

CONFORMATIONAL EFFECTS IN ORGANOALUMINUM-PROMOTED PINACOL-TYPE REARRANGEMENT

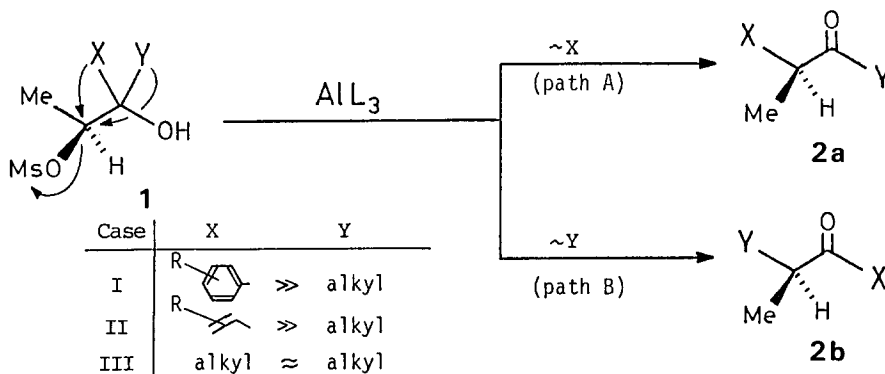
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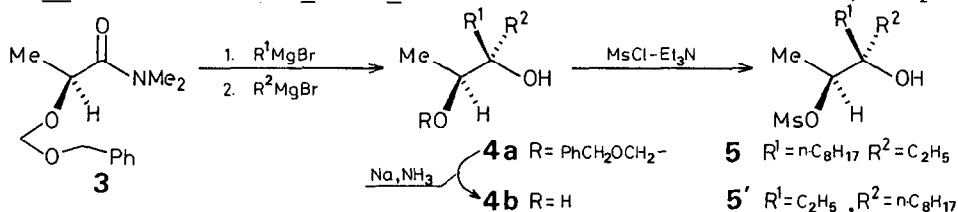
Summary: Conformational effects on the reaction course were examined in organoaluminum-promoted pinacol-type rearrangement, using stereo-defined unsymmetrical β -mesyloxy alcohols as the probe, where combinational use of DIBAL-Et₂AlCl achieved highly selective migration.

Conformations of a given molecule pose significant effects over the reactivity and the reaction course, inclusively referred as the "stereoelectronic effects" whose evaluation is essential in designing organic reactions.¹⁾

In the continuing research on the organoaluminum-promoted pinacol-type rearrangement, our attention was focussed on the conformational effects in this 1,2-migration process, mainly from the mechanistic interests. In determining the reaction course of the unsymmetrically-substituted substrate **1** ($X \neq Y$), the migratory aptitude (MA) was the primary factor to give rise to the exclusive migration of X, the group of the higher MA. This rule was valid for Case I, II even when the stereo-center of the migrating terminus was random, which was explained by the flexibility of the seven-membered chelate intermediate.^{2a,b)} On the other hand, the conformational effect should be the dominant factor when X and Y are of the similar MA, and hence, are competing (such as in Case III). Here we describe the manifestation of this effect by using the stereo-defined substrate as the probe, leading to the selective migration in Case III.



Stereo-defined β -mesyloxy alcohol 5 was prepared by way of the chelation-controlled Grignard reaction.⁴⁾ The diastereomer 5' was also prepared by changing the order of the Grignard reactions. By further purification at the stage of 4b,⁵⁾ the de's of 5 and 5' were rendered to be over 98 %, respectively.



As the model substrates in hand, the reaction course of the 1,2-migration process was examined: Substrate 5 was allowed to react with organoaluminum reagents to effect the pinacol-type rearrangement, and the ratios of the possible rearranged products 6a (C_8H_{17} -migration) and 6b (C_2H_5 -migration) were determined by HPLC.⁶⁾ Fair selectivity ($\text{6a} / \text{6b} = 6.3 / 1$) for the C_8H_{17} -migration was achieved by utilizing Et_2AlCl , the preferred reagent for the migration of alkyl groups.³⁾ During the course of our study, the possibility arose that two moles of the aluminum reagent are synergistically involved in the migration process, one for the alkoxide formation, the other as the Lewis-acidic promoter (binary activation: Fig 1). Based on this consideration, the combinational use of the two different organoaluminum reagents was attempted as shown in Table 1. The highest selectivity was achieved by using the DIBAL - Et_2AlCl combination: The $(i\text{-Bu})_2\text{Al}$ -alkoxide of 5 was first generated by the action of DIBAL on 5 at -78°C , which was successively treated with Et_2AlCl to effect the 1,2-migration ($-78^\circ\text{C} \rightarrow 0^\circ\text{C}$). The rearranged products were obtained in their reduced form (by

Fig 1

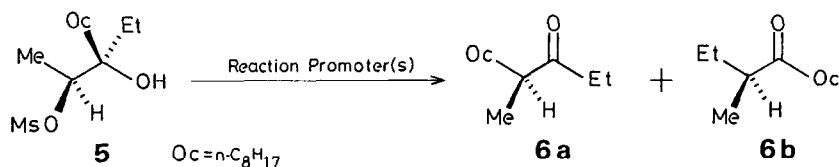
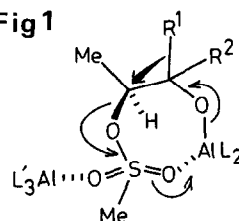


Table 1. Effect of Reaction Promoter(s)

Reaction Promoter(s) ^{a)}	6a / 6b
Et_2AlCl	6.3 / 1
$\text{Me}_3\text{Al} - \text{Et}_2\text{AlCl}$	8.2 / 1
$\text{Et}_3\text{Al} - \text{Et}_2\text{AlCl}$	5.3 / 1
$i\text{-Bu}_3\text{Al} - \text{Et}_2\text{AlCl}$	4.0 / 1
DIBAL - Et_2AlCl	14.1 / 1

a) Carried out in CH_2Cl_2 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$.

Table 2. Solvent Effect^{a)}

Solvent	6a / 6b
CH_2Cl_2	14.1 / 1
CHCl_3 ^{b)}	21.2 / 1
toluene	10.3 / 1
hexane	26.3 / 1

a) Using DIBAL - Et_2AlCl , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$.

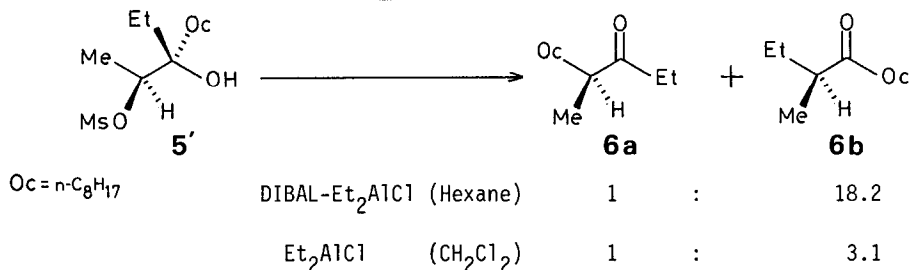
b) Reaction temp.: $-65^\circ\text{C} \rightarrow 0^\circ\text{C}$.

the excess DIBAL), which were thoroughly oxidized (PDC / DMF)⁸⁾ back to **6a** / **6b** and analyzed. In contrast, substantial decrease of the selectivity was encountered in the cases of the $R_3Al - Et_2AlCl$ combination.

This tendency could be attributable to the readiness and the extent of the alkoxide formation at the low temperature. Actually, the gas-evolution measurements supported this assumption: The degree of the alkoxide formation between **5** and various organoaluminum reagents at $-78^\circ C$ for 1h was as follows: DIBAL (~100 %), Et_3Al (84 %), Et_2AlCl (45 %), and $(i-Bu)_3Al$ (17 %).⁹⁾ Thus, the clean formation of the alkoxide intermediate is essential for the selective migration, which may lead to the restriction of the conformational freedom.¹⁰⁾ These facts are of considerable interest with respect to the mechanism of the organoaluminum-mediated pinacol-type rearrangement.

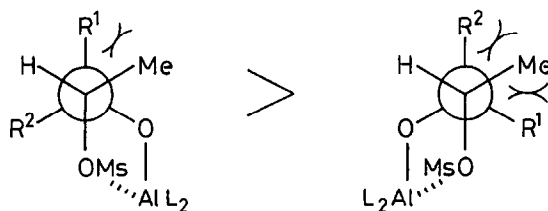
The selectivity was further optimized by screening the solvent effects; the best selectivity as large as 26 / 1 was observed in hexane (Table 2).

In order to gain further insight, the rearrangement of the isomeric starting material **5'** was examined. In these cases, as expected, selective migration of ethyl group was observed, although the selectivities were lower in comparison with the corresponding cases of **5** under the same definite reaction conditions.



The present situations are rationalized by the chelate model as depicted in Fig 2, judging from the data obtained here and the unlikelihood of the free carbocation intermediate.³⁾ The energy difference of the chelate conformers might be the primary factor in the determining the reaction course by assuming the antiperiplanar relationship between the migrating and the leaving groups. This makes a sharp contrast to the related cases, the deaminative pinacol-type rearrangement, where the ground state conformation is reflected to the intermediate viz. the open carbocation.¹¹⁾

Fig 2



Aside from the mechanistic standpoints, the present feature of this 1,2-rearrangement is of potential utility for the asymmetric synthesis of chiral molecules of the general formula $R(\text{CH}_3)\overset{*}{\text{C}}\text{HCOR}'$, such as 4-methyl-3-heptanone, the alarm pheromone of the leaf-cutting ant, Atta texana.¹²⁾

In summary, the conformational effect in the chelate intermediate directed the reaction course of the organoaluminum-promoted pinacol-type rearrangement. Further study on this process and its application to the synthesis of the chiral natural products is now under way in our laboratory.

References and Notes

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- 2) a) K. Suzuki, E. Katayama, & G. Tsuchihashi, *Tetrahedron Lett.*, 24, 4997 (1983).
b) K. Suzuki, E. Katayama, & G. Tsuchihashi, *ibid.*, 25, 1817 (1984).
- 3) Rearrangement of alkyl groups was smoothly promoted by Et_2AlCl , however, only the symmetrical cases ($X=Y$) were described: G. Tsuchihashi, K. Tomooka, & K. Suzuki, *Tetrahedron Lett.*, 25, 4253 (1984).
- 4) W. C. Still & J. H. McDonald, III, *Tetrahedron Lett.*, 21, 1031 (1980).
- 5) Preference of the chelation-controlled product was 97 / 3 in each cases (-78°C , in toluene). Purification was done by converting 4b to 3,5-dinitrobenzoyl mono-ester derivative; (1) 3,5- $(\text{NO}_2)_2\text{C}_6\text{H}_3\text{COCl}$ / pyr, (2) separation on SiO_2 column (hexane - $\text{AcOEt} = 7 / 1$), (3) $\text{NaOH} / \text{MeOH}$.
- 6) Conditions for the HPLC analysis: ZORBAX SIL (Du Pont Instruments, 46 / 250), hexane - $\text{CH}_2\text{Cl}_2 = 20 / 1$.
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- 10) The reaction course, that is, the selectivity may be dependent on the ligands on the chelated aluminum (L), however, the net effect of this sort could not be estimated at present due to the incomplete alkoxide formation in the trialkylaluminum cases.
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