Preparation of Soluble Polymeric Supports with a Functional Group for Liquid-Phase Organic Synthesis

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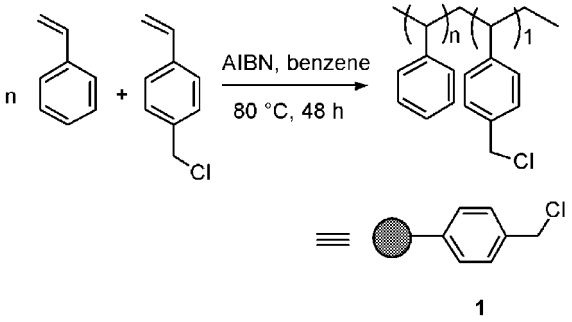
Abstract: Soluble copolymers of styrene with functional groups were prepared by radical co-polymerization of styrene with various substituted styrenes. They were characterized by NMR spectroscopy and their molecular weight was determined by size exclusion chromatography.

Key words: polymerization, soluble copolymer, polystyrene, functional group

The use of solid polymeric supports, dedicated to organic synthesis, affords the advantage of a simplified purification of the products, based on the facile separation of the support from the reaction mixture. However, the broadly employed solid polystyrene beads, initially developed by Merrifield,[1] have shown some limitations. Consequently, some attempts to develop alternatives to these resins have recently been made. Particularly, polymers with higher loading, specific solubility,[2] swelling properties,[3] or increased chemical and mechanical stability[4] have been used. Thus, Janda et al. have shown that soluble supports were readily applicable to small organic molecule synthesis in liquid-phase methodology.[5,6] The use of soluble polymeric supports affords the application of homogeneous reaction conditions, as well as the product characterization by routine analytical methods. These soluble supports have proven to be convenient polymeric materials for applications dealing with supported reagents[7] and catalysts.[8] Such copolymers are easily prepared by radical polymerization (Scheme 1) and with glassware usually used for organic synthesis. The analysis of polymers by routine NMR spectroscopy is easily performed in various deuterated solvents. However, these polymers can present the disadvantages of reticulation in some experimental conditions and consequently lose their specific physical properties. So, they are mainly useful in quite short sequences, usually of less than six steps.[5,6]

Although several co-polymerizations with amino group substituents have been reported,[8] most of the work was focalized on the modification of the polystyrene bearing a chloromethyl substituent. The co-polymerization of styrene with a monomer bearing the desired functionality



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Scheme 1

corresponds to an economy of several steps. However, such an approach is only interesting when a variety of monomer can be used in the polymerization step without reticulation of the polymer or lose of the functional groups. We report here the preparation of copolymers of styrene with substituted styrenes bearing one or two functional groups and show the compatibility of the functional groups with the co-polymerization reaction.

Preparation of the monomers.

Various functional groups can be easily introduced onto a styrene, by some well-known organic reactions. According to the literature, 4-vinylbenzylalcohol,[9] 4-vinylbenzylamine,[10] but-3-enyl-4-vinylbenzene,[11] 4-vinylbenzoic acid,[12] the styrenic monomer bearing the Wang linker[13] and isopropyl 4-styrenesulfonate[14] have been prepared as reported. 4-Vinylbenzyl azide **2** has been synthesized by nucleophilic substitution of 4-vinylbenzylchloride with sodium azide, in dimethylsulfoxide, at 80 °C.[15] From *p*-styrenesulfonylchloride,[16] allylamine and and triethylamine in dichloromethane, the sulfonamide **3** has been prepared,[17] then converted to the sulfonamide **4** with propargyl bromide in the presence of cesium carbonate (Scheme 2).[18]

Preparation of copolymers

To study the co-polymerization of styrene with substituted styrenes, we used the experimental conditions reported by Janda et al.[5] in the preparation of copolymer **1**. For most experiments, the reactions were performed with 33 equiv. of styrene and 1 equiv. of the substituted styrene and were carried out twice in order to evaluate the reproducibility of the molecular weight, the loading and the chemical yield.[19] The radical co-polymerization of mono-

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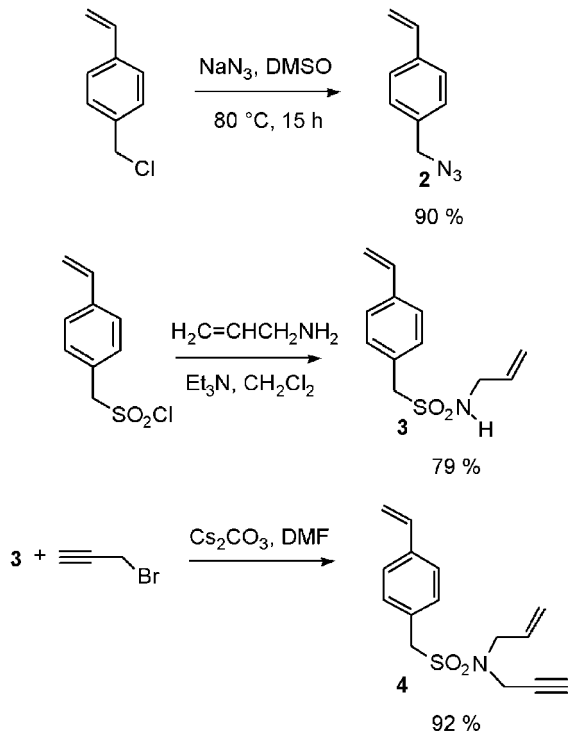
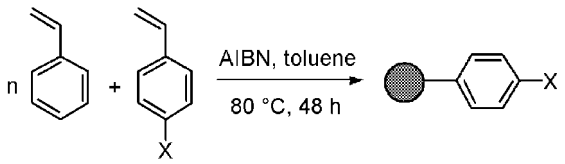


Scheme 2

mer with substituted styrenes has been achieved successfully in all the cases, even in the presence of other unsaturations (Scheme 3). Copolymers **5**–**13** are readily soluble in most of commonly used organic solvents, and easily recovered by precipitation in methanol. Molecular weights have been determined by size exclusion chromatography (SEC) (Table).

Apart from the sample containing a primary amine **7**, the average molecular weight of the synthesized copolymers is in the same range as the molecular weight of the reference sample **1**. The polydispersity is good for most of the samples (**1**, **6**–**11**, **13**). The yields range between 20% and 55% and, in most cases, the loading is not dependent on the nature of the functional group.



Scheme 3 **1**: X = CH_2Cl, **5**: X = CH_2OH, **6**: X = CH_2N_3, **7**: X = CH_2NH_2, **8**: X = $CH_2OpC_6H_4CH_2OH$, **9**: X = $(CH_2)_2CH{=}CH_2$, **10**: X = CO_2H, **11**: X = $SO_3{}^iPr$, **12**: X = $SO_2N(H)CH_2CH{=}CH_2$, **13**: X = $SO_2N(CH_2CH{=}CH_2)$-$(CH_2C{\equiv}CH)$

The radical co-polymerization reaction conditions are thus compatible with various functional groups. Alcohol, carboxylic acid, azide, alkene or sulfonamide groups can be incorporated into the macromolecular chain as pendant groups during the step of co-polymerization. Such preparations of various functionalized soluble supports enable to design the requisite monomer with much more synthetic tools than those afforded by the subsequent chemical modification of polystyrene **1**.

Table Preparation of Copolymers **1**, **5**–**13**

Sample	Mw (D)[a]	I = Mw/Mn	Loading (mmol/g)	Yield (%)
1	39000	1.4	0.32[b]	52
5	47000	2.1	0.24[b]	52
6	33300	1.6	0.18[b]	40
7	19000	1.4	0.30[b]	37
8	29000	1.6	0.28[b]	25
9	35000	1.5	0.50[c]	44
10	45000	1.5	0.37[b]	35
11	45000	1.1	1.1[c]	20
12	40000	2.0	0.32[b]	55
13	44000	1.5	0.32[b]	49

[a] SEC determination in THF.
[b] Ratio 33.
[c] Ratio 10.

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(15) **4-Vinylbenzyl Azide 2**: A mixture of 2 g (13 mmol) of 4-vinylbenzylchloride, 1.7 g (26 mmol) of sodium azide and 0.2 g (1.3 mmol) of sodium iodide in 25 mL of DMSO was stirred at 80 °C for 15 h, cooled, and treated with 25 mL of water and 75 mL of ether. The organic phase was separated, washed with water and then dried with magnesium sulfate. Yield 90%. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, 2 H, *J* = 8.1, Ar-H); 7.25 (d, 2 H, *J* = 8.1, Ar-H); 6.71 (dd, 1 H, *J* = 10.7, 17.8, CH=C); 5.75 (d, 1 H, *J* = 17.8, C=CH_2); 5.25 (d, 1 H, *J* = 10.7, C=CH_2); 4.29 (s, 2 H, CH_2N_3). ^{13}C NMR ($CDCl_3$): δ 138.3, 136.9, 135.4, 129.1, 127.3, 115.1, 55.2.

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(17) **Sulfonamide 3**: Allylamine (1.1 mL, 14.2 mmol) was added to a solution of *p*-styrene-sulfonylchloride (1.44 g, 7.11 mmol) in a solution of dichloromethane–triethylamine (13 mL, 10:3). The mixture was stirred for 15 h at room temperature, and then acidified by a 0.25 N aqueous HCl solution (10 mL). The organic products were extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried with magnesium sulfate. After evaporation of the solvent, the residue was purified by chromatography on silica gel (CH_2Cl_2). The monomer was isolated as a colorless oil (1.25 g, Yield 79%). ^{1}H NMR ($CDCl_3$): δ 7.83 (d, 2 H, *J* = 8.4, Ar-H); 7.52 (d, 2 H, *J* = 8.4, Ar-H); 6.75 (dd, 1 H, *J* = 10.9, 17.5, (Ar)-CH=C); 5.88 (d, 1 H, *J* = 17.5, (Ar)-C=CH_2); 5.72 (m, 1 H, *J* = 17.3, 10.2, 5.6, CH=CH_2); 5.42 (d, 1 H, *J* = 10.9, (Ar)-CH=CH_2); 5.16 (d, 1 H, *J* = 17.3, CH=CH_2); 5.07 (d, 1 H, *J* = 10.2, CH=CH_2); 4.83 (s, 1 H, NH); 3.60 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 142.4, 139.3, 135.9, 133.5, 128.1, 127.4, 118.3, 118.0, 46.3.

(18) **Sulfonamide 4**: A 80% w/w solution of propargyl bromide (97 mg, 0.65 mmol) in toluene was added to a mixture of allyl *p*-styrenesulfonamide (120 mg, 0.48 mmol) and cesium carbonate (213 mg, 0.65 mmol) in DMF (1.2 mL). The mixture was stirred for 15 h at room temperature, then 9 mL of ethyl acetate was added. The mixture was washed with a saturated ammonium chloride aqueous solution and the organic products were extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and then dried with magnesium sulfate. After evaporation of the solvent, the residue was purified by chromatography on silica gel (CH_2Cl_2). The monomer **4** was obtained as a colorless oil (123 mg, Yield 92%). ^{1}H NMR ($CDCl_3$): δ 7.84 (d, 2 H, *J* = 8.3, Ar-H); 7.53 (d, 2 H, *J* = 8.3, Ar-H); 6.76 (dd, 1 H, *J* = 10.9, 17.6, (Ar)-CH=CH_2); 5.88 (d, 1 H, *J* = 17.6, (Ar)-CH=CH_2); 5.74 (ddt, 1 H, *J* = 17.3, 10.2, 5.6, CH=CH_2); 5.44 (d, 1 H, *J* = 10.9, (Ar)-CH=CH_2); 5.29 (d, 1 H, *J* = 17.3, CH=CH_2); 5.07 (d, 1 H, *J* = 10.2, CH=CH_2); 4.05 (d, 2 H, *J* = 2.6, CH_2-CCH); 3.60 (d, 2 H, *J* = 5.6, CH_2); 1.63 (t, 1 H, *J* = 2.6, CCH).

(19) **General Procedure for the Preparation of Copolymers 5–13**: AIBN (11.6 mg, 0.07 mmol) was added to a solution of styrene (1.43 g, 13.8 mmol) and monomer (0.42 mmol) in toluene (5.3 mL), and the mixture was stirred for 40 h at 70 °C under inert atmosphere. After evaporation of the solvent, dichloromethane (4.5 mL) was added to the residue and the solution was dropped into methanol (23 mL) with strong stirring, at room temperature, to precipitate the polymer. The resulting suspension was filtered, washed with methanol and dried under vacuum.

Copolymers 5–13. Selected data. For all the copolymers **5**–**13**: ^{1}H NMR ($CDCl_3$): δ 7.3–6.2 (brd signal, Ar-H PS); 2.2–1.2 (brd signal, -CH-CH_2- PS). ^{13}C NMR ($CDCl_3$): δ 147.0–145.0, 129.1–126.0, 47.0–40.5. **5**: ^{1}H NMR ($CDCl_3$): δ 4.60 (s, 2 H, CH_2O). ^{13}C NMR ($CDCl_3$): δ 66.0 (CH_2OH). **6**: ^{1}H NMR ($CDCl_3$): δ 4.21 (s, 2 H, CH_2N_3). ^{13}C NMR ($CDCl_3$): δ 133.1, 55.2. **7**: ^{1}H NMR ($CDCl_3$): δ 3.74 (s, 2 H, CH_2NH_2). **8**: ^{1}H NMR ($CDCl_3$): δ 4.97 (s, 2 H, CH_2O); 4.61 (s, 2 H, CH_2OH). ^{13}C NMR ($CDCl_3$): δ 159.2, 134.6, 133.9, 129.7, 115.5, 70.6, 65.6. **9**:^{1}H NMR ($CDCl_3$): δ 5.89 (brd s, 1 H, CH=CH_2); 5.02 (brd s, 2 H, CH=CH_2); 2.65 (s, 2 H, Ph-CH_2), 2.35 (brd s, 2 H, CH_2-CH=CH_2). ^{13}C NMR ($CDCl_3$): δ 139.0, 115.4, 36.3, 35.7. **11**: ^{1}H NMR ($CDCl_3$): δ 7.52 (brd s, 2 H, Ar-H); 4.65 (brd s, 1 H, CH); 2.2-1.2 (CH_3). **12**: ^{1}H NMR ($CDCl_3$): δ 7.54 (brd s, 2 H, Ar-H); 5.71 (brd s, 1 H, CH=CH_2); 5.14 (m, 2 H, CH=CH_2); 3.52 (brd s, 2 H, CH_2-CH=C). **13**: ^{1}H NMR ($CDCl_3$): δ 7.46 (brd s, 2 H, Ar-H); 5.72 (brd s, 1 H, CH=CH_2); 5.28 (m, 2 H, CH=CH_2); 4.03 (brd s, 2 H, CH_2-CCH); 3.78 (brd s, 2 H, CH_2-CH=CH_2); 2.2-1.2 (-C≡CH). ^{13}C NMR ($CDCl_3$): δ 136.4, 132.5, 120.7, 78.7, 74.4, 49.6, 36.4.