Polymer Bulletin 20, 435–441 (1988)

Polymer Bulletin

Preparation of polymer-supported amino acid

Shinichi Itsuno, Takashi Wakasugi, and Koichi Ito

School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi, 440 Japan

SUMMARY

Insoluble polymer-supported amino acids have been synthesized by simple one-pot synthesis. Amino acids were solubilized in organic solvent by trimethylsilylation. Solubilized amino acids (L-Tyr, L-Ser, D-HPG, L-Cys) having functional groups such as OH or SH were easily attached to crosslinked polystyrene beads through benzyl ether or thioether linkage. Other amino acids without extra functional groups could be attached to the polymer through benzyl amine linkage.

INTRODUCTION

Crosslinked polystyrene resins having chiral pendant groups have been demonstrated over the past fifteen years as being useful supported reagents or catalysts for asymmteric syntheses (1-7) as well as powerful packing materials for the direct resolution of enantiomers in liquid chromatography (8-11). Optically active amino acids, which are commonly found in nature, are the most abundant and hence relatively inexpensive. The synthetic utility of α-amino acids as the chiral reagents and catalysts have been demonstrated(12). For example, amino acids such as L-proline (L-Pro) and L-phenylalanine (L-Phe) are the efficient catalyst of chiral intramolecular aldolization of triketones(13,14). In the presence of L-Phe in acetic acid the asymmetric cyclization of 2-methyl-2-(3-oxopentyl)-1,3-cyclohexadione results in 80% chemical and 87% optical yield (13). Amino acids have been also used as chiral auxiliaries of several asymmetric syntheses such as halolactonization (15) and alkylation reactions(16).

Although polymer-supported amino acids and peptides are very popular in solid phase peptide synthesis, usually amino acids are anchored to polystyrene beads through ester linkage. In this paper we wish to report a convenient preparation method of polymer supported amino acid having

free amino and carboxylic acid functionalities. Synthesis of the polymer-supported amino acid is made difficult by the fact both (chloromethyl)polystyrene and amino acids are solid insoluble reagents. We have been able to solve this problem satisfactorily using trimethyl-silylation of amino acids. Trimethylsilyl group is not only a solubilizing agent but also a protecting group for COOH of amino acids. Under these conditions excellent yields of the insoluble polymer-bound amino acids are obtained. They may be used as chiral ligand or catalyst for asymmetric syntheses as well as chiral stationary phase of resolution by chromatography.

EXPERIMENTAL

N,N-Dimethylformamide (DMF) and N-methylpyrrolidone (NMP) were purified by distillation from CaH_2. L-Tyrosine (L-Tyr), L-serine (L-Ser), L-threonine (L-Thr), L-cysteine (L-Cys), D-hydroxyphenylglycine (D-HPG), L-hydroxyproline (L-HPro), L-proline (L-Pro), chlorotrimethylsilane, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and sodium hydride (NaH) were used without purification. 2% Crosslinked (chloromethyl)-polystyrene was prepared by the method in the literature(17). The degrees of functionalization of the polymers (DF) given below represent the fraction of aromatic rings that possess the desired functionalities.

Polymer-supported L-Tyrosine: To a suspension of L-Tyr(0.05mol, 9.05g) in NMP chlorotrimethylsilane (0.05 mol, 6.3 ml) was added at room temperature. A clear solution was obtained after 2 h of stirring at room temperature. To this homogeneous solution 2 equiv of NaH (0.1 mol) was added portionwise at 0 °C for 15 min. Crosslinked (chloromethyl)polystyrene with DF=0.68 [$(C_{10}H_{10})_{0.02}$·$(C_8H_8)_{0.30}$·$(C_9H_9Cl)_{0.68}$] (4.96 meq Cl/g, 4.03 g) was added at once and whole mixture was stirred for 3 days at room temperature. The polymer was treated with 1N HCl aqueous solution to complete removal of trimethylsilyl group, followed by neutralization with aqueous ammonia. Obtained polymer on glass filter was washed with MeOH, THF, THF-H_2O, $CHCl_3$, and MeOH respectively. After drying in vacuo at 40°C for 24 h the white beads of polymer supported L-Tyr 3 (6.6 g, theor. 6.92 g) was obtained. Beilstein test of the polymer showed no chlorine atom remained. The infrared spectrum of the resin included the COO^- absorption at 1595 cm^{-1} Anal. Calcd. for $(C_{10}H_{10})_{0.02}$·$(C_8H_8)_{0.30}$·$(C_{18}H_{19}NO_3)_{0.68}$:C,75.51; H,6.63; N,4.03. Found C,75.58; H,6.53; N,4.00; Cl,0.

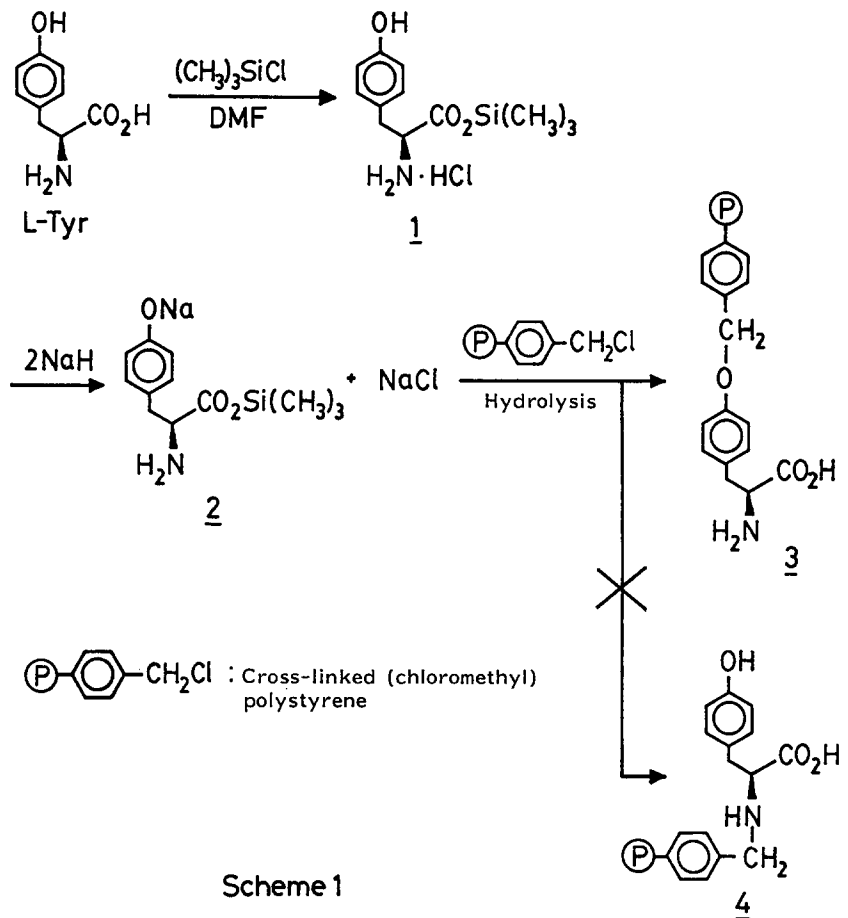
Polymer-supported L-Alanine: L-Alanine p-toluenesulfonate salt was prepared from L-Ala (0.04 mol) and p-toluenesulfonic acid (TsOH) (0.06 mol). L-Ala TsOH (5 mmol, 1.3 g), HMDS (5mmol, 1 ml) and 20 ml of NMP were mixed and stirred at room temperature under nitrogen atmosphere for 2 h. Without isolation of N,O-bis(trimethylsilyl)-L-alanine, NaH (5 mmol) was added portionwise at 0 °C and then crosslinked

(chloromethyl)polystyrene with DF=0.68 (4.96 meq Cl/g, 0.5 g) was added and stirring was continued for 3 days at room temperature. Water (5 ml) was added and the polymer was washed with THF-H_2O, THF-1N HCl, H_2O, NH_4OH, H_2O, THF, MeOH and, then, dried under vacuum at 40°C for 24h, yielding 0.6 g (theor. 0.63 g) as a white powder 11. Beilstein test showed no chlorine atom remained in the polymer. IR(KBr) peaks absent at 1265 cm^{-1} for chloride precursor, peak present at 1600 cm^{-1} (s, COO^-). Anal. Calcd. for $(C_{10}H_{10})_{0.02}$·$(C_8H_8)_{0.30}$·$(C_{12}H_{15}NO_2)_{0.68}$: C,74.52; H,7.44; N,5.49. Found C,74.56; H,7.34; N,5.38; Cl,0.

Polymer-supported L-Proline: To a suspension of L-Pro (60 mmol, 6.9 g) in NMP (200 ml) chlorotrimethylsilane (60 mmol, 7.56 ml) was added at room temperature. A clear solution was obtained within a half hour. NaH (120 mmol) was added portionwise, followed by addition of (chloromethyl)-polystyrene with DF=0.68 (4.96 meq Cl/g, 6.05 g). After 24h stirring at room temperature the polymer was washed on glass filter with THF-H_2O, THF-1NHCl, H_2O, THF-NH_4OH, H_2O, THF, MeOH, and then dried under vacuum at 40°C for 24 h,yielding 8.2 g (theor. 8.41 g) as a pale yellow powder 12: IR (KBr) peaks absent at 1265 cm^{-1} for chloride precursor, peaks present at 1580 cm^{-1} (s, COO^-) Anal: Calcd. for $(C_{10}H_{10})_{0.02}$·$(C_8H_8)_{0.30}$·$(C_{14}H_{17}NO_2)_{0.68}$: C,76.16 ;H,7.47 ;N,4.98. Found C,76.35 ;H,7.32 ;N,5.00 ;Cl,0.

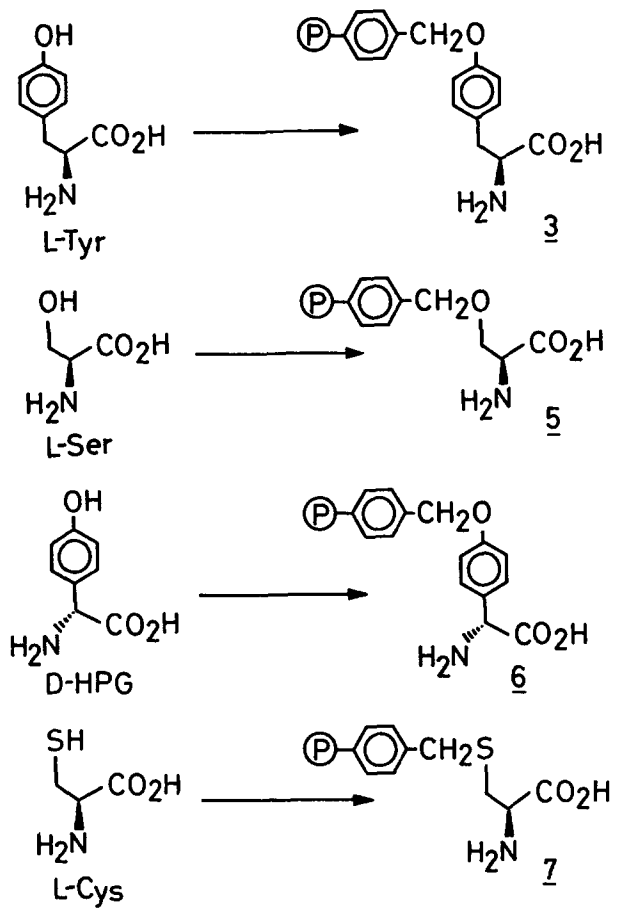
RESULTS & DISCUSSION

There are several naturally occurring amino acids with a hydroxy or mercapto substituent attached to the group in the α-position. These functional groups could be used to make linkage between polymer and amino acid. Unfortunately, amino acids actually exist as inner salts (zwitterions). Because of this highly polar innersalts structure they are insoluble in any nonpolar organic solvents. In order to solubilize these amino acids, we chose a chemoselective trimethylsilylation of them. For example, the reaction between equimolar amounts of chlorotrimethylsilane and of L-Tyr which is amino acid having phenolic hydroxy group, would give trimethylsilyl ester of L-Tyr selectively due to the different acidity of functional groups of NH_2 < OH < COOH. Easy removal of trimethylsilyl group after attachment reaction to the polymer is also another advantage of this method. In fact, mixing of L-Tyr with chlorotrimethylsilane in DMF at room temperature resulted in a clear solution of trimethylsilyl ester 1 within a few hours. Then, hydroxyphenyl group of 1 was able to be converted into sodium phenoxide which reacted easily with crosslinked (chloromethyl)polystyrene at room temperature to give polymer-supported L-Tyr 3 after removal of trimethylsilyl group by hydrolysis (Scheme 1). This procedure may be the easiest way of one-pot synthesis of attaching amino acid into



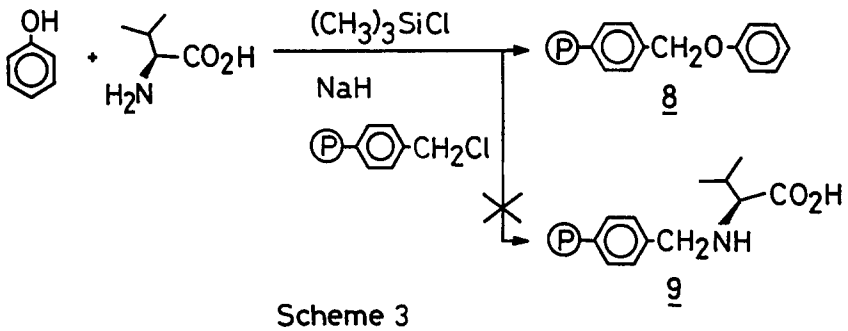
Scheme 1

insoluble polymer. Trimethylsilyl group acts as a protecting group of COOH and also a solubilizing group during coupling reaction between polymer and amino acid. Without silylation insoluble amino acid is not able to react with cross linked polystyrene. In addition, NaH does not react with amino acid in DMF. IR spectra of the obtained polymer 3 showed the peaks corresponding to polystyrene and the characteristic peaks of amino acid (NH_3^+:3130-3030 cm^{-1}, COO^-:1600-1560 cm^{-1}). The same procedure was applied to other amino acids such as L-Ser, L-Cys, D-HPG, L-Thr, and L-HPro (Scheme 2). In the case of L-Thr and L-HPro, IR peaks of the final polymer contained 1720 cm^{-1} corresponding to ketone carbonyl which would be formed by undesired Claisen condensation of trimethylsilyl ester under basic condition. Alkoxide anion of secondary alcohol in L-Thr and L-HPro may be strong enough to eliminate α-hydrogen of these amino acids. Actually, at higher temperature (80°C) this side reaction was observed even in the case of L-Tyr and L-Ser. Under basic condition there is another possibility of side



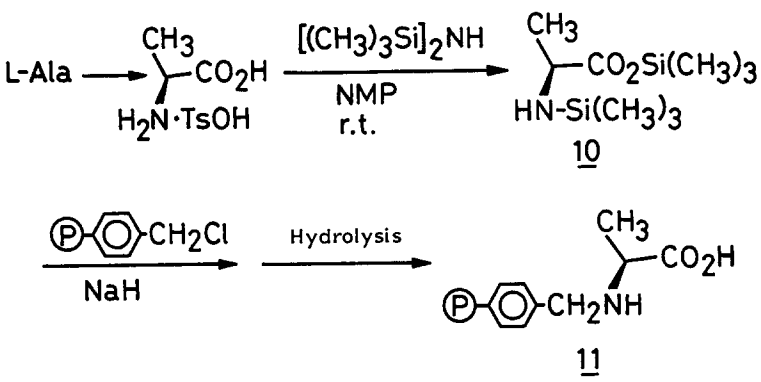
Scheme 2

reaction that amino group of 2 might react with chloromethyl group of the polymer to give different structure of the polymer **4**. This structure **4** could be avoided by following experimental results. Instead of L-Tyr, when the mixture of phenol and L-Val were treated in the same manner, product was only phenoxy polystyrene **8** confirmed by IR spectra and elemental analysis of the final polymer (Scheme 3). This experimental result supports that L-Tyr should be attached to the polymer through only benzyl phenyl ether linkage as depicted in Scheme 1.

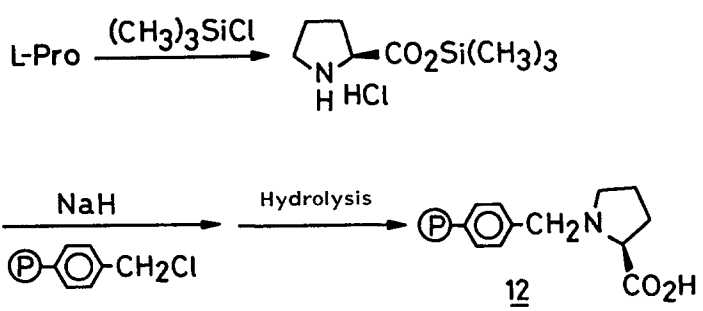


Scheme 3

Amino acids without hydroxy or mercapto groups can be also attached to insoluble polymer through benzylamine linkage. However, reactivity of the primary amino group of amino acid is not strong enough to react with polymeric chloride, even when amino acid is solubilized by trimethylsilylation . The vigorous conditions such as high temperature and long reaction time are required to make the linkage between amino acid and polymer. These conditions usually result in racemization of the amino acid. Instead of mono(trimethylsilyl)amino acid we chose



Scheme 4



Scheme 5

bis(trimethylsilyl)amino acid which contains secondary amino functionality being able to react more easily with (chloromethyl)polystyrene. For example, L-Ala TsOH was converted into bis(trimethylsilyl)-L-alanine **10** which can react with (chloromethyl)polystyrene in the presence of base under mild condition to give polymer supported L-Ala **11** as shown in Scheme 4. In the case of L-Pro already having secondary amino group in itself soluble monosilylester reacts with (chloromethyl)polystyrene to give polymer supported L-Pro **12** (Scheme 5).

REFERENCES

1. S. Itsuno, J.M.J. Frechet, J.Org.Chem. **52**, 4140 (1987)
2. S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, Polymer **28**, 1005 (1987)
3. P. Hodge, E. Khoshdel, J. Waterhouse, J.M.J. Frechet, J.Chem.Soc.,Perkin Trans. 1, 2327 (1985)
4. P. Lecavalier, E. Bald, Y. Jiang, J.M.J. Frechet, Reactive Polymer, 3, 315 (1985)
5. G. Parrinello, J.K. Stille, J.Am.Chem.Soc. **109**, 7122 (1987)
6. M. Calms, J. Daunis, R. Jacquier, G. Nkusi, J. Verducci, P. Viallefont, Tetrahedron Lett. **27**, 4303 (1986)
7. M. Masui, A. Ando, T. Shioiri, Tetrahedron Lett. **29**, 2853 (1988)
8. W.H. Pirkle, J. Finn, in "Asymmetric Synthesis", vol1, p57 Ed. By J.D. Morrison, Academic Press New York, (1983)
9. V.A. Davankov, S.V. Rogozhin, A.V. Semechkin, T.P. Sachkova, J.Chromatog. **82**, 359 (1973)
10. G. Dotsevi, Y. Sogah, D.J. Cram, J.Am.Chem.Soc. **97**, 1259 (1975)
11. O. Charmot, R. Audebert, C. Quivoron, J.Polym.Sci.,Polym. Lett. **24**, 59 (1986)
12. G.M. Coppola, H.F. Schuster, "Asymmetric Synthesis", John Wiley & Sons, Inc. New York (1987)
13. R. Uma, S. Swaminathan, K.Rajagopalan, Tetrahedron Lett. 25, 5825 (1984)
14. Z.G. Hajos, D.R. Parrish, J.Org.Chem. **39**, 1615 (1974)
15. S. Terashima, S. Jew, Tetrahedron Lett., 1005 (1977)
16. S. Hashimoto, K. Koga, Tetrahedron Lett., 573 (1978)
17. K.W. Pepper, H.M. Paisley, M.A. Young, J.Chem.Soc. 4097 (1953)

Accepted September 7, 1988 S