Pergamon

Tetrahedron Vol. 50, No. 25, pp. 7535-7542, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0362-W

Functionalization of Polystyrene Resins with Chiral Fragments derived from Tartaric Acid.

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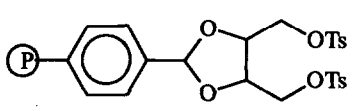
Abstract: Several methods have been assayed for the anchoring of chiral fragments derived from tartaric acid to polystyrene/divinylbenzene resins. In order to further modify the initially anchored chiral groups, binding to the polymer backbone through an ether linkage is preferred to the usual acetalic linkage. Resins containing different chiral groups have been prepared with degrees of functionalization ranging from 0.5 to 0.8 meq/g (DF ≈ 0.05-0.11). The use of the *O*-monobenzyl ether of dimethyl tartrate gives the best results for the initial anchoring reaction.

Reactive polymers have received much attention in recent years.[1-4] Preparation of novel functionalized polymers designed to act as polymer-supported reagents or catalysts, as well as starting materials for solid phase synthesis and other applications continues being a very active area of research. Introduction of chirality in polymers is of great importance in order to develop reactive polymers for asymmetric synthesis,[5,6] chromatographic separation of enantiomers[7] and molecular recognition.[8] This can be accomplished via main-chain chirality[9] or, more often, by anchoring chiral fragments in the polymeric backbone.[5,6] Chiral groups derived from tartaric acid are very frequently found in chiral auxiliaries, enantioselective catalysts, etc..[10] A limited number of polymer-supported tartaric acid derivatives have been described. In fact, some of the earlier polymeric chiral phosphines used as ligands for asymmetric catalytic reduction with transition metals were prepared from the supported tartaric acid derivative **1**.[11,12] The anchoring of the tartaric fragment through the formation of an acetalic group is easily accomplished by reaction of a diol with a polymeric aldehyde but is expected to present the important drawback of the low stability of that group to strongly acidic conditions. An alternative reported procedure for the introduction of tartaric acid fragments in polystyrene-divinylbenzene resins is the formation of a polymeric ester as shown in **2**.[13,14] In this case, the anchoring bond is more stable but it has been shown that monoesterification is not easily achieved and, for most groups, both carboxyl groups are bound to the polymeric backbone (**2**, R = polystyrene-divinylbenzene). Thus, functionalization is accompanied by additional crosslinking which can affect to the activity of the polymeric species formed.



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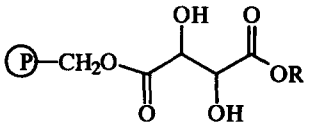

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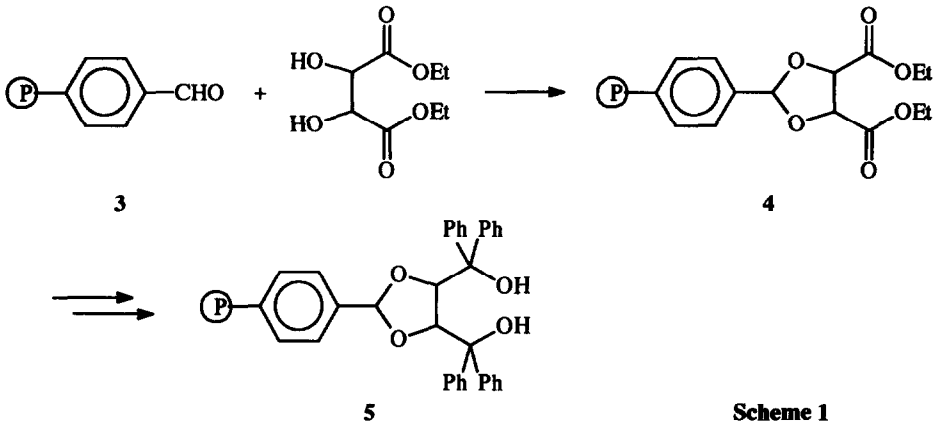
In order to avoid these problems, we have developed some novel methods which allow to functionalize polystyrene resins with chiral fragments derived from tartaric acid. In the work with functionalized polymers, reagents and experimental conditions have to be selected carefully, as polymer-bound species cannot be purified and polymer-supported by-products have to be avoided. In the case of the functionalization with chiral fragments, additional care needs to be taken and only reactions which proceed cleanly in solution without loss of chiral integrity can be selected.

According to the above mentioned literature data, in an initial series of experiments we attempted to prepare a polymer-bound diol derived from tartaric acid using the procedure shown in scheme 1. This procedure represents only a minor modification of the general route used in solution for the preparation of these compounds.[15]

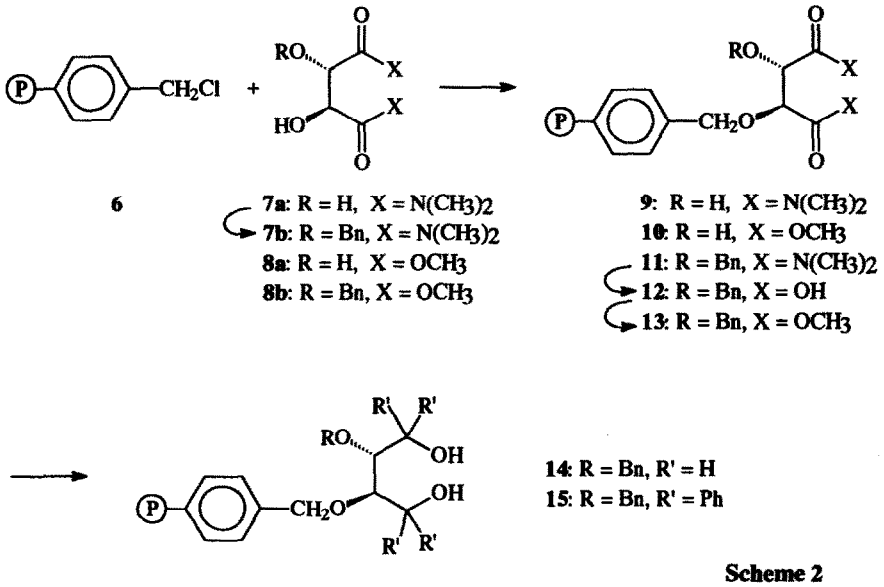


3 4 5

Scheme 1

Starting from a Merrifield resin (1 meq. of Chlorine/g, 1% divinylbenzene, DF = 0.11), the polymeric benzaldehyde **3** was prepared as described by Fréchet[16] (1.006 meq./g, DF = 0.11) by oxidation of the chloromethyl groups with DMSO. This polymer was then reacted with an excess of the dimethyl ester of tartaric acid in refluxing benzene containing a catalytic amount of p-toluenesulfonic acid.[11] The IR spectrum of the resulting resin **4** showed the complete disappearance of the carbonyl band corresponding to the aldehyde, supporting that quantitative acetalization had taken place. However, when this polymer was treated with phenylmagnesium chloride to afford polymeric diol **5**, attempts to remove magnesium salts from inside of the polymer beads resulted in a partial or total loss of the chiral fragment by hydrolysis of the acetalic group.

In view of these results, a different approach was considered. The general procedure studied is presented in Scheme 2. Reaction of the alkoxylate of a *O*-monofunctionalizated tartaric acid derivative (**7** and **8**) with a chloromethylated resin would afford an ether anchoring bond which should be much less affected by the usual acidic and basic conditions used for the next steps.



Scheme 2

Direct monoalkylation of N,N,N',N'-tetramethyl tartaramide, **7a**, and dimethyl tartrate, **8a**, with polymeric benzyl chloride **6** to give resins **9** and **10** was attempted using different reagents and conditions. However, only very low degrees of funcionalization were always obtained.

The monobenzylated N,N,N',N'-tetramethyl tartaramide **7b** (R = Bn, X = $N(CH_3)_2$) has been prepared in fair yields by Fyles as a key intermediate in the preparation of some polycarboxylate crown ethers derived from tartaric acid.[17] Monoprotection of the tartaramide **7a** was accomplished by the use of one equivalent of sodium hydride in dry DMF and subsequent addition of an excess of benzyl bromide. We obtained slightly improved results using one equivalent of sodium hydride, tetrabutylammonium iodide and a catalytic amount of 18-crown-6 in similar conditions to the ones described by Yamamoto for the synthesis of optically active diethyl tartrate dibenzyl ether.[18] From this monobenzylated derivative **7b**, attachment to the polymeric backbone was carried out by alkylation of its alkoxylate with a chloromethylated polymer **6**. Anchoring of the tartaramide moiety can be easily monitored by IR spectroscopy through the disappearance of the C-Cl band at ca. 1260 cm^{-1} and the appearance of the amide carbonyl band at 1635 cm^{-1}, as well as by elemental analysis for N that allowed a quantitative analysis of polymer **11**. Binding was first attempted by the use of the method of Fyles, but better results were again obtained by the method devised by Yamamoto. Phase transfer reagents and specially tetrabutylammonium iodide were essential for good yields, but even in the presence of these catalysts conversion of the chloromethyl groups into the desired functionality was never complete (see table 1). No clear improvement was observed when THF was changed by dioxane, a solvent that is known to better swell the resin.

Table 1.- *Results Obtained in the Attachment of Tartaramide 7b to the Merrifield's Polymer 6.*

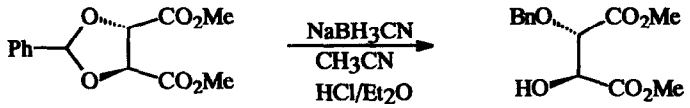
Ratio 7b:6	*reaction time (hr)*	*Method*	*Catalyst*	*loading[b] (meq/g)*	*DF[c]*	*conversion yield (%)*
1:1	24	A	----	-----	-----	-----
3:1	24	A	----	0.12	0.013	15
3:1	24	B	----	0.18	0.020	23
3:1	48	B	18C6	0.18	0.020	23
3:1	48	B	18C6/INBu4	0.42	0.051	53
3:1	72	B	18C6/INBu4	0.42	0.051	53

a) Method A: reaction in DMF, according to Fyles[17]; Method B: reaction in THF, according to Yamamoto[18]. *b)* Calculated from elemental analysis for nitrogen. Maximum loading capacity for 100% functional conversion was 0.8 meq/g. *c)* The DF of a polystyrene-bound reagent is a measure of the proportion of aromatic styrene rings that carry the desired functionality. For instance, for a Merrifield's resin containing 1 meq Cl/g, 11% of the styrene units are functionalized and DF = 0.11.

Complete conversion of the tartaramide **11** into the polymeric diacid **12** was not easily accomplished. The highly acidic conditions described for the hydrolysis of several soluble tartaramides[17b] seem to be not fully compatible with the hydrophobic nature of the polymeric backbone. However, hydrolysis of **11** with a 2.5 M HCl solution in H_2O/dioxane 1/1 afforded the expected resin **12** (0.43 meq/g, DF = 0.051) which showed the complete disappearance of the amide carbonyl band and the presence of the C=O band characteristic of the acid above 1700 cm^{-1}. The polymeric benzyl ether derivative of tartaric acid **12** was then efficiently converted into diols **14** and **15** having structural units which are found in a number of asymmetric catalysts. Reduction of the diacid with $LiAlH_4$ afforded a novel resin **14** (R = Bn, R' = H) containing no carbonyl bands in the IR (0.44 mmol of diol/g, DF = 0.051).[19] The quantitative conversion **12**→**14** was also determined by conversion of the hydroxy groups into their 3,5-dinitrobenzoates and elemental analysis for N of the resulting polymer.[20] On the other hand, treatment of **12** with a mixture of MeOH and $SOCl_2$ gave polymer **13** in quantitative yields for conversion of the functional groups. Reaction of **13** with an excess of phenyl magnesium chloride finally afforded resin **15** (R = Bn, R' = Ph) quantitatively as shown by the absence of any carbonyl band (0.39 mmol of diol/g, DF = 0.051).[21]

Thus, starting from tartaramide **7b**, the less efficient step in the synthetic procedure depicted in scheme 2 seems to be the anchoring to the polymer to form **11**. Hydrolysis of **11** to **12** is also a process which is not easily accomplished. In order to overcome these difficulties a similar synthetic scheme but starting from a different monoprotected tartaric acid derivative (**8b**) was studied.

Several methods have been described for the selective monoalkylation of dialkyl tartrates. In our hands, monobenzylation of dimethyl tartrate by means of dibutyltin oxide, cesium fluoride and an excess of benzyl bromide gave only moderate yields for large-scale preparations.[22] Much better yields of the benzyloxy derivative **8b** were obtained by reductive opening of the *O*-benzylidene tartrate **16** with sodium cyanoborohydride in acetonitrile in presence of hydrogen chloride in diethyl ether, under the conditions described by Barton and Géro.[23]



8b

Scheme 3

Anchoring of **8b** by reaction of its alkoxylate with the chloromethylated resin **6** directly afforded polymer **13**. A survey of bases and conditions was carried out to optimize this step and revealed that the use of cesium fluoride in dioxane and 18-crown-6 and tetrabutylammonium iodide as catalysts gave an essentially quantitative conversion of **6** to **13** (0.75 meq of tartaric derivative/g, DF = 0.10). Direct conversion of resin **13** to polymeric diol **14** was achieved by reduction with $LiAlH_4$ in similar conditions to that used for reduction of diacid **12**. Complete reduction was monitored by the absence of carbonyl bands in **14** and by transformation of hydroxy groups into their 3,5-dinitrobenzoates. The same procedure described earlier was used for the quantitative transformation of **13** to **15**. Polymers **14** and **15** synthesized in this way were similar to the ones prepared in the procedure starting form tartaramide **7b** except that higher functionalization degrees were obtained according to the increased efficiency of the anchoring step. For resin-bound diol **14** a loading of ca. 0.8 meq/g (DF = 0.10) was calculated, and for **15** the loading was ca. 0.65 meq/g (DF = 0.10).

In summary, different synthetic procedures for the functionalization of polystyrene-divinylbenzene resins with a variety of chiral fragments derived from tartaric acid have been developed and evaluated. The best results have been obtained from the resin synthesized by reaction of a chloromethylated resin with the monobenzyl ether of dimethyl tartrate, **8b**. The use of the *O*-monobenzylated tartaramide **7b** is less convenient as the anchoring step is less efficient and produce polymers with lower functionalization degrees, and also because the synthesis of diols from the tartaramide requires more steps than the use of the diester. Direct monoalkylation of diester **7a** and tartaramide **8a** is not efficient, and, additionally, dialkylation accompanied by an increase in crosslinking cannot be avoided when using this procedure.

Experimental Section

(2R,3R)-N,N,N',N'-Tetramethyl-2-benzyloxy-3-hydroxysuccinamide (7b). A solution of tartaramide **7a** (10 g, 49 mmol) in dry THF (150 mL) was added dropwise to a suspension of NaH (1.56 g, 80% in mineral oil, 52 mmol) in dry THF (50 mL) with stirring at room temperature under an Ar atmosphere. The mixture was then stirred at room temperature for 1 h until a clear solution was obtained and tetrabutylammonium iodide (2.01 g, 5.5 mmol), 18-crown-6 (16 mg, 5.9×10^{-2} mmol) and benzyl bromide (8.38 g, 49 mmol) were added. The resulting mixture was refluxed for 8 h and then the solvent was vacuum evaporated. The residue was dissolved in water (200 mL) and the aqueous solution was extracted with hexanes (3×), ether (3×) and dichloromethane (3×). The dichloromethane solution was dried over $MgSO_4$, concentrated in vacuo and dried overnight in a vacuum oven to give the monobenzyl ether **7b** as a slightly yellowish oil (10.1 g, 34 mmol, 69%). $[\alpha]_D^{25}$= +52.7° (c = 0.35, ethanol) (lit[17b] +53.2°). IR (cm^{-1}) 3100-3500, 1647, 1498, 1455, 1400; 1H NMR (200 MHz) ($CDCl_3$, δ) 2.79 (s, 3H), 2.88 (s, 3H), 2.96 (s, 3H), 3.20 (s, 3H), 3.97 (d, 1H), 4.32 (d, 1H), 4.36 (d, 1H), 4.74 (d, 1H), 4.75 (dd, 1H), 7.29 (m, 5H). MS (EI, m/z) 295 $(M+1)^+$.

Preparation of polymer-bound tartaramide 11. A solution of *O*-monobenzylated tartaramide **7b** (3.1 g, 10.5 mmol) in dry THF (40 mL) was added to a suspension of NaH (0.315 g, 80% in mineral oil, 10.5 mmol) at room temperature under an Ar atmosphere. The mixture was stirred at room temperature for 1 h and then tetrabutylammonium iodide (0.427 g, 1.2 mmol), 18-crown-6 (3.3 mg, 1.2×10^{-2} mmol) and a Merrifield's resin (3 g, 1% crosslinked, 1 meq Cl/g, DF = 0.11, 3 meq)[$(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_9Cl)_{0.11}$] were added. The resulting mixture was refluxed for 48 h under an Ar atmosphere, and then the resin was filtered, washed with THF (3×), THF/H_2O (2:1) (3×), THF/H_2O (1:1) (3×), THF/H_2O (1:2) (3×), THF (3×), acetone (3×) and CH_2Cl_2 (3×) and vacuum dried at 60°C to afford polymer **11**, containing 0.42 meq of tartaramide/g of polymer (DF≈0.051). IR (cm^{-1}): 3025, 2918, 2844, 1635, 1594,1483, 1105, 1085, 1024, 751, 691, 524. Anal. Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{24}H_{30}N_2O_4)_{0.11}$: N, 2.23; Found: N, 1.18. Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_{10})_{0.059}(C_{24}H_{30}N_2O_4)_{0.051}$: N, 1.18.

Preparation of polymer-bound tartaric acid dibenzyl ether 12. Polymer-bound tartaramide **11** (3 g, 0.42 meq/g, 1.26 meq of tartaramide) was suspended in a 2.5 M solution of HCl in H_2O/dioxane (1:1)(60 mL) and the mixture was refluxed with stirring, under an Ar atmosphere, for 48 h. The resin was filtered, washed with H_2O/dioxane (1:1) (3×), H_2O (3×), MeOH (3×) and CH_2Cl_2 (3×) and vacuum dried to give polymer **12** containing 0.43 meq of functional group/g of polymer (DF ≈ 0.051). IR (cm^{-1}): peak absent at 1630-1645, peaks observed at 2400-3500, 1743, 1596, 1481, 1437, 1053. Anal Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_{10})_{0.059}(C_{20}H_{20}O_6)_{0.051}$: N absent; Found: N absent.

Preparation of polymer-bound dimethyl tartrate dibenzyl ether 13.

Method A: (From polymer-bound tartaric acid 12). A solution of $SOCl_2$ (7 mL) in dry benzene (2 mL) was added dropwise to a suspension of polymer-bound tartaric acid **12** (2 g, 0.43 meq/g, 0.86 meq of tartaric group) in dry MeOH (15 mL) with stirring at 0°C under an Ar atmosphere. The mixture was then refluxed for 24 h and the resulting resin was filtered and washed with MeOH (3×), MeOH/H_2O (2:1)(3×), MeOH/H_2O (1:1)(3×), MeOH/H_2O (2:1)(3×), acetone and CH_2Cl_2 (3×). The polymer was vacuum dried at 60°C to give resin **13** containing 0.43 meq of tartaric ester/g (DF ≈ 0.051). IR (cm^{-1}) absence of acid bands in the 2400-3500 region, peaks at 1716, 1595, 1483,1438, 1201, 1192, 1173, 1026,1016.

Method B: (From dimethyl 2-O-benzyl-L-tartrate 8b). A mixture of dimethyl 2-*O*-benzyl-L-tartrate (8.5 g, 32 mmol) and CsF (4.8 g, 32 mmol) was vacuum dried and a solution of tetrabutylammonium iodide (1.18 g, 3.2 mmol) and 18-crown-6 (0.84 g, 3.2 mmol) in dry dioxane was added under an Ar atmosphere. After stirring at room temperature for a few minutes, a Merrifield's resin (11 g, 1% crosslinking, 1 meq Cl/g, DF = 0.11, 11 meq) [$(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_9Cl)_{0.11}$] was added and the resulting mixture was refluxed for 24 h. The polymer was then filtered, washed with dioxane (3×), THF (3×), THF/H_2O (2:1)(3×), THF/H_2O (1:1)(3×), THF/H_2O (2:1)(3×), THF (3×), MeOH (3×), CH_2Cl_2 (3×) and acetone (3×) and vacuum dried to give resin **13** containing 0.75 meq of tartrate/g (DF ≈ 0.10). Anal. Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{22}H_{24}O_6)_{0.11}$: C, 84.98; H, 7.23; O, 7.81. Found: C, 85.5; H, 7.22; O, 7.28. Calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_9Cl)_{0.01}(C_{22}H_{24}O_6)_{0.10}$: C, 85.3; H, 7.25; O, 7.23.

Preparation of polymer-bound (2*S*,3*S*)-2,3-Bis(phenylmethoxy)-1,4-butanediol (14). A suspension of polymer **13** (obtained by method B, 3 g, 0.75 meq/g, DF = 0.10, 2.25 meq) and $LiAlH_4$ (0.342 g, 9 mmol) in dry THF (50 mL) was refluxed for 24 h under an Ar atmosphere. After cooling, the mixture was quenched by the successive addition of H_2O (3 mL), a 15% aqueous solution of NaOH (3 mL) and H_2O (7 mL). The resulting polymer was filtered, washed with a 3 M aqueous solution of HCl (3×), conc. HCl (3×), H_2O (3×), THF (3×), CH_2Cl_2 (3×) and MeOH (3×) and vacuum dried to give resin **14** containing 0.78 meq of butanediol group/g (DF ≈ 0.10). IR (cm^{-1}) peak absent in the 1700 region, peaks at 3100-3600, 3024, 2920, 2849, 1600, 1492, 1452, 1028, 1019, 758, 697, 540.

Preparation of polymer-bound (2*R*,3*R*)-2,3-Bis(phenylmethoxy)-1,1,4,4-tetraphenyl-1,4-butanediol (15). A 2 M solution of PhMgCl in THF (10 mL, 20 mmol) was added dropwise over 30 min to a suspension of polymer **13** (obtained by method B, 1 g, 0.75 meq/g, DF = 0.10, 0.75 meq) in dry THF (60 mL) with stirring at room temperature under an Ar atmosphere. The mixture was then slowly heated and then kept under reflux for 12 h. The resin was then filtered, washed with 1 M HCl (3×), THF (3×), MeOH (3×) and acetone (3×) and vacuum dried to give polymer **15** containing 0.65 meq of tetraphenyl butanediol/g (DF ≈ 0.10). IR (cm^{-1}) peak absent in the 1700 region, peaks at 3100-3500, 3024, 2920, 2850, 1601, 1493, 1451, 1028, 1019, 757, 697, 538.

Acknowledgments: Financial support has been provided by the CICYT (project MAT93-0224).

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(*Received in UK* 29 *March* 1994; *accepted* 22 *April* 1994)