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Graphical Abstract

An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

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An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

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Abstract—A straightforward and general synthesis of trityl alcohols in which one of the aryl rings is substituted with a vinyl group is presented. The synthesis of the alcohols involves the direct addition of the Grignard reagent prepared from 4-bromostyrene to substituted benzophenones. These compounds were used to incorporate trityl linker groups into polystyrene-based organic synthesis supports. Both non-cross-linked and cross-linked (Janda/Jel™) polystyrene have been prepared using these monomers. © 2004 Elsevier Science. All rights reserved

1. Introduction

In polymer-supported synthesis, linker moieties are required for the attachment of the synthesis substrate to the polymer support. Commonly these linker groups are based on standard protecting groups used in traditional solution-phase synthesis.1 Trityl groups2 are often used in this context since they can serve as protecting groups for alcohols,3 acids,4 amides,5 amines,6 amino acids,7 hydroxamic acids,8 imidazoles,9 nucleotides,10 thiols,11 and thioureas.12 The most common trityl group functionalized polymers used in this regard are cross-linked unsubstituted trityl resin13 and 2-chlorotrityl resin.14

The polymer bound trityl alcohol groups of such resins are usually introduced by one of three methods: (1) The sequence of lithiation of a halogenated phenyl group of a preformed polymer, followed by treatment with a benzophenone.15 (2) The sequence of Friedel-Crafts acylation of a preformed polymer with a benzoyl chloride followed by the addition of an aryl Grignard reagent.10,16 (3) Direct lithiation of cross-linked polystyrene using a 1:1 complex of n-BuLi and TMEDA, followed by reaction with a benzophenone.17 However, a significant drawback of all of these methods is that since they derivate preformed polymers, it is difficult to determine the final composition of the product polymer and to accurately control the its homogeneity and loading level.18 Therefore, in order to prepare better defined polymers with easily controllable levels of trityl group incorporation, the functional monomer, (4-ethenylphenyl)diphenyl methanol (1a) (Scheme 1), has been prepared and co-polymerized with styrene and divinylbenzene under suspension polymerization conditions to afford polystyrene trityl resin by Kurth et al.19 Their first reported synthesis of 1a involved the addition of t-BuLi to 4-bromostyrene followed by reaction of the thus formed aryl lithium species with benzophenone.19a The same authors also reported a procedure involving the use of potassium, potassium iodide and anhydrous magnesium chloride to activate 4-bromostyrene.19b Later, Rimmer et al. reported that the first synthesis of 1a was not readily reproducible due to anionic polymerisation of the starting material, and that an inverse addition procedure (4-bromostyrene added to t-BuLi) afforded acceptable and reproducible yields of 1a.20 Most recently, Janda et al. have reported the only other method for the preparation of 1a which involves a 4 step synthetic sequence starting with 4-vinylbenzyl alcohol.21 While these reported syntheses do produce the desired product, they are less than optimal, especially when considering the reported difficulty in reproducing the results, the costs and hazards associated with using t-BuLi and potassium, and the length of the most recent synthesis. Furthermore, they have not been demonstrated to be general methods for the preparation of substituted trityl monomers, as they only report the synthesis of 1a.

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We are interested in the preparation and applications of polymers that incorporate monomers derivatized with various functional groups\textsuperscript{22}\textsuperscript{-24} and have successfully used the Grignard reagent formed from 4-bromostyrene to prepare monomers containing sulfide\textsuperscript{23} and phosphine\textsuperscript{24} groups. Herein we report our results regarding using this reagent to prepare 1a and derivatives of it and the incorporation of these into both cross-linked and, for the first time, non-cross-linked polystyrene polymers.

2. Results and discussion

Obviously, the most direct method for preparing compounds 1 is via the nucleophilic addition of a styrene equivalent to a substituted benzophenone. Hence this was the method used in the first reported synthesis of such compounds.\textsuperscript{19a} However, the nucleophile used was an aryl lithium and such a strongly nucleophilic species readily initiates anionic polymerization of styrene molecules and makes this method low yielding and unreliable.\textsuperscript{20} Therefore we chose to examine the addition of the relatively less nucleophilic styrene Grignard reagent, prepared simply from 4-bromostyrene and magnesium,\textsuperscript{25} to a series of benzophenones (Scheme 1).

![Scheme 1. Synthesis of monomers 1a-f.](image)

Gratifyingly, these reactions afforded good yields (65-82%) of the desired products (1a-g), even when the benzophenones were substituted with deactivating electron donating groups. As might be expected, the benzophenones substituted with electron withdrawing substituents afforded slightly higher yields (1c-g). In all of these reactions, 4-bromostyrene was used in excess of the benzophenone since any unreacted Grignard reagent was converted to easily isolable Grignard reagents formed from 4-bromostyrene and magnesium,\textsuperscript{25} to a series of benzophenones (Scheme 1).

Suspension co-polymerization of 1a, 1e and 1f with styrene and the Janda/el\textsuperscript{TM} cross-linker, 1,4-bis(4-vinylphenoxy)butane, afforded JJ-Tr-OH (3a), JJ-2-Cl-Tr-OH (3b), and JJ-4-Cl-Tr-OH (3c), respectively (Scheme 2).\textsuperscript{27-29} It is important to note that the loading levels of 3b and 3c based on elemental analysis of chlorine, are slightly lower than expected (theoretical 1.5 mmol/g each, observed 1.3 mmol/g (3b), and 1.1 mmol/g (3c)). This implies that, in contrast to 1c, monomers 1e and 1f are incorporated somewhat more slowly than styrene is during polymerization process. These differences in reactivity must therefore be taken into account when preparing polymers with specific loading levels. In order to determine the rate of incorporation of 1a into 3a, we treated 3a sequentially with TBDMSI/DMSO\textsuperscript{16c,30} and BnNH\textsubscript{2} to form 4 and 5, respectively. Elemental analysis of both 4 (chlorine, 5.4%) and 5 (nitrogen, 2.1%) indicates that 3a has a loading level close to the theoretical 1.5 mmol/g.

![Scheme 2. Synthesis of polymers 2-5.](image)

Reagents and conditions: (a) AIBN, toluene, 80 °C. (b) chlorobenzene, benzoyl peroxide, water, acacia gum, NaCl, 85 °C. (c) TBDMSI, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, rt. (d) BnNH\textsubscript{2}, THF, rt.
3. Conclusions

In summary, we have developed an improved, general and reproducible method for the synthesis of a variety of substituted triphenyl methanols that contain a vinyl group. These compounds can be used to directly introduce trityl linker groups into both soluble and insoluble polystyrene cross-linked polymers. The utility of such linkers in the new non-cross-linked polymers 2a-b in polymer-supported peptide/organic synthesis is currently being assessed.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N₂ atmosphere. Tetrahydrofuran was distilled under a N₂ atmosphere over calcium hydride Merck silica gel 60 (230-400 mesh) was used for chromatography. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F254. The NMR spectra were recorded using a Bruker DRX 300 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. El-MS data was recorded on a Finnigan MAT 96 mass spectrometer.

4.2. (4-Ethenylphenyl)diphenyl methanol (1a). Procedure A. Benzophenone (12.4 g, 68 mmol) was added dropwise at 0 °C to a solution of the Grignard reagent prepared from 4-bromostyrene (14.0 g, 76 mmol) and Mg (2.2 g, 92 mmol) in dry THF (250 mL). After TLC analysis indicated electrophile consumption was complete, the reaction mixture was diluted with diethyl ether (1 L), and then washed sequentially with water (500 mL), 10% aqueous HCl (500 mL), saturated aqueous NaHCO₃ (500 mL) and brine (500 mL). The organic layer was dried over MgSO₄, filtered and concentrated in vacuo to afford 1a as a white solid (12.6 g, 44 mmol, 65%). Mp 72-73 °C. ¹H NMR (300 MHz, CDCl₃) δ 2.77 (s, 1H, exchangeable with D₂O), 5.24 (dd, 1H, J = 10.9, 0.9 Hz), 5.74 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 7.17-7.36 (m, 14H). ¹³C NMR (75 MHz, CDCl₃) δ 81.9, 114.1, 125.8, 127.3 (2C), 127.9 (4C), 128.0 (4C), 128.2 (2C), 128.7 (2C), 136.4, 144.3, 146.8 (2C). HR EI-MS: calcd for C₂₁H₁₇O, 286.1358; found 286.1356.

4.2.2. (4-Ethenylphenyl)-(4-methylphenyl)phenyl methanol (1b). This was prepared by procedure A using 4-methylbenzophenone (1.4 g, 6.9 mmol) to afford 1b as a pale yellow solid (1.3 g, 4.5 mmol, 65%). Mp 74-76 °C. ¹H NMR (300MHz, CDCl₃) δ 2.34 (s, 3H), 2.73 (s, 1H, exchangeable with D₂O), 5.40 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 7.10-7.36 (m, 13H). ¹³C NMR (75 MHz, CDCl₃) δ 21.0, 81.8, 114.0, 125.7 (2C), 127.2, 127.8 (2C), 127.90 (2C), 127.92 (2C), 128.1 (2C), 128.7 (2C), 136.3, 136.44, 137.0, 143.9, 146.6, 146.9. HR EI-MS: calcd for C₂₂H₂₃O, 300.1514; found 300.1512.

4.2.3. (4-Ethenylphenyl)-(4-methoxyphenyl)phenyl methanol (1c). This was prepared by procedure A using 4-methoxybenzophenone (6.5 g, 31 mmol) to afford 1c as a pale yellow liquid (6.5 g, 21 mmol, 67%). ¹H NMR (300 MHz, CDCl₃) δ 2.76 (s, 1H, exchangeable with D₂O), 3.78 (s, 3H), 5.23 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.68 (dd, 1H, J = 17.6, 10.9 Hz), 8.61-8.75 (m, 13H). ¹³C NMR (75 MHz, CDCl₃) δ 55.3, 81.6, 113.3 (2C), 114.0, 125.8 (2C), 127.2, 127.8 (2C), 127.9 (2C), 128.0 (2C), 129.2 (2C), 136.4, 136.5, 139.1, 146.7, 147.0, 158.8. HR EI-MS: calcd for C₂₂H₂₅O₃, 316.1463; found 316.1459.

4.2.4. Bis(4-methoxyphenyl)phenyl methanol (1d). This was prepared by procedure A using 4,4’-dimethoxybenzophenone (1.5 g, 6.1 mmol) to afford 1d as a pale yellow liquid (1.6 g, 4.6 mmol, 75%). ¹H NMR (300 MHz, CDCl₃) δ 3.79 (s, 6H), 5.23 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.67 (dd, 1H, J = 17.6, 10.9 Hz), 8.61-8.75 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 55.4 (2C), 81.4, 113.3 (4C), 114.1, 125.8 (2C), 128.1 (2C), 129.2 (4C), 136.47, 136.51, 139.5 (2C), 147.0, 158.8 (2C). HR EI-MS: calcd for C₂₂H₂₁O₅, 346.1569; found 346.1545.

4.2.5. (2-Chlorophenyl)-(4-ethenylphenyl)phenyl methanol (1e). This was prepared by procedure A using 2-chlorobenzophenone (1.4 g, 6.9 mmol) to afford 1e as a colourless liquid (1.5 g, 6.1 mmol) to afford 1e as a pale yellow liquid (1.6 g, 4.6 mmol, 75%). ¹H NMR (300 MHz, CDCl₃) δ 7.39 (s, 6H), 5.23 (dd, 1H, J = 10.9, 0.9 Hz), 5.73 (dd, 1H, J = 17.6, 0.9 Hz), 6.67 (dd, 1H, J = 17.6, 10.9 Hz), 8.61-8.75 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 55.4 (2C), 81.4, 113.3 (4C), 114.1, 125.8 (2C), 128.1 (2C), 129.2 (4C), 136.47, 136.51, 139.5 (2C), 147.0, 158.8 (2C). HR EI-MS: calcd for C₂₂H₁₉ClO, 344.1569; found 344.1545.
136.3, 136.8, 145.4, 146.1, 146.4. HR EI-MS: calecd for C_{21}H_{17}ClO, 354.0578; found 354.0576.

4.2.7. Bis(4-chlorophenyl)phenyl methanol (1g). This was prepared by procedure A using 4,4’-dichlorobenzophenone (1.7 g, 6.8 mmol) to afford 1g as a pale yellow liquid (2.0 g, 5.6 mmol, 82%). 1H NMR (300 MHz, CDCl3) δ 2.72 (s, 1H, exchangeable with D2O), 5.27 (dd, 1H, J = 10.9, 0.7 Hz), 5.75 (dd, 1H, J = 17.6, 0.7 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 7.14-7.35 (m, 12H). 13C NMR (75 MHz, CDCl3) δ 81.2, 114.6, 126.0 (2C), 127.9 (2C), 128.2 (4C), 129.2 (4C), 133.5 (2C), 136.1, 137.0, 144.8 (2C), 145.5. HR EI-MS: calcd for C_{21}H_{16}Cl2O, 354.0578; found 354.0576.

4.3.1. Poly(styrene-co-[4-ethenylphenyl]diphenylmethanol) (2a). Procedure B. To a solution of styrene (18.2 g, 175 mmol) and 1a (5.0 g, 17 mmol) in toluene (100 mL) was added AIBN (0.3 g, 1.7 mmol). The mixture was purged with N2 for 30 min and the solution was stirred at 90 °C for 24 h. The solution was concentrated in vacuo and then the residue was taken up in 10 mL of THF. This solution was added dropwise to vigorously stirred cold methanol (200 mL). The white precipitate was filtered and dried to afford 2a as a white powder (11.6 g, 50%). 1H NMR (300 MHz, CDCl3) of 2a was determined by 1H NMR to be 8.8:1 (styrene: 1a). This corresponds to a loading level of 0.8 mmol/g of polymer.

4.3.2. Poly(styrene-co-[4-ethenylphenyl]-[4-methoxyphenyl]phenylmethanol) (2b). This was prepared by procedure B using styrene (16.5 g, 158 mmol), 1c (5.0 g, 17 mmol) and AIBN (0.3 g, 1.6 mmol) in toluene (100 mL) to afford 2b as a white powder (8.8 g, 45%). 1H NMR (300 MHz, CDCl3) of 2b was determined by 1H NMR to be 8.8:1 (styrene: 1c). This corresponds to a loading level of 0.8 mmol/g of polymer.

4.4.1. Poly(styrene-co-[4-ethenylphenyl]diphenylmethanol-co-1,4-bis[4-vinylphenoxy]butane) (Janda/Jel-Tr-Cl-2-Tr-OH, 3a). Procedure C. A solution of acacia gum (6.0 g) and NaCl (2.75 g) in warm deionion water (45 °C, 150 mL) was added benzylamine (0.2 g, 1.5 mmol). Stirring was continued for 3 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, diethyl ether, and hexanes. The shrunken beads 4 (2.2 g) were dried in vacuo. Elemental analysis was used to determine the chlorine content (5.4%) and thus the loading level of 1.5 mmol Cl/g of 4.

4.4.2. Poly(styrene-co-[2-chlorophenyl]-[4-ethenylphenyl]phenylmethanol-co-1,4-bis[4-vinylphenoxy]butane) (Janda/Jel-2-Cl-Tr-OH, 3b). This was prepared by procedure C using of 1f (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford 3b (7.3 g, 73%). Elemental analysis was used to determine the chlorine content (4.6%) and thus the loading level of 1.3 mmol Cl/g of 3b.

4.4.3. Poly(styrene-co-[4-chlorophenyl]-[4-ethenylphenyl]phenylmethanol-co-1,4-bis[4-vinylphenoxy]butane) (Janda/Jel-4-Cl-Tr-OH, 3c). This was prepared by procedure C using of 1h (4.8 g, 15.0 mmol), styrene (5.7 mL, 50 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford 3c (7.2 g, 72%). Elemental analysis was used to determine the chlorine content (3.7%) and thus the loading level of 1.1 mmol Cl/g of 3c.

4.5. Poly(styrene-co-[4-ethenylphenyl]diphenyl chloride-co-1,4-bis[4-vinylphenoxy]butane) (Janda/Jel-Tr-Cl, 4). To a magnetically stirred suspension of 3a (2.0 g) in anhydrous CH2Cl2 (20 mL) at rt and under a N2 atmosphere was added tert-butyl(dimethyl)silyle chloride (2.3 g, 15.0 mmol) and dimethyl sulfoxide (0.5 g, 6.0 mmol). Stirring was continued for 3 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, diethyl ether, and hexanes. The shrunken beads 4 (2.2 g) were dried in vacuo. Elemental analysis was used to determine the chlorine content (5.4%) and thus the loading level of 1.5 mmol Cl/g of 4.

4.6. Poly(styrene-co-[4-ethenylphenyl]diphenyl benzylamine-co-1,4-bis[4-vinylphenoxy]butane) (Janda/Jel-Tr-NHCH2Ph, 5). To a magnetically stirred suspension of 4 (0.2 g, 0.3 mmol) in THF (5 mL) at rt was added benzylamine (0.2 g, 1.5 mmol). Stirring was continued for 24 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, methanol, diethyl ether, and hexanes. The shrunken beads 5 (0.2 g) were dried in vacuo. elemental analysis was used to determine the nitrogen content (2.1%) and thus the loading level of 1.5 mmol N/g of 5.

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Chemical Company for supplying many of the reagents used in this study.

References


2. For an excellent review of recent applications of bifunctional trityl protecting groups, see: Shchepinov, M. S.; Korshun, V. A.


18. Trityl linkers have also been introduced onto preformed polystyrene beads via an intermediate ether linkage (Hidai, Y.; Kan, T.; Fukuyama, T. Tetrahedron Lett. 1999, 40, 4711-4714) and an amide linkage (Zikos, C. C.; Fiderigos, N. G. Tetrahedron Lett. 1994, 35, 1767-1768.)


26. Reference 14a describes the use of a linker with two chloro substituents.

27. Janda/jel is a registered trademark of the Aldrich Chemical Co.


