Pergamon

Tetrahedron Letters, Vol. 37, No. 31, pp. 5569-5572, 1996

0040-4039/96 \$15.00 + 0.00

PII: S0040-4039(96)01158-6

Aldol Reactions on Solid Phase. Sc(OTf)3-Catalyzed Aldol Reactions of Polymer-Supported Silyl Enol Ethers with Aldehydes Providing Convenient Methods for the Preparation of 1,3-Diol, β-Hydroxy Carboxylic Acid, and β-Hydroxy Aldehyde Libraries

Shū Kobayashi,* Iwao Hachiya, Masaru Yasuda

Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Abstract: *Aldol reactions on solid phase have been achieved. In the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$), polymer-supported silyl enol ethers reacted with aldehydes to afford the corresponding β-hydroxy thioester derivatives, which were reduced to 1,3-diol and β-hydroxy aldehyde derivatives, or hydrolyzed to β-hydroxy carboxylic acid derivatives.* Copyright © 1996 Elsevier Science Ltd

While large numbers of useful synthetic reactions have been developed, a few have been applied to the reactions on solid phase so far.[1] Therefore, development of basic carbon-carbon bond-forming reactions on solid phase is one of the most important tasks, especially in combinatorial synthesis of lower molecular organic compounds.[2] In our previous paper, we reported the first synthesis of polymer-supported silyl enol ethers (thioketene silyl acetals) and their reactions with imines for the construction of an amino alcohol library.[3] Since silyl enol ethers are versatile reagents in organic synthesis,[4] other carbon-carbon bond-forming reactions using the polymer-supported silyl enol ethers have been investigated. In this paper, we describe aldol reactions with aldehydes for the construction of 1,3-diol, β-hydroxy aldehyde, and β-hydroxy carboxylic acid libraries.

The aldol reaction of silyl enol ethers with aldehydes (Mukaiyama aldol reaction)[5] is known as one of the most important and fundamental carbon-carbon bond-forming reactions. Although the original report requires a stoichiometric amount of $TiCl_4$ to promote the reaction, we found that a catalytic amount of scandium triflate ($Sc(OTf)_3$)[6] accelerates this reaction efficiently.[7] In the aldol reaction of polymer-supported silyl enol ethers with aldehydes, it was also revealed that $Sc(OTf)_3$ effectively catalyzed the reaction. The effect of the amount of the catalyst and reaction temperature in the model reaction of copoly-(styrene-1%-divinylbenzene) resin-based silyl enol ether **1**[3] with benzaldehyde is shown in Table 1. While a low yield was obtained at room temperature, the yield was improved at lower temperatures. Moreover, use of 20 mol% of $Sc(OTf)_3$ gave better results than use of 10 mol% of the catalyst. Silyl enol ether **1** reacted with benzaldehyde in dichloromethane at -78 °C to afford the corresponding aldol adduct, which was reduced with $LiBH_4$ to give the 1,3-diol. The yield was determined to be 82%, based on the loading level of the silyl enol ether.[3]

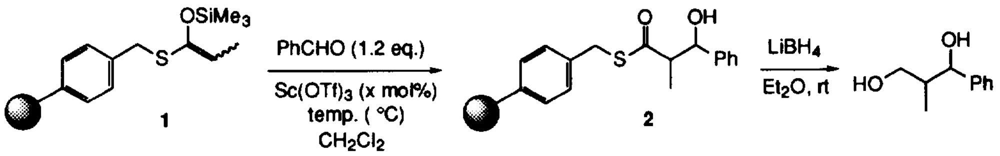
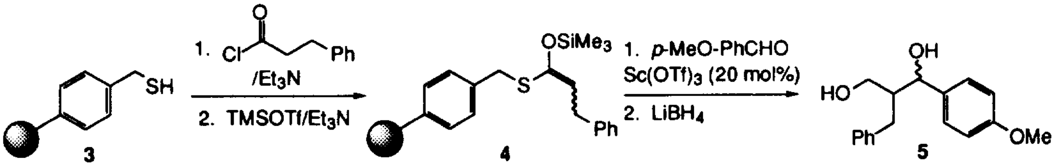


Table 1. Effect of the amount of the catalyst and temperature

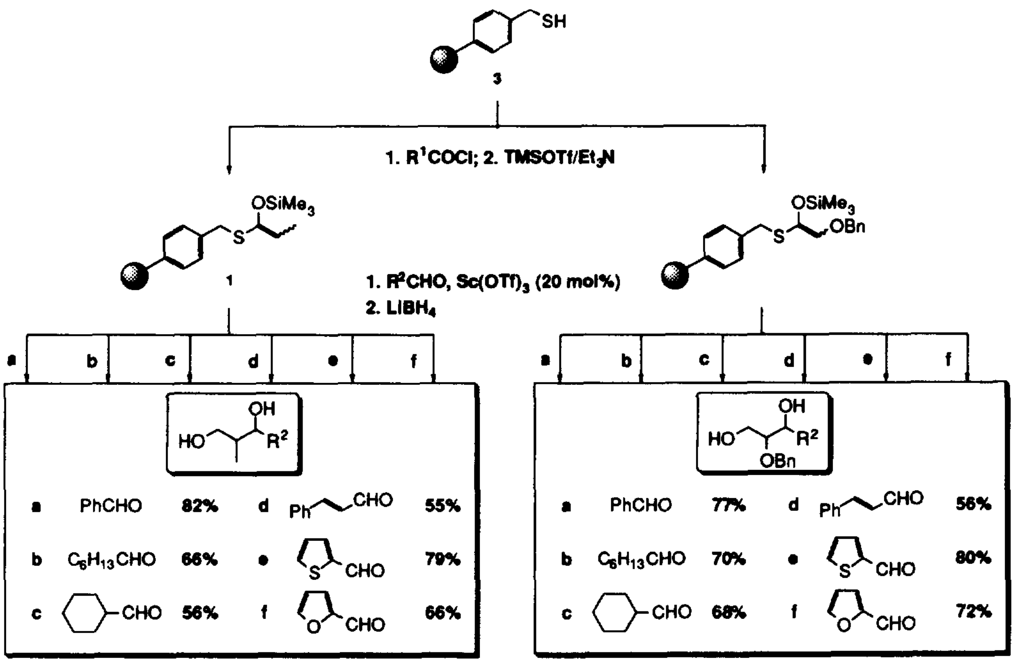
$Sc(OTf)_3$/x mol%	Temp./°C	Yield/%
10	rt	20
10	-10	63
10	-40	73
10	-78	73
20	-78	82

As polymer-supported silyl enol ethers are prepared from thiol **3**,[3] preparation of a 1,3-diol library is performed starting from **3**. An example is shown in Scheme 1 using two acid chlorides and six typical aldehydes including aromatic, aliphatic, α,β-unsaturated, and heterocyclic aldehydes. In all cases, the reactions proceeded smoothly to afford the corresponding 1,3-diols in good yields.[8] In addition, polymer-supported silyl enol ether **4**, which was prepared from **3** and hydrocinnamoyl chloride, reacted with *p*-anisaldehyde, followed by reduction with $LiBH_4$ to afford 1,3-diol **5** in a 72% yield based on the starting chloromethyl resin (76% yield based on **4**). An aldol reaction using a zinc enolate on solid phase was recently reported to give the same diol (**5**) in a 26% yield.[9]

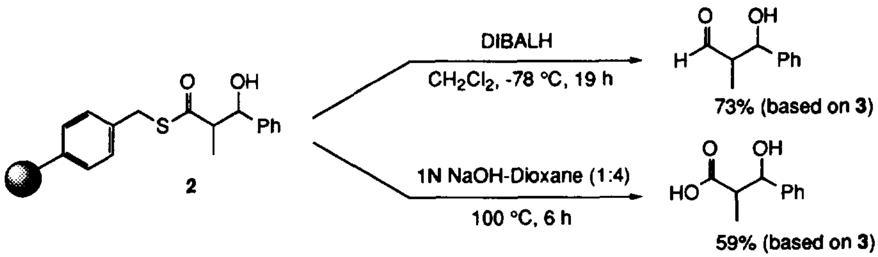


Following is a typical experimental procedure for the reaction of **1** with benzaldehyde: A mixture of benzaldehyde (25.4 mg, 0.24 mmol), **1** (224.0 mg, 0.20 mmol), and $Sc(OTf)_3$ (19.6 mg, 20 mol%) in dichloromethane (2 ml) was stirred for 20 h at -78 °C. The reaction was then quenched by adding dioxane-water-HCl. The resin was washed with water, dioxane, and Et_2O successively, and dried under reduced pressure. The resin was then treated with lithium borohydride (21.8 mg, 1.0 mmol) in ether (4 ml) at rt for 12 h. Phosphate buffer (pH = 7) was added and the aqueous layer was extracted with ether. The organic layers were combined and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by preparative TLC to afford the corresponding 1,3-diol (27.2 mg, 0.16 mmol, 82% yield). The resin was recovered as a thiol form (**3**), which could be used for the second reaction.

While 1,3-diols are successfully cleaved from the support by treatment with $LiBH_4$, it is also possible to produce β-hydroxy aldehydes or β-hydroxy carboxylic acids directly (Scheme 2).



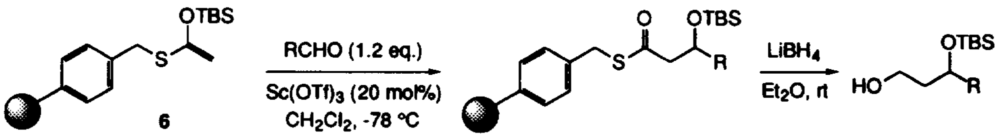
Scheme 1. 1,3-Diol Library Based on Aldol Reactions



Scheme 2. Conversion to β-Hydroxy Aldehyde or β-Hydroxy carboxylic Acid

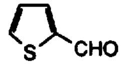
When α-substituted silyl enol ethers were used, the desired aldol reactions proceeded smoothly. On the other hand, a lower yield was observed when an α-unsubstituted silyl enol ether was used in the reaction with benzaldehyde. In order to improve the yield, several reaction conditions were examined and finally it was found that the yield was improved when *t*-butyldimethylsilyl enol ether **6** was used (Table 2).[10]

In summary, the aldol reaction of polymer-supported silyl enol ethers with aldehydes, a basic carbon-carbon bond-forming reaction on solid phase, has been successfully carried out using Sc(OTf)$_3$ as a catalyst. It has also been demonstrated that the reaction is useful for the construction of 1,3-diol, β-hydroxy aldehyde, and β-hydroxy carboxylic acid libraries. It is noted that on solid phase, the Lewis acid-catalyzed aldol reaction is superior to the aldol reaction of zinc enolates with aldehydes under basic conditions.



TBS = $^{t}BuMe_2Si$

Table 2. Aldol Reactions of 6 with Aldehydes

RCHO	Yield/%
PhCHO	69[a]
	91[b]
	95[c]

Containing 1,3-diols; a) 9%; b) 13%; c) 14%

Further studies to prepare useful libraries using the present aldol reaction as well as to develop new methodologies for combinatorial synthesis are now in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. I. H. thanks the JSPS fellowship for Japanese Junior Scientists.

References and Notes

1) *Reviews:* a) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17-42. b) Hermkens, P. H. H.; Ottenheijm, H. C.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554.

2) *Reviews:* a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401. b) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135-8173. c) Lowe, G. *Chem. Soc. Rev.* **1995**, *37*, 309-317. d) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600.

3) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809-2812.

4) *Reviews*: a) Rasmussen, J. K. *Synthesis* **1977**, 91-110. b) Fleming, I. *Chimica* **1980**, *34*, 265-271. c) Brownbridge, *Synthesis* **1983**, 1; 85-104. d) Weber, W. P. *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983. e) Colvin, E. W. *Silicon in Organic Synthesis*, Butterworths, London, 1981.

5) Mukaiyama, T.; Banno, K.; Narasaka, K. *Chem. Lett.* **1973**, 1101-1104.

6) a) Thom, K. F., US Patent 3615169 (1971); *CA* **1972**, *76*, 5436a. b) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755-3758. c) Kobayashi, S. *Synlett* **1994**, 689-701.

7) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472-474.

8) Moderate diastereoselectivities (1/1~2/1) were observed. Relative configuration assignment was not made.

9) Kurth, M. J.; Ahlberg, L. A.; Chen, C.; Melander, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang, R.; Nakatsu, T.; Green, C. *J. Org. Chem.* **1994**, *59*, 5862-5864.

10) The reactions were quenched by adding water.

(*Received in Japan* 29 *May* 1996; *accepted* 10 *June* 1996)