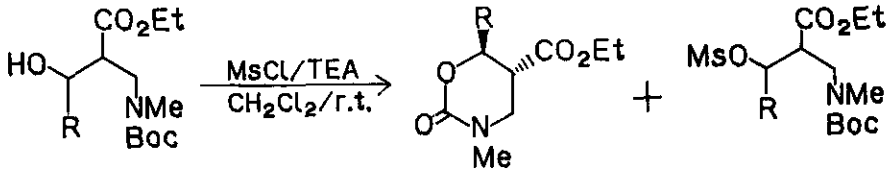
AN ABNORMAL REACTION OF N-tert-BUTOXYCARBONYL GROUP: MECHANISTIC CONSIDERATION FOR THE PREPARATION OF 2-OXOTETRAHYDRO-1,3-OXAZINE

Yoshitaka Matsubara, Ryuji Yoneda, Shinya Harusawa, and Takushi Kurihara*

Osaka University of Pharmaceutical Sciences, 2-10-65, Kawai, Matsubara, Osaka 580, Japan

Abstract —— Threo- and erythro-selective aldol condensations of 3-aminopropionate (**1**) with benzaldehyde (**2**) gave β-hydroxy ester (**3**) as a mixture of diastereomers (threo/erythro: 79/21 and 26/74). Upon treatment with methanesulfonyl chloride and triethylamine, threo-**3** was converted to 2-oxotetrahydro-1,3-oxazine (**4**) via mesylate, while erythro-**3** gave the corresponding mesylate (**5**). A plausible mechanistic consideration is also described.

Our previous work has shown[1] that when ethyl 2-(N-tert-butoxycarbonyl-N-methyl)-aminomethyl-3-hydroxy-3-aryl(or vinyl)propionates were treated with methanesulfonyl chloride (MsCl) and triethylamine (TEA), 6-aryl(or vinyl)-5-ethoxycarbonyl-2-oxotetrahydro-1,3-oxazines were obtained accompanied by the mesylates. In the case of benzylic alcohol, the obvious substituent effect was observed; namely substitution of hydrogen on the benzene ring by the electron-releasing groups resulted in a unilateral formation of 1,3-oxazines in high yields, whereas the electron-withdrawing group had a tendency to produce much amount of the mesylates.



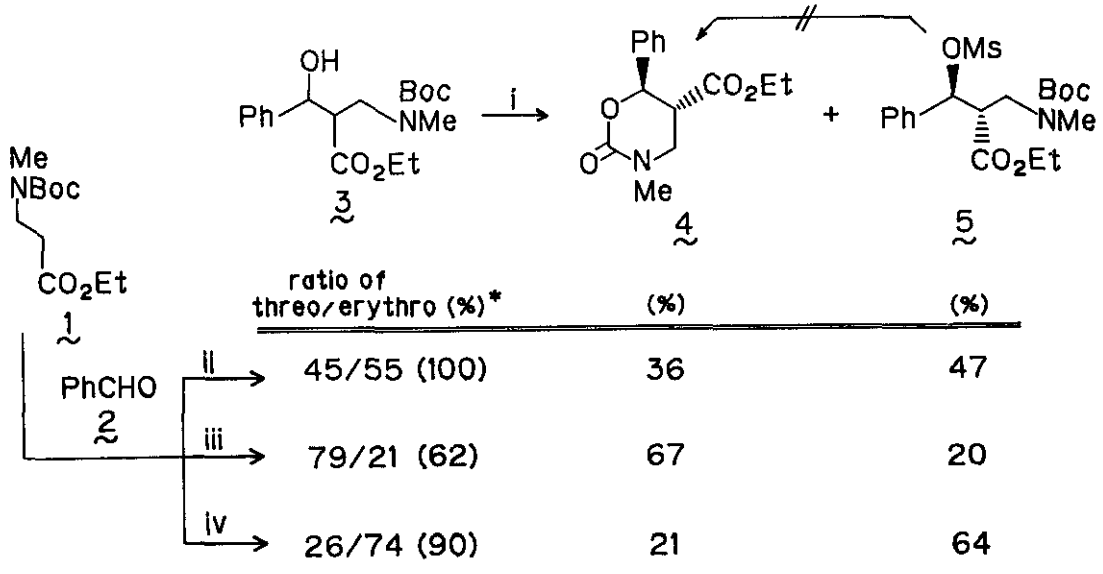
R = Ar, CH_2=CH

In this paper, we report the mechanistic consideration for the formation of 2-oxotetrahydro-1,3-oxazines.

Aldol condensation of ethyl 3-(N-tert-butoxycarbonyl-N-methyl)aminopropionate (**1**) with benzaldehyde (**2**) in the presence of lithium diisopropylamide (LDA) at -78 °C

in THF gave alcohol(3), which was a mixture of diastereomers (threo-3 and erythro-3) in a ratio of 45 : 55 determined by N-methyl signals (δ2.84 and 2.75) in the ^{1}H nmr spectrum (300 MHz in $CDCl_3$). However, diastereomers were not separated by column chromatography. As mentioned in the previous communication,[1] 3 was reacted with MsCl (1.5 eq) and TEA (3 eq) in CH_2Cl_2 at room temperature to give 2-oxo-tetrahydro-1,3-oxazine (4) and mesylate (5) in 36% and 47% yields. Under the same conditions for mesylation the isolated mesylate (5) was not derived to the heterocyles (4). Thus, it was reasonably supposed that one of the threo- or erythro-isomers of 3 was converted into the oxazine (4) via corresponding mesylate which must be unstable to isolate, and the other gave the stable mesylate (5). In order to confirm the above hypothesis diastereoselective aldol condensation of 1 with 2 was examined. The threo-selective and erythro-selective aldol condensations were carried out according to the methods of Chan[2] and Evans[3], respectively, to give the aldol products in 62% and 90% yields. Each of them were then treated with MsCl/TEA under the same conditions as above to give a mixture of 4 and 5, the results of which are summarized in the Table.

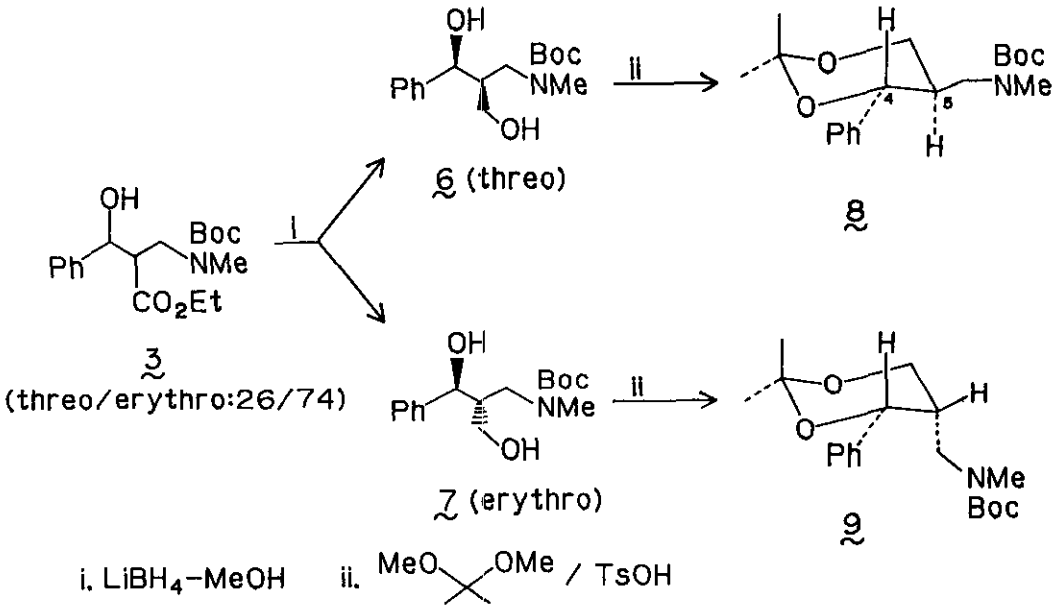
Table. Diastereoselective Aldol Condensations



i. MsCl/TEA, ii. LDA, iii. LDA/TMSCl/$TiCl_4$, iv. LDA/Cp_2ZrCl_2

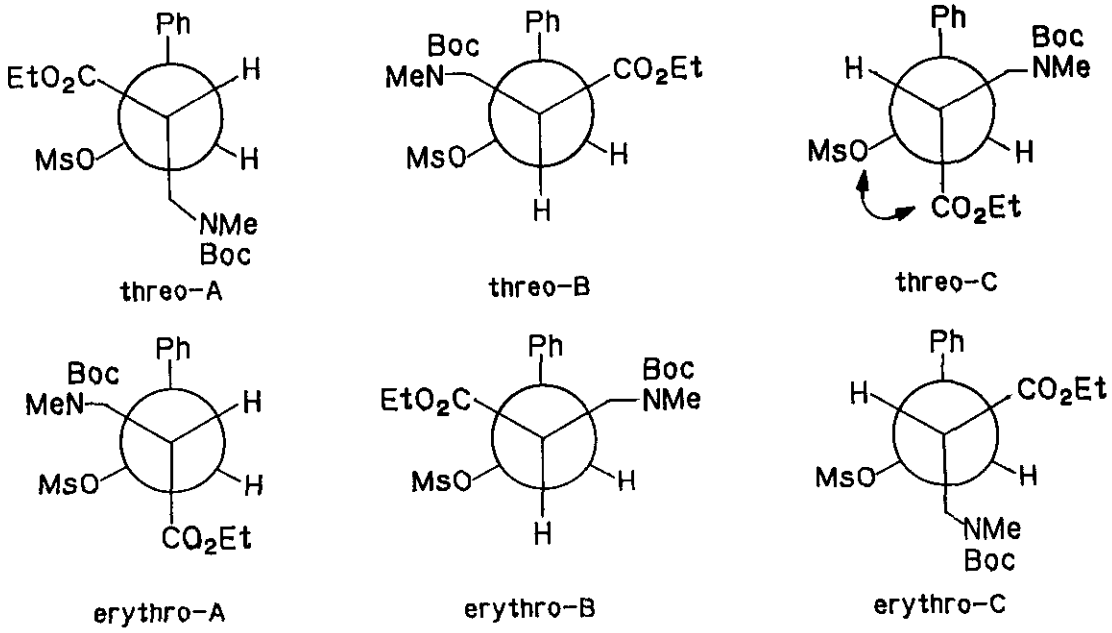
* All yields refer to isolated product.

As is clearly shown, the threo-selective condensation product yielded predominantly oxazine (**4**), while the mesylate (**5**) was obtained as the major product from the erythro-selective condensation product. The assignment of the stereostructures of threo-**3** and erythro-**3** was made as follows: Lithium borohydride-methanol reduction[4] of the erythro-selective aldol product in ether gave the diols, which were separated by column chromatography on silica gel to give **6** (22%) and **7**(63%). The diols (**6** and **7**) were treated with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid (TsOH) to give 1,3-dioxane derivatives (**8** and **9**), whose vicinal coupling constants ($J_{4,5}$) in **8** had a larger values (12 Hz) than that (3 Hz) of **9**. On the basis of these results, the stereochemistry of **3** was concluded that the major product is erythro-**3** and the minor one is threo-**3**, and our experimental results for diastereoselective aldol condensation are in good accord with the reported.[2,3]

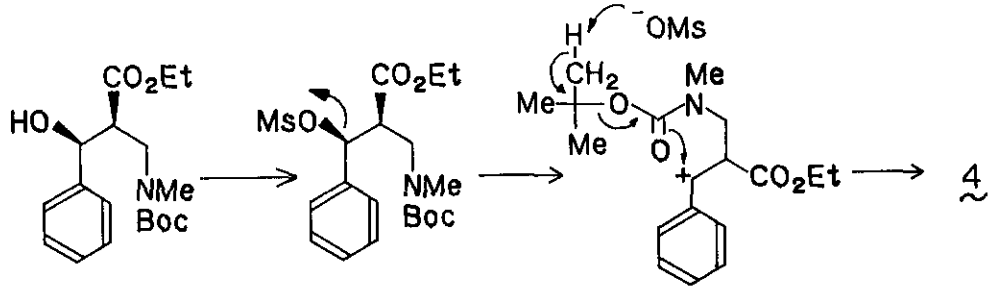


Finally it was found that 2-oxotetrahydro-1,3-oxazine (**4**) is derived from threo-**3** by treatment with MsCl/TEA, while erythro-**3** gives the corresponding mesylate (**5**). The considerable difference will be nicely explainable as follows: among Newman projections of the mesylates, threo-C and erythro-C should be more stable than the other two conformers, respectively. If we assume that electrostatic interaction between the mesyloxy and ethoxycarbonyl groups is the determining factor, the most stable conformer should be erythro-C. Thus, demesyloxylation from the threo-C is

Fig. Newman Projections of Mesylates



enhanced by electrostatic repulsion to yield a cation intermediate, which is stabilized by the aromatic double bond. Deprotonation from tert-butyl group assisted by the mesyloxy anion followed by cyclization resulted in the formation of 2-oxotetrahydro-1,3-oxazine (**4**). The large coupling constant ($J^{2,3}$=11 Hz) of the mesylate (**5**) are in good agreement with the expected value for erythro-C.



In general, the Boc group is known as a representative protective group removed by strong acidic conditions.[5] Therefore, the formation of 1,3-oxazine under rather basic conditions is noteworthy.

REFERENCES

1. T. Kurihara, T. Terada, Y. Matsubara, and R. Yoneda, Heterocycles, 1987, **26**, 641.
2. T.H. Chan, T. Aida, P.W.K. Lau, V. Gorys, and D.N. Harpp, Tetrahedron Lett., **1979**, 4029.
3. D.A. Evans and L.R. McGee, Tetrahedron Lett., 1980, **21**, 3975.
4. K. Soai and A. Ookawa, J. Org. Chem., 1986, **51**, 4000.
5. T.W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, New York, 1981, p 232.

Received, 24th November, 1987