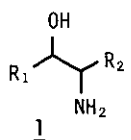
DIASTEREOSELECTIVE SYNTHESIS OF TRANS-4,5-DISUBSTITUTED OXAZOLIDIN-2-ONES AND VICINAL AMINO ALCOHOLS THROUGH ALKYLATION OF N-ACYL-IMINIUM ION INTERMEDIATES

Shinzo Kano,* Yoko Yuasa, and Shiroshi Shibuya

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract —— Treatment of 5-substituted 4-ethoxyoxazolidin-2-ones (10a-f, 13a,b) with allyltrimethylsilane in the presence of titanium tetrachloride gave the corresponding trans-4,5-disubstituted oxazolidin-2-ones (14a-f, 16a,b), respectively, with high diastereoselectivity. Methallylation of 13a,b with methallyltrimethylsilane yielded 16c,d, respectively. Ring cleavage of 14a-f afforded the corresponding threo vicinal amino alcohols (17a-f), respectively.

Vicinal amino alcohols are biologically important class of compounds as exemplified by ephedrine (1a) and related compounds[1] and statin (1b).[2] For the preparation of vicinal amino alcoholic structures. anionic center of 2a possessing the appropriate substituent at nitrogen has been used to introduce a hydroxyalkyl group at the α-position of nitrogen.[3] On the other hand, N-acyliminium salts[4] have been widely applied to a formation of carbon-carbon bond at the α-position. Fused oxazolidin-2-ones such as 3a,b,[5] prepared by cyclization of the iminium ion (2b), were used to a synthesis of α-(α'-hydroxyalkyl)-N-heterocycles by cleavage of the oxazolidinone ring. We investigated an alkylation of 2b in the expectation that the alkylation would proceed from the less hindered face of 2b. Ring cleavage of the alkylation products, trans-4,5-disubstituted oxazolidin-2-ones, attained the diastereoselective synthesis of vicinal amino alcohols. The results of our studies are described in this paper.



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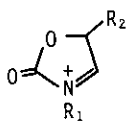
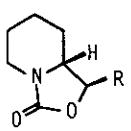
a: R_1=C_6H_5, R_2=Me

b: R_1=CH_2COOH, R_2=$CH_2CH(Me)_2$

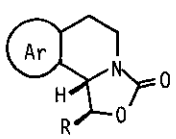
2a: X=NO; CH=N-CMe_3



2b: R_1=CH_2CH_2Ar; CH_2CH_2CH=$CHSiMe_3$
R_2=Me; Et; n-Pr; C_6H_5



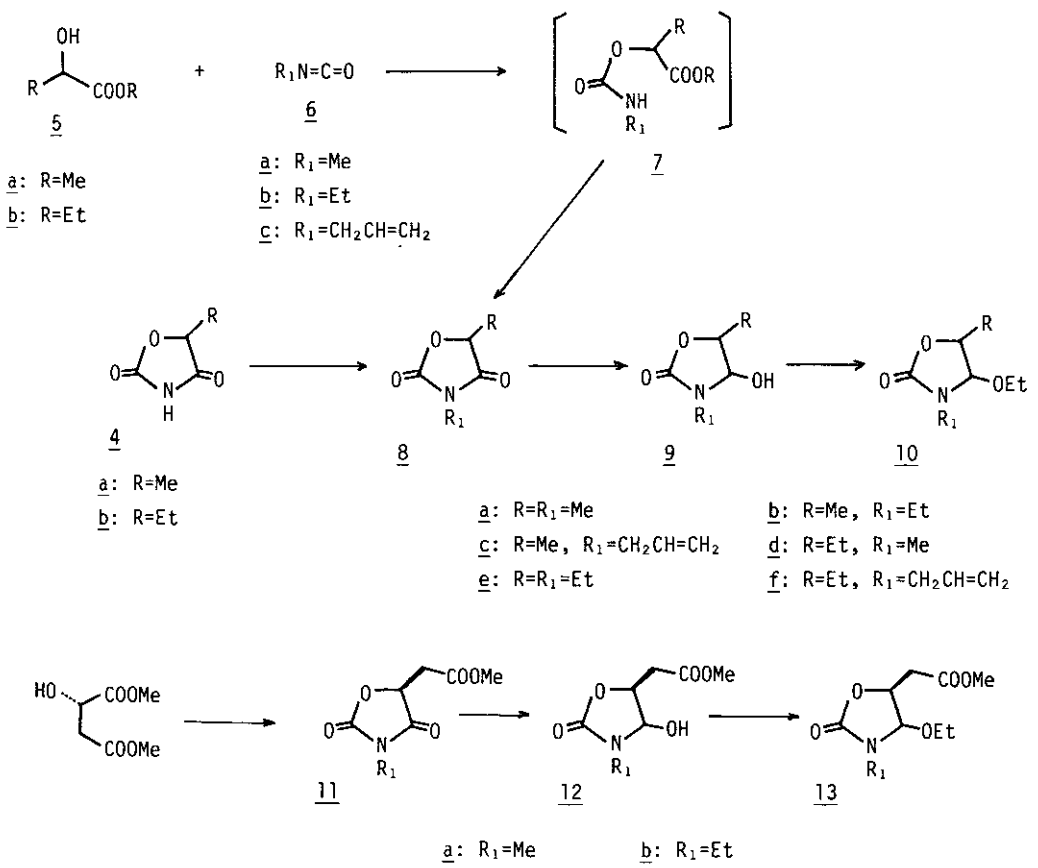
3a: R=Me; Et



3b

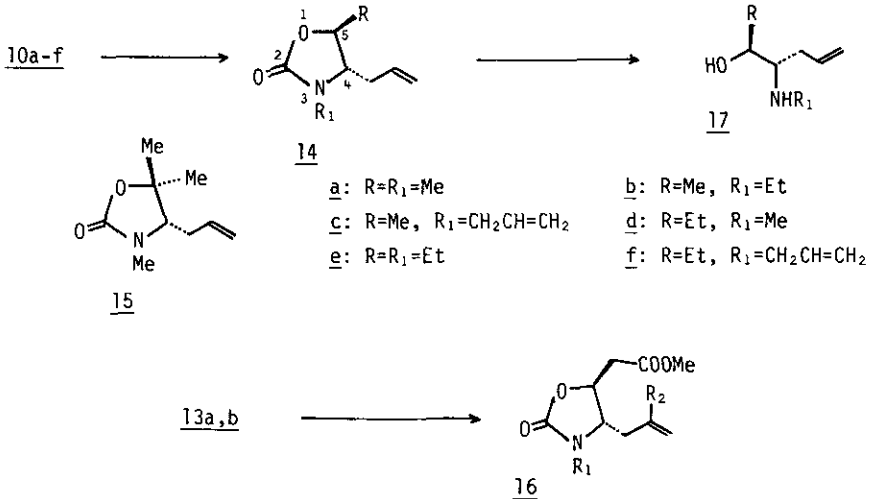
R=Me; Et; n-Pr; C_6H_5
Ar=benzene or Heteroaromatic

The 5-substituted 4-ethoxyoxazolidin-2-ones (10a-f, 13a,b), used for generation of the iminium salts, were prepared as follows. Alkylation of 5-methyloxazolidin-2,4-dione (4a)[6] MeI (EtI for 8b and allyl bromide for 8c), KOH, dimethyl sulfoxide, room temperature, 10 h afforded 8a-c[7] in 78-80 % yield. The same reaction by the use of 5-ethyloxazolidin-2,4-dione (4b)[6] instead of 4a gave 8d-f. The reaction of methyl lactate (5a) with isocyanates (6a-c; 1.2 equiv) in toluene under reflux for 3 h, followed by further heating at 175-180°C in the presence of pyridine (15 equiv) for 10 h also gave 8a-c via 7a-c in 80-83 % yield from 5a. The same reaction of ethyl α-hydroxybutyrate with 6a-c afforded 8d-f, respectively. The reaction of methyl ester of (S)-(-)-malic acid with 6a,b afforded the oxazolidin-2,4-diones (11a,b) in 60 and 62 % yield, respectively. Reduction of 8a-f and 11a,b with $NaBH_4$ in methanol at 0°C (-20°C for 11a,b) yielded the corresponding 4-hydroxy derivatives (9a-f, 12a,b), respectively. Treatment of 9a-f and 12a,b with ethanol (pH 2.0, 0°C, 3 h) yielded the corresponding 4-ethoxy derivatives (10a-f; 90-92 % yield, 13a, 50 % yield, 13b, 48 % yield), respectively, as an oil in all cases. These 4-ethoxyoxazolidin-2-ones were subjected to alkylation reaction. Allyltrimethylsilane and methallyltrimethylsilane were used as the nucleophilic alkylation reagent.



Treatment of 10a with $TiCl_4$ (1.2 equiv, 0°C, CH_2Cl_2, 10 min), followed by addition of allyltrimethylsilane (1.2 equi, 0°C ⟶ room temperature, 10 h) afforded 3,5-dimethyl-4-allyloxazolidin-2-one (14a) in 88 % yield as a single diastereomer as an oil, ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J=7 Hz), 2.88 (3H, s), 2.26-2.49 (2H, m), 3.17-3.36 (1H, m), 4.11-4.39 (1H, m), 5.09-5.29 (2H, m), 5.54-5.97 (1H, m), IR ($CHCl_3$) 1750 cm^{-1}. The relative configuration of 5-CH_3 and 4-allyl groups was determined by comparison with the ^{1}H NMR ($CDCl_3$) spectrum of 3,5,5-trimethyl analogue (15) prepared by allylation of 3,5,5-trimethyl-4-ethoxyoxazolidin-2-one under the same conditions. Two singlets due to 5-CH_3 group were observed at δ 1.37 and 1.43. The cis-oriented CH_3 group relative to 4-allyl group resonated at the lower field. Thus, the relative configuration at 4- and 5-positions of 14a was determined as trans. In this reaction, allylation was found to proceed from the less hindered face of the iminium ion as expected. The reaction of 10b-f with allyltrimethylsilane under the same conditions as 10a afforded the corresponding 5-substituted 4-allyloxazolidin-2-ones (14b-f),[7] respectively, in 80-83 % yield as an oil in all cases. Treatment of 13a,b with allyltrimethylsilane under the same conditions as above gave 16a,b as an oil in 73 and 75 % yield, respectively. Furthermore, the reaction of 13a,b with methallyltrimethylsilane afforded 4-methallyl derivatives (16c,d) as an oil in 68 and 65 % yield, respectively. Ring cleavage of 14a-f by heating in 10 % EtOH-NaOH under reflux for 10 h gave the corresponding vicinal threo amino alcohols (17a-f),[7] respectively, in 90-92 % yield in all cases.

An enantioselective synthesis of statin (1b) and its N-substituted analogs is under progressive.



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7. All new compounds gave the satisfactory spectral data (^1H NMR, IR, and Mass spectra). In the mass spectra of 14a-f and 16a-d, molecular ion peaks werenot observed in their EI mass spectra, but M^++1 peaks were clearly observed in their CI mass spectra. In the ^1H NMR spectra of 14b,c the signals due to 5-CH_3 were observed at δ 1.33 as doublets (J=7 Hz). The signals due to CH_3 at the methallyl group of 16c,d were observed at δ 1.78. IR ($CHCl_3$) spectra of 14a-f showed absorbtion band at 1750 cm^{-1}.
8. An enantioselective synthesis of statin (1b) and a variety of N-susbstituted analogous compounds will be reported elsewhere soon.

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