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2-Polystyrylsulfonyl ethanol supports for the solid-phase syntheses of hydantoins and ureas

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Abstract—Reaction of sodium polystyrylsulfinate **1** with 2-chloroethanol gave the 2-arylsulfonyl ethanol resin **2**, which was converted to the polymer-supported amine **5**. Amine **5** was coupled with an isocyanate or an isothiocyanate to give the polymer-supported urea derivatives **6**. Treatment of the resin **6** with 6N HCl gave hydantoins **7**, while reaction of the same resin with 4N NaOH then HCl gave the urea derivatives **8**. © 2001 Elsevier Science Ltd. All rights reserved.

Efforts have been made towards the discovery of novel tethers for connecting hydroxyl groups to polymer supports and the materials obtained are useful for derivatization to ether and ester resins.[1–6] Hydroxyl groups can be attached directly to polymers via 'unfunctionalized' tethers and examples are the Wang resin,[2] Sasrin resin,[3] and Rink acid resin.[4] Alternatively, tethers with functional groups can be inserted between hydroxyl groups and supports, and these functional groups offer an additional handle for releasing the desired molecules from the polymers. For example, 2-polystyrylsulfonyl ethanol **2** has been used in the solid-phase synthesis of oligonucleotides.[5] Bramdstetter and co-workers have explored the use of a polystyrene-supported β-hydroxylethylene thioether, which can be released by thioether oxidation and alkaline treatment. Tesser and co-workers prepared 2-polystyrylmethylenesulfonylethanol resin by the reaction of the Merrifield resin with thioethanol followed by the oxidization with MCPBA.[6] We report an efficient method for the synthesis of **2** by the direct coupling of 2-chloroethanol with resin **1**.[7] The resin **2** can easily couple with carboxylic acids to form ester linkages, which can be cleaved by using both aqueous basic and acidic conditions.

2-Polystyrylsulfonylethanol **2** was prepared by treatment of polystyrylsulfinate resin **1** with 2-chloroethanol in DMF in the presence of tetrabutylammonium iodide and potassium iodide.[8] The efficiency of hydroxyl group attachment on the resin was 1.59 mmol/g, which was determined by using 3,5-dinitrobenzoyl chloride. Reaction of **2** with Boc-protected glycine under general DCC/DMAP coupling conditions gave resin **3**,[9] which was converted to **4** by the treatment with 6N hydro-

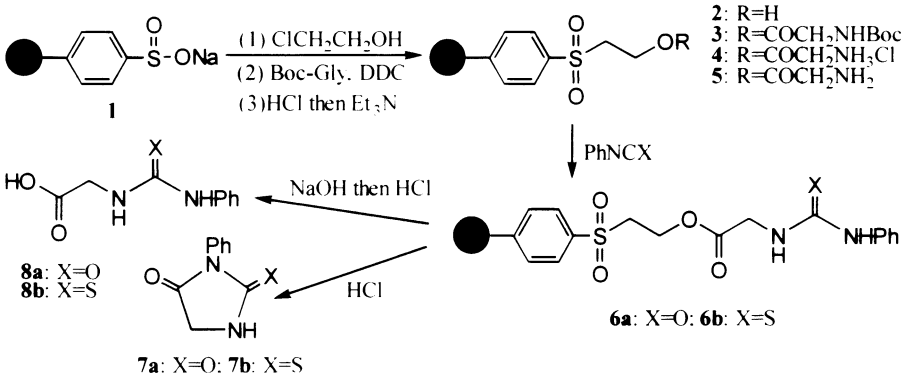

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Table 1. The results of solid-phase synthesis of (thio)hydantoins and (thio)urea from **6**

Compound	Mp (°C)[a]	Elemental analysis (%)						Yield (%)[b]
		Found			Calc.			
		C	H	N	C	H	N	
7a	158–158.5 (154–156)	61.2	4.62	15.5	61.4	4.54	15.9	29
7b	196–197 (195–196)	55.1	5.02	13.8	55.7	5.15	14.4	20
8a	247–250 (dec.) (245–248 (dec.))	55.7	4.20	14.6	56.2	4.17	14.6	30
8b	140–141 (141)	51.0	4.98	12.3	51.4	4.76	13.3	21

[a] Literature melting point in parentheses.
[b] Isolated overall yield.

chloric acid in dioxane. The ester group in **4** appears to survive under these conditions probably due to the formation of ammonium salts. The resin obtained was treated with benzoyl chloride/pyridine in DCM to mask the uncoupled hydroxyl groups.

Resin **5** was obtained by neutralization of **4** with Et_3N in DCM, the amount of triethylamine (<2 equiv.) being minimized to reduce alcohol elimination. The corresponding vinyl sulfone resin was obtained from resin **5**. Polymer-supported urea **6a** was prepared by the treatment of **5** in DMF with phenyl isocyanate (5 equiv., based on the loading of amine) under a nitrogen atmosphere at room temperature for 8 h. Reaction of **5** with phenyl isothiocyanate required an elevated temperature (90°C) to give polymer-supported thiourea **6b**. Direct treatment of compounds **6a** and **b** with 6N aqueous hydrochloric acid in dioxane released the corresponding hydantoin **7a** and thiohydantoin **7b**, respectively.[10] Base treatment (4N NaOH in dioxane) of the same polymer resin **6a** or **b** produced compounds **8a** or **b** after acid neutralization.[11] The results are summarized in Table 1.

To summarize, 2-polystyrylsulfonylethanol resin **2** can be easily prepared by an S_N2 displacement of 2-chloroethanol with sulfinic acid resin **1**. This resin is useful for its conversion to the urea **6**, which can release both **7** and **8** using simple acidic and basic reagents.

Acknowledgements

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7. Resin **1**, which is available from Hecheng Co. of Nankai University, PRC, has the following properties: 1% DVB cross-linked, 1.88 mmol SO_2Na/g.
8. Resin **1** (5 g) was suspended in a mixture of DMF (10 mL) and THF (20 mL) for 30 min with mechanical stirring. To the suspension were added 2-chloroethanol (6 mL), tetrabutylammonium iodide (0.8 g), and potassium iodide (4.4 g). The mixture was refluxed at 90°C under an N_2 atmosphere for 48 h. After filtration, the resin was washed sequentially with DMF, H_2O, EtOH, acetone, DCM, and Et_2O, and then dried under reduce pressure over P_2O_5 at 40°C.
9. Resin **2** (0.50 g) was swelled in DMF (5 mL) for 30 min. To the resulting suspension were added Boc-Gly (0.35 g), DCC (0.41 g) and DMAP (0.245 g). The mixture was mechanically shaken at 30°C for 4 h. The resin was filtered out and washed twice in succession with DMF, EtOH, DCM, and Et_2O, and then dried over P_2O_5 at 40°C overnight.
10. To urea resin **6a** (0.50 g) was added HCl (6N) in dioxane (5 mL). After the suspension was stirred at 80°C for 6 h, the resin was filtered out and washed three times with methanol. The combined aqueous and organic phases were neutralized with sodium carbonate and then evaporated to dryness. The residue was dissolved in DCM. After removal of insoluble materials, the solvent was evaporated to give a crude product. 3-Phenylhydantoin (white needles) can be obtained by recrystallization from water.
11. To urea resin **6a** (0.50 g) was added a mixture of NaOH (4N), dioxane, and methanol (v/v/v = 1:30:9, 5 mL). The suspension was mechanically shaken at room temperature for 15 min. Resin materials were filtered out and washed several times with methanol. The combined aqueous and organic phases were neutralized with aqueous HCl, and then evaporated to dryness. The residue was dissolved in methanol. The filtered organic phase was dried to give **8a**, which can be recrystallized from water.