NOVEL RING EXPANSION REACTION OF EPOXIDES AND OXETANES ACCOMPANIED BY REARRANGEMENT OF ETHEREAL FUNCTIONAL GROUPS

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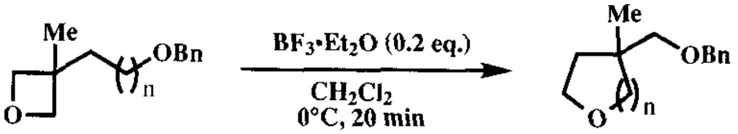
Abstract - Small cyclic ethers, epoxides and oxetanes, possessing ethereal groups on the side chain, was found to rearrange by means of *Lewis acid catalysts*, $BF_3 \cdot EtO_2$, to give ring expanded cyclic ethers accompanied by transfer of the ethereal groups. Formation of tetrahydro-furan and pyran ring and transposition of benzylic and allylic groups of the etheral function were observed to be favorable.

Many examples of intramolecular oxygen atom participation in displacement reactions have been reported.[1] Particularly, epoxides and oxetanes which contain oxygen functionalities on the side chain were known to easily undergo ring expansion reactions[2,3] due to a high strain energy (27.28 for oxirane and 25.51 Kcal/mol for oxetane) [4] which is a major driving force for cleavage of the C-O bond of the rings. For example, ring expansion of epoxides involving intramolecular participation of hydroxyl and ester groups to give tetrahydro-furan [2a,b] and pyran derivatives [2c] and transformation of oxetanes with ester and ethereal groups respectively to orthoesters having trioxabicyclo[2.2.2]octane skeleton [3a] and a tetrahydrofuryl alcohol [3b] have been reported. Among the reported ring expansions of small cyclic ethers, formation of 2-tributylstanyloxymethyloxetane and 3-tributylstanyloxytetrahydrofuran from 4-tributylstanyloxy-1-butene oxide under drastic conditions (210°C) detected by Moulines [3c] is only the case in which transposition of the terminal ethereal function in a side chain occured. In the course of our studies on the ring opening reaction of 3-substituted oxetanes, we observed that 3-methyl-3-(2-benzyloxyethyl)oxetane (**1**) on treatment with a Lewis acid afforded 3-methyl-3-benzyloxymethyl-tetrahydrofuran (**2**). This report describes novel ring expansion reactions of epoxides and oxetanes accompanied by transposition of *the ethereal groups on the side chain under mild reaction conditions.*

As shown in Scheme 1, an oxetane (**1**)[5] was treated with $BF_3 \cdot EtO_2$ (0.2 equiv.) in CH_2Cl_2 at 0°C for 20 min to give a 3,3-disubstituted tetrahydrofuran (**2**) in 66% yield. Screening of Lewis *acid catalysts on the reaction of*

Scheme 1

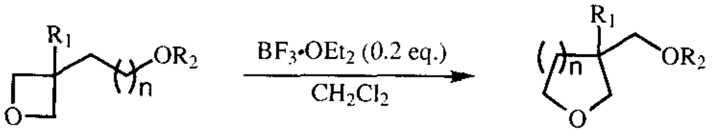


1 : n=1
3 : n=2

2 : n=1 ; 66%
4 : n=2 ; 77%

3-methyl-3-(3-benzyloxypropyl)oxetane (**3**) revealed that $BF_3 \bullet EtO_2$ is the most effective among the catalysts examined.[6] With $BF_3 \bullet EtO_2$ and $SnCl_4$, the rearranged product, tetrahydropyran derivative (**4**) was obtained in 77% and 34% yields, respectively. Other Lewis acids, $AlCl_3$, $ZnCl_2$, $MgBr_2 \bullet EtO_2$, $TiCl_4$, and $ZrCl_4$, hardly promoted the reaction and the substrate (**3**) was recovered unchanged. As the reaction solvent, CH_2Cl_2 gave a higher yield (77%) of the product (**4**) than other solvents, toluene (56%), ether (62%), and MeCN(41%) under the same conditions (0°C, 15 min). Results for oxetanes[5] bearing various length of side chain at the 3-position and different kinds of terminal ethereal groups under the conditions using $BF_3 \bullet EtO_2$ and CH_2Cl_2 as a Lewis acid catalyst and reaction solvent, respectively, are summarized in Table 1. Conversion of the oxetanes into tetrahydro-furan and pyran ring

Table 1



entry	n	R_1	R_2	temp (°C)	time (min)	yield (%)
1	1	Me	Bn	0	20	66
2	2	Me	Bn	0	15	77
3	3	Me	Bn	20	20 h	49
4	4	Me	Bn	20	98 h	---a)
5	2	Me	n-$C_{10}H_{21}$	0	15	0b)
6	2	Me	CH_2CH_2Ph	20	23 h	58
7	2	Me	CH(Me)Ph	0	30	64
8	2	Ph	Bn	0	15	75
9	2	Ph	$CH_2CH=CH_2$	0	30	79
10	2	Ph	$CH_2C(Me)=CH_2$	0	30	79
11	2	Ph	$CH_2CH=CMe_2$	0	30	29
12	2	Bn	Bn	0	15	82
13	2	Bn	$CH_2CH=CH_2$	0	30	79
14	2	Bn	$CH_2C(Me)=CH_2$	0	30	75
15	2	Bn	$CH_2CH=CMe_2$	0	30	26
16	2	Bn	$CH_2C \equiv CH$	0	1.5 h	28

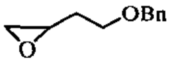
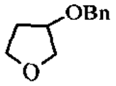
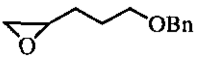
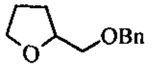
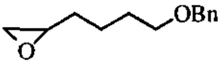
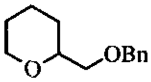
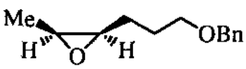
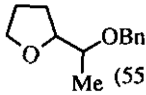
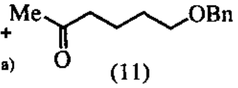
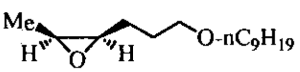
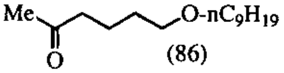
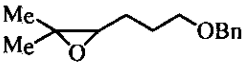
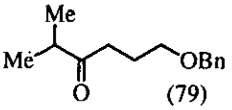
a) The starting oxetane was consumed but the desired product was not observed in the crude mixture of products. b) The starting oxetane was recovered unchanged.

proceeded smoothly (entries 1,2), although slugish into oxepane skeleton (entry 3) and absolutely no detection of oxocane derivative (entry 4). Ready transposition of the ethereal benzylic and allylic group including α-phenethyl and methallyl group to the carbinol side chain at the 3-position of expanded ring was observed (entries 7-10, 12-14), whereas no reaction took place with an oxetane having the alkyl (n-decyl) ethereal group at the terminal position (entry 5). An oxetane with β-phenethyloxy side chain also gave the corresponding rearranged product in a moderate yield (entry 6).

In turn, attention was forcused on the reaction of epoxides which have ethereal group at the terminal position of the side chain. Results from the reaction of epoxides[7] are summarized in Table 2. Mono-substituted epoxides with benzyloxy terminal group were transformed to products derived by ring expansion with concomitant transposition of the terminal benzyl group in low to moderate yields (entries 1-3). It is of interest that the product in the entry 1, although obtained in a low yield, appears to be derived by the 5-endo-tetragonal mode which is predicted to be disfavored.[8] Reactions of 1,2-disubstituted epoxides bearing benzyloxy and n-alkyloxy group as a terminal ethreal function exhibited a striking contrast. Thus, a tetrahydrofuran derivative was obtained predominantly from a 1,2-disubstituted epoxide with terminal benzyloxy group through the 5-exo-tetragonal mode (entry 4), while a methyl ketone was produced exclusively from a 1,2-disubstituted epoxide with terminal n-nonyloxy group (entry 5).

Table 2

$$\text{Epoxy-Ether} \xrightarrow[\text{Et}_2\text{O}]{\text{BF}_3\text{•OEt}_2\text{ (0.2 eq.)}} \text{Product}$$

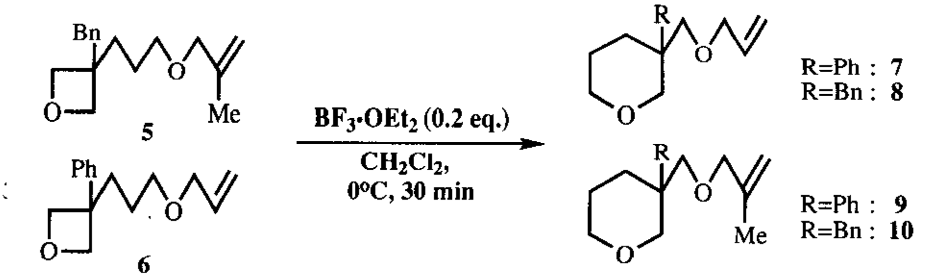
entry	Epoxy-Ether	temp (°C)	time (h)	Product (% yield)
1		20	2	 (25)
2		0	1	 (73)
3		0	1.5	 (48)
4		0	30 min	 (55)[a)] +  (11)
5		0 ~ 20	2.5	 (86)
6		0	30 min	 (79)

a) The product proved to be a sole diastereoisomer on the basis of ^{1}H-NMR analysis but the stereochemistry of the product has not been determined.

Such rearrangement of epoxides to ketones promoted by Lewis acids is common reaction,[9] whereas the highly regioselective formation of the methyl ketone is probably initiated by an intramolecular assistance of the terminal ethereal oxygen function.[10] For a tri-substituted epoxide even with terminal benzyloxy group, rearrangement to a ketone was a predominant course (entry 6).

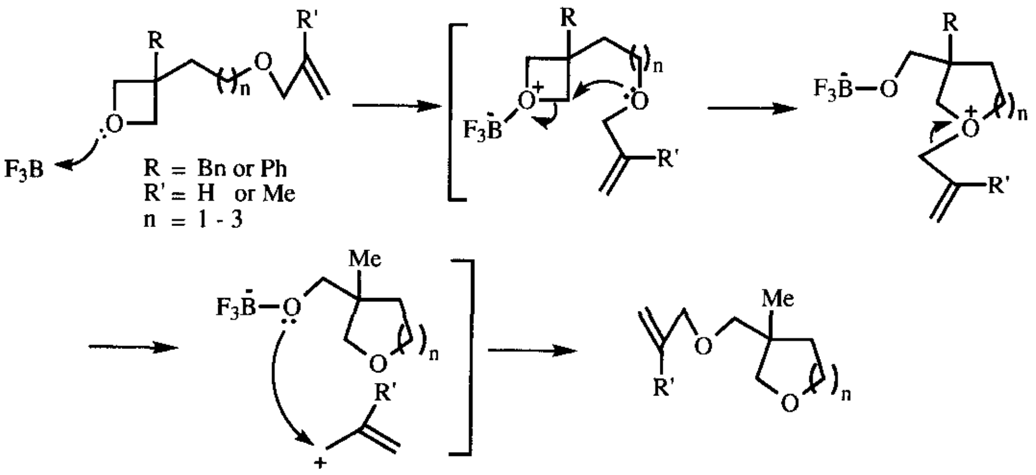
For clarification of the mechanism of the reaction, a cross-over experiment was carried out, as shown in Scheme 2, using a mixture of two oxetanes each other with different kind of substituents and ethereal side chains on the quaternary carbon at the 3-position. Treatment of a mixture of oxetanes (**5**) and (**6**) with a catalytic $BF_3 \cdot EtO_2$ afforded four products (**7**-**10**) in a ratio of 6:5:7:9.

Scheme 2



Favorable transposition of the ethereal benzylic and allylic group, ready ring enlargement to tetrahydro-furan and pyran, and the results from the above cross-over experiment strongly suggest that the reaction involves not only intra- but also inter-molecular rearrangement of benzyl and allylic group *via* the oxonium transition state as depicted for the oxetane model in Scheme 3.

Scheme 3



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3. (a) E. J. Corey and Natrarajan Raju, *Tetrahedron Lett.*, 1983, **24**, 5571. (b) A. K. Saksena, A. K. Ganguly, V. M. Girijavallabhan, R. E. Pike, Y. -T. Chen, and M. S. Puar, *Tetrahedron Lett.*, 1992, **33**, 7721. (c) J.-P. Bats and J. Moulines, *Tetrahedron Lett.*, **1976**, 2249.
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5. Oxetanes investigated were synthesized according to the literatures: S. M. Ludeman, D. L. Bartlett, and G. Zon, *J. Org. Chem.*, 1979, **44**, 1163; P. Picard, D. Leclercq, J.-P. Bats, and J. Moulines, *Synthesis*, **1981**, 550.
6. The general procedure for investigation on the catalytic activity of Lewis acids follows : A Lewis acid (0.2 eq.) was added to the CH_2Cl_2 (10 ml) solution of 3-methyl-3-(3-benzyloxypropyl)oxetane (**3**)[5] (100 mg, 0.454 mmol) at 0 °C. The mixture was stirred until the starting oxetane was disappeared by tlc monitoring, and quenched with water.
7. Epoxides investigated were synthesized from the corresponding olefin alcohols, *via* OH-protection with benzyl ether followed by oxidation with mCPBA. Olefin alcohols, 3-buten-1-ol, 4-penten-1-ol, 1-hexen-1-ol, and *trans*-4-hexen-1-ol, are commercially avialable and 5-methyl-4-hexen-1-ol was synthesized according to the literature: W. Cocker, N. W. A. Geraphty, T. B. H. Mucmurry, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. I*, **1984**, 2245.
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