

A NEW POLYMER – BOUND 1,2 – DIOL AS A PROTECTING AGENT FOR SYMMETRICAL DIALDEHYDE*

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ABSTRACT

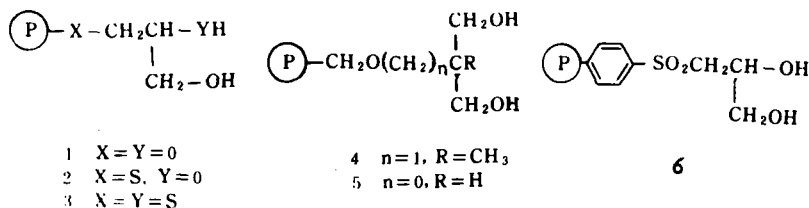
A novel polymer-bound 1,2-diol, 3-polystyrylsulfonyl-1,2-propanediol (**6**) had been prepared by the reaction of sodium polystyrylsulfinate with allyl bromide, followed by oxidation and hydrolysis or directly with 3-chloro-1,2-propanediol in the presence of a phase transfer catalyst, *n*-tetrabutylammonium iodide. The capacity of resin **6** for terephthalaldehyde reached 1.43 mmol/g. The aldehydic groups attached to polymer **6** reacted with hydroxylamine hydrochloride or reduced by sodium borohydride giving *p*-formylbenzaloxime (yield: 89%) and *p*-formylbenzalcohol (yield: 73.4 %), respectively. The high yields of these polymer-supported reactions showed that the polymer **6** possessed the effective isolation of its reactive sites.

INTRODUCTION

Since Merrifield's pioneer work on solid-phase synthesis^[1], polymeric reagents and their use in organic synthesis have attracted much attention^[2]. Polymer-supported protecting groups have been one of the interesting subjects by synthetic chemists^[3-5], as they possess the potential for effective isolation of the reactive sites, ease of product separation, simple workup and regenerability.

Several polymer-bound 1,2-diols^[1-3] and 1,3-diols^[4-5] had been synthesized and used in monoprotecting symmetrical dialdehydes to prepare unsymmetrical products^[6-10].

Polymeric diol **1** was successfully applied in monoprotection of aryl dialdehydes;



however, the capacity of the diol group on **1** was too low (ca. 0.35 mmol/g) to be used practically^[6]. The diol resin **2** was reported by Hodge that it had a capacity of 0.65 — 1.37 mmol/g for ketone^[7]. The loading of aldehyde on resin **3** prepared by Chen^[8] reached 1.2 mmol/g, but its regenerability was not reported. The 1,2-diol

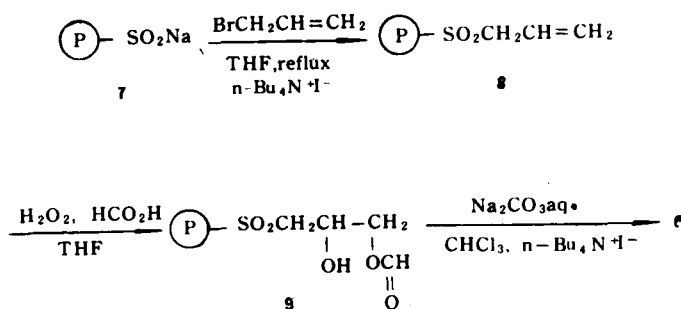
functional groups attached to 40% crosslinked polyacrylate had a loading of 1.3 mmol/g for terephthaldehyde; unfortunately its monoprotecting ratio was only one third of the above value and after reaction, the degradation of the polymer was observed^[9].

In this paper we report the synthesis of a new type of 1, 2-diol, i. e., 3-polystyrylsulfonyl - 1, 2-propanediol (6) and its monoprotecting property for terephthaldehyde.

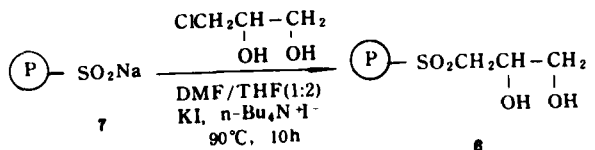
SYNTHESIS OF 3-POLYSTYRYLSULFONYL - 1,2-PROPANEDIOL (6)

Two synthetic routes were designed to prepare 3-polystyrylsulfonyl - 1, 2-propanediol (6) starting from sodium polystyrylsulfinate which was synthesized by the improved reaction of 2% DVB crosslinked polystyrene in CS₂ with SO₂ catalyzed by AlCl₃^[11]. In Route I, sodium polystyryl - sulfinate resin (2.30 mmol/g) first reacted in THF with allyl bromide in the presence of phase-transfer catalyst, n-Bu₄N⁺I⁻ according to Frechet's report^[12], giving polymer-bound olefin followed by oxidation with hydrogen peroxide in formic acid, and then the product was hydrolyzed with aqueous sodium carbonate in chloroform yielding the 1,2-diol resin 6. In Route II, the sodium sulfinate resin directly reacted with 3-chloro-1,2-propanediol in the presence of potassium iodide and n-Bu₄N⁺I⁻ yielding resin 6 (Scheme I).

ROUTE I



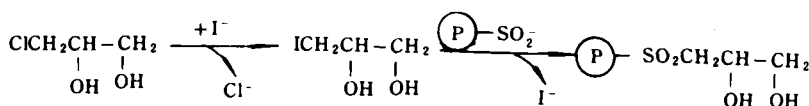
ROUTE II



Scheme I

It was found that even if the phase-transfer catalyst was added, no reaction took place between sodium sulfinate resin and 3-chloro-1,2-propanediol without potassium iodide in Route II. So we supposed that potassium iodide might be a co-catalyst and the following reaction could promote the reaction (Scheme II).

Co-catalysis of KI

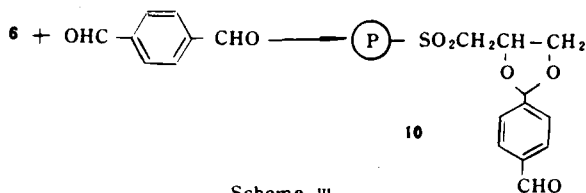


Scheme II

Compared with the preparation of the diols 1-5, the preparation of the diol 6 has the attractive feature that it only requires to use cheaper sodium sulfinate resin instead of chloromethylated polystyrene. The functionalization is conducted under the phase-transfer catalysis, the solvents need not be dried, the conversion of sulfinate groups is high, and the presence of potassium iodide in Route II makes the reaction condition mild and more effective than the procedure used by Frechet^[12].

ATTACHMENT AND DETACHMENT REACTIONS OF TEREPHTHALDEHYDE

The polymer-bound diol 6 reacted successfully with terephthalaldehyde to give an acetal. The reaction was carried out through the diol 6 in chloroform with an excess of the dialdehyde containing toluene-*p*-sulfonic acid as catalyst and magnesium sulfate as dehydrating agent at 40 °C for 48 h (Scheme III). The dialdehyde bound to the polymer 10 was cleaved by 4*M* HCl in dioxane. It was observed that the polymer-bound diol 6 prepared from Route II is more reactive than that from Route I (Table 1).



Scheme III

Table 1 Comparison of the reactivity of polymer-bound diol 6 prepared by Route I and II

Polymer-bound 1,2-diol ^{a)} (mmol/g)	Amount of dialdehyde bound to polymer 10 ^{b)} (mmol/g)
1.40 (from Route I)	0.82
1.71 (from Route II)	1.11

^{a)} Determined by the reaction of 6 with 3,5-dinitro-benzaldehyde.

^{b)} Reaction condition: 6 (1 mmol), terephthalaldehyde (6 mmol), *p*-TsOH (0.6 mmol), MgSO₄ (13 mmol), 40 °C, 48 h.

The reactive site-isolation is one of the advantages in applying polymeric protecting groups in organic synthesis. The monoprotecting ratio is an important index of the site-isolation. In this study, infrared spectra were used for evaluation of the ratio of monoprotecting terephthaldehyde. The carbonyl band corresponding to free aldehydic C=O stretching is at 1700 cm^{-1} . The band at 1080 cm^{-1} appears to be attributed to the C-O-C stretching vibrations of the acetal groups. The band at 1300 cm^{-1} is characterized to the $>\text{SO}_2$ asymmetrical stretching vibrations which are not concerned with the acetalation. The ratio of the heights of the bands at 1700 and 1300 cm^{-1} (H_{1700}/H_{1300}) shows the relative amount of free aldehydic groups on polymer 10 (corresponding to a relative amount of single-binding terephthaldehyde), and the ratio of the heights of bands at 1080 and 1300 cm^{-1} indicates a relative amount of double-binding terephthaldehyde. From the data of Entry 1 in Table 2 obtained by cleavage of oximating product of resin 10, we can calculate the monoprotecting aldehyde amount per unit of H_{1700}/H_{1300} , and the double-binding aldehyde amount per unit of H_{1080}/H_{1300} . The other data were derived from the amounts and values of H_{1700}/H_{1300} and H_{1080}/H_{1300} . It was found that the degree of the acetalation of terephthaldehyde with the diol 6 depends on the solvent used and reaction temperature (Table 2). The amount of free aldehydic groups attached to polymer 10 decreased in the following order: $\text{CHCl}_3 > \text{THF} > \text{C}_6\text{H}_6$. By raising the reaction temperature, the amount of both the aldehydic groups of dialdehyde linking onto the polymer is increased (Entry 4).

Table 2 Effect of solvents and reaction temperature on the amount of terephthaldehyde attached to resin 6^{a)}

Entry	Solvent	Dehydrating agent	Temp. (°C)	Time (h)	$\frac{H_{1700}}{H_{1300}}$	$\frac{H_{1080}}{H_{1300}}$	Amount of -CHO group ^{b)} (mmol/g)	Amount of double-bound dialdehyde ^{b)} (mmol/g)
1	CHCl_3	MgSO_4	40	48	1.00	1.25	1.26 ^{c)}	0.17 ^{c)}
2	THF	MgSO_4	40	48	0.85	1.31	1.10	0.18
3	C_6H_6	MgSO_4	40	48	0.75	1.25	0.94	0.17
4	C_6H_6	—	reflux	24			1.10	0.36

^{a)} Reaction condition: 6: dialdehyde: TsOH: $\text{MgSO}_4 = 1: 6: 0.6: 13(\text{mmol})$.

^{b)} The data calculated from the heights of the absorption bands at 1700 , 1080 , and 1300 cm^{-1} in IR spectra except Entry 1.

^{c)} The data obtained by cleavage of oximating product of resin 10.

Table 3 Effect of cleavage of acetal bonds on resin 10 catalyzed by different acids on the regeneration of protecting groups

Entry	Cleaving condition ^{a)}	Initial amount of dialdehyde bound to resin 10 (mmol/g)	Amount of first cleaved dialdehyde (mmol/g)	Amount of second cleaved dialdehyde (mmol/g)	Regenerating activity ^{b)} (%)
1	A	1.43	0.90	0.25	28
2	B	1.43	1.43	1.04	73
3	C	1.43	1.43	1.43	100
4	D	1.43	— ^{c)}	— ^{c)}	

^{a)} Cleaving condition: A— 2MHCl (aq.)—dioxane (1:1), r.t., 44h; B— 4MHCl (aq.)—dioxane (1:1), 60°C , 24h; C— $\text{HCOOH}-\text{CHCl}_3$ (2:3), r.t., 24h; K_2CO_3 (aq.)— $n-\text{Bu}_4\text{N}^+\text{I}^-$; D—TsOH (catalyst amount)—dioxane— H_2O , 90°C , 30h.

^{b)} Regenerating activity = the amount of second-cleaved dialdehyde/the amount of first cleaved dialdehyde.

^{c)} Only a very little amount of dialdehyde was cleaved.

literatures^[6-9]. It is showed that resin 1 reported by Leznoff^[6] containing ca. 0.35 mmol of the diol groups per gram of the resin could be successfully used to protect one aldehydic group of terephthaldehyde. In our experiment the capacity of terephthaldehyde on the resin 6 is up to 1.43 mmol/g and the monoprotecting ratio reaches 89%. The polymer-supported 1,2-diol 6 has been found to monoprotect terephthaldehyde with an excellent site-isolation, and therefore may be of practical value.

Table 4 Comparison of monoprotecting ratio of 1,2-diol resins for terephthaldehyde

Diol resin	Crosslinkage (%)	Amount of dialdehyde bound to resin (mmol/g)	Monoprotecting ratio ^{a)} (%)	Lit.
1	2	0.35	100	[6]
1	40	1.30	33	[9]
2	1	0.92	52	[7]
3	1	1.20	85	[8]
6	2	1.43	89	

^{a)} Based on the maximum yield of the reaction product.

EXPERIMENTAL

Infrared spectra were recorded on a Nicolet 5DX Fourier Transfer Infrared spectrometer and KBr pellets were used. NMR spectra were recorded on PMX60 SI spectrometer in CDCl₃ using TMS as the internal standard. Silica gel (300 — 400 mesh) was used for the flash column chromatography.

Preparation of resin 7

Resin 7 was prepared by direct reaction of a 2% DVB crosslinked polystyrene with SO₂ (gas) in the presence of AlCl₃ according to the procedure in the literature^[11]. The capacity of sulfinate on resin 7 was 2.30 mmol/g based on sulfur content.

Route 1

Preparation of polystyryl allyl sulfone 8[11]

To a 100 ml three-necked flask was added 3.0 g of 7, THF (30ml), allyl bromide (3.0 ml) under nitrogen atmosphere. The mixture was refluxed for 24 h and then cooled to room temperature. After filtration and repeated washings with THF, acetone, alcohol and ether, the polymer was dried in vacuo. IR: 1639 (C=C), 1310, 1143(SO₂), 989, 935 (C=C-H) cm⁻¹.

Preparation of resin 9

A 1.0 g of polymer 8 was suspended in 17 ml of THF and 17 ml of formic acid. After addition of 4.7 ml of 30% aqueous hydrogen peroxide in 0.5h, the mixture was stirred at room temperature for 0.5h, then 40 °C for 12h. After removing the solvent phase the polymer was washed successively with THF, alcohol, water, acetone and dried in vacuo giving yellowish resin 9. IR: 3509 (OH), 1729 (C=O), 1310, finally ether, and 1138 (SO₂) cm⁻¹ and the bands at 1639, 989, 935 cm⁻¹ disappeared.

Preparation of resin 6

To 0.9 g of resin 9 in 10 ml of chloroform was added 10% aqueous potassium

carbonate (10 ml), tetrabutylammonium iodide (0.2 g). The suspension was stirred at room temperature for 24 h. After filtration and washings with chloroform, acetone, alcohol, water, 50% dioxane-water, alcohol, acetone, and ether, the polymer was dried at 40 °C over P_2O_5 in vacuo. IR: 3445 (OH), 1307, 1145 (SO_2) cm^{-1} .

Route II

Preparation of resin 6

To 5.5 g of resin 7 suspended in DMF (10 ml) and THF (20 ml) was added 3-chloro-1, 2-propanediol (5 ml), tetrabutylammonium iodide (6 g) and potassium iodide (3.3 g). The mixture was refluxed under nitrogen for 48 h, and then cooled to room temperature. After removal of solvent phase, the polymer was successively washed with THF, alcohol, water, acetone and ether; then dried in vacuo. The IR spectra of the resin 6 obtained was the same as that of the polymer prepared by Route I.

Determination of capacity of hydroxyl groups on resin 6 was carried out by the following procedure: the mixture of resin 6 (0.3 g), 3,5-dinitrobenzoyl chloride (1.4 g) and anhydrous pyridine (7 ml) was stirred under nitrogen at 100 °C for 8 h, cooled and filtered. The polymer was washed with pyridine, alcohol, hot water, 50% dioxane-water, acetone and ether, and dried at 40 °C over P_2O_5 in vacuo. The nitrogen content by elemental analysis: 4.36% (corresponding to 2.24 mmol/g of the hydroxyl capacity of resin 6 and a 99.6% of conversion of sodium sulfinate on resin 7).

Preparation of polymer 10

The mixture of resin 6 (9.0 g), terephthaldehyde (15.0 g), anhydrous sodium sulfate (30.0 g), p-toluenesulfonic acid (1.0 g) and chloroform (70 ml) was stirred at 40 °C under nitrogen for 48 h. After filtration and washings with pyridine in water, alcohol, water, 50% dioxane-water, acetone and ether, the polymer obtained was dried at 40 °C over P_2O_5 in vacuo. IR: 2734 (C-H in CHO), 1700 (C=O) cm^{-1} . The capacity of polymer 10 for terephthaldehyde was determined by cleavage of the acetal linkages with 85% $HCO_2H-CHCl_3$ (1:1) at 40 °C for 24 h, and found to be 1.43 mmol/g resin 10.

Preparation of polymer 11 and cleavage of the acetal linkages

Polymer 10 (1.0 g) and sodium borohydride (0.33 g) were suspended in a 1:1 mixture of THF and ethanol (20 ml). The suspension was stirred under nitrogen at room temperature for 24 h and then at 60 °C for 3 h, cooled to room temperature. After filtration and washings with ethanol, water, dioxane-water, acetone and ether, the polymer was dried in vacuo. Infrared spectra analysis of the polymer confirmed that no free aldehydic groups remained. The acetal linkages of 11 were cleaved as follows. A suspension of 11 (1.0 g) in 4M HCl (10 ml) and dioxane (10 ml) was stirred at 60 °C for 24 h. After filtration, the resin was washed repeatedly with solvents. After combining the filtrates, the organic phase was again washed with water and dried over anhydrous magnesium sulfate; then evaporated and separated by preparative flash chromatography using silica gel (300—400 mesh) [eluent: ethyl acetate-petroleum ether (3:7)], yielding 0.143 g of pure p-hydroxymethylbenzaldehyde 12 which was confirmed by IR and ^1H NMR. yield: 73.4%.

Preparation of polymer 13 and cleavage of the acetal linkages

Resin 10 (1.0 g) suspended in anhydrous pyridine (10 ml) was treated with excess hydroxylamine hydrochloride (0.37 g) under nitrogen at 80 °C for 24 h. After filtration, the polymer was successively washed with pyridine, ethanol, water, ethanol, acetone and ether; then dried in vacuo. The structure of the oximated polymer 13 was identified by infrared spectra which showed the absence of free aldehydic groups. Cleavage of the acetal linkages was carried out as mentioned above with 1.0 g of resin 13. After workup and purification by flash chromatography (eluent: 5% methanol in dichloromethane), a yield of 0.190 g (89%) of *p*-formylbenzaloxime 14 was obtained. M.P.: 123 — 125 °C. The IR and ¹HNMR spectra of 14 were identified as the pure form.

CONCLUSION

A new polymer-bound diol, 3-polystyrylsulfonyl-1,2-propanediol has been prepared efficiently by the reaction of sodium polystyrylsulfinate with 3-chloro-1,2-propanediol and was successfully used in the monoprotection of terephthalaldehyde to prepare unsymmetrical compounds in very good yields. The cleaving agent consisting of formic acid and chloroform was found to be useful for the cleavage of polymer-bound aldol bonds.

Keywords:

3-polystyrylsulfonyl-1,2-propanediol, polymer-supported protecting group, solid-phase organic synthesis, cleavage of aldol linkages

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