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Efficient Synthesis of 2,3-*trans*-Tetrahydropyrans and Oxepanes: Rearrangement-Ring Expansion of Cyclic Ethers Having a Chloromethanesulfonate

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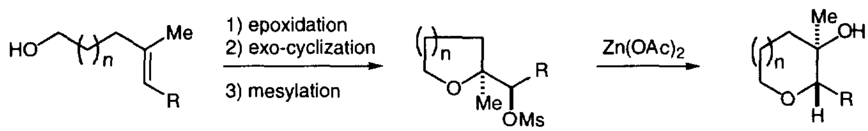
Abstract

$Zn(OAc)_2$-treatment of cyclic ethers having a chloromethanesulfonate as an efficient leaving group on the side chain effected a stereoselective rearrangement reaction to give the ring-expanded ethers, 2,3-*trans*-tetrahydropyrans and oxepanes, in good yield.

Keywords: Rearrangements; Tetrahydropyrans; Oxepanes; Stereocontrol

Recently, many marine polycyclic ethers exemplified by brevetoxin B [1] have attracted the attention of synthetic organic chemists due to their unusual structural framework, novel functionalities, and potent biological activities. The most characteristic feature of this class of marine natural products involves *trans*-fused polycyclic ether ring systems. Thus, various methods for constructing these systems have been extensively studied [2]. We recently succeeded in developing an efficient method for the syntheses of 2,3-*trans*-tetrahydropyrans and oxepanes **iii**, based on the $Zn(OAc)_2$-mediated rearrangement-ring expansion of the mesylates **ii**, which were prepared from **i** by epoxidation, exo-cyclization, and mesylation [3]. We now report a more efficient procedure using chloromethanesulfonates instead of the mesylates for this unique rearrangement-ring expansion reaction.



i (n=1 or 2) ii iii (n=1 or 2)

We have already reported that treatment of the mesylate **ii** (n=1 or 2) with $Zn(OAc)_2$ in AcOH-H_2O (1:1) under reflux effected the rearrangement-ring expansion, giving 2,3-*trans*-cyclic ether **iii** in high yield [3a]. The reaction, however, needs reflux conditions, which gave

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unsatisfactory yields in some cases in natural product synthesis [4]. Therefore, a more efficient procedure for the present rearrangement-ring expansion was investigated. We have recently found that the chloromethanesulfonate (monochlate) [5] served as an extremely efficient leaving group for the inversion of secondary alcohols [6]. Thus, this new leaving group was applied to the present rearrangement-ring expansion reaction.

Treatment of the tetrahydrofuran **1** [3a] with chloromethanesulfonyl chloride ($ClCH_2SO_2Cl$=McCl) [5] in the presence of 2,6-lutidine in CH_2Cl_2 at 0 °C gave a monochlate **2**, which was then subjected to the rearrangement-ring expansion reaction. The results are shown in Table 1 in comparison with those of the corresponding mesylate **3**. Upon treatment of the monochlate **2** with $Zn(OAc)_2$ in AcOH-H_2O, the expected rearrangement took place very smoothly even at 50 °C, giving the ring-expanded ether, 2,3-*trans*-tetrahydropyran **4a,b** in 85% combined yield (**4a**: 77%, **4b**: 8%) from **1** (run 1), while the reaction of the corresponding mesylate **3** under the same reaction conditions gave **4a** in only 13% yield along with the recovered starting material **3** in 67% yield (run 5), although under reflux conditions **3** afforded 75% yield of **4a** (run 7) [3a]. The reaction of the monochlate **2** provided **4a,c** (56%) even under the conditions without $Zn(OAc)_2$ (run 2), while that of the mesylate **3** without $Zn(OAc)_2$ resulted in hydrolysis of the acetate (36%) and the recovery of **3** (61%) (run 6). These results suggested that the monochlate served as an efficient leaving group for the present reaction. We then examined the effect of solvents and reagents for the reaction of the monochlate **2**. The rearrangement of **2** with $Zn(OAc)_2$ also proceeded in dioxane-H_2O (1:1) at 50 °C to give **4a** in 97% yield (run 3) [7]. Thus, these neutral conditions should be useful for the synthesis of cyclic ethers having labile functional groups. Among several Lewis acids examined, $Sc(OTf)_3$ in dioxane-H_2O was found to effect the rearrangement to give **4c** in

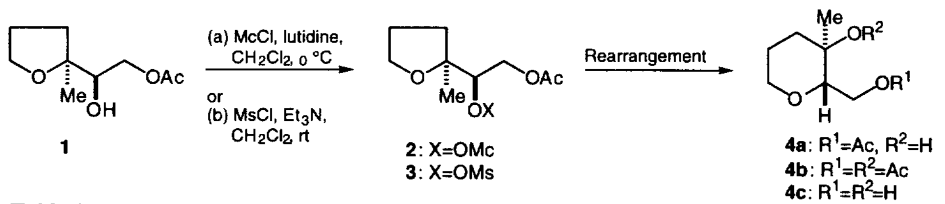

Table 1
Rearrangement of tetrahydrofuran **1** to tetrahydropyran **4**

Run	Substrate	Reagent[a]	Reaction Conditions	Yield of Product 4[b]		
1	**2**: X=Mc	$Zn(OAc)_2$	AcOH-H_2O, 50 °C, 4 h	85% (**4a**: 77%, **4b**: 8%)		
2		-----	AcOH-H_2O, 50 °C, 7 h	56% (**4a**: 26%, **4c**: 30%)		
3		$Zn(OAc)_2$	dioxane-H_2O, 50 °C, 6 h	97% (**4a**)		
4		$Sc(OTf)_3$	dioxane-H_2O, 50 °C, 7 h	90% (**4c**)		
5	**3**: X=Ms	$Zn(OAc)_2$	AcOH-H_2O, 50 °C, 24 h	13% (**4a**)	(**3**: 67%)[c]	
6		-----	AcOH-H_2O, 50°C, 7 h	---	(**3**: 61%)[c]	(36%)[d]
7		$Zn(OAc)_2$	AcOH-H_2O, reflux, 6 hr	75% (**4a**)[e]		

a) Four equiv of $Zn(OAc)_2$ or two equiv of $Sc(OTf)_3$ was used.
b) Overall yield from the alcohol **1**.
c) Yield of the recovered starting material **3**.
d) Hydrolysis product of the acetate in **3**.
e) Result from reference 3a. Yield after acetylation of the rearranged product.

90% yield (run 4) [8].

We next examined the rearrangement of the tetrahydropyrans **5** and **6** to the oxepanes **11** and **12**. The results are shown in Table 2. The rearrangement of the monochlate **7**, prepared from **5**, with $Zn(OAc)_2$ took place effectively in $AcOH$-H_2O under reflux for 30 min to give the ring-expanded ether, 2,3-*trans*-oxepane **11a,c** in 89% combined yield (run 1). The reaction also proceeded at 80 °C with or even without $Zn(OAc)_2$, giving **11** in 87% and 72% yields, respectively (run 2 and 3), while the corresponding mesylate **8** resulted in the recovery of **8** (60%) (run 6). Treatment of the monochlate **7** with $Zn(OAc)_2$ or $Sc(OTf)_3$ in dioxane-H_2O afforded **11c** in 82% yield (run 4 and 5).

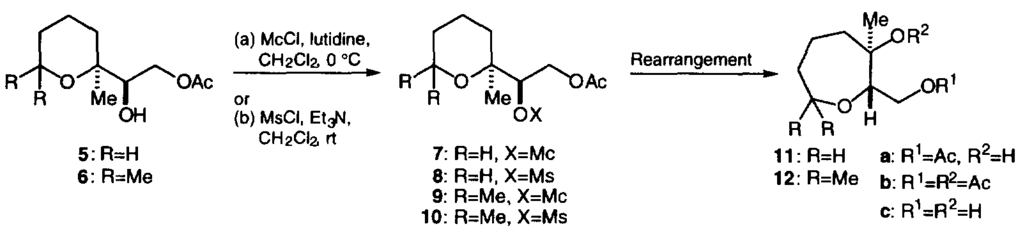

Table 2
Rearrangement of tetrahydropyran, **5** or **6**, to oxepane, **11** or **12**

Run	Substrate	Reagent[a]	Reaction Conditions	Yield of Product **11** or **12**[b]
1	**7**: X=Mc	$Zn(OAc)_2$	$AcOH$-H_2O,reflux, 30 min	89% (**11a**: 79%, **11c**: 10%)
2		$Zn(OAc)_2$	$AcOH$-H_2O, 80 °C, 3.5 h	87% (**11a**: 68%, **11b**: 19%)
3		-----	$AcOH$-H_2O, 80 °C, 2.5 h	72% (**11a**: 37%, **11c**: 35%)
4		$Zn(OAc)_2$	dioxane-H_2O, 80°C, 4 h	82% (**11c**)
5		$Sc(OTf)_3$	dioxane-H_2O, 80 °C, 6.5 h	82% (**11c**)
6	**8**: X=Ms	$Zn(OAc)_2$	$AcOH$-H_2O, 80 °C, 6 h	--- (**8**: 60%)[c]
7		$Zn(OAc)_2$	$AcOH$-H_2O, reflux, 8 h	95% (**11a**: 53%, **11b**: 42%)[d]
8	**9**: X=Mc	$Zn(OAc)_2$	$AcOH$-H_2O, rt, 24 h	92% (**12a**)
9		-----	$AcOH$-H_2O, 50 °C, 2 h	90% (**12a**: 80%, **12b**: 10%)
10		$Zn(OAc)_2$	dioxane-H_2O, rt, 4 d	90% (**12c**)
11		-----	dioxane-H_2O, 50 °C, 7 h	95% (**12a**: 58%, **12c**: 37%)
12		$Sc(OTf)_3$	dioxane-H_2O, rt, 12 h	82% (**12a**: 50%, **12c**: 32%)
13	**10**: X=Ms	$Zn(OAc)_2$	$AcOH$-H_2O, rt, 4 d	19% (**12a**) (**10**: 64%)[c]
14		$Zn(OAc)_2$	$AcOH$-H_2O, reflux, 2 h	90% (**12a**)[d]

a) Four equiv of $Zn(OAc)_2$ or two equiv of $Sc(OTf)_3$ was used.
b) Overall yield from the alcohol **5** or **6**.
c) Yield of the recovered starting material **8** or **10**.
d) Result from reference 3a.

The rearrangement of the monochlate **9**, prepared from 2,2,6,6-tetrasubstituted ether **6**, proceeded more easily [9]. Upon treatment of **9** with $Zn(OAc)_2$ in $AcOH$-H_2O, the reaction proceeded completely even at room temperature for 24 h to give **12a** in 92% yield (run 8), while the same reaction of the mesylate **10** gave only 19% yield of **12a** after 4 d along with the recovered **10** (64%) (run 13). The monochlate **9** provided **12a,b** in 90% combined yield even without $Zn(OAc)_2$ at 50 °C for 2 h (run 9). The treatment of the monochlate **9** with $Zn(OAc)_2$ or $Sc(OTf)_3$ in dioxane-H_2O also provided **12** in good yield (run 10-12).

Thus, the rearrangement-ring expansion reaction of the monochlate effectively proceeds under milder conditions than that of the mesylate. The reaction using a monochlate as the substrate can use $Zn(OAc)_2$ and $Sc(OTf)_3$ as the reagent and AcOH-H_2O and dioxane-H_2O as the solvent. The rearrangement reaction using the monochlate with $Zn(OAc)_2$ in AcOH-H_2O was successfully applied to the synthesis of CD-ring system by double ring expansion in the total synthesis of hemibrevetoxin B [10]. Applications of the present method to natural product synthesis are now in progress in this laboratory.

Typical procedure of the rearrangement-ring expansion reaction: To a solution of **1** (20.9 mg; 0.11 mmol) in CH_2Cl_2 (0.3 mL) were added 2,6-lutidine (0.1 mL; 0.88 mmol) and chloromethanesulfonyl chloride (0.05 mL; 0.55 mmol) at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture was diluted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. To a solution of the residue in AcOH (1.5 mL)-H_2O (1.5 mL) was added $Zn(OAc)_2 \cdot 2H_2O$ (96.6 mg; 0.44 mmol) and the mixture was stirred at 50 °C for 4 h. The mixture was extracted with EtOAc and the organic extracts were washed with brine, dried over $MgSO_4$, and evaporated azeotropically with toluene *in vacuo*. The residue was purified on flash column chromatography (silica gel FL60D; EtOAc:hexane=1:7) to give **4b** (2.0 mg; 8%) and **4a** (16.0 mg; 77%).

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[5] We abbreviated chloromethane sulfonate and $ClCH_2SO_2$ to monochlate and Mc, respectively, by reference to the abbreviations for trifluoromethane sulfonate (triflate) and CF_3SO_2 (Tf).

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[7] The ring expansion reaction of **2** with $Zn(OAc)_2$ also proceeded in MeCN-H_2O (50 °C, 6 h, 75%; reflux, 30 min, 93%) or in acetone-H_2O (50 °C, 6 h, 69%; reflux, 2 h, 88%).

[8] The ring expansion reactions of **2** with several Lewis acids in dioxane-H_2O at 50 °C were examined; $ZnCl_2$ (4 equiv, 6 h; 49% (**4c**)), $Zn(OTf)_2$ (4 equiv, 6 h; 79% (**4a**: 28%, **4c**: 51%)), $Yb(OTf)_3$ (2 equiv, 6 h; 78% (**4a**: 18%, **4c**: 60%)), $La(OTf)_3$ (2 equiv, 8 h; 53% (**4c**)), $Sc(OAc)_3$ (2 equiv, 9h, 63% (**4a**: 40%, **4c**: 23%).

[9] The 1,3-diaxial repulsion by the substituents would cause an acceleration of this rearrangement.

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