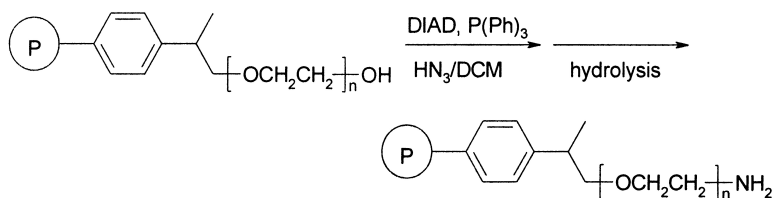Report

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Reports

Efficient Methods of Converting Hydroxyl Groups into Amino Groups in Poly(ethylene glycol)-Grafted Polystyrene Resin

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The development of proper solid supports for the construction of combinatorial peptide/chemical libraries[1,2] remains demanding. Poly(ethylene glycol)-grafted polystyrene (PS-g-PEG) resin is one such choice for a solid support because it has excellent properties, such as good solvation[3] in various solvents, and is biocompatible with biological molecules such as peptides, enzymes, and cells. We have previously reported a novel process for the preparation of polystyrene resins having a β-hydroxyl group (PS-PO) and of PS-g-PEG resins from these.[4] The process can efficiently introduce β-hydroxyl groups onto polystyrene resin via a one-step reaction with a relatively high loading of hydroxyl group, up to 2.4–2.7 mmol/g.[5] The final levels of hydroxyl group loading after addition of ethylene oxide to PS-PO resin are also easily controlled by adjusting the amount of catalyst and propylene oxide in the first step and the amount of ethylene oxide in the second.

Even though solid-phase organic syntheses are possible using the hydroxyl group of a PS-g-PEG resin, its weak nucleophilicity restricts the resin from wide application. Therefore, it is necessary to convert the hydroxyl group into

other functional groups, such as amino or sulfhydryl group. Various methods[6–8] are possible for converting the hydroxyl group into the amino group. Changing the hydroxyl group of the PS-g-PEG resin to a halide or a sulfonate and then reacting it with phthalimide or metal azide will give phthalimide or azide resins.[7] This can be converted into the amino resin by hydrazinolysis or reduction using various reagents.[9] Recently, Gooding et al. have reported the conversion of a hydroxyl group into an amino group on PS-g-PEG resins (ArgoGel).[10] However, these methods have to be performed in three stages to obtain the amino resins and to overcome the problems associated with heterogeneous reaction conditions. We here report on efficient methods for transforming PS-g-PEG–OH resins into PS-g-PEG–NH$_2$ resins.

Results and Discussion. The 2-(1-methyl)hydroxyethyl group was directly introduced into the polystyrene resin by Friedel–Crafts alkylation with propylene oxide and SnCl$_4$ as a catalyst, as reported previously.[4] The initial substitution levels were 1.7 and 2.7 mmol/g. Various PS-g-PEG resins with different PEG content were prepared by adding ethylene oxide to the PS-PO resins in the presence of KOH. To convert the hydroxyl group of PS-g-PEG resin into an amino group, several well-known reactions were tried, such as transforming the hydroxyl groups into halides or tosylates and then to a phthalimide and finally to the amino group via hydrazinolysis. However, all the methods used gave unsatisfactory results with low yields (Table 1).

We believe that the poor yields are due to the specific properties of the grafted PEG chains in nucleophilic substitution reactions. For example, PEG chains inside the resins might form complexes with counterions of nucleophiles, such as potassium and sodium. Moreover, the PEG chains have a tendency to coaggregate at elevated temperatures,[11] preventing the terminal functional groups from reacting with the added reagents under heterogeneous reaction conditions.

To prevent these complexities with the PEG chains, we opted to use metal ion free conditions, the Mitsunobu

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Scheme 1. Preparation of PS-g-PEG−NH$_2$ from PS-g-PEG−OH Resin via Conventional Mitsunobu Reaction Followed by Hydrazinolysis
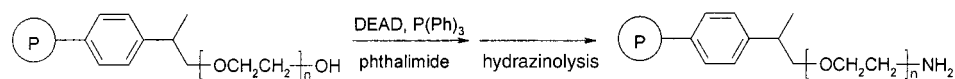
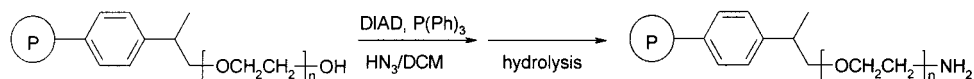**Scheme 2.** Preparation of PS-g-PEG−NH$_2$ from PS-g-PEG−OH Resin via Mitsunobu−Staudinger Reaction

Table 1. Result of Amine Transformation of PS-g-PEG−OH Resin[a]

| run | halogenating methods | degree of substitution (mmol/g) | |
		initial −OH	final −NH$_2$
1	TsCl	0.61[b]	
2	PCl$_3$	0.48[c]	0.03
3	SOBr$_2$	0.48[c]	0.05
4	CBr$_4$/P(Ph)$_3$	0.48[c]	0.10
5	CBr$_4$/P(Ph)$_3$	0.55[d]	0.10

[a] The hydroxyl groups were converted to halides or tosylates and then to a phthalimide and finally to the amino group via hydrazinolysis. [b] 52% PEG content. Degree of hydroxyl substitution of PS-PO was 1.27 mmol/g. Degree of substitution was determined as reported earlier (ref 5). [c] 82% PEG content. Degree of hydroxyl substitution of PS-PO was 2.70 mmol/g. [d] 67% PEG content. Degree of hydroxyl substitution of PS-PO was 1.70 mmol/g.

Table 2. Result of Mitsunobu Reaction and Hydrazinolysis on PS-g-PEG−OH Resin[a]

| | Mitsunobu reaction[b] | | degree of substitution (mmol/g) | |
run	DEAD (equiv)	temp (°C)	initial −OH	final −NH$_2$[c]
1	20	64	0.48[a]	0.27
2	20	25	0.48[a]	0.42
3	6	25	0.48[a]	0.44
4	4	40	0.48[a]	0.24
5	4	28	0.48[a]	0.43
6	4	25	0.48[a]	0.45
7	3	25	0.48[a]	0.44
8	2	25	0.48[a]	0.36

[a] 82% PEG content. Degree of hydroxyl substitution of PS-PO resin was 1.27 mmol/g. Degree of substitution was determined as reported earlier (ref 5). [b] For Mitsunobu reaction: reaction time, 24 h at room temp; ca. 4 equiv of phthalimide was used. [c] For hydrazinolysis: reaction time, 18 h; 43 equiv of hydrazine was used.

Table 3. Result of Mitsunobu−Staudinger Reaction on PS-g-PEG−OH Resin

| | Mitsunobu−Staudinger reaction | | | | degree of substitution (mmol/g) | |
run	DIAD (equiv)	temp (°C)	reaction time (h)	hydrolysis (h)	initial −OH	final −NH$_2$
1	3	25	15	3	0.45[a]	0.45
2	2	25	15	3	0.45[a]	0.45
3	3	20	15	3	0.25[b]	0.25

[a] 82% PEG content. Degree of hydroxyl substitution of PS-PO resin was 1.27 mmol/g. Degree of substitution was determined as reported earlier (ref 5). [b] About 1.5 N of HN$_3$/DCM solution was used.

reaction,[12] to transform the hydroxyl group of the PS-g-PEG resin into an active leaving group. Mitsunobu reactions have been applied previously for aryl ether formation on TentaGel resin.[13] The Mitsunobu reaction has one more advantage such that it requires no heating and very mild reaction conditions. Thus, PS-g-PEG−OH resin was converted to PS-g-PEG-phthalimide resin with diethyl azodicarboxylate (DEAD), triphenylphosphine, and phthalimide in THF. All the reagents were added into the same reaction vessel stepwise. After the phthalimide and triphenylphosphine were added to the preswollen PS-g-PEG−OH resin in THF, DEAD was then added dropwise. Hydrazinolysis of the resulting phthalimide resin in refluxing ethanol efficiently yielded the PS-g-PEG−NH$_2$ resin. The reaction schemes are depicted in Scheme 1 and the results are summarized in Table 2. As illustrated in Table 2, the conversion reactions proceeded smoothly except runs 1 and 4, which involve reaction temperatures above 25 °C.

Even though the reaction conditions required to convert the hydroxyl group to the phthalimide group are mild and very effective, the next step, the hydrazinolysis reaction, requires 18 h of refluxing. Moreover, excessive washing is required to remove the hydrazide byproduct. To simplify the preparation and to shorten the reaction time, a combination of Mitsunobu reaction and Staudinger reaction[14] was chosen and performed in the same reaction vessel (Scheme 2). Specifically, 3 equiv of diisopropyl azodicarboxylate (DIAD) and 3 equiv of HN$_3$ were added to the swollen resin in THF, and then 6 equiv of triphenylphosphine in THF were added dropwise. After the reaction mixture was stirred for 15 h at room temperature, 1 N HCl solution was added to hydrolyze

the iminophosphorane intermediate. The hydrolysis reaction was completed within 3 h, and the results are summarized in Table 3.

As illustrated in Table 3, all the reactions proceeded quantitatively. Compared to the former reaction scheme, the advantages of this combination reaction are a shorter reaction time and higher conversion yield. In the case of this reaction, DIAD produced better results than DEAD.

In conclusion, the Mitsunobu reaction and hydrazinolysis were successfully applied to transform the hydroxyl groups of PS-g-PEG−OH resin into amino groups. However, in view of time saving and simplicity, a combination of the Mitsunobu and the Staudinger reactions offers an even better method. We even obtained high-loading PS-g-PEG−NH$_2$ resins (above 0.4 mmol/g) using this new method without any difficulty.

Preparation of 2-(1-methyl)hydroxyethylpolystyrene (PS-PO) Resin. After being thoroughly washed, polystyrene−

1% divinylbenzene copolymer beads (BioRad Co., Biobead S-X1, 200−400 mesh, 5 g, 47.5 mmol) were swollen in dichloromethane (80 mL) in a three-necked round-bottomed flask, and $SnCl_4$ (0.5−1.0 equiv) was added to the resin mixture with stirring. Propylene oxide (0.5−1.0 equiv) in 20 mL of dichloromethane was then added dropwise in 10 min with stirring. After 5 h of reaction, 100 mL of MeOH was added to quench the remaining catalysts and the resin was washed with EtOH (×3), 0.1 N aqueous HCl (×3), water (×3), MeOH (×2) and was dried in vacuo. The loading levels were determined by the DMT-Cl titration method.[15]

Preparation of Poly(ethylene glycol)-Grafted Polystyrene (PS-g-PEG) Resin. The PS-PO resin (5 g) and KOH (1.1 equiv) were added to dioxane (150 mL) in a pressure reactor (Parr model 4561, 300 mL) and purged with nitrogen for 30 min at 100 °C to remove moisture. Ethylene oxide (30−50 mL) was added to the reactor, and the reaction mixture was maintained at 110 ± 1 °C with stirring. After 9 h, the resin was washed with dioxane/water (1:1, ×3), 0.1 N aqueous HCl (×3), water (×3), EtOH (×5), and dichloromethane (×3) and was then dried in vacuo. The grafting levels were determined by weight increase and the DMT-Cl titration method.[15]

Preparation of Hydrazoic Acid Solution.[16] A paste is prepared from 65 g (1 mol) of NaN_3 and 65 mL of warm water in a three-necked flask fitted with an efficient stirrer, a dropping funnel, a thermometer, and a gas-exit tube. After 400 mL of dichloromethane was added, the mixture was cooled to 0 °C, and 0.5 mol of concentrated H_2SO_4 was added dropwise with control of the temperature at 0−5 °C. The organic layer was separated and dried over sodium sulfate. The concentration of HN_3 solution was determined by transferring an aliquot of the sample solution with a pipet to a glass-stoppered bottle, shaking it with distilled water, and titrating with a standard alkali. *Caution: After inhalation of hydrazoic acid vapor, the acute effects noted in humans are ocular irritation, bronchitis, headache, hypotension, weakness, and collapse.*

General Procedure for the Preparation of Amino Resins. Method A. Hydrazinolysis after the Conventional SN_2 Reaction. The PS-g-PEG resin (0.6 g, 0.48 mmol/g), $SOBr_2$ (1.34 g, 6.45 mmol), pyridine (1.05 g, 12.48 mmol), and purified benzene were mixed in a round-bottomed flask and refluxed for 15 h. The resin was filtered and washed with EtOH (×2) and dichloromethane (×3). The resin, potassium phthalimide (0.3 g, 1.62 mmol), and purified DMF (40 mL) were mixed and refluxed for 28 h. The resin was filtered and washed with dichloromethane (×3), hot water (×3), and EtOH (×3) and was then dried in vacuo. The amount of amine group was determined by picric acid titration.[17]

Method B. Hydrazinolysis after Mitsunobu Reaction. The PS-g-PEG resin (1.0 g, 0.48 mmol/g), triphenylphosphine (0.51 g, 1.94 mmol), phthalimide (0.29 g, 1.94 mmol), and purified THF were mixed in a round-bottomed flask at 0 °C, and diethyl azodicarboxylate (0.31 mL, 1.94 mmol) was added dropwise. After the addition, the temperature was maintained at 25 °C for 24 h. The resin was filtered and washed with THF (×3), dichloromethane (×3), and EtOH

(×3). The resin, hydrazine hydrate (1.03 g, 20.62 mmol), and EtOH (20 mL) were mixed and refluxed for 18 h. The resin was filtered and washed with hot EtOH (×2), hot water (×2), and dichloromethane (×3) and was then dried in vacuo. The amount of amine was determined by picric acid titration.[17]

Method C. Mitsunobu−Staudinger Reaction. To a mixture of the PS-g-PEG resin (1.0 g, 0.48 mmol) in THF-(10 mL) was added 1 M solution of hydrazoic acid in dichloromethane (1.5 mL), followed by addition of diisopropyl azodicarboxylate (0.3 mL, 1.5 mmol) in THF (2 mL). To the resulting mixture was added to a solution of triphenylphosphine (0.79 g, 3.0 mmol) in THF (5 mL) with stirring. After 1 h of being stirred at room temperature, the reaction mixture was heated at 50 °C for 3 h. Aqueous 1 N HCl (1 mL) was added, and the temperature was maintained at 50 °C for another 3 h. The resin was filtered and dried in vacuo. The amount of amine was determined by picric acid titration.[17]

References and Notes

(1) (a) Geysen, H. M.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3998−4002. (b) Geysen, H. M.; Barteling, S. J.; Meloen, R. H. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 178−182. (c) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5135. (d) Frank, R. *Tetrahedron* **1992**, *48*, 9217−9232. (e) Fodor, S. P. A.; Leighton, R. J.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767−773. (f) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487−493. (g) Chen, C. L.; Strop, P.; Lebl, M.; Lam, K. S. *Methods Enzymol.* **1996**, *267*, 211−219.
(2) (a) Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30* (2), 113−216. (b) Meldal, M. *Tetrahedron Lett.* **1992**, *33*, 3077−3080. (c) Kempe, M.; Barany, G. *J. Am. Chem. Soc.* **1996**, *118* (30), 7083−7093. (d) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40* (35), 6329−6332.
(3) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82−84.
(4) Lee, Y. S.; Park, B. D.; Lee, H. I. U.S. Patent 5,466,758, 1995.
(5) Park, B. D.; Lee, H. I.; Ryoo, S. J.; Lee, Y. S. *Tetrahedron Lett.* **1997**, *38* (4), 591−594.
(6) (a) Hendrickson, J. B.; Joffee, I. *J. Am. Chem. Soc.* **1973**, *95*, 4083−4084. (b) Oliver, K. L.; Young, W. G. *J. Am. Chem. Soc.* **1959**, *81*, 5811−5817. (c) Kice, J. L.; Scriven, R. L.; Koubek, E.; Barnes, M. *J. Am. Chem. Soc.* **1970**, *92*, 5608−5614. (d) Chow, R. C. L.; Tarbell, D. S. *J. Org. Chem.* **1967**, *32*, 2188−2193.
(7) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327−4329.
(8) Slusarska, E.; Zwierzak A. *Liebigs Ann. Chem.* **1986**, 402−405.
(9) (a) Suzuki, H.; Takaoka, K. *Chem. Lett.* **1984**, 1733−1736. (b) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590−591. (c) Hedayatullah, M.; Guy, A. *Tetrahedron Lett.* **1975**, 2455−2458. (d) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633−3634. (e) Gartiser, T.; Selve, C.; Delpuech, J.-J. *Tetrahedron Lett.* **1983**, *24*, 1609−1610.

(10) Gooding, O. W.; Baudart, S.; Deegan, T. L.; Heisler, K.; Labadie, J. W.; Newcomb, W. S.; Porco, J. A., Jr.; Eikeren, P. *J. Comb. Chem.* **1999**, *1*, 113−122.

(11) Park, B. D.; Lee, Y. S. *React. Funct. Polym.* **2000***, 44*, 41−46.

(12) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(13) Krchňák, V.; Flegelová, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36* (35), 6193−6196.

(14) (a) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861−886. (b) Scriven, E.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297−368. (c) Zimmer, H.; Singh, G. *J. Org. Chem.* **1963**, *28*, 483−486. (d) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F.; *Tetrahedron* **1981**, *37*, 437−472. (e) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190−192.

(15) Chu, S. S.; Reich, S. H. *Bioorg. Med. Chem. Lett.* **1995**, *5* (10), 1053−1058.

(16) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1, p 46.

(17) Grant, G. A. In *Synthetic Peptides: A User's Guide*; Freeman and Company: New York, 1992; p 126.