S_N2 Type Hydrolysis of Secondary Alkyl Halides and Sulfonates in Hydrothermal Water

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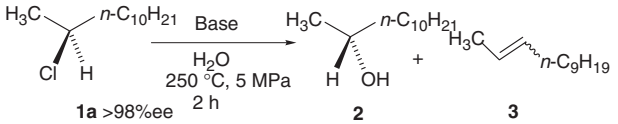
Optically active secondary alkyl halides and sulfonates were treated with alkaline hydrothermal water at 250 °C in sealed vessel. The hydrolysis mostly proceeded with inversion of stereochemistry.

Hydroxide ion is one of the most common base in chemistry and also considered to be one of the most gentle nucleophile in organic synthesis. It is reported, however, that it plays an important role as a nucleophile in super critical and hydrothermal water.[1,2] A loss of hydrogen bond network may increase the nucleophilicity. In addition, these super heated water possesses the higher dissolving ability of non-polar organic compounds because of its lower dielectric constant relative to the ambient water.[3] We have reported hydrolysis of dichloromethane in alkaline water under hydrothermal condition.[1a] The nucleophilic attack of hydroxide ion to the carbon of dichloromethane in S_N2 manner was concluded to be the main reaction route. In this communication, the same condition was applied to the optically active secondary halide or sulfonate to investigate the stereochemistry of hydrolysis reaction.

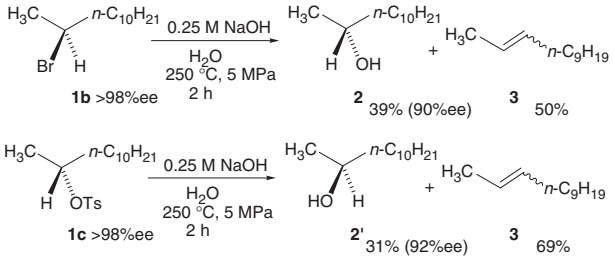
As shown in Table 1, (*S*)-2-chlorododecane (**1a**, >98%ee)[4] was treated with basic water. A mixture of **1a** (2.0 mmol) and basic water (20 mL) was added in a 30-mL-Teflon vessel which was placed in stainless autoclave.[1a,5,6] The whole was heated at 250 °C for 2 h. After the whole was cooled to room temperature, the obtained mixture was extracted with hexane. The combined organic phases were washed with sat. NH_4Cl aq and dried over Na_2SO_4. After concentration in vacuo, $CHBr_3$ (0.1 mmol) was added to the concentrated mixture as an internal standard for ^1H NMR analysis in order to determine the product distribution. The enantiomeric purity of **2** was determined by ^{19}F NMR analysis after conversion into Mosher's ester.[7]

In all cases, hydrolysis reaction competed with elimination reaction which afforded alkene **3**. The hydrolysis reaction proceeded with inversion of stereochemistry in 81–86%ee. To examine the effect of leaving group, (*S*)-2-bromododecane (**1b**) and (*R*)-2-dodecanyl tosylate (**1c**) were examined for the hydrolysis under hydrothermal condition. As shown in Scheme 1, these good leaving groups improved the stereospecificity slightly, but increased the ratio of elimination product **3**.

Table 1. Hydrolysis of (*S*)-2-chlorododecane



Base	Yield of **2** /%	%ee	Yield of **3** /%
2.0 M LiOH	25	83	75
2.0 M NaOH	66	86	34
0.25 M NaOH	60	81	34
2.0 M KOH	40	86	42
2.0 M CsOH	40	83	30

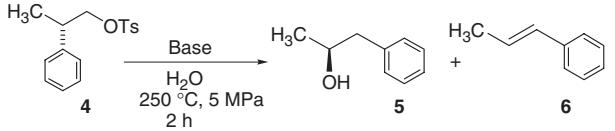


Scheme 1. Effect of leaving group.

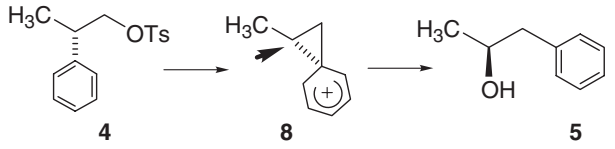
The loss of stereospecificity in the hydrolysis reaction of Table 1 and Scheme 1 implies an existence of S_N1 like reaction. The possibility of racemization that comes from S_N2 type reaction by the conjugated base (i.e. Cl^-, Br^-, and TsO^-) may be excluded, because of their low concetration and low nucleophilicity. In these S_N1 like reactions, carbocation intermediate even in a basic condition should contribute the reaction pathway in some extent. We tried to examine the effect of neighbouring group which may stabilize the carbocation.[8] As shown in Table 2, (*S*)-2-phenylpropyl tosylate (**4**) was treated with basic water under hydrothermal condition. Phenyl group will stabilize carbocation on β-position through benzenium ion.[9] The product of the hydrolysis reaction was secondary alcohol **5** in 53–56%ee. The formation of the product was explained as shown in Scheme 2.

In Table 3, results of hydrolysis of (*R*)-3-phenyl-2-propyl tosylate (**7**) under hydrothermal condition are shown. The hydrolysis product was secondary alcohol **5** with slight stereospecificity. The results can be explained as shown in Scheme 3. A direct nucleophilic attack gave **5** with inversion stereochemistry, while the neighbouring phenyl group made a route to the enantiomer

Table 2. Hydrolysis of (*S*)-2-phenylpropyl tosylate



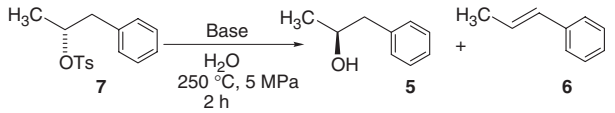
Base	Yield of **5** /%	%ee	Yield of **6** /%
0.2 M NaOH	63	56	30
0.2 M CsOH	61	53	35



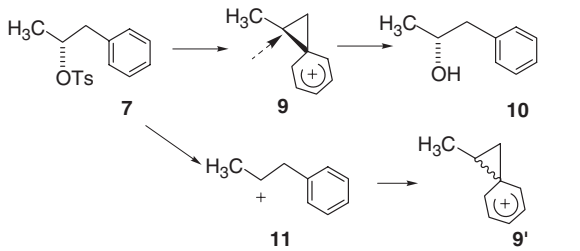
Scheme 2. Hydrolysis of **4** via benzenium ion **8**.

10 possible through stereospecifically formed benzenium ion **9** (Scheme 3). At the stage of formation of benzenium ion, however, secondary cation formation, whose route to the elimination product **6** was checked by the neighbouring phenyl group, also causes racemization (**9′**).

Table 3. Hydrolysis of tosyl (*S*)-1-phenyl-2-propyl tosylate



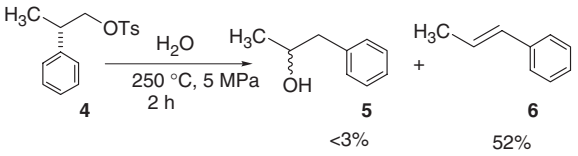
Base	Yield of **5** /%	%ee	Yield of **6** /%
0.2 M NaOH	25	4	45
0.2 M CsOH	40	12	40



Scheme 3. Hydrolysis of **7** via benzenium ion **9** and formation of recamic benzenium **9′**.

Even though the nucleophilicity of hydroxide ion is increased under hydrothermal condition, the existence of base is crucial for these reaction. As shown in Scheme 4, without an addition of base, **4** gave only the alkene **6**.

We previously reported the hydrolysis of dichloromethane with basic water under hydrothermal condition.[1] In this case, the kinetic study explained the reaction pathway according to S_N2 reaction. In the present work, main pathway of hydrolysis of secondary halide and tosylate with basic water under hydrothermal condition was also shown to be S_N2 like, as the inversion of stereochemistry was observed. We can also show the existence of benzenium ion even in the basic water under hydrothermal condition. Although the hydrothermal condition seems to be drastic, delicate intermediate such as benzenium ion can survive during the reaction.



Scheme 4. Hydrolysis of **4** without base.

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References and Notes

1 a) Y. Yamasaki, H. Enomoto, N. Yamasaki, and M. Nakahara, *Bull. Chem. Soc. Jpn.*, **73**, 2687 (2000). b) Y. Yamasaki, H. Enomoto, N. Yamasaki, and M. Nakahara, *Chem. Lett.*, **1999**, 83.
2 H. Oka, S. Yamago, J. Yoshida, and O. Kajimoto, *Angew. Chem., Int. Ed. Engl.*, **41**, 623 (2002).
3 D. Bröll, C. Kaul, A. Krämer, P. Krammer, T. Richter, M. Jung, H. Vogel, and P. Zehner, *Angew. Chem., Int. Ed. Engl.*, **38**, 2998 (1999); N. Akiya and P. E. Savage, *Chem. Rev.*, **102**, 2725 (2002); P. E. Savage, *Chem. Rev.*, **99**, 603 (1999).
4 Prepared from (*R*)-2-dodecanol which was prepared from (*R*)-propylen oxide and *n*-nonylmagnesium bromide in the presence of copper iodide.
5 S. Matsubara, Y. Yokota, and K. Oshima, *Chem. Lett.*, **33**, 294 (2004).
6 B. K. Mehta, K. Yanagisawa, M. Shiro, and H. Kotsuki, *Org. Lett.*, **5**, 1605 (2003).
7 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
8 D. N. Kevill and M. J. D'Souza, *J. Chem. Soc., Perkin Trans. 2*, **1997**, 257; M. Fujio, N. Goto, T. Dairokuno, M. Goto, Y. Saeki, Y. Okusako, and Y. Tsuno, *Bull. Chem. Soc. Jpn.*, **65**, 3072 (1992).
9 D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2129 (1952).

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