Suspension Copolymerization as a Route to Trityl-Functionalized Polystyrene Polymers

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Since the initial report of Merrifield[1] which utilized solid support polymers in the sequential synthesis of oligopeptides, cross-linked functionalized polymers have received tremendous attention as synthetic templates and recyclable catalytic reagents.[2] Growing interest in the polymer-supported preparation of large libraries of compounds for drug discovery further illustrates the use of functionalized polymers in synthetic organic chemistry.[3,4] Styrene-based polymers are by far the most widely used solid supports in chemical synthesis and ion exchange. While there are numerous reports concerning the synthesis, characterization, and functionalization of styrene-based polymers,[5] the need for functionalized polymers is rapidly increasing. One important route to functionalized solid supports is copolymerization[6] of functionalized monomers; an attractive advantage of copolymerization over postfunctionalization of preformed polymer is that it can afford highly predictable and reproducible loadings. We report here the suspension copolymerization of a trityl alcohol derivative (**1**) to give a trityl-functionalized styrene/divinylbenzene resin (**2**).[7]

Suspension copolymerization is achieved through the dispersion of aqueous insoluble monomer(s) in an aqueous phase. Mechanical agitation is usually provided to ensure formation of uniform droplets of the dispersed organic phase. Typically, there is little or no mass transfer between the aqueous/organic phases, and the radical initiator, solubilized in the organic phase, promotes polymerization by thermally induced homolytic cleavage to yield radicals. Initiation, propagation, and termination steps proceed in each individual organic droplet.[8] The aqueous phase is charged with a stabilizer, usually a water soluble polymer such as methyl cellulose or poly(vinyl alcohol) or salts of poly(methacrylic acid), which adsorbs on the surface of monomer droplets and suppresses droplet coagulation.[9] The organic droplets are formed with agitation of the biphasic solution by rapid stirring during polymerization. While many factors influence suspension co-polymerization, the geometry and shape of the polymerization flask and impeller have a pronounced effect on the quality and size distribution of the final resinous bead.

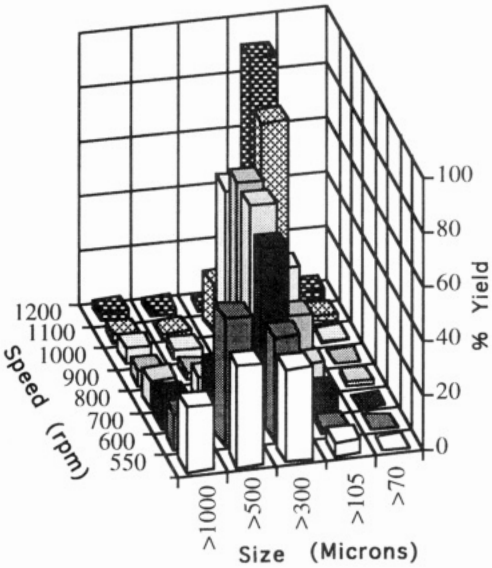

Figure 1. Size distribution of polymer beads as a function of impeller speed.

A typical suspension polymerization of styrene cross-linked with 2% divinylbenzene is achieved by dissolving stabilizer in warm water. This solution is placed in a three-necked Morton flask; indentations force the suspended mixture in toward the rotating stir blade, thus ensuring a more homogeneous shearing environment for monomer droplets which results in more uniform droplet sizes. After the solution is deoxygenated with bubbling N_2 gas, the organic monomers [styrene, styrene derivative, and divinylbenzene (2% by weight)] are added. The impeller is lowered into the biphasic solution, and the biphasic solution is stirred at a constant rate with a mechanical motor. Next the radical initiator, benzoyl peroxide, is added, and the flask is sealed with a condenser on one side neck and a rubber septum on the other. The polymerization flask is lowered into a 90 °C preheated oil bath, and the system is kept under a continuous flow of nitrogen for the duration of the polymerization. When polymerization is complete, the beads are collected and sized with Teflon screens.

Numerous factors dictate the bead size obtained in suspension polymerization. Smaller beads are obtained by increasing the water to organic ratio and/or by decreasing the amount of cross-linking monomer.[5a] While the size and shape of the flask and impeller are important in determining bead size distribution, the impeller speed can also be critical. Figure 1 illustrates the size distribu-

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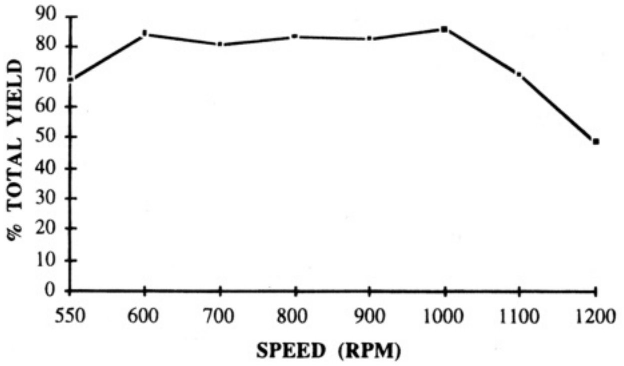

Figure 2. Impeller speed (rpm) versus yield of resinous beads (1000 μm to 105 μm).

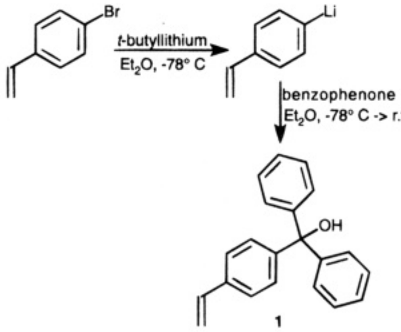

Figure 3. Synthesis of functionalized monomer **1**.

tion achieved under standard polymerization conditions at varying impeller speeds. Note that it is possible to target a specific range of bead sizes and tailor the polymerization process to obtain a preponderance of a particular bead size. Bead size reproducibility was investigated by performing the suspension polymerization of styrene with 2% divinylbenzene four times at 800 rpm. The mass yield of isolated polymer at each bead size range remained constant (yield of beads: >1000 μm = 9.7 ± 3.0; <1000 and >500 = 4.6 ± 1.5; <500 and >300 = 53.7 ± 4.1; <300 and >105 = 31.1 ± 4.5; <105 and >70 = 0.9 ± 0.3). The total bead yield was also investigated at each propeller speed. As Figure 2 illustrates, the bead yield was >80% for impeller speeds of 600−1000 rpm. The yield dropped at higher speeds due to excessive shearing of the polymer beads.

Monomers with additional functionalization can be incorporated in this polymerization scheme, yielding polymers functionalized for use in synthetic organic chemistry. In analogy with earlier reports,[7] we previously prepared a trityl chloride-functionalized polystyrene support (polystyrene/2% divinylbenzene copolymer) by derivatization of preformed resin.[3a] As reported here, we have synthesized "styryl-containing" trityl alcohol **1** for incorporation as a monomer component in suspension copolymerization. Figure 3 illustrates the reaction scheme used to prepare (4-ethenylphenyl)diphenylmethanol (**1**). The pure functionalized monomer was then added to a styrene/divinylbenzene mixture and submitted to suspension copolymerization.

The amount of added functionalized monomer **1** was compensated for by reducing the amount of styrene in the polymerization system. Thus, to synthesize a 0.50 mmol/g trityl-functionalized polymer, a mass ratio of 12.3:60.8:2.7 monomer **1**:styrene:divinylbenzene was used. Polymerization of **1** was affected at 700 rpm with a 79% total bead yield. The distribution of bead sizes was within the range expected from Figure 1, and the incorporation of monomer **1** within the polymeric backbone was demonstrated by the presence of an hydroxyl group in the IR spectrum (KBr; 3463 cm^{-1}). Prior to IR spectroscopy, the resin was washed extensively and rigorously dried in a vacuum oven (P_2O_5, 50 °C).

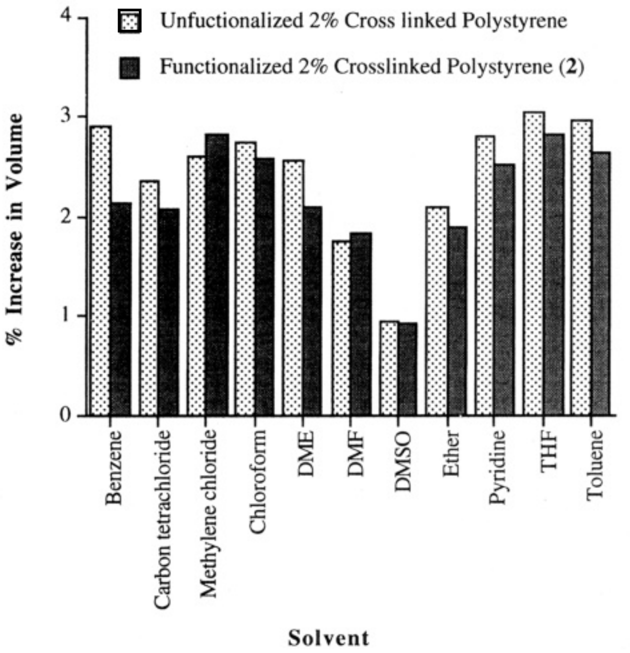

Figure 4. Swelling of 2% styrene/divinylbenzene polymers (<300 and >105 μm) with various organic solvents.

Bead swelling of functionalized polymers in organic solvents is considered to be important for efficient chemistry to occur on microporous solid supports as swelling allows for effective diffusion of solution-phase reagents to polymer-bound functionalities. As a probe of the effect of trityl incorporation upon polymer swelling, a variety of solvents were tested for their ability to swell both the functionalized and unfunctionalized 2% crosslinked styrene/divinylbenzene polymers prepared in this study. While both resins are 2% cross-linked on a weight basis, on a mole percentage basis (i.e., moles of crosslink/total moles of monomers) the crosslink density of the trityl-functionalized resin is slightly higher than the crosslink density of the unfunctionalized resin (≈1.8% versus ≈1.6%, respectively). This difference may explain why the trityl-functionalized resin swells to a lesser extent in most solvents that the unfunctionalized styrene benzene polymer (see Figure 4).

This trityl-functionalized polymer was employed in a sequence of reactions (Figure 5), and the results were compared to a parallel solution-phase sequence of reactions. Trityl chloride polymer **3** was prepared from trityl alcohol polymer **2** by refluxing with acetyl chloride in benzene.[7] This reaction was carried out with four separated bead sizes; <1000 and >500 μm, <500, and >300 μm, <300 and >105 μm, and <105 and >70 μm. The chloride content for each bead size of polymer **3** was determined as described by Stewart and Young[10] and were found to be similar (0.51 mmol/g, 0.52 mmol/g, 0.52 mmol/g, and 0.52 mmol/g, respectively), indicating equal functional group accessibility. More importantly, chloride content determination on polymer **3** indicates that

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[10] Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*; W. H. Freeman and Co.: San Francisco, 1969; p 55.

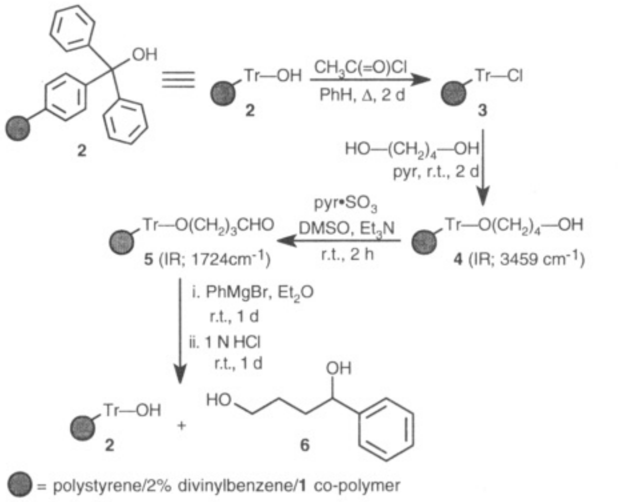

Figure 5. Demonstration synthesis utilizing the trityl alcohol polymer **2**.

bead loading is very close to the theoretically calculated value (0.50 mmol/g) based on the amount of monomer **1** used.[11]

1,4-Butanediol was attached to polymer **3**, and excess reagent was removed by Soxhlet extraction (24 h) with ether. Reappearance of an hydroxyl stretch in the IR (KBr; 3459 cm^{-1}) of resin **4** after rigorous drying (vacuum oven, P_2O_5, 50 °C) confirmed attachment of 1,4-butanediol. Subsequent oxidation of the alcohol-bound polymer to aldehyde **5** was effected by sulfur trioxide–pyridine reagent. The FTIR of polymer **5** clearly indicated formation of the aldehyde with the appearance of C=O stretching frequency at 1724 cm^{-1}. The resulting aldehyde was reacted with phenylmagnesium bromide, and subsequent treatment of the polymer with 2.5 N HCl for 24 h hydrolyzed the product from the solid support. The ^1H-NMR of the crude product after aqueous workup indicated excellent product purity. After purification of 1-phenyl-1,4-butanediol by prep TLC, the overall yield of 1-phenyl-1,4-butanediol (**6**) was 32%.[12] The same sequence of reactions performed in solution phase with trityl alcohol gave an overall yield of 24%. The regenerated trityl alcohol polymer **2** was again reacted with refluxing acetyl chloride in benzene to regenerate trityl chloride polymer **3**. Analysis for chloride content established that the regenerated polymer was functionalized at 0.510 mmol/g (as compared to 0.520 mmol/g originally).

Experimental Section

General. The mechanical motor used in suspension polymerization was a Janke & Kunkel IKA-WERK Model RE 16 equipped with an rpm gauge IKA-TRON Model DZM-1 (Staufen, Germany). This motor provides constant speed at all stages of the polymerization, thus compensating for any minor changes in the viscosity of the solution. The impeller and the 45/50 sealed shaft adapter for the propeller were also purchased from IKA (Staufen, Germany). Food grade gelatin was purchased from Research Organics, Inc. (Cleveland, OH). All starting materials were purchased from Aldrich, Inc. and used without further purification (unless stated otherwise). The solvent used for reactions were freshly distilled under dry nitrogen immediately prior to use.

General Polymerization Procedure. Gelatin (0.670 g) was dissolved in 70 °C deionized water (225 mL). After the gelatin was completely dissolved, the solution was placed in a three-necked Morton flask (500 mL, center neck size 45/50, outside neck sizes 24/40). Teflon sleeves of appropriate size were inserted in each neck of the Morton flask since freezing of joints during polymerization can be a problem. The solution was purged with nitrogen for 20 min to flush out solubilized oxygen. The monomers, styrene (73 g, 0.70 mol) and divinylbenzene (55%, 2.7 g, 2% by weight of styrene), were mixed and added to the Morton flask. The propeller was lowered into the solution through the center 45/50 neck, and the biphasic solution was stirred at a constant speed (550 → 1200 rpm) as indicated by an rpm gauge attached to the motor. Benzoyl peroxide (0.75 g) was added, and the stirring was continued for 5 min before the flask was lowered into a preheated oil bath maintained at 90 °C. The Morton flask was sealed with a water condenser on one side neck and a rubber septum on the other side neck. The system was kept under a continuous nitrogen flow for the duration of the polymerization. After 5 h the motor was stopped, the newly formed beads were allowed to settle, and the flask was flushed with running water allowing any light weight solidified gelatin to wash out. The beads were sized with Teflon screens beginning with 1000 μm which filtered coagulated and large irregular sized particles. The filtrate was then passed through 500, 300, 105, and 70 μm Teflon screens, sequentially. Polymerization of functionalized monomer **1** was effected as described above except that the mass of styrene used was reduced by the mass of monomer **1** used. Thus, in order to obtain a 0.500 mmol/g polymer, 12.3 g of **1** was mixed with 60.8 g of styrene and 2.7 g of divinylbenzene.

Synthesis of (4-Ethenylphenyl)diphenylmethanol (1). 4-Bromostyrene (20.0 g, 0.105 mol) was dissolved in dry ether (500 mL), and the solution was put under nitrogen and cooled to −78 °C with an acetone/dry ice bath. *tert*-Butyllithium (1.7 M, 0.231 mol) was added to the reaction flask, and transmetalation to 4-styryllithium was instantaneous yielding a red-colored solution. Benzophenone (19.6 g, 0.110 mol), previously dried in a vacuum oven, was dissolved in ether (30 mL) and added slowly to the reaction vessel via a syringe pump. The acetone/dry ice bath was removed, and the reaction was allowed to warm to room temperature. After 4 h, the reaction mixture was washed with 1% H_2SO_4 (300 mL) and saturated NaCl (300 mL), dried with anhydrous Na_2SO_4, and filtered. Removal of solvent under reduced pressure yielded a yellow oil as crude product which was purified by flash silica chromatography to give **1** in 55% (15.1 g) overall yield [^1H NMR (300 MHz, $CDCl_3$) 2.84 (1 H, D_2O exchangeable), 5.29 (1 H), 5.78 (1 H), 6.75 (1 H), 7.23–7.42 (14 H).[13]

Synthesis of 1-Phenyl-1,4-butanediol (6) from Polymer 2. Polymer-bound 1-butanal ether **5** was synthesized as described previously from trityl alcohol polymer **2** [prepared by suspension polymerization of (4-ethenylphenyl)diphenylmethanol (**1**, trityl alcohol monomer) with styrene and divinylbenzene]. Polymer **5** (6.6 g, 0.51 mmol/g) was suspended in dry ether (90 mL), and the solution was purged with nitrogen for 10 min. Phenylmagnesium bromide (3 M, 5.5 mL) was added, and the reaction mixture was kept under nitrogen on an orbital shaker. The reaction progress was monitored by FTIR (small samples of polymer were withdrawn from the reaction flask, rinsed thoroughly with dry ether, dried under vacuum, ground with KBr, and analyzed by FTIR). After three days, the aldehyde C=O stretching frequency at 1724 cm^{-1} had completely disappeared and was accompanied by the reappearance of a large OH peak (3440 cm^{-1}). The reaction was quenched and the product was hydrolyzed from the polymer by addition of a 3:1 THF:20% HCl solution (95 mL). The latter solution was stirred continuously for 20 h, after which the polymer was removed by filtration, and the filtrate was neutralized with the slow addition of Na_2CO_3. FTIR of recovered polymer indicated the recovery of the original trityl alcohol polymer [**2**; IR (KBr) 3463, 3081, 3058, 3023, 2919, 2850, 1600, 1492, 1450 cm^{-1}]. The filtrate was

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(11) The slightly higher experimental value obtained for the mmol equiv functionality of polymer **2** could be due to several factors. These factors might be the higher rate of styrene evaporation during polymerization as compared to monomer **1** or residual chloride trapped within the polymer prior to chloride content analysis (the polymer was extensively washed in a soxhlet extractor).

(12) We expect that diblocking of 1,4-butanediol contributes to this modest overall yield; see reference 7c.

(13) Rakshys, J. W., Jr. U.S. Patent 3,716,501, 1973.

extracted with ether (3 × 50 mL), and the combined organics were washed with saturated NaCl (50 mL), dried with anhydrous Na_2SO_4, and filtered. After removal of solvent under reduced pressure, a yellowish oil was obtained. NMR of the crude product showed good purity (>80%) of the final product. The crude product was applied to a prep TLC plate and developed with 20% ethyl acetate in hexane. 1-Phenyl-1,4-butanediol (179 mg) was isolated as the major product in 32% yield [^1H NMR (300 MHz, $CDCl_3$) 1.68 (2 H), 1.87 (2 H), 2.40 (2 H, D_2O exchangeable), 3.68 (2 H), 4.73 (1 H), 7.25–7.36 (5 H); IR (KBr) 3324, 2923, 2869, 1600, 1450, 1419 cm^{-1}; LRMS m/z 166 (5), 149 (21), 107 (100).[14]

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