Pergamon

SCIENCE @ DIRECT®

Tetrahedron Letters 44 (2003) 8623–8625

TETRAHEDRON
LETTERS

Hydrolysis of acetals in water under hydrothermal conditions

Kimihiko Sato,[a] Tsutomu Kishimoto,[b] Minoru Morimoto,[b] Hiroyuki Saimoto[b] and Yoshihiro Shigemasa[b,*]

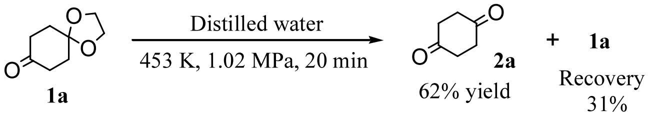
[a]*Industrial Research Institute of Tottori Prefecture, 7-1-1 Wakabadai-minami, Tottori 689-1112, Japan*
[b]*Department of Materials Science, Faculty of Engineering, Tottori University, Koyama, Tottori 680-8552, Japan*

Received 4 August 2003; revised 3 September 2003; accepted 5 September 2003

Abstract—A simple method for the hydrolysis of acetals and ketals was accomplished in neutral water or aqueous media by hydrothermal treatment without using acidic reagents. The deacetalization reaction was effectively accelerated in the presence of calcium chloride. Because no acidic catalysts were employed, neutralization of the reaction mixture was not necessary after the reaction. This sequence was successfully applied to the hydrolysis of chitosan, a biodegradable polyaminosaccharide.

Formations of acetals are valuable not only as synthetic intermediates but also as common methods for the protection and the isolation of polyols and carbonyl compounds.[1,2] Although a number of procedures have been developed for deacetalization, most of these methods need acidic media or oxidative conditions.[3,4] Liquid water in the sub- or supercritical region is an environmentally friendly solvent, and minimizes the utilization of acidic, basic, oxidative reagents in the decomposition of polymers and organic wastes.[5,6] Synthetic utility of the sub- or supercritical water has been recently reported.[7–9] Because hydrothermal conditions at 393–453 K do not enhance undesired fragmentation reactions, and were available by a relatively cheaper experimental device compared with that for the supercritical study;[10,11] we have tried to transform several organic compounds in neutral water under hydrothermal conditions and found that acetals and ketals were hydrolyzed to give the corresponding hydroxy and carbonyl compounds. Furthermore, we report the application of hydrothermal methods to partial hydrolysis of chitosan, a natural polyaminosaccharide.[12,13]

As shown in Scheme 1, treatment of 1,4-dioxaspiro-[4.5]decan-8-one (**1a**) in distilled water at 453 K gave 1,4-cyclohexanedione (**2a**) in 62% yield along with recovered **1a** (31%). Comparison of entry 1 with entries 2–4 in Table 1 revealed that utilization of calcium chloride as an additive improved the transformation and that 0.5 mol equivalent of calcium chloride was enough. Although employment of sodium chloride (entry 5) as an additive gave **2a** in the lower yield, barium chloride (entry 6) was as effective as calcium chloride. Among entries 3, 7, and 8 in Table 1, treatment of **1a** at 453 K gave **2a** in better yield compared with the treatment at 433 or 473 K. Although the reaction mechanism has not been clarified, the larger ionic product in the subcritical region may permit a sufficient supply of H^+ for the acid catalyzed hydrolysis of acetals, while dissociation of water provides an equal amount of H^+ and ^-OH.[14,15] According to the previous report,[16] calcium chloride might play as a weak Lewis acid, which activates the acetal group. As shown in entries 9–11 in Table 1, dimethyl acetal **1b**, diethyl acetal **1c**, and diethyl ketal **1d** were also hydrolyzed in high yields. Tetrahydropyranyl moiety in **3a** was removed to give a primary alcohol **4a** (entry 12 in Table 1). Also in cases of a secondary alcohol and a phenol (entries 13 and 14 in Table 1), deprotection of hydroxy groups was demonstrated in good yields. In contrast to the ester hydrolysis in sub- or supercritical water,[8,15] the ester group in **3c** was retained, and the acetal group in **3c** was selectively hydrolyzed under hydrothermal conditions.



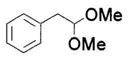
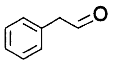
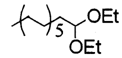
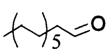
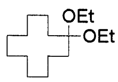
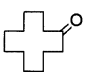
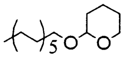
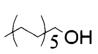
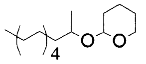
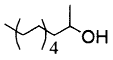
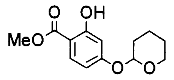
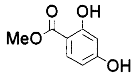
Scheme 1.

Keywords: acetals; ketals; hydrolysis; deprotection; chitosan.

* Corresponding author. Tel./fax: +81 857 31 5254; e-mail: shigemas@chem.tottori-u.ac.jp

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.087

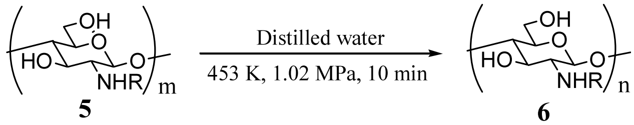
Table 1. Hydrolysis of acetals under hydrothermal conditions[a]

Entry	Substrate	Solvent	$CaCl_2$ / mol equiv	Temperature / K	Product	Isolated yield / %
1	**1a**	H_2O	0	453	**2a**	62[b]
2	**1a**	H_2O	0.1	453	**2a**	89
3	**1a**	H_2O	0.5	453	**2a**	94
4	**1a**	H_2O	2.0	453	**2a**	92
5	**1a**	H_2O	0.5[c]	453	**2a**	85
6	**1a**	H_2O	0.5[d]	453	**2a**	96
7	**1a**	H_2O	0.5	433	**2a**	22[e]
8	**1a**	H_2O	0.5	473	**2a**	81
9	 **1b**	H_2O/EtOH 1/1	0.5	453	 **2b**	90
10	 **1c**	H_2O/1,4-dioxane 1/4	0.5	453	 **2c**	97
11	 **1d**	H_2O/1,4-dioxane 1/4	0.5	453	 **2d**	92
12	 **3a**	H_2O/1,4-dioxane 1/4	0.5	453	 **4a**	96
13	 **3b**	H_2O/1,4-dioxane 1/4	0.5	453	 **4b**	94
14	 **3c**	H_2O/EtOH 2/3	0.5	453	 **4c**	94

[a] Substrate: 10 mg/ml, 10 ml; hydrothermal conditions: 453 K, 1.01 MPa, 20 min. Before the reaction, if the apparent pH* was 6.0 – 6.9, the initial pH* was adjusted to 7.0 by adding aqueous NaOH, where pH* means pH of a mixture of water and organic solvent and was not corrected. [b] Recovery of **1a**, 31%. [c] NaCl was used instead of $CaCl_2$. [d] $BaCl_2$ was used instead of $CaCl_2$. [e] Recovery of **1a**, 70%.

In a typical procedure, a solution of 1,1-diethoxycyclododecane (**1d**) (100 mg, 0.39 mmol) and calcium chloride dihydrate (29 mg, 0.20 mmol) in a mixture of distilled water and 1,4-dioxane (1:4 (vol/vol), 10 ml) was packed in a 20-ml volumetric bottle sealed by a silicone cap. Hydrothermal treatment of the sample in the bottle was performed in an airtight-autoclave HTP-50/250 (HISAKA WORKS Ltd.). Based on the temperature program, the bottle was warmed from room temperature to the reaction temperature in 20 min, and the temperature maintained for 20 min (453 K, 1.01 MPa). Then the reaction mixture was cooled down to room temperature in 5 min. Extractive workup followed by silica gel column chromatography gave cyclododecanone (65 mg, 92% yield).

This method was successfully applied to the hydrolysis of chitosan, which has been industrially produced from chitin, a β-(1-4)-linked natural polysaccharide composed of 2-acetoamido-2-deoxy-β-D-glucopyranose (*N*-acetyl-D-glucosamine) residues, by the deacetylation reaction.[17] Although chitosan could be hydrolyzed by acid treatment or enzymatic hydrolysis,[18,19] in the former method it is difficult to control the molecular weight, and the latter method is very expensive. As shown in Scheme 2, commercially available chitosan (**5**) (Chitosan 10B from Funakoshi Co., Ltd.; degree of deacetylation, 96%; weight averaged molecular weight (*M*w), 630000; and number averaged molecular weight (*M*n), 160000) was suspended in distilled water (8 mg/ml, 4 ml), and then subjected to hydrothermal treat-



5

R = H (96%) and Ac (4%)

*M*n 160000

6

*M*n 32000

Scheme 2.

ment (453 K, 1.01 MPa, 10 min). The gel permeation chromatography analysis of the hydrolyzate **6** using pullulan as the standard revealed that the molecular weight of the chitosan decreased to *M*w 105000 and *M*n 32000. It is noteworthy that chitoan, which was hydrolyzed by hydrochloric acid to give considerable amount of monomer and dimer, was hydrothermally hydrolyzed in *endo* manner. Because chitosans of relatively low molecular weights show better solubility than the high molecular weight homologs, and are useful as Pd-carriers for electroless plating technology,[20] the present method is promising as a simple and convenient way to prepare this class of chitosans.

Acknowledgements

This work was partially supported by the Ministry of Economy, Trade and Industry of Japan (Regional Consortium Project: 14C6003), the Ministry of Education, Science, Sports and Culture of Japan (Grant-in-Aid for Scientific Research (C) No. 10650851 and 14580820), and the Takahashi Industrial and Economic Research Foundation.

References

1. Wulff, G.; Schmid, J.; Venhoff, T. *Macromol. Chem. Phys.* **1996**, *197*, 259–274.
2. Iwata, A.; Tang, H. Q.; Kunai, A.; Ohshita, J.; Yamamoto, Y.; Matui, C. *J. Org. Chem.* **2002**, *67*, 5170–5175.
3. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp. 297–329.
4. Mirjalili, B. F.; Zolfigol, M. A.; Bamonir, A. *Russ. J. Org. Chem.* **2002**, *38*, 761–762.
5. Ehara, K.; Saka, S. *Cellulose* **2002**, *9*, 301–311.
6. Yesodharan, S. *Curr. Sci.* **2002**, *82*, 1112–1122.
7. Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750.
8. Oka, H.; Yamago, S.; Yoshida, J.; Kajimoto, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 623–625.
9. Kabyemela, B. M.; Adschiri, T.; Malaluan, R. M.; Arai, K.; Ohzeki, H. *Ind. Eng. Chem. Res.* **1997**, *36*, 5063–5067.
10. Katritzky, A. R.; Nichols, D. A.; Siskin, M.; Murugan, R.; Balasubramanian, M. *Chem. Rev.* **2001**, *101*, 837–892.
11. Sato, K.; Saimoto, H.; Morimoto, M.; Shigemasa, Y. *Sen'I Gakkaishi* **2003**, *59*, 104–109.
12. Omura, Y.; Shigemoto, M.; Akiyama, T.; Saimoto, H.; Shigemasa, Y.; Nakamura, I.; Tsuchido, T. *Biocontrol Sci.* **2003**, *8*, 25–30.
13. Terada, N.; Morimoto, M.; Saimoto, H.; Okamoto, Y.; Minami, S.; Shigemasa, Y. *Polym. Adv. Technol.* **2003**, *14*, 40–51.
14. Holzapfel, W. B. *J. Chem. Phys.* **1969**, *50*, 4424–4428.
15. Lestis, H. P.; Glaser, R.; Liotta, C. L.; Eckert, C. A. *J. Chem. Soc., Chem. Commun.* **1999**, 2063–2064.
16. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768–6769.
17. Morimoto, M.; Saimoto, H.; Shigemasa, Y. *Trends Glycosci. Glycotechnol.* **2002**, *14*, 205–222.
18. Shigemasa, Y.; Saito, K.; Sashiwa, H.; Saimoto, H. *Int. J. Biol. Macromol.* **1994**, *16*, 43–49.
19. Saimoto, H.; Takamori, Y.; Morimoto, M.; Sashiwa, H.; Okamoto, Y.; Minami, S.; Matsuhashi, A.; Shigemasa, Y. *Macromol. Symp.* **1997**, *120*, 11–18.
20. Omura, Y.; Renbutsu, E.; Morimoto, M.; Saimoto, H.; Shigemasa, Y. *Polym. Adv. Technol.* **2003**, *14*, 35–39.