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Polystyrene Grafted Fluoropolymer MicroTubes: New Supports for Solid-Phase Organic Synthesis with Useful Performance at High Temperature

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New solid supports for organic synthesis have been developed by radiolytically grafting polystyrene onto inert fluoropolymer tubes. The grafted tubes have been functionalized and utilized in two solid-phase organic reactions performed at high temperatures.

Solid-phase organic synthesis[1] has been developing rapidly since the concept of combinatorial chemistry and biology[2] began to attract increasing attention in the drug discovery community. The most widely used solid supports for organic synthesis today are divinylbenzene cross-linked polystyrene resin beads and their derivatives.[3] In the development of memory encoded MicroReactor technologies for high-throughput combinatorial organic synthesis and biological screening,[4,5] we have searched for chemically and mechanically stable solid matrixes that have the desired chemical properties to act as solid supports in organic syntheses. Useful synthesis supports would retain the appropriate mechanical properties to be conveniently fabricated with microdigital[5] or optical[6] memory devices. We now report our preliminary results on the preparation and derivatization of surface grafted fluoropolymer matrixes and their applications in solid-phase organic synthesis at elevated temperature.

Radiolytic grafting is a well-documented process for graft copolymerization.[7] Grafted solid supports have been reported for application in peptide[8] and oligonucleotide[6] syntheses. We chose fluoropolymer tubes as our grafting substrate for the following reasons. First, for organic synthesis, high mechanical, thermal, and chemical stability is required. Fluoropolymers, polytetrafluoroethylene (PTFE), and ethylenetetrafluoroethylene (ETFE) are among the most stable polymers. Second, the base substrate must have acceptable reactivity toward radiolytic grafting. Polyethylene and polypropylene have similar reactivity while fluoropolymers are less reactive toward radiation grafting, even though acceptable grafts can still be obtained via optimized grafting conditions.[6] Third, the substrate must be able to readily associate with micromemory devices. Since the current radio frequency memory chips are in a cylindrical form,[4,5] polymer tubes with a slightly bigger i.d. (3.5 to 4 mm) were used so that the memory chips can be conveniently enclosed. By controlling radiation grafting conditions, long polystyrene chains with minimum cross-linking can be grafted onto the surfaces of the fluoropolymer tubes. The nearly linear polystyrene chains on the insoluble polymer tubes would more readily solvate in organic solvents and might be more accessible to reagents than cross-linked polystyrene resin beads.

It has been reported that under the radiation conditions the degree of swelling of the polymer would affect the rate of grafting.[7] Thus, high-strength fluoropolymer tubes (i.d. = 3.6 mm, o.d. = 4.8 mm, 25 mm in length) were washed with methylene chloride (DCM) and air-dried. Methanol was chosen as the nonswelling solvent for polystyrene in our experiment. MicroTubes were immersed in a mixture of styrene, methanol, and mineral acid and γ-irritated with a Co^{60} source (patent pending, "Methods for Radiation Grafting to Polymeric Surfaces").[6,7] The radiated polymer tubes were then thoroughly washed with DCM to remove the excess monomer and homopolymer formed in the solution until the washing is clear of any UV-detectable materials and air-dried overnight.

The above polystyrene grafted fluoropolymer tubes were aminomethylated [9] using the Tscherniac−Einhorn reaction[10] followed by hydrazinolysis. Thus, the tubes were first treated with *N*-(hydroxymethyl)phthalimide (0.12 mM) and trifluoromethanesulfonic acid (0.5%, v/v) in trifluoroacetic acid/DCM (1:1, v/v; 100 mL/100 tubes) at room temperature for various lengths of time. The solution was removed, and the tubes were thoroughly washed with methylene chloride (×3) and dried under vacuum. The resulting phthalimidomethylated fluoropolymer tubes were then reacted with hydrazine (5%, v/v) in refluxing ethanol for 20 h. The reaction was cooled to room temperature, and the tubes were washed thoroughly with 20% piperidine/*N*,*N*-dimethylformamide (DMF) and DCM until the solution was free of phthalhydrazide by UV detection and dried under vacuum overnight. The disappearance of the C═O stretch (1709 cm^{-1})[11] in the IR spectrum indicated complete conversion of the phthal-

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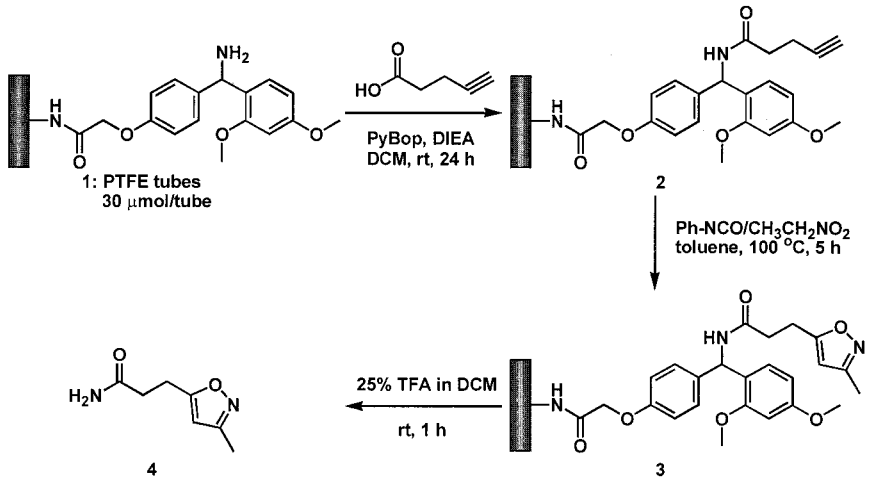
Scheme 1. [3 + 2] Cycloaddition on Polystyrene Grafted PTFE Tubes



imide to the free amine. Fmoc analysis (by capping the amino groups on the tubes with Fmoc−Cl, thoroughly washing away excess reagents, removing the tube-bound Fmoc groups with 20% piperidine/DMF, and spectrophotomically measuring the concentration of the released 9-fluorenylmethylidene/piperidine adduct) indicated an average loading of 30 μmol per PTFE tube and 35 μmol per ETFE tube with less than 10% variation.

A variety of linkers can be appended onto the above aminomethyl fluoropolymer (Rink amide, PAL, HMPB, BAL, safety catch, etc.). Other functionalities such as chloromethyl (Merrifield type) and 4-hydroxymethylphenoxy (Wang type) have also been obtained.[12] These functionalized and linker-modified fluoropolymer tubes have been successfully utilized by us in the synthesis of heterocyclic molecules. We report the excellent performance of the polystyrene grafted PTFE and ETFE tubes in nonpolar/aromatic solvents at elevated temperatures.

Formation of isoxazoles and isoxazolines through [3 + 2] cycloaddition of nitrile oxides with alkynes and alkenes on polystyrene resins has previously been reported.[13] When nitroalkyl compounds are used as the precursors of the nitrile oxides, the reactions need to be performed in toluene at 100 °C. Under this condition, grafted polypropylene and polyethylene supports will completely disintegrate. Thus, polystyrene grafted PTFE and ETFE MicroTubes were used for this reaction (Scheme 1). Aminomethylated PTFE/ETFE MicroTubes were coupled with Rink amide linker,[14] and the unreacted amine groups were capped with 0.5 M Ac_2O and 0.5 M DIEA in DCM at room temperature for 2 h (or until a negative ninhydrin test result was achieved).[15] The loading was measured to be 30 μmol/35 μmol per PTFE/ETFE tube by Fmoc group deprotection (20% piperidine in DMF) and UV measurement. PTFE tubes with Rink amide linker (**1**) were treated with 4-pentynoic acid (0.1 M)/DIEA (0.2 M)/PyBop (0.1 M) in DCM at room temperature for 24 h to yield the alkyne tubes **2**. These tubes were then reacted with nitroethane (0.1 M)/phenyl isocyanate (0.1 M)/Et_3N (0.12 M)/in toluene at 100 °C for 5 h, yielding the tube-bound isoxazole **3**, which was cleaved using standard conditions to afford isoxazole amide **4** at 76% overall yield based on the initial loading of microtube **1**. HPLC (CH_3CN:H_2O, from 25:75 to 100:0) analysis indicated that the crude cleavage product was obtained in over 90% purity confirmed by NMR.[16]

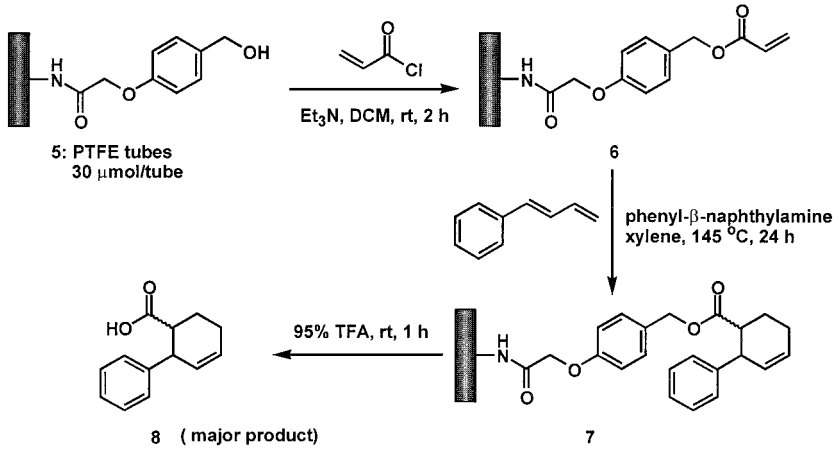
A [4 + 2] cycloaddition between tube-bound alkene **6** and 1-phenylbutyldiene[17] was similarly performed on 4-hydroxymethylphenoxyacetic acid (HMPA)-modified PTFE and ETFE tubes **5**[18] in xylene at an even higher temperature (145 °C, 24 h).[19,20] The desired cyclohexyl compound **8**[21] was isolated in an overall yield of 46% based on the initial loading of **5** (Scheme 2).

We have demonstrated that polystyrene grafted fluoropolymer matrixes can be readily prepared using the process of radiolytic grafting. These matrixes have been used successfully in high-temperature organic reactions. They are mechanically and chemically stable and can be readily fabricated with microencoding devices (radio frequency tags,[4,5] 2D bar codes[6]) to form the desired MicroReactors utilized in nonchemically encoded combinatorial synthesis. The PTFE and ETFE supports are especially stable to solvents and temperatures and are useful when nonpolar/aromatic solvents and elevated temperatures are required. Even without the encoding devices, these matrixes bring advantages as general solid supports in organic synthesis over conventional resin beads owing to their ease of handling in agitation, transferring, and washing. Their use should provide an attractive alternative in solid-phase organic synthesis.

Experimental Section

General. 4-Hydroxymethylphenoxyacetic acid **(**HMPA linker) was obtained from Novabiochem (San Diego), *p*-[(*R*,*S*)-α-[1-(9*H*-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]phenoxyacetic acid (Rink amide linker) and benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBop) were purchased from Midwest Biotech (Fishers). All the other chemicals were purchased from Aldrich (Milwaukee, WI) and used without further purification. Polymer tubes were purchased from Cole-Palmer (Vernon Hills, IL). ^{1}H NMR and MS spectra were obtained separately from NuMega Resonance Labs, Inc., and Mass Consortium Corporation (San Diego). UV spectra were measured using an HP 8453 spectrophotometer. HPLC analysis was performed using a HP 1050 HPLC. IR spectra

Scheme 2. [4 + 2] Cycloaddition on Polystyrene Grafted PTFE Tubes



were obtained using a Perkin-Elmer Spectrum 1000 IR spectrometer.

General Reaction and Washing Conditions. Reactions with the MicroTube were generally performed using 1 mL of solvent per tube. Agitation was achieved by shaking on a Gio gyrotory shaker (Fisher Scientific) at 150 rpm. Between each reaction step, the MicroTube was washed by repeating the following washing cycle three times: DCM × 5 min, methanol × 5 min. The last washing solvent was either ethyl ether or DCM. Amount of washing solvents was 1−2 mL per tube.

Amino MicroTube Preparation. Polystyrene was first covalently attached onto MicroTubes using the γ-radiation technique. Methanol was chosen as the nonswelling solvent for polystyrene in our experiment.[7] Twenty-five Teflon (PTFE) or PTFE−ETFE copolymer tubes, 3.6 mm (i.d.) × 4.8 mm (o.d.) × 25 mm (length), were immersed in 25 mL of 50% styrene/methanol (v:v) containing 0.1 M sulfuric acid in a 50 mL glass bottle. The solution was carefully degased by bubbling with argon at a rate of 5 cm^3/min for 5 min. The glass bottle was sealed with Teflon tape and γ-irritated with a Co^{60} source (patent pending, "Methods for Radiation Grafting to Polymeric Surfaces"). Polystyrene (PS) grafted fluoropolymer tubes were washed thoroughly with DCM to remove residual monomer and nonattached polystyrene from radiation grafting. After drying, the tubes were weighted and polystyrene loading or tube weight increase was determined as 35 mg per tube. MicroTubes were aminomethylated using the Tscherniac−Einhorn reaction[10] followed by hydrazinolysis. One thousand tubes were put into a 2 L round bottle flask, 1 L of 1:1 (v/v) trifluoroacetic acid (TFA):DCM was added as solvents, and then 24.8 g (4 equiv based on 35 μmol/per tube) of *N*-(hydroxymethyl) phthalimide and 5 mL of trifluoromethanesulfonic acid were added. The reaction was sealed and shaken at room temperature for 24 h. A 1 mm × 1 mm piece of tube surface was cut off using a razor blade and analyzed with attenuated total reflectance (ATR)-FTIR. The IR spectrum revealed the expected C═O stretch at 1714 cm^{-1}, indicating the presence of phthalimide. The predetermined loading can be obtained by changing the concentrations of reagents, catalyst, and reaction time. The hydrazinolysis of these tubes was accomplished by refluxing in 1000 mL of 5:95 (v/v) hydrazine:ethanol for 24 h, and the absence of the C═O stretch in the IR spectrum indicated the complete conversion of the phthalimide to free amine. The amine loading was measured by first coupling Fmoc−Cl onto the tubes: five MicroTubes were placed into a 12 mL vial, and then anhydrous DCM (5 mL), Fmoc−Cl (129 mg, 0.1 M), and DIEA (174 μL, 0.2 M) were added. The reaction was completed at room temperature in 1 h. After reaction, MicroTubes were washed thoroughly using the washing protocol described above, and the Fmoc group was removed (using 6 mL of 20% piperidine/DMF per tube, room temperature, 1 h). Finally, the released 9-fluorenylmethylidine/piperidine adduct was spectrophotometrically measured at 301 nm. The average loading is 35 μmol/tube (with standard deviation ≤ 3.5 μmol).

Rink Amide AM Linker (Knorr Linker) Coupling (1). Using the method shown in Scheme 1, five aminomthylated PTFE tubes (ETFE tubes were also used for all the reactions reported here) were placed into a 8 mL vial, and 5 mL of anhydrous DCM was added, followed by the addiation of DIEA (100 μL, 0.2M), Knorr linker (270 mg, 0.1M), and PyBop (260 mg, 0.1M). The reaction was shaken at 200 rpm overnight. The unreacted amine group was capped using 0.5 M DIEA/0.5 M acetic anhydride at room temperature for 2 h (or until a negative ninhydrin test[15] was obtained). After being washed, the tubes were treated with 6 mL of 20% piperidine/DMF individually for 1 h. An average loading of 30 μmol/per tube and yield of 86% (based on starting tube loading) was obtained. After being washed, the tubes were dried under vacuum overnight. The FTIR spectrum (Figure 1) of tube **1** indicated the amide bond formation at 1654 cm^{-1}.

MicroTubes (2). 4-Pentynoic acid was coupled to MicroTube **1** using the following conditions: 0.1 M 4-pentynoic acid, 0.1 M PyBop, 0.2 M DIEA, DCM, room temperature, 20 h. Ninhydrin test was used to confirm the complete reaction conversion. The tubes were washed and dried before the next step.

Nitrile Oxides Cycloaddition (3).[13] Two of the MicroTubes **2** and a stirring bar were placed into a 50 mL round bottle flask. Addition of toluene (20 mL), phenyl isocyanate (238 mg, 0.1 M), nitroethane (150 mg, 0.1 M), and triethylamine (330 μL, 0.12 M) followed. The reaction mixture was heated at 100 °C for 5 h with gentle stirring

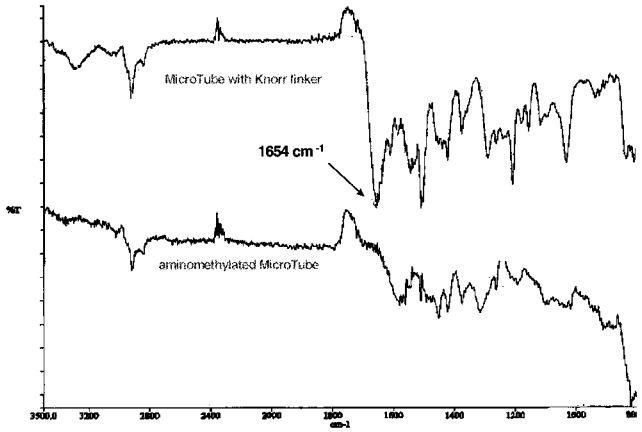


Figure 1. FTIR spectra of Rink amide linker attached microtube and aminomethylated microtube.

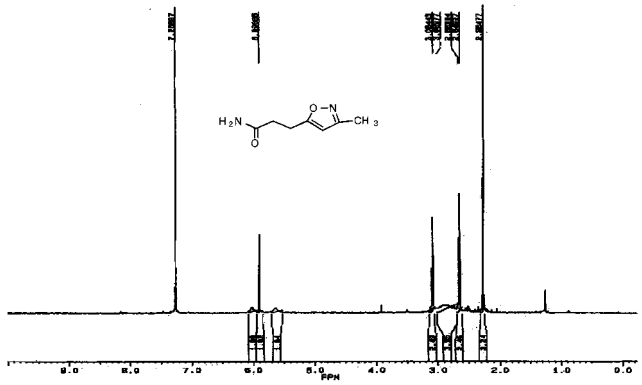


Figure 2. Proton NMR of compound **4** ($CDCl_3$ was used as solvent).

(300 rpm) to form tube-bound isoxazole **3**. The final compound was cleaved off the tube using 2 mL of 50:50 of TFA:DCM at room temperature for 1 h, the solvents were removed, and the compound was dried under vacuum for overnight. The overall yield of the final compound **4** was 3.5 mg/per tube or 76% (based on the loading of **1**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.2 (s, 3H), 2.5 (t, 2H), 3.1 (t, 2H), 5.7 (b, 1H), 5.8 (s, 1H), 6.1 (b, 1H). MS *m*/*e* (Figure 2): 155 (MH^+). HPLC (CH_3CN/H_2O) results indicated that the crude cleavage product was obtained in over 90% purity confirmed by NMR.

MicroTube with 4-Hydroxymethylphenoxyacetic Acid (HMPA) Linker (5). Using the method shown in Scheme 2, tube **5** was prepared using a method similar to that of a Knorr linker starting with aminomethylated PTFE and ETFE microtubes. The loading of the hydroxyl group was measured by Fmoc protection (0.1 M Fmoc−Cl, pyridine, room temperature, 2 h), then deprotection with 20% piperidine/DMF, and spectrophotometric measuring of the released 9-fluorenylmethylidine/piperidine adduct as described earlier.

MicroTube (6). Five dried MicroTubes of **5** were placed into a 8 mL vial, and 5 mL of dried DCM was added as solvent, followed by the addition of triethylamine (138 μL, 0.2 M) and acryloyl chloride (61 μL, 0.15 M, slow addition). The reaction was shaken at room temperate for 2 h. After being washed, the MicroTubes of **6** were dried under vacuum overnight.

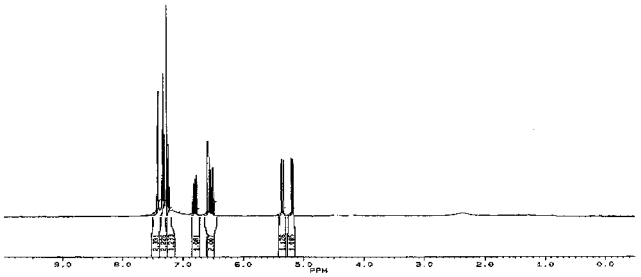


Figure 3. Proton NMR of 1-phenyl-1,3-butadiene ($CDCl_3$ was used as solvent).

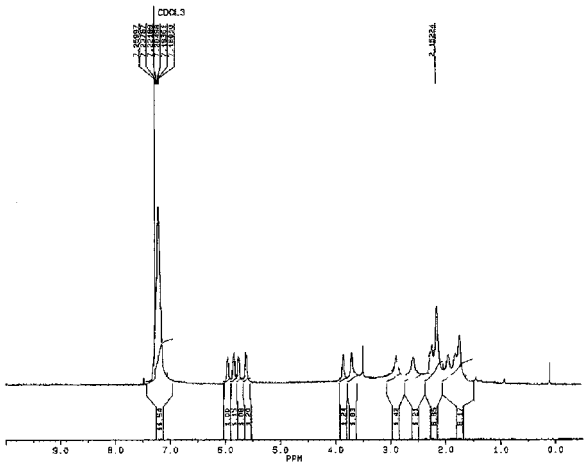


Figure 4. Proton NMR of compound **8** ($CDCl_3$ was used as solvent).

1-Phenyl-1,3-butadiene. A 3.57 g (0.01 mol, 1.2 equiv) sample of methyltriphenyl phosphinium bromide was reacted with 1.83 g (0.01 mol, 1.2 eq.) of sodium bis(trimethylsilyl) amide in anhydrous tetrahydrofuran (THF) at room temperature for 30 min. Then 1.1 g (0.0083 mol, 1.0 equiv) of *trans*-cinnamaldehyde was added into the reaction solution slowly. The reaction was continued for another 2 h at room temperature. The product was purified using a chromatography column, and DCM was used as solvent. Yield: 46%. ^{1}H NMR (Figure 3, $CDCl_3$, 500 MHz): δ 5.2 (d, 1H), 5. 4 (d, 1H), 6.4 to 6.6 (m, 2H), 6.7 to 6.8 (q, 1H), 7.2 (t, 1H), 7.3 (t, 2H), 7.4 (d, 2H). MS *m*/*e*: 131 (MH^+).

Diels−Alder Cycloaddition Reaction (7). Yedidia[19] previously reported the Diels−Alder cycloaddition reaction of polymer-bound benzyl acrylate with 1-phenyl-1,3-butadiene. The reaction temperature was 145 °C. Since the PTFE tubes would be chemically and thermally stable at over 200 °C, this high-temperature cycloaddition reaction was chosen as the second example of our demonstration. Five MicroTubes **6** were refluxed in 50 mL of *o*-xylene for 24 h at 145 °C in the presence of 2% phenyl-β-naphthylamine and 1-phenyl-1,3-butyldiene (650 mg, 0.1 M). The obtained MicroTubes **7** were washed thoroughly with benzene and DCM, and the final product was cleaved using 2 mL/tube of 95:5 (v/v) of TFA:H_2O at room temperature for 1 h. Product **8** was purified using preparative TLC, and the mixture of 95% DCM/5% MeOH/0.5% HOAc was used as solvent. The NMR showed the major addition product was a mixture of cis and trans isomers of 2-phenyl-3-cyclohexenecarboxylic acid. The overall yield was 2.7 mg/tube or

45% (based on tube **5**), determined using ^{1}H NMR with tetramethylsilane as internal standard. ^{1}H NMR (Figure 4, $CDCl_3$, 500 MHz): δ 1.7−2.3 (m, 2 CH_2), 2.6−2.9 (m, 1H), 3.7−3.8 (m, 1H), 5.6−5.9 (m, 2 H, vinylic), 7.1−7.3 (m, 5H, aromatic). MS *m*/*e*: 225 (MNa^+).

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References and Notes

(1) For excellent books and reviews, see: (a) *A Practical Guide to Combinatorial Chemistry*; DeWitt, S. H., Czarnik, A. W., Eds.; American Chemical Society: Washington, DC, 1997. (b) *Combinatorial Chemistry: Synthesis and Application*; Wilson, S. H., Czarnik, A. W., Eds.; Wiley & Sons: New York, 1997. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527. (d) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (e) Balkenhohl, F.; Bussche-Hünnefeld, C. von dem; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (f) Hermken, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.

(2) (a) Schultz, J. S.; Schultz, J. S. *Biotechnol. Prog.* **1996**, *12*, 729. (b) Fenniri, H. *Curr. Med. Chem.* **1996**, *3*, 343.

(3) (a) Gutte, B.; Merrifield, R. B. *J. Biol. Chem.* **1971**, *246*, 1922. (b) Bayer, E.; Rapp, W. *Poly (Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications*; Harris, J. M., Ed.; Plenum Press: New York, 1992; Chapter 20.

(4) Zhao, C. F.; Parandoosh, Z.; David, G. S.; Knoles, S.; Xiao, X.-y.; Nova, M. P.; Czarnik, A. W. MicroTubes for Combinatorial Chemistry Synthesis and Solid-Phase Scintillation Proximity Assay. Poster for Discovery 98 (Emerging Technologies for Drug Discovery), May 18−21, 1998, San Diego, CA.

(5) (a) Nicolaou, K. C.; Xiao, X.-y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289. (b) Xiao, X.-y.; Nova, M. P. *Combinatorial Chemistry: Synthesis and Applications*; Wilson, S. R., Czarnik, A. W., Eds.; John Wiley & Sons: New York, 1996; p 135. (c) Moran, E. J.; Sarshar, S., Cargill, J. F.; Shahbaz, M. M.; Lio, A., Mjalli; A. M. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 10787.

(6) Xiao, X.-y.; Zhao, C. F.; Potash, H.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 780.

(7) (a) *Graft Copolymers*; Battaerd, H. A. J., Tregear, G. W. Interscience Publishers: New York, 1972. (b) Berg, R. H.; Almdal, Pedersen, W. B.; Holm, A.; Tam, J. P.; Merrifield, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 8024. (c) Matchi, S.; Kamel, I.; Silverman, J. *J. Polym. Sci. Part A-1*, **1970**, *8*, 3329.

(8) Geysen, H. M.; Meloen, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3998.

(9) Mitchell, A. R.; Kent, S. B.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845.

(10) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.

(11) A small piece of tube sample (1 mm × 1 mm, cut off from tubes using a razor blade) was used for IR measurement. IR spectra of tube samples can be easily obtained similar to resin samples by using an ATR-FTIR spectrometer.

(12) Li, R.; Xiao, X.-y.; Czarnik, A. W. *Tetrahedron Lett*. **1998**, *39*, 8581.

(13) Pei, Y.; Moos, W. H. *Tetrahedron Lett.* **1994**, *35*, 5825.

(14) Rink amide AM linker was coupled using 0.1 M linker, 0.2 M DIEA, and 0.1 M PyBop in DCM at room temperature for overnight.

(15) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem*. **1970**, *34*, 595.

(16) ^{1}H NMR of compound **4** ($CDCl_3$, 500 MHz): δ 2.2 (s, 3H), 2.5 (t, 2H), 3.1 (t, 2H), 5.7 (b, 1H), 5.8 (s, 1H), 6.1 (b, 1H). MS *m*/*z*: 155 (MH^+).

(17) 1-Phenyl butyldiene was prepared as the following: 1.2 equiv of methyltriphenyl phosphnium bromide was reacted with 1.2 equiv of sodium bis(trimethylsilyl) amide in anhydrous THF at room temperature for 30 min. Then 1.0 equiv of *trans*-cinnamaldehyde was slowly added into the above reaction solution. The reaction was stirred for another 2 h at room temperature. The product was purified using flash chromatography column (DCM:ethyl acetate = 90:10). Yield: 46%. ^{1} H NMR ($CDCl_3$, 500 MHz): δ 5.2 (d, 1H), 5. 4 (d, 1H), 6.4−6.6 (m, 2H), 6.7−6.8 (q, 1H), 7.2 (t, 1H), 7.3 (t, 2H), 7.4 (d, 2H). MS *m*/*e*: 131 (MH^+).

(18) Preparation of microtubes with HMPA linker (**5**): (a) 0.1 M HMPA, 0.1 M PyBop, 0.2 M DIEA, DCM, rt, overnight; (b) 0.5 M acetic anhydride, 0.5 M DIEA, DCM, rt, 2 h; (c) 0.1 M LiOH, THF:H_2O = 4:1, rt, 16 h.

(19) Yedidia, V.; Leznoff, C. C. *Can. J. Chem*. **1980**, *58*, 1144.

(20) Reaction conditions: 0.1 M *E*-phenyl-1,3-butyldiene, 2% phenyl-β-naphthylamine, *o*-xylene, 145 °C, 24 h.

(21) ^{1}H NMR of compound **8** ($CDCl_3$, 500 MHz): δ 5.2 (d, 1H), 5. 4 (d, 1H), 6.4−6.6 (m, 2H), 6.7−6.8 (q, 1H), 7.2 (t, 1H), 7.3 (t, 2H), 7.4 (d, 2H). MS *m*/*z*: 131 (MH^+).

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