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New supports for solid-phase organic synthesis: development of polystyrene resins containing tetrahydrofuran derived cross-linkers

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Abstract

Polystyrene resins containing flexible tetrahydrofuran derived cross-linkers are presented. These cross-linkers were designed to render the resins more 'organic solvent-like' and thus impart increased swelling/solvation characteristics in the resins with regard to common solvents used in solid-phase organic synthesis. © 1999 Elsevier Science Ltd. All rights reserved.

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With the advent of combinatorial chemistry and automated synthesis there has been renewed interest in polymer-supported reactions.[1] Resins that are commonly used in solid-phase organic synthesis (SPOS) were adopted from the field of solid-phase biopolymer synthesis and most have thus been optimized to work with highly polar solvents and reagents that are not always conducive to, or necessary for, the synthesis of small organic molecules. The resins are typically lightly cross-linked divinyl benzene-polystyrene beads and they are often derivatized with grafts of hydrophilic polyethyleneglycol (PEG).[2,3] There have been few resins designed de novo specifically for use as general platforms for SPOS in common organic solvents.

One group of such resins utilizes bifunctional styrene derivatized PEG chains to cross-link polystyrene as a means for improving general resin performance.[4–7] Improved swelling and mechanical properties have been observed with these resins. However, the choice of PEG-based cross-linkers can interfere with the use of strong bases and organometallic reagents, and imparts hydrophilic properties not always desirable for organic synthesis. To circumvent the inherent problems associated with PEG, an alternative flexible polytetrahydrofuran (PTHF) cross-linker could be used to prepare a new class of resins. Herein we report the preparation and characterization of such cross-linked polystyrene resins.

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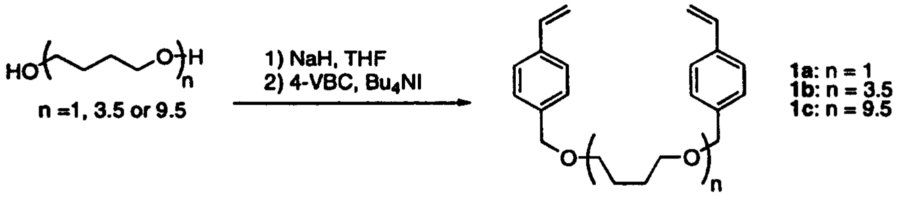
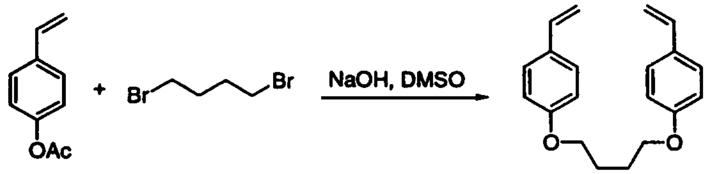
THF-based cross-linkers **1a–c** were prepared by Williamson ether synthesis in 70–85% yield from diols (Scheme 1).[8,9] Cross-linkers **1b** and **1c** are the products from commercially available PTHF (mw 250) and PTHF (mw 650), respectively. The three different molecular weight diols were used to study possible chain-length dependant swelling and chemical properties. It should be noted that the cross-linkers **1b** and **1c** are defined mixtures of oligomers that result in well defined resins, as opposed to some recently reported PEG-based cross-linkers and resins.[6] Phenyl ether containing cross-linker **2** was prepared as shown in Scheme 2.[10] Cross-linker **2** contains a highly stable phenyl ether linkage and was designed to provide expanded compatability with reagents and chemistries compared to **1a–c**. Various mole fractions of **1a–c** and **2** were suspension copolymerized[7] with styrene and 4-vinylbenzyl chloride (VBC) to form resins **3a–c** and **4** (Table 1), respectively, which contain the common benzyl chloride functionality.



Scheme 1. Synthesis of cross-linking agents **1a–c**



2

Scheme 2. Synthesis of cross-linking agent **2**

The degree to which a resin absorbs a particular solvent and swells is considered to be a good measure of site accessibility and thus resin functionalization.[11] Table 1 compares the swelling of **3a–c** and **4** to three commonly used supports of the same bead size (100–200 mesh) and approximately the same loading level (ca. 0.9 mmol/g) in solvents typically used for organic synthesis. From Table 1, it is clear that utilization of flexible cross-linkers **1a–c** and **2** allows for resins **3a–c** and **4** to have outstanding swelling properties in all solvents where swelling was observed. As previously reported,[8] the amount of swelling decreases as the level of cross-linking increases, although even the 10% cross-linked resins swell significantly. Interestingly, resin swelling is not dependent on the chain length of the cross-linker.

To investigate the chemical stability of these resins, a series of unfunctionalized resins **5a–c** and **6**, analogous to **3a–c** and **4**, respectively, were prepared by copolymerizing styrene with **1a–c** or **2**. These beads were found to be stable to a variety of common chemical reagents (>20 mmol reagent/g resin at rt for 4 h): mCPBA, Dibal-H, MeI, Ac_2O, aq. NaOH, aq. HCl, and 50% TFA/CH_2Cl_2. The only reagents found to degrade the structural integrity of resins **5a–c** were TMSOTf and BuLi. Importantly, only resins **5a–c** cross-linked with 1 and 2 mol% **1a–c** were degraded upon treatment with BuLi. Resins **5a–c** cross-linked with 5 and 10 mol% **1a–c** were unaffected by this treatment. Furthermore, resins **6** cross-linked with 1 and 2 mol% **2** also exhibited stability to BuLi. Finally, all resins were mechanically stable to magnetic stirring over a 48 h period.

In summary, we have synthesized flexible THF derived cross-linking agents and used them to prepare a new class of resin that is designed specifically for use in SPOS. A simple alteration in the cross-linking

Table 1
Volumes of swollen resins

Resin - Cross-linking (%)	Volume of Swollen Resin (mL/g)[a]				
	Dioxane	THF	DMF	Benzene	CH_2Cl_2
Merrifield-1[b]	**6.0**	**6.4**	**4.8**	**6.6**	**6.0**
Merrifield-2[b]	5.4	5.4	4.2	6.6	5.8
Tentagel HMP-1[b]	4.8	4.4	4.4	4.0	5.8
3a-1	**11.8**	**13.4**	**8.8**	**12.6**	**11.8**
3a-2	7.0	7.0	5.0	7.6	6.6
3a-5	5.2	5.6	3.8	5.8	4.8
3a-10	4.2	4.2	3.2	4.8	4.4
3b-1	**10.4**	**10.4**	**8.0**	**12.2**	**10.6**
3b-2	7.4	8.2	5.6	9.6	7.8
3b-5	5.6	5.8	3.6	7.2	5.8
3b-10	4.0	4.0	3.0	5.0	4.6
3c-1	**12.6**	**12.6**	**8.2**	**13.8**	**12.4**
3c-2	8.4	8.4	5.4	8.0	7.8
3c-5	5.4	5.8	3.6	5.8	5.6
3c-10	5.6	5.4	3.2	5.8	5.6
4-1	**14.8**	**14.0**	**10.4**	**14.6**	**15.0**
4-2	7.8	7.4	6.0	8.2	7.4

(a) Volumes were measured in syringes equipped with a sintered frit after equilibrating for 1 h.[11] Resins **3a-c** and **4** did exhibit modest swelling in ethyl ether and 1:1 THF:water. Water, acetonitrile, and ethanol were also examined, but no swelling was observed. All resins had dry volumes of approximately 1.5 mL/g. (b) Resin was purchased from NovaBiochem and used as received.

reagent has allowed the preparation of resins that exhibit excellent swelling characteristics in common organic solvents as compared to the commercially available resins examined. Noteworthy is that the process of preparing these resins is efficient and inexpensive. The utilization of our resins in SPOS is currently under investigation. We have successfully applied aminomethyl versions of our resins to the synthesis of a phthalide library via a directed *ortho*-lithiation strategy and this will be reported in due course.[12]

Resin Preparation: Resin **3c**–2%: A solution of acacia gum (18.0 g) and NaCl (11.25 g) in water (450 mL) was placed in a 500 mL flanged reaction vessel equipped with a floating magnetic stirrer[7] and deoxygenated by purging with N_2. A solution of VBC (4.59 g, 30.0 mmol), styrene (23.4 mL, 204 mmol), **1c** (4.14 g, 4.69 mmol), benzoyl peroxide (0.45 g) in chlorobenzene (30 mL) was injected into the rapidly stirred aqueous solution. This mixture was heated at 85°C for 16 h. The crude polymer was collected and washed in a Soxhlet extractor with water, THF and hexanes. The beads (25.92 g, 86%) were dried in vacuo and sieved to afford resin in three size ranges: 50–100 mesh (11.31 g, 38%), 100–200 mesh (10.51 g, 35%) and 200–400 mesh (1.31 g, 4%). MAS ^{1}H NMR (600 MHz, 4 mg per mL $CDCl_3$, 4 s relaxation delay with water suppressed by using a 0.5 s pre-saturation pulse during the relaxation delay) δ=3.75, 1.82.

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