

S0040-4039(96)00435-2

Polymer-Supported Silyl Enol Ethers. Synthesis and Reactions with Imines for the Preparation of an Amino Alcohol Library

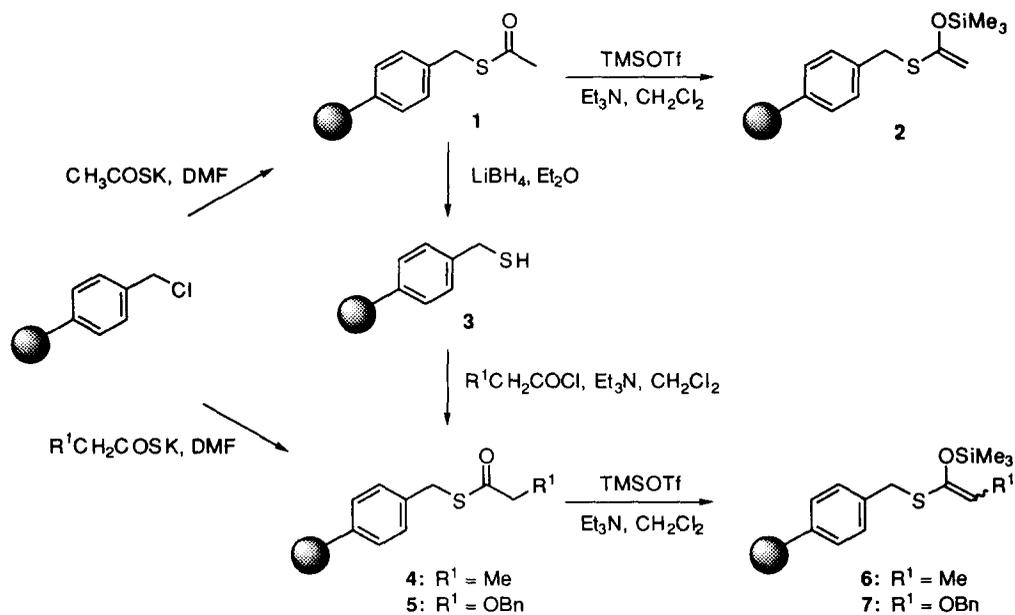
Shū Kobayashi,* Iwao Hachiya, Shū Suzuki, and Mitsuhiro Moriwaki
Department of Applied Chemistry, Faculty of Science,
Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162

Abstract: Polymer-supported silyl enol ethers (thioetene silyl acetals) were prepared from chloromethyl copoly-(styrene-1%-divinylbenzene) resin. The silyl enol ethers reacted with imines in the presence of a catalytic amount of scandium triflate ($\text{Sc}(\text{OTf})_3$) to afford β -amino thioesters, which were reduced to amino alcohols in good yields. These reactions provide a convenient method for the preparation of an amino alcohol library. Copyright © 1996 Elsevier Science Ltd

Silyl enol ethers are versatile reagents in organic synthesis.¹ They are used as isolable enolate equivalents and many useful reactions using silyl enol ethers have been developed.¹ In the course of our investigations to exploit efficient methods for combinatorial synthesis,² we planned to immobilize silyl enol ethers to a polymer. In this paper, we disclose the first example of polymer-supported silyl enol ethers and describe their reactions with imines for the preparation of an amino alcohol library.

Polymer-supported silyl enol ethers (thioetene silyl acetals) were prepared according to Scheme 1. Chloromethyl copoly-(styrene-1%-divinylbenzene) resin (1.15 mmol/g) was treated with potassium thioacetate in DMF. Formation of thioester **1** was indicated by IR spectra showing a strong carbonyl stretching vibration at 1693 cm^{-1} . A chlorine titration showed that **1** was obtained in a 95% yield. Thioester **1** thus obtained was then combined with TMSOTf and triethylamine³ in dichloromethane to afford silyl enol ether **2**.⁴ Similarly, silyl enol ethers **6** and **7** were prepared from **4** and **5**, respectively. Silyl enol ethers **6** and **7** were alternatively synthesized from thiol **3** according to the Scheme. Thiol **3** was prepared by reducing **1** using LiBH_4 in Et_2O at room temperature (rt). Several trials to hydrolyze thioester **1** under basic conditions failed.

Silyl enol ethers thus prepared were tested in the reaction with imines. It has been reported that silyl enol ethers react with imines in the presence of a Lewis acid to afford β -amino ketones, esters, and thioesters.⁵ Reduction of the adducts gives the corresponding amino alcohols, therefore these reactions using the polymer-supported silyl enol ethers provide a new method for the preparation of an amino alcohol library. We chose the reaction of **2** (0.88 mmol/g) with *N*-benzylideneaniline as a model and several Lewis acids were tested (Table 1). Although typical Lewis acids such as TiCl_4 , SnCl_4 , and $\text{BF}_3\cdot\text{OEt}_2$ gave poor results, a catalytic amount of a new type of Lewis acid such as $\text{Sc}(\text{OTf})_3$ ⁶ or $\text{Hf}(\text{OTf})_4$ ⁷ gave better results.



Scheme 1. Synthesis of Polymer-Supported Silyl Enol Ethers

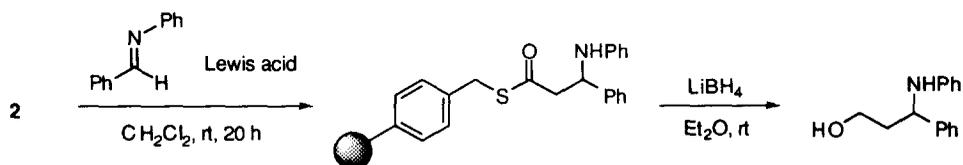


Table 1. Effect of Lewis Acids

Lewis Acid (mol%)	Yield (%)	Lewis Acid (mol%)	Yield (%)
SnCl_4 (100)	2	$\text{Zr}(\text{OTf})_4$ (10)	23
TiCl_4 (100)	3	$\text{Hf}(\text{OTf})_4$ (10)	70
$\text{BF}_3 \cdot \text{OEt}_2$ (100)	10	$\text{Sn}(\text{OTf})_2$ (10)	40
$\text{Sc}(\text{OTf})_3$ (10)	65	TMSOTf (10)	47

Several imines and polymer-supported silyl enol ethers were then screened using $\text{Sc}(\text{OTf})_3$ as a catalyst, and the results are summarized in Table 2. Although the reaction conditions have not yet been optimized, the desired amino alcohols were obtained in good yields after reduction.⁸

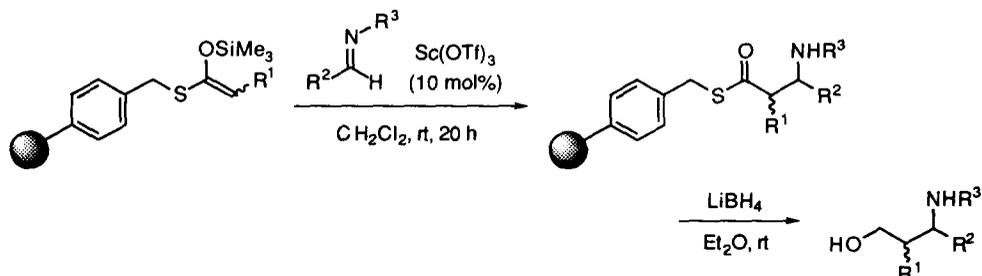


Table 2. The Reactions of Polymer-Supported Silyl Enol Ethers with Imines

R ¹	R ²	R ³	Yield (%)	R ¹	R ²	R ³	Yield (%)
H	Ph	Ph	65	Me	Ph	Ph	78
H	2-furyl	Ph	65	Me	2-furyl	Ph	68
H	2-thiophene	Ph	55	Me	c-C ₆ H ₁₁	Ph	77
H	c-C ₆ H ₁₁	Ph	68	Me	Ph	p-MeOPh	64
H	Ph	PhCH ₂	42	Me	p-ClPh	p-MeOPh	68
H	Ph	p-MeOPh	50	BnO	Ph	Ph	67
H	p-ClPh	p-MeOPh	52	BnO	2-furyl	Ph	77
H	p-MeOPh	p-MeOPh	51	BnO	2-thiophene	Ph	71
H	2-furyl	p-MeOPh	67	BnO	c-C ₆ H ₁₁	Ph	79
				BnO	Ph	p-MeOPh	66

Following is a typical experimental procedure for the reaction of **7** with *N*-benzylideneaniline: to **7** (234.2 mg, 0.20 mmol⁹) and $\text{Sc}(\text{OTf})_3$ (9.8 mg, 10 mol%) in dichloromethane (2 ml) was added *N*-benzylideneaniline (36.2 mg, 0.24 mmol) at rt. The mixture was stirred for 20 h at this temperature, and the reaction was then quenched by adding saturated aqueous sodium hydrogen carbonate. The resin was washed with water, dioxane, and Et₂O 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) and then 1N NaOH were added and the aqueous layer was extracted with ether. The organic layers were combined and dried (Na₂SO₄). After removal of the solvent, the crude product was purified by preparative TLC to afford the corresponding amino alcohol (44.7 mg, 0.13 mmol, 67% yield). The resin was recovered as a thiol form (**3**), which could be used for the formation of **1**, **4**, and **5**.

In summary, we have prepared the first polymer-supported silyl enol ethers. They reacted with imines to afford β-amino thioesters, which were reduced to give amino alcohols. These reactions provide a useful method for the preparation of an amino alcohol library. Further studies using the silyl enol ethers in other synthetic reactions as well as to prepare other types of silyl enol ethers 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.

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- 8) Moderate diastereoselectivities (1/1~3/1) were observed. Relative configuration assignment was not made at this stage. Cf. 6a, b).
- 9) The loading of **5** is quantitated after reduction of the thioester with LiBH₄. Formation of **7** from **5** proceeded quantitatively (determined by IR).

(Received in Japan 29 January 1996; revised 23 February 1996; accepted 29 February 1996)