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Efficient Pinacol Rearrangement Mediated by Trimethyl Orthoformate

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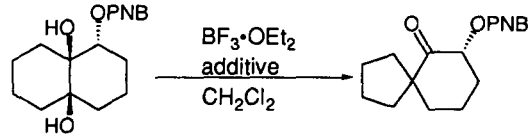
Abstract: An efficient pinacol rearrangment mediated by trimethyl orthoformate has been developed. The reactions of various types of diols with catalytic amount of a Lewis acid in the presence of an ortho ester afforded the rearranged product in good yields *via* a cyclic ortho ester intermediate.

The pinacol rearrangement reaction is one of the oldest known transformations of the carbon skeleton. Typically, the diols (pinacols) are treated with a Brønsted acid or a Lewis acid to give the pinacolone. Intrinsic dehydration occurs during the reaction.[1] Excess Lewis acid is then usually required to complete the reaction and this makes the reaction disadvantageous. However, recent remarkable progress in the stereoselective synthesis of pinacols, for example, by pinacol coupling using low valent metals[2] or samarium diiodide,[3] or by the dihydroxylation of olefins using OsO_4 in the presence of a chiral ligand,[4] would make this rearrangement reaction itself quite attractive, if this drawback is overcome. Recently, Mukaiyama et al. developed an efficient pinacol rearrangement using a catalytic amount (0.2 eq.) of $SbCl_5$-$AgSbF_6$, where bis-silylethers of diols are used and siloxane is produced instead of H_2O.[5] Sands et al. developed another catalytic method (0.5 eq. of BF_3•OEt_2) using $MgSO_4$ as a dehydrating agent.[6] But in this case the formation of H_2O was not suppressed. We present here another answer to the disadvantage of pinacol rearrangement using an ortho ester as a mediator.

In the course of our synthetic studies of spirocarbocyclanes by stereoselective skeletal rearrangement under acidic conditions,[7] we examined the pinacol rearrangement of **1** with BF_3•OEt_2 (Table 1). As a result, a spiro compound **2** was obtained in 60% yield through the carbocation at the β-position of the acyloxy group,[8] but eight

Table 1. Effect of additives on the pinacol rearrangement of 1



1 **2**

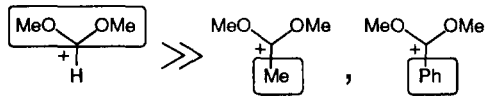
Entry	Additive	BF_3•OEt_2 (eq.)	Conditions	Yield (%)
1	none	8	0°C - reflux, 3 h	60
2	$MgSO_4$	10	0°C - r.t., 48 h	15 (68)[a]
3	MS 4 Å	1	0°C - r.t., 48 h	NR
4	$PhC(OMe)_3$	1	0°C - r.t., 48 h	NR
5	$MeC(OMe)_3$	1	0°C - r.t., 48 h	NR
6	$HC(OMe)_3$	1	0°C - r.t., 48 h	83

[a] Yield in the parenthesis is recovered starting material.

equivalents of BF_3•OEt_2 and reflux conditions were required (entry 1). We next examined the reported improved-method. Sands's method did not work well (entry 2). Mukaiyama's method could not be applied to this system since silylation of the 1,2-diol hardly occurred because of the bulkiness of the substrate. Then, use of molecular sieves also did not have any effect (entry 3). We then examined the reaction in the presence of an ortho ester with the aim of activation of the diol and capture of H_2O.[9] Although $PhC(OMe)_3$ and $MeC(OMe)_3$ did not show any effects (entries 4 and 5), $HC(OMe)_3$ promoted the reaction very well and afforded the rearranged product **2** in 83% yield at 0°C-r.t. with only 1 equivalent of BF_3•OEt_2 (entry 6).[10]

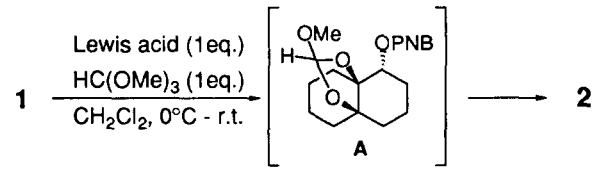
Difference of the reactivity among the three ortho esters is rationalized as follows. In the case of $HC(OMe)_3$, the reaction proceeded *via* a cyclic ortho ester intermediate **A** (refer to Table 2),[11] whose formation was observed on TLC and its structure was determined by comparison with the authentic one prepared by the reaction of **1** and $HC(OMe)_3$ in the presence of a catalytic amount of *p*-TsOH. On the other hand, no cyclic ortho ester intermediate was formed in the case of $PhC(OMe)_3$ and $MeC(OMe)_3$. This must be due to the difference in the reactivities of the dioxycarbenium ions towards tertiary alcohols due to their bulkiness (Figure 1).

Fig. 1. Reactivity of the Dioxycarbenium Ions towards *tert*-Alcohols



We then examined the effect of a Lewis acid in the presence of $HC(OMe)_3$ as an additive (Table 2). Every Lewis acid afforded **2** in good yield and $SnCl_4$ gave the best results (entry 2). It is noteworthy that the presence of $HC(OMe)_3$ is essential to accelerate this reaction.

Table 2. Effect of Lewis acids in the presence of $HC(OMe)_3$

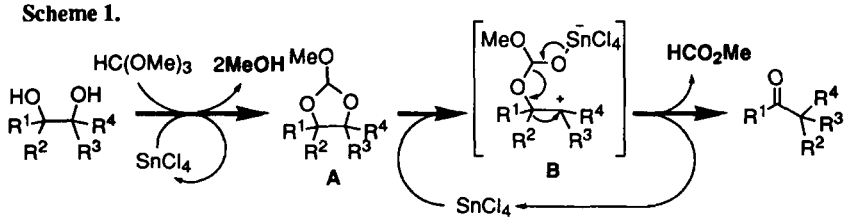


Entry	Lewis acid	Time	Yield of **2** (%)	
1	BF_3•OEt_2	48 h	83	(NR)[a]
2	$SnCl_4$	2 h	85	(trace)
3	TMSOTf	2 h	74	(NR)
4	$EtAlCl_2$ (2eq.)	8 h	70	(NR)

[a] Result in parenthesis is observed in the absence of $HC(OMe)_3$.

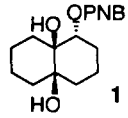
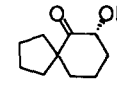
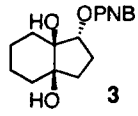
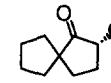
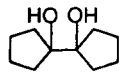
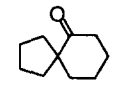
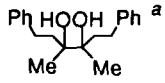
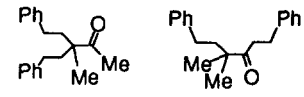
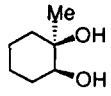
The above results would suggest the reaction mechanism as depicted in Scheme 1. Namely, first, formation of cyclic intermediate **A** and further conversion to cationic intermediate **B**[12] produced the rearrangement product. During the reaction, 2 equivalents of MeOH and 1 equivalent of HCO_2Me formed, but no H_2O. The formation of MeOH and HCO_2Me was confirmed by the ^1H NMR experiment.

Scheme 1.



From a mechanistic consideration, this rearrangement reaction seems to proceed under a catalytic Lewis acidic condition. We then examined the generality of the reaction using several types of diols. The results are shown in Table 3. In all cases, the reactions smoothly proceeded to give the corresponding ketones in good to excellent yields. This ortho ester method is effective not only for the bicyclic systems **1** and **3** but also for the typical tetra- and tri-substituted diols **4**~**6** for the pinacol rearrangement (entries 3~5).

Table 3. Pinacol Reaction of Various Diols with $SnCl_4$ in the presence of $HC(OMe)_3$

Entry	Substr	Equiv. of $SnCl_4$	Conditions	Product	Yield (%)
1	 **1**	0.4	0°C - r.t., 52 h	 **2**	82
2	 **3**	0.2	0°C - r.t., 7 h	 **7**	97
3	 **4**	0.2	-20°C, 5 min	 **8**	90
4	 [a] **5**	0.4	0°C - r.t., 4 d	 **9** 67 (52:15) **10**	
5	 **6**	0.4	0°C - r.t., 9 h	 **11**	66

[a] 1:1 diastereomer mixture was used.

In conclusion, we have developed an efficient and mild reaction system for the pinacol rearrangement reaction. The characterestic point of the reaction is no formation of water during the reaction and the reaction proceeds using a catalytic amount of a Lewis acid. The method presents a new solution to the disadvantage of the pinacol rearrangement and will promise the successful transformation of various types of 1,2-diols.

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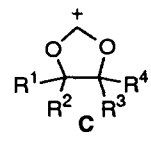
8. For remarkable effect of acyloxy group on the stability of cationic intermediate, see ref. 7.
9. For the effect of an ortho ester towards the reactions which proceed under dehydrative conditions, see: Fujioka, H.; Kitagawa, H.; Kondo, M.; Matsunaga, N.; Kitagaki, S.; Kita, Y. *Heterocycles* **1993**, *35*, 665; Fujioka, H.; Kitagawa, H.; Kondo, M.; Kita, Y. *ibid.* **1994**, *37*, 743.
10. **Typical experimental procedure:** To a solution of diol (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added $HC(OMe)_3$ (1.0 mmol), and $BF_3{\cdot}OEt_2$ or other Lewis acid (0.1~1.0 mmol) at -20 °C or 0 °C under N_2, and the reaction mixture was stirred at room temperature for the period shown in the table. After having been diluted with CH_2Cl_2, saturated aqueous $NaHCO_3$ was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$ or Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate) to give the pure product.
11. Ortho ester **A** can be easily detected on TLC.
12. Although the formation of another cationic intermediate **C** might take place, **C** is disadvantageous for the rearrangement reaction and orthoester **A** is reproduced with co-existent MeOH, then rearrangement would proceed *via* **B**.
    [see: Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, 61, 4469.]



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