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Synthesis of tetrahydrofurans by regio- and stereoselective cyclization of epoxyalcohols using magnesium halide

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Abstract—A novel synthetic method for several tetrahydrofuran derivatives by intramolecular cyclization of epoxyalcohols is described. The presence of a catalytic amount of magnesium halide altered the regio- and stereoselectivity of the cyclization reaction.

Intramolecular cyclization of epoxyalcohols is a useful reaction for the construction of oxygen-containing heterocycles. Actually, many natural compounds and related biologically active compounds have been synthesized according to this strategy.[1] As an epoxy ring possesses two reactive carbons, different membered heterocycles are formed depending on its regioselective nature. Therefore, the regioselectivity of the cyclization has been paid considerable attention.[2] Previously, we have reported a novel synthesis of 3-hydroxyazetidines by intramolecular cyclization of 2,3-epoxyamines using magnesium halide.[3] Our results show that the presence of a catalytic amount of magnesium halide alters a both the regio- and stereoselectivity compared with the results of the known reactions. Consequently, we expected this method would be applicable to the synthesis of oxygen-containing heterocyclic systems. In this letter we described a novel regio- and stereoselective synthesis of tetrahydrofurans.

Epoxyalcohol cyclizations are known to prefer the *exo* mode of ring closure over the *endo* mode, in accord with Baldwin's rules.[4] For example, it is reported that 1-(2,3-epoxypropyl)cyclohexane-1-ol (**1a**) with aqueous sodium hydroxide gives only spiro-oxethane derivatives (**3**).[5]

Initially, we attempted a method for the intramolecular cyclization of **1a**. A mixture of **1a** with 10 mol% of magnesium bromide in THF was refluxed for 20 h. The spiro-tetrahydrofuran derivatives (**2a**) were obtained in 69% yield. Formation of an oxethane derivative was not observed (Table 1, entry 1). The three possible transition states are depicted in Fig. 1. Cyclization by aqueous sodium hydroxide proceeds via the transition state **A** (4-*exo*-tet ring closure) exclusively. The transition state **B** (5-*endo*-tet ring closure) is not preferable because the angle α, which consists of the leaving oxygen of the oxirane, the reaction carbon center and the nucleophilic oxygen anion, is not allowed to take a linear arrangement in its conformation in the transition state. On the contrary, our method will take the transition state **C** (5-*exo*-tet ring closure), which has no difficulties to take the linear arrangement in the transition state. To explain the high regioselectivity, we assumed that the existing of the equilibrium between the starting epoxyalcohols and the halohydrin intermediates. The unpreferable regioisomeric halohydrin intermediate could not form the oxetanes caused by the ring strain. Only the other preferable halohydrin intermediate could form the tetrahydrofurans. Another possibility could point out that the high regioselective bromination was achieved by the chelation mechanism. However, we could not find out further evidences of the existing of the chelate intermediate.[6]

As for the stereoselectivity, the intramolecular cyclization of epoxy alcohols proceeds with inversion according to an S_N2 mechanism (Scheme 1, Eq. (1)). On the other hand, our method would proceed with retention caused by double inversion (Eq. (2)). The initial step of this reaction proceeds with ring-opening of epoxide by the halide anion. Then, the ring closure process would take place with the substitution of the halogen by the intramolecular hydroxyl group. Therefore, the stereo-

Keywords: epoxyalcohols; cyclization; magnesium halides, epoxides; furans.

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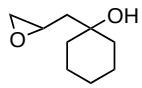
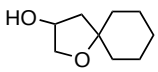
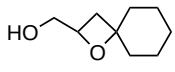
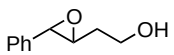
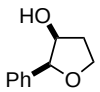
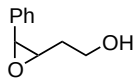
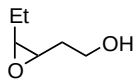
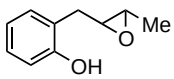
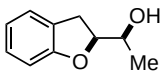
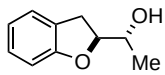
Table 1. Synthesis of cyclic ether by reaction of epoxyalcohol with magnesium halide[a]

Entry	Substrate	MgX_2	Solvent	Time/h	Products/Yield% [b](ratio)[c]
1	 **1a**				 **2a**  **3**
		$MgBr_2$	THF	20	69 (>98 : 2)
2	 **1b**				 **2b**  **2c**
		$MgBr_2$-Et_2O	THF	7days	73 (76 : 24)
3		MgI_2	THF	40	84 (85 : 15)
4		MgI_2	Dioxane	5	70 (54 : 46)
5	 **1c**	MgI_2	THF	65	65 (4 : 96)
6	 **1d**				 **2d**  **2e**
		MgI_2	THF	72	60 (2 : >98)
7	 **1e**				 **2f**  **2g**
		MgI_2	THF	24	73 (65 : 35)

[a] All reactions were performed at reflux with 10 mol% MgX_2.
[b] Combined yield of diastereoisomers.
[c] Determined by ^1H NMR. The indication >98:2 means that a single diastereoisomer was observed.

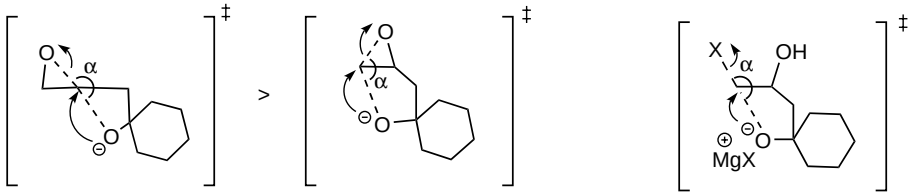
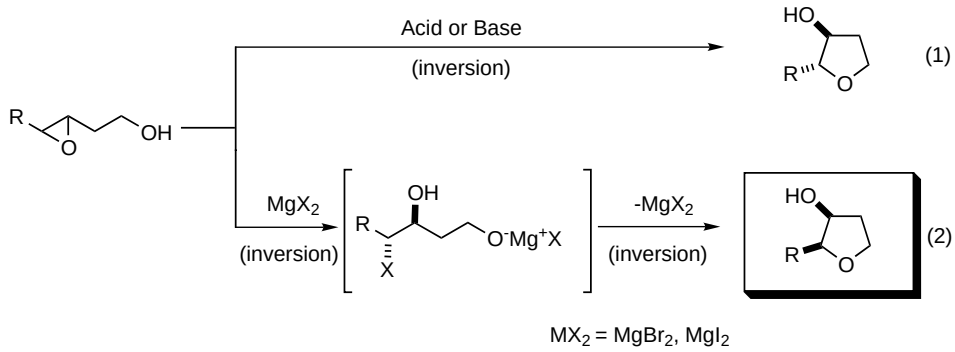


Figure 1. Transition states for the cyclization of 3,4-epoxyalcohols.



Scheme 1.

chemical outcome of Eqs. (1) and (2) will give opposite results.

Phenyl- and ethyl-substituted 3,4-epoxyalcohols (**1b**–**d**) were then subjected to several experiments directed towered a cyclization reaction. Epoxyalcohol **1b** gave a mixture of stereoisomeric tetrahydrofuran derivatives in 76% combined yield (**2b**:**2c** = 76:24, entry 2).

Employing MgI_2 instead of $MgBr_2{\cdot}Et_2O$, we observed improved selectivity and yield (84%, **2b**:**2c** = 85:15). In addition, the reaction time was shortened (entry 3). When the reaction was conducted in refluxed 1,4-dioxane instead of THF, the reaction was completed in 5 h. However, it was less selective (**2b**:**2c** = 54:46, entry 4). The low stereoselectivity could be explained by the two following reasons: (a) The participation of S_N1 mechanism, especially at the bromination of the phenyl substituted derivatives **1b** can be supposed. Upon comparison to previously studied reactions of this type, the data collected show that a little participation of S_N1 mechanism on the benzylic position has been observed.[3] (b) The phenyl substituted alcohol **1b** easily cyclize to afford **2c** without bromination by magnesium halide. However, we could not conclude which effects were more influential. The stereoisomer **1c** gave also a stereo isomeric tetrahydrofuran derivative in 65% yield stereospecifically (**2b**:**2c** = 4:96, entry 5). In an analogous fashion, **1d** gave **2e** dominantly (entry 6). Next, we assessed the scope of the reaction for a phenolic derivative. *trans*-2-(2,3-Epoxybutyl)phenol was refluxed in THF for 24 h in the presence of 10 mol% of magnesium iodide. A mixture of *syn*- and *anti*-2-(hydroxyethyl)dihydrobenzofuran derivatives (**2f** and **2g**) was obtained in 73% combined yield (**2f**:**2g** = 65:35, entry 7). The stereoselectivity is not satisfactory, but the configuration of the main product was the result of double inversion. The structure and stereochemistry of these products were confirmed by ^1H NMR, ^{13}C NMR, IR and MS with comparison of the products obtained by KOH-catalyzed cyclization reactions.

In summary, we have presented an alternative synthetic route for the preparation of tetrahydrofurans synthesized by using a catalytic amount of magnesium halide.

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