydes with ammonia and ketones.* However, the 3-oxazolines produced from these methods contained 4-aryl group and a general method for the preparation of 4-methyl (or 4-alkyl) 3-oxazolines (such as 1) was not available. Herein, we report a synthesis of 1 from the condensation 2-aminopropanol (2)1).[9] th ketones follow

Table 1. Reaction Conditions for the Condensation of 2-Amino-1-propanol and Various Ketones, and Yields of Oxazolidines 4 and 3-Oxazolines 1.

Ketone 3 (equiv)	2-Amino-1-propanol (2) (equiv)	Solvent (temp., time)	Oxazolidine 4 (yield)'	3-Oxazoline 1 (yield)'
3-Pentanone (4.0)	(1.0)	none (50°C, 3h)	98%	61%
Cyclohexanone (1.05)	(1.0)	benzene (80°C, 4h)	83%	93%
Acetylcyclohexane (1.0)	(1.0)	benzene (80°C, 4h)	93%	90%[c]
Acetophenone (1.0)	(1.5)	benzene (80°C. 48h)	92%[b]	40%
p-Nitroacetophenonc (1.0)	(1.2)	benzene (80°C, 22h)	quantitative	79%

a. Isolated
b. Determined by ^{1}H NMR
c. Determined by ^{1}H NMR, from column chromatography only 30% of pure compound was isolated

Condensation of 2-amino-1-propanol (2) with ketones 3 in refluxing benzene (axeotropic removal of water) (with 3-pentanone; no solvent, 50°C, 3 h) gave excellent yields of the 3-oxazolidines 4. Yields and reaction conditions are summarized in Table 1. N-Chlorination of 4 with *tert*-butyl hypochlorite (1.2 equiv) and sodium bicarbonate (1.2 equiv) in ether at 0°C for 3 h immediately followed by 2.2 equiv of potassium superoxide (KO_2)[10] and a catalytic amount of 18-crown-6 in ether at 25°C gave 3-oxazolines 1 (Table 1).

3-Oxazolines 1 can be converted into various α-sulfinyl ketimines (such as 5) which can lead to the preparation of chiral β-amino alcohols, a-amino acids, piperidines, and pyrrolidines.[11] For instance, treatment of 3-oxazoline la with 2.2 equiv of LDA in THF at -78°C followed by d-(+)-(*R*)-menthyl *p*-toluenesulfinate (6) provided a 76% yield of sulfinyl ketimine 5; $[\alpha]_D^{22} = -160°$ (c 2.5, CH_2Cl_2), mp 74-75°C (Scheme 2). Interestingly, ketimine 5 can be stereoselectively reduced with Dibal-H in THF to give 65%

yield (based on recovered starting ketimine 5) of amines 7 and 8 in a ratio of 94:6,[12] along with small amount of the sulfide derivative of 5. The absolute configuration at C-2 of 7 was determined by converting it into (*R*)-(-)-2-[(1-ethylpropyl)amino]-1-propanol [(*R*)-9][13] by desulfurization with Raney nickel in EtOH under 1 atm. of hydrogen.

The following experimental procedure for the preparation of 3-oxazoline 1a from amino alcohol 2 and 3-pentanone is representative.[14]

A solution of 2.4 g (0.032 mol) of 2-amino- I-propanol(2) and 11 g (0.128 mol) of 3-pentanone was heated at 50°C under argon for 3 h. Most of the excess 3-pentanone was removed by distillation at 60°C/200 mm Hg (85°C bath temperature) and the remaining trace of the material was removed under reduced pressure (30 mm Hg) at 50°C bath to leave 4.47 g (98% yield) of oxaxolidine 4a as an oil. This material was used in the next step without further purification. An analytical sample can be obtained by distillation, bp 50°C/20 mm Hg: ^{1}H NMR ($CDCl_3$; 400 MHz) δ 3.95 (dd, *J* = 7.4, 6.5 Hz, 1 H, CHO), 3.4 (m, 1 H, CHN), 3.1 (dd, *J* = 8.6, 7.4 Hz, 1 H, CHO), 1.65 (m, 3 H, CH,, NH), 1.55 (q, *J* = 7.4 Hz, 2 H, CH_2), 1.2 (d, *J* = 6.3 Hz, *Me*), 0.93 (t, *J* = 7.4 Hz, 3 H, Me), 0.88 (t, *J* = 7.4 Hz, 3 H, Me); ^{13}C NMR (CDCl,) 8 99.7 (s, CNO), 72.6 (t, CH_2O), 53.3 (d, CHN), 302. (t), 30 (t), 17.5 (q), 8.9 (q), 8.12 (q). To a cold (0°C) mixture of 17.9 g (0.125 mol) of oxaxolidine 4a and 12.4 g (0.148 mol) of $NaHCO_3$ in 400 mL of ether under argon, was added slowly a cold (0°C) solution of 5.97 g (0.147 mol) of *t*-BuOCl in 100 mL of ether via catmula. The mixture was stirred at 0°C for 3 h, filtered through Celite, and the filtrate concentrated on a rotary evaporator. The ^{1}H NMR spectrum of the oily product obtained indicated it was the desired *N*-chloro oxaxolidine. This oil was dissolved in 500 mL of ether under argon, and 19.12 g (0.269 mol) of KO_2 and 0.4 g (1.5 mmol) of 18-crown-6 were added. After the mixture was stirred at 25°C for 12 h, the solvent (ether) was removed by distillation under normal pressure and the product obtained by distillation under reduced pressure to give 11.5 g (65% yield) of 1a; bp 57°C/23 mm Hg; ^{1}H NMR (CDCl,) δ 4.5 (s, 2 H, CH_2O), 2.0 (s, 3 H, Me), 1.6 (m, 4 H, 2 CH_2), 0.8 (t, *J* = 7.4 Hz, 6 H, 2 Me); ^{13}C NMR (CDCl,) 8 167.6 (s), 77.5 (t, CO), 31.6 (t, 2 C), 15.5 (q), 7.4 (q, 2 C).

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9. A similar scheme for the preparation of 2,5-dihydro-4-methyl-5-phenyloxazole from norephedrine and aqueous formaldehyde has been reported. Although reaction conditions are different: Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y.; Gould, I. R. *J. Am. Chem. Soc.* **1986**, *108*, 6739.
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11. This work will be published in due course.
12. When 5 was reduced with 2 equiv of $NaCNBH_3$-AcOH in CH_2Cl_2, a I: 1 ratio of 7 and 8 (99% yield) were formed; in contrary, with $LiEt_3BH$ in THF at -78°C (40 h) and 0°C (12 h), a 2:9 ratio of 7 and 8 were obtained. Pure 7: $[\alpha]_D^{22} = -141.6°$ (c 0.75. CH_2Cl_2); ^{1}H NMR (CDCI,) δ 7.52 (d, *J* = 8 Hz, 2 H, Ar),

7.33 (d, J = 8 Hz, 2 H, Ar), 3.73 (dd, J = 11, 5 Hz, 1 H, CHO), 3.59 (dd, J = 11, 4 Hz, 1 H, CHO), 3.26 (m, 1 H, CHN), 2.95 (dd, J = 13, 5 Hz, 1 H, CHS), 2.88 (dd, J = 13, 6 Hz, 1 H, CHS), 2.42 (s, 3 H, *p*-Me), 2.37 (m, 1 H, CHN), 1.7 (broad s, 2 H, OH, NH), 1.5~1.35 (m, 4 H, 2 CH,), 6.88 (t, J = 7 Hz, 3 H, Me), 0.85 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 141.6 (s, Ar), 140.3 (s, Ar), 130.0 (d. Ar), 124.0 (d, Ar), 63.39 (t, CO), 61.22 (t, CS), 57.29 (d, CN), 52.9 (d, CN). 26.28 (t), 26.2 (t), 21.3 (q, p-Me), 9.87 (q), 9.68 (q). Pure 8: $^{22}CH_2Cl_2$); ^{1}H ($CDCl_3$) δ J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 2 H), 3.71 (dd, J = 11, 4 Hz, 1 H, CHO), 3.46 (dd, J = 11, 4 Hz, 1 H, CHO), 3.25 (m, 1H, CHN), 2.87 (m, 2 H, CS), 2.47 (m, 1 H, CHN), 2.42 (s, 3 H,p-Me). 1.8 (br. s, 2 H, OH, NH), 1.5 ~ 1.3 (m, 4 H, CH_2), 0.91. (t, J = 7 Hz, 3 H, Me), 0.9 (t, J = 7 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 141.6 (s, 2 C), 130.1 (d, 2 C), 123.93 (d, 2 C). 63.47 (t, CO), 61.74 (t, CS), 57.3 (d, CN), 51.97 (d, CN), 26.47 (t. CH_2), 26.16 (t), 21.37 (q, *p*-Me), 9.93 (q), 9.9 (q).

13. Antipode (*S*)-9 was unequivocally synthesized from (*S*)-(+)-2-amino-1-propanol with 3-pentyl mesylate and K_2CO_3.

14. Oxazolidines 4b ~ e were prepared by refluxing 2 and ketones 3b ~ e in benzene for the periods of time indicated in Table 1 and azeotropically removing H_2O. After the reactions were completed, benzene was removed by distillation under reduced pressure. **4b:** bp 35°C/0.2 mm Hg; ^{1}H NMR ($CDCl_3$) δ 3.95 (dd, J = 7.6 Hz, 6.4 Hz, 1 H, CHO), 3.48 (m, 1 H, CHN), 3.14 (dd, J = 8.4 Hz, 7.6 Hz, 1 H, CHO), 1.64-1.53 (m, 10 H), 1.22 (d, J = 7.2 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$) δ 96.3 (s), 71.6 (t, CO), 52.8 (d, CN), 37,6 (t), 35.8 (t), 25.3 (t), 23.9 (t), 23.5 (t), 17.8 (q). lb: bp 33~35°C/1 mm Hg; IR (neat) ν 1664 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.48 (s, 2 H, CH_2O), 2.02 (s, 3 H, Me), 1.7~1.58 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 166.8 (s, C=N), 110.5 (s), 75 (t, CO), 36.3 (t. 2 C), 24.95 (t), 23.2 (t, 2 C), 15.8 (q). **4c:** bp 45°C/0.2 mm Hg; ^{1}H NMR ($CDCl_3$) δ (2 stereoisomers in a ratio of 48:52) 3.94 (dd, J = 7.5, 6.7 Hz, 1 H, CHO, 2 isomers), 3.5 ~ 3.2 (m, 1 H, CHN), 3.12 (dd, J = 8.5, 7.5 Hz, 1 H, CHO, 1 isomer), 2.99 (dd, J = 8.5, 7.5 Hz, 1 H, CHO, 1 isomer), 1.9 ~ 1.0 (m, 11 H), 1.23 (d, J = 5.3 Hz, 3 H, Me, 1 isomer), 1.18 (s, 3 H, Me, 2 isomers), 1.17 (d, J = 5.4 Hz, 3 H, Me, 1 isomer); ^{13}C NMR ($CDCl_3$) δ (2 isomers) 99.3 (s), 72.2, 72.03 (t, CH_2O), 53.6, 53.03 (d, CHN). 48.16, 46.72 (d), 28.6, 28.35 (t), 28.06, 27.84 (t), 26.48, 26.38 (t). 22.87.22.12 (q), 17.87, 17.08 (q). **1c:** IR (neat) v 1674 (C=N) cm"; ^{1}H NMR (CDCI,) δ 4.51 (d, J = 14 Hz, 1 H, CHO), 4.41 (d, J = 14 Hz, 1 H, CHO). 2.03 (s, 3 H, Me), 1.76 ~ 1.6 (m, 6 H), 1.32 (s, 3 H, Me), 1.2 ~ 1.0 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 166.92 (s, C=N), 113.84 (s), 77.0 (t, CH_2O), 47.31 (d), 27.16 (t), 26.92 (t), 26.29 (CH_2, CH,), 23.47 (q, Me). **4d:** ^{1}H NMR (CDCI,) δ (2 stereoisomers in a ratio of 60:40) 7.6 ~ 7.56 (m, 2 H, Ph), 7.5 ~ 7.24 (m, 3 H, Ph), 4.14 (dd, J = 7.5, 6.5 Hz, 1 H, CHO, minor isomer), 3.83 (t, J = 7.1 Hz, 1 H, CHO, major isomer), 3.6 (m, 1 H, CHN, minor isomer), 3.29 (t, J = 7.1 Hz, 1 H, CHO, major isomer), 3.14 (m, 1 H, CHN, major isomer), 3.19 (dd, J = 8.1, 7.5 Hz, 1 H, CHO, minor isomer), 1.99 (broad s, 1 H, NH), 1.65 (s, 3 H, Me, major isomer), 1.60 (s, 3 H, Me, minor isomer), 1.24 (d, J = 6.2 Hz, 3 H, Me, minor isomer), 1.15 (d, J = 6.2 Hz, 3 H, Me, major isomer); ^{13}C NMR (CDCI,) δ 132.5 (s, Ph), 128.2, 128.0 (d, Ph), 127.13 (d, Ph), 125.7, 124.9 (d, Ph), 97.74 (s, CNO), 72.61, 72.0 (t. CH_2O), 53.84, 53.32 (d, CHN), 29.41.29.01 (q. Me), 17.98, 17.63 (q, Me). **Id:** IR (neat) ν 1661 (C=N) cm^{-1}; ^{1}H NMR (CDCI,) δ 7.57 ~ 7.52 (m, 2 H), 7.39 ~ 7.27 (m, 3 H), 4.70 (d, J = 14 Hz, 1 H, CHO), 4.53 (d, J = 14 Hz, 1 H, CHO), 2.07 (s, 3 H, Me), 1.74 (s, 3 H. Me); ^{13}C NMR ($CDCl_3$) δ 167.6 (s, C=N), 144.23 (s, Ph), 128.3 (d, Ph), 127.4 (d, Ph), 125.0 (d, Ph), 112 (s, CNO), 76.37 (t, CO), 29.17 (q. Me), 15.89 (q, Me). **4e:** mp 48 ~ 49%; ^{1}H NMR ($CDCl_3$) δ [2 stereoisomers in a ration of 2: 1 (trans:cis)] 8.15 (d, J = 9 Hz, 2 H, Ar), 7.75 (d. J = 9 Hz, 2 H, Ar), 4.13 (dd, J = 8, 6.8 Hz, 1 H, CHO, cis), 3.82 (t, J = 7 Hz, 1 H, CHO, trans), 3.6 ~ 3.5 (m, 1 H, CHN), 3.29 (dd, J = 7.9, 7 Hz, 1 H, CHO, trans), 3.17 (t, J = 7, 8 Hz, 1 H, CHO, cis), 3.1 (broad s, 1 H, NH), 1.63 (s, 3 H, Me, trans), 1.58 (s, 3 H, Me, cis); 1.24 (d, J = 6.3 Hz, 3 H, Me, trans), 1.03 (d, J = 6.5 'Hz, 3 H, Me, cis); ^{13}C NMR ($CDCl_3$) δ 152.7 (s, Ar, trans), 147.3 (s, Ar, cis), 126.9, 126.43 (d, Ar), 123.4, 123.3 (d, Ar), 96.9 (s, CNO), 72.3 (t, CH_2O), 53.5 (d, CHN), 29.18, 29.0 (q, Me), 18.7, 17.6 (q, Me). **1e:** IR (neat) v 1664 (C=N) cm"; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 7 Hz, 2 H, Ar), 7.71 (d, J = 7 Hz, 2 H, Ar), 4.72 (d, J = 14 Hz, 1 H, CHO), 4.53 (d, J = 14 Hz, 1 H, CHO), 2.09 (s, 3 H, Me), 1.71 (s, 3 H, Me); ^{13}C NMR (CDCI,) δ 168.7 (s, C=N), 128 (s, Ar), 126.9 (s, Ar), 126.1 (d, Ar), 123.4 (d, Ar), 110.8 (s. CNO), 76.7 (t, CH_2O), 29.2 (q, Me), 17.63 (q. Me).

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