Pergamon

Tetrahedron Letters, Vol. 38, No. 4, pp. 591-594, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02399-4

Convenient Method for Preparing Polystyrene having β-Hydroxy Group : Its Application to the Synthesis of Polyethylene Glycol-Grafted Polystyrene Resin

Byeong-Deog Park[a], Hyeong-Ik Lee, Sun-Jong Ryoo, and Yoon-Sik Lee[*]

[a]Aekyung Central Research Center, Taejeon 300-200, Korea
Dept. of Chemical Technology, Seoul National University, Seoul 151-742, Korea

Abstract: An effiecient method for preparing β-hydroxy polystyrene resin is described. Friedel-Crafts alkylation of polystyrene resin with propylene oxide in the presence of a Lewis acid catalyst affored 2-(1-methyl) hydroxyethyl polystyrene (PS-PO). Addition of ethylene oxides to the PS-PO in the presence of base gave PS-g-PEG resins. The resin contained 60-80%(w/w) of PEG and showed excellent stability in highly acidic media. © 1997, Elsevier Science Ltd. All rights reserved.

Nowadays, the use of combinatorial libraries of peptides, nucleotide and small molecules has become a very powerful tool for the development of therapeutic agents[1]. For the construction of peptide libraries, polystyrene beads grafted with polyethylene glycol (PS-g-PEG)[2] have been widely used as solid supports. This is due to the excellent properties of PS-g-PEG: good solvation properties in various solvents and good biocompatibility with enzymes, and cells.[3]

PS-g-PEG resins were prepared by directly reacting chloromethylated polystyrene, known as Merrifield resin[4], with polyethylene glycol[5]. In another process, hydroxy group was introduced onto polystyrene, and used as a precursor of PS-g-PEG resin for the addition polymerization of ethylene oxide thereto. Conventionally, Merrifield resin has been adopted to introduce the hydroxy group onto polystyrene[6]. Bayer *et al.*[7] has previously reported a hydroxylation process from Merrifield resin by using tetraethylene glycols which are previously treated by bases, such as KOH or NaOH. However, there are several drawbacks to these processes. One is the crosslinking reaction by dihydroxy groups of polyethylene or tetraethylene glycols. This reaction reduces the substitution degree of functional groups. Another disadvantage, a more critical one, is that polyethylene or tetraethylene glycols are grafted to the polymer backbone as benzyl ether linkages, which would be unstable and cleaved releasing polyethylene glycols in the presence of strong acid, such as trifluoroacetic acid, trifluoromethanesulfonic acid, hydrofluoric acid, which are normally used in peptide synthesis. This unstability in acid medium limits the use of Boc-amino acids during solid phase peptide synthesis. Moreover, the process for preparing Merrifield resin from polystyrene requires the use of chloromethylether, which is a suspected carcinogen.

Therefore, it is important not to have PS-g-PEG resin precursor containing the hydroxy group at the α position to the polymer backbone. Even though a process for introducing hydroxy group at β position has been disclosed[8], it consists of at least three steps. Another more important requirement for preparing the precursor for PS-g-PEG resin is the high initial loading of the functional groups. Generally, the final substitution degree of hydroxy groups in the PS-g-PEG drops to about 20% of the initial level after an addition of 80%(w/w) of PEG onto the polystyrene resin. Now, we would like to report an easy method to introduce β-hydroxy groups to the polystyrene backbone via one step reaction,

which can also offer high substitution degrees.

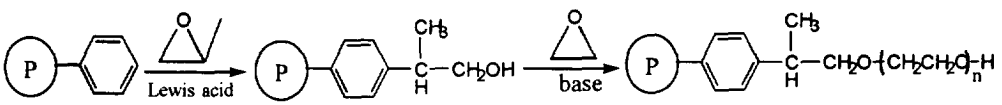
Recently, we found that 2-(1-methyl)hydroxyethyl group can be directly introduced to polystyrene resin by Friedel-Crafts alkylation with propylene oxide[9] in the presence of a Lewis acid catalyst such as $SnCl_4$. It is shown in Scheme 1 and the results are summarized in Table 1.

Table 1. The Degree of Substitution of 2-(1-methyl)hydroxyethyl Group on Polystyrene Resin with Various Amounts of Catalysts[a]

Run	Catalyst	Temp. (℃)	Amount of Catalyst(eq)[b]	Amount of PO (eq)[b]	Sub'n degree[c] (mmol/g)
1	$SnCl_4$	40	0.4	0.4	1.07
2	$SnCl_4$	40	1.1	1.1	1.12
3	$SnCl_4$	40	1.6	1.6	1.27
4	$SnCl_4$	40	2.6	2.6	1.41
5	$SnCl_4$	40	5.0	5.0	1.88
6	$SnCl_4$	40	10.0	10.0	2.23
7	$SnCl_4$	0	1.0	1.0	1.42
8	$SnCl_4$	0	1.4	1.4	1.98
9	$SnCl_4$	0	2.0	2.0	2.38
10	$AlCl_3$	40	0.4	0.4	[d]

[a]Reaction condition: solvent, methylene chloride; reaction time, 5 hour. [b]The amount of catalysts and propylene oxide(PO) added to the phenyl groups in polystyrene resin(5g, 47.5 mmol). [c]Calculated from N content of the PS-PO resin after reacting with 10 eq. of phenyl isocyanate. [d]N% value was below 1%.

Scheme 1



PS-PO Resin PS-g-PEG Resin

$SnCl_4$ was first introduced to a suspension of polystyrene beads in methylene chloride, and propylene oxide diluted in methylene chloride was slowly added onto it. When the order was reversed, the hydroxy groups were introduced at very low level. Moreover, the reaction medium turned brown and viscous which indicated that polypropylene glycols might be formed as side reactions. Nakajima *et al.*[10] had reported about the side reaction between propylene oxide and Lewis acid. The added Lewis acid in the presence of propylene oxide seemed to catalyze the polymerization of propylene oxide more easily. When the Lewis acid catalyst is added first, the catalyst seem to diffuse inside the beads making a complex with the phenyl rings of polystyrene[11]. Then, the added propylene oxide would diffuse into the polystyrene bead more freely until it forms a complex with the catalyst, finally yielding 2-(1-methyl)hydroxyethyl group to the polystyrene resin.

We also have tested several other Lewis acids such as BCl_3, BF_3, AlF_3, $AlCl_3$, $AlBr_3$, $FeCl_3$, $SbCl_5$, $ZnCl_2$, ZnI_2, $HgCl_2$ for the ring substitution reaction. Among the Lewis acids tested, none of them gave satisfying results as that of $SnCl_4$. In case of $AlCl_3$ which is stronger than $SnCl_4$ in catalytic effect[11], the substitution degree of the hydroxy group was rather much lower than that of $SnCl_4$. In this reaction, if a strong catalyst is used, side reactions such as homopolymerization might predominate and reduce the substitution yield.

Comparing to chloromethylation or aminomethylation processes where average substitution degrees do not normally exceed above 1.5 mmol/g[4b,12], this process can give higher substitution degrees up to 2.4-2.7 mmol/g at β position[12] by a single step reaction, and they are easily controllable by changing the amount of catalyst and propylene oxide (Table 1). Among other factors, the control of temperature seems to be very critical. When the reactions were carried at 40℃, even though we could obtain reasonably high substitution degree (2.23 mmol/g), large amounts of catalyst and propylene oxide were necessary and most of the propylene oxides were not reacted on the phenyl rings. It is supposed that oligomerization of propylene oxide occurs as side reactions. When large amount of catalyst and propylene oxides were used, a brown colored viscous oily material was produced. On the contrary, the reaction at 0℃ gave high substitution degree. Ethylene oxide was also used as a reactant. But, the substitution degrees of hydroxy group were very low. This is probabley due to the unstability of transition state from Lewis acid-activated ethylene oxide.

In order to test the usefulness of this process, we have prepared polyethylene glycol-grafted polystyrene (PS-g-PEG) resins from 2-(1-methyl)hydroxyethyl polystyrene (PS-PO) by adding ethylene oxides to the β-hydroxy groups. Thus, after treating PS-PO with KOH in an autoclave, ethylene oxide were added and polymerized to the resins at 110 ℃ yielding PS-g-PEG resins which contained 60-80% (w/w) of PEG.

The stabilities of the PS-g-PEG resins in strong acid medium were measured.[13] Comparing with the result of PS-g-PEG resin originated from Merrifield resin, we found that our PS-g-PEG resins were exceedingly stable in 50% of trifluoroacetic acid, trifluoromethanesulfonic acid.[14] The high stability in acidic medium makes this resin versatile in peptide coupling reaction with Boc amino acids as well as in the construction of chemical library which requires strong acid treatment.

In summary, propylene oxide with $SnCl_4$ catalyst can introduce high degree of β-hydroxy groups to polystyrene, up to a maximum of 2.7 mmol/g resin. The process is easily controllable and simple. Moreover, the PS-g-PEG resin prepared from PS-PO revealed good stability in acidic medium.

Experimental

2-(1-Methyl)hydroxyethyl polystyrene (PS-PO)

After thorough washing[4b], polystyrene-1% divinylbenzene copolymer beads (BioRad Co., Biobead S-X1, 200-400 mesh, 5g, 47.5 mmol) were swollen in methylene chloride (80 ml) in 3-necked round bottomed flask, and $SnCl_4$ or $AlCl_3$ was added to the resin mixture with stirring. Propylene oxide in 20 ml methylene chloride was then added dropwise in 10 minutes with stirring. After 5 hours of reaction, 100 ml of MeOH was added to quench the remaining catalysts and the resin was washed with EtOH(×3), 0.1*N* aq. HCl(×3), water(×3), MeOH(×2) and dried in vacuum.

Polyethylene glycol-grafted polystyrene (PS-g-PEG)

The PS-PO resin (5 g) and KOH (1.1 eq.) were added in dioxane (150 ml) in a pressure reactor (Parr Model 4561) and purged with nitrogen gas for 30 min. at 100℃ to remove moisture. Ethylene oxide (50 ml) was added to the reactor and the reaction mixture was maintained at 110 ± 1℃ with stirring. After 9 hours, the resin was washed with dioxane/water (1:1, ×3), 0.1*N* aq. HCl (×3), water(×3), ethanol(×5), and methylene chloride(×3) and dried in vacuum. The grafting levels were determined by weight increase.

Acknowledgements : This work was supported by Korea Science & Engineering Foundation.(Grant 93-0300-03-01-3)

References and Notes

1. (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (b) Cortese R. *Combinatorial Libraries: Synthesis, Screening, and Application Potential*; W. de Gruyter: New York **1995**. (c) Gallo, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gorden, E. M. *J. Med. Chem.* **1994**, *37*, 1233-1251.
2. (a) Bayer, E. *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 113-216. (b) Barany, G.; Albericio, F.; Biancalana, S.; Bontems, S. L.; Chang, J. L.; Eritja, R.; Ferrel, M.; Fields, C. G., *et al. Peptides: Chem. & Biol., Proc. of 12th Am. Pept. Sympo.*; Smith, J. A.; Rivier, J. E. Eds.; ESCOM: Leiden, pp603-604, **1992**. (c) Zhang, L.; Rapp, W.; Bayer, E. *Peptide 1990: Proc. of 21th Eur. Pept. Symp* ; Giralt E.; Andreu D. Eds.; ESCOM: Leiden. pp196-197, **1991**. (d) Rapp, W.; Zhang, L.; Haebich, R.; Bayer, E. *Peptide: Proc. of 20th Eur. Pept. Sympo.*; Jung, G.; Bayer, E. Eds.; W. de Gruyter: Berlin, pp199-201, **1989**. (e) Bayer, E.; Rapp, W. *German Patent* DOS 3714258 (1988). Bayer, E.; Rapp, W. *US Patent* 4,408,405 (1990).
3. (a) Inada Y.; Takahashi K.; Yoshimoto T.; Ajima A.; Matsushima A.; Saito Y. *TIBTECH* 1986, 190-195. (b) Pillai V. N. R.; Mutter M. *Naturwissenschaften* **1981**, *68*, 558-566.
4. (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154. (b) Mitchell A. R.; Kent S. B. H.; Engelhard M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845-2852.
5. (a) Becker, H.; Lucas, H. W.; Maul, J.; Pillai, V. N. R.; Mutter, M. *Makromol. Chem.* **1983**, *184*, 2603-2617. (b) Warshavasky, A.; Kaliv, R.; Doshe, A.; Berkovitz, H.; Patchornik, A. *J. Am. Chem. Soc.*, **1979**, *101*, 4249-4258.
6. Letsinger, R. L.; Kalus, I. *J. Am. Chem. Soc.*, **1964**, *86*, 3884-3885.
7. (a) Bayer, E.; Hemmasi, B.; Albert K.; Rapp W.; Dengler, M.; *Peptides: Structure & Function, Proc. of 8th Am. Pept. Sympo.*; Hruby V.J.; Rich D.H. Eds.; Pierce Chem. Co., pp87-90, **1983** (b) Bayer, E.; Dengler, M.; Hemmasi, B. *Int. J. Pept. Protein Res.* **1985**, *25*, 178-186.
8. Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877-3882.
9. (a) Lee, Y. S.; Park B. D.; Lee H. I. *U.S. Patent* 5,466,758 (1995).
   (b) As a model reaction, benzene(100mmol) was reacted with propylene oxide (200mmol) in the presence of $SnCl_4$(200mmol) in methylene chloride at 0℃ for 5 hr. Reaction mixture was washed thoroughly with conc. HCl in crushed ice and water and then vacuum distilled. Colorless oils (bp 35-55℃, 3-4 torr) were collected and analyzed by GC-MS. Main peak was 2-phenyl-1-propanol(ca 70% by gc) : m/z 136(M), 105(Ph-CH-CH_3). Trace amount of 1-phenyl-2-propanol (not detectable as a peak) was also found : m/z 136(M), 121(Ph-CH_2-CH-OH), 91(Ph-CH_2).
10. (a) Nakajima, T.; Suga, S. *Tetrahedron* **1969**, *25*, 1807-1816. (b) Masuda, S.; Nakajima, T. Suga, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1089-1094.
11. Decker, D. C.; Kooistra, D. A.; Greene, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 9284-9285.
12. The substitution degrees of the resulting PS-PO resin were determined as follows: PS-PO resin (*ca* 200 mg) which was previously swollen in methylene chloride(5 ml) was reacted with excess phenyl isocyanate (1 ml) for 12 hours at rt. The substitution degrees were calculated from the N% of the resulting carbamate.
13. Small samples of the resin were treated with strong acid in a given time, washed, and dried in vacuum. The amount of PEG was calculated from the C% analysis data.
14. Treating with 50% trifluoroacetic acid/methylene chloride, PS-g-PEG which was originated from Merrifield resin lost 20% of PEG in 120 min. while our resin retained most of PEG during the same period.

(*Received in Japan* 24 *September* 1996; *accepted* 6 *December* 1996)