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<td>Choi, MKW; Toy, PH</td>
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An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

Matthew Kwok Wai Choi and Patrick H. Toy*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, People’s Republic of China
An improved and general synthesis of monomers for incorporating trityl linker groups into polystyrene synthesis supports

Matthew Kwok Wai Choi and Patrick H. Toy*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, People’s Republic of China

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 halogentated 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 derive from 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 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.

* Corresponding author. Tel.: +852-2857-2167; fax: +852-2857-1586; e-mail: phtoy@hkucc.hku.hk.
We are interested in the preparation and applications of polymers that incorporate monomers derivatized with various functional groups and have successfully used the Grignard reagent formed from 4-bromostyrene to prepare monomers containing sulfide and phosphine 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. 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. Therefore we chose to examine the addition of the relatively less nucleophilic styrene Grignard reagent, prepared simply from 4-bromostyrene and magnesium, to a series of benzophenones (Scheme 1).

Scheme 1. Synthesis of monomers 1a-f.

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 removable styrene. When it was used as the limiting reagent, the excess benzophenone was more tedious to separate from the desired alcohol. It should be noted that the synthesis of only monomer 1a has been previously reported and that monomer 1d represents a new linker group. To our knowledge, no previously used trityl linker in solid-phase synthesis contained more than one electron donating group in addition to the alkyl group from the polystyrene backbone, to modulate the electron density at the incipient carbocation center. Therefore the use of these types of more highly substituted linkers may allow for the synthesis substrates to be more selectively or mildly cleaved from the polymers.

We next examined the use of our monomers in the preparation of both non-cross-linked and cross-linked polystyrenes (Scheme 2). Co-polymerization of 1a with styrene in the presence of AIBN afforded soluble polymer 2a, which is reported here for the first time. In order to determine the efficiency of incorporation of the functional monomers in this polymerization process, monomer 1e was co-polymerized with styrene to afford 2b. Analysis of 2b by 1H NMR shows that reaction of a 10:1 ratio of styrene:1e results in the observed incorporation of these monomers in a ratio of 8.8:1. This indicates that monomers with electron donating substituents are slightly more reactive than styrene in the polymerization process.

Suspension co-polymerization of 1a, 1e and 1f with styrene and the Janda/el™ 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). 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 loading 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 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 TBDMSCI/DMSO and BnNH2 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.
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 polymers. Given the wide range of substituted benzophenones that are commercially available or easily synthesized, our methodology allows access to a great number of new trityl linkers having varying acid sensitivities, which should further enhance the applicability of such linkers. 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 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. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) 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: calebd for C₂₃H₂₃O, 306.1538; found 306.1541.

4.2.2. (4-Ethenylphenyl)-(4-methylphenyl)phenyl methanol (1b). This was prepared by procedure A using 4-methoxybenzophenone (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 (300 MHz, 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), 136.38, 136.44, 137.0, 143.9, 146.6, 146.9. HR EI-MS: calebd for C₂₂H₂₀O, 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), 6.81-7.35 (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: calebd for C₂₂H₂₀O₂, 316.1463; found 316.1459.

4.2.4. Bis(4-methoxyphenyl)methanol (1d). This was prepared by procedure A using 4,4' -dimethoxybenzophenone (1.5 g, 6.1 mmol) as a pale yellow liquid (1.6 g, 4.6 mmol, 75%). ¹H NMR (300 MHz, CDCl₃) δ 2.71 (s, 1H, exchangeable with D₂O), 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), 6.81-7.36 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 55.3 (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: calebd for C₂₅H₂₄O₂, 346.1569; found 346.1545.

4.2.5. (2-Chlorophenyl)-(4-ethylphenyl)phenyl methanol (1e). This was prepared by procedure A using 2-chlorobenzophenone (7.5 g, 35 mmol) to afford 1e as a colourless liquid. (8.5 g, 27 mmol, 77%). ¹H NMR (400 MHz, CDCl₃) δ 4.39 (s, 1H, exchangeable with D₂O), 5.20 (dd, 1H, J = 10.9, 0.8 Hz), 5.71 (dd, 1H, J = 17.6, 0.8 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 6.74-7.34 (m, 13H). ¹³C NMR (100 MHz, CDCl₃) δ 82.4, 114.1, 125.9 (2C), 126.4, 127.4, 127.7 (2C), 127.96 (2C), 128.0 (2C), 129.1, 131.3, 131.4, 133.2, 136.4, 136.6, 143.6, 145.2, 145.5. HR EI-MS: calebd for C₂₃H₂₁ClO₂, 320.0968; found 320.0971.

4.2.6. (4-Chlorophenyl)-(4-ethylphenyl)phenyl methanol (1f). This was prepared by procedure A using 4-chlorobenzophenone (7.5 g, 35 mmol) to afford 1f as a pale yello liquid. (8.0 g, 25 mmol, 72%). ¹H NMR (300 MHz, CDCl₃) δ 2.75 (s, 1H, exchangeable with D₂O), 5.25 (dd, 1H, J = 10.9, 0.7 Hz), 5.76 (dd, 1H, J = 17.6, 0.7 Hz), 6.69 (dd, 1H, J = 17.6, 10.9 Hz), 7.13-7.41 (m, 13H). ¹³C NMR (75 MHz, CDCl₃) δ 81.6, 114.4, 126.0 (2C), 127.6 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 129.4 (2C), 130.2, 133.3,
136.3, 136.8, 145.4, 146.1, 146.4. HR EI-MS: calec for C21H17ClO, 320.0968; found 320.0960.

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%). \[1^1H\text{NMR } (300\text{ MHz, CDCl}_3) \delta 2.72 (s, 1H, exchangeable with D$_2$O), 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). \[1^3C\text{NMR } (75\text{ MHz, CDCl}_3) \delta 81.2, 114.6, 126.0 (2C), 127.9 (2C), 128.2 (4C), 129.2 (4C), 133.5 (2C), 136.1, 137.0, 144.8 (2C), 145.5. \] HR EI-MS: calcd for C21H16Cl2O, 354.0578; found 354.0576.

4.3.1. Poly(styrene-co-[4-ethenylphenyl]diphenyl chloride-co-1,4-bis[4-vinylphenoxy]butane) (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 N$_2$ for 30 min and the solution was stirred at 90 °C for 24 h. The solution was concentrated in vacuo. 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%). \[1^H\text{NMR } (300\text{ MHz, CDCl}_3) \delta 1.25-2.16 (bm, 33H), 3.74 (bs, 58H). Polyomers 2 are soluble in THF, EtOAc, CH$_2$Cl$_2$, DMF. They are not soluble in methanol, ethanol, ether, water.

4.3.2. Poly(styrene-co-[4-ethenylphenyl]-[4-methoxyphenyl]phenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (2b). This was prepared by procedure B using styrene (16.5 g, 158 mmol), cross-linker (0.4 g, 1.5 mmol), and AIBN (0.2 g) in chlorobenzene (10 mL) to afford 2b as a white powder (8.0 g, 80%). The mixture was continued for 24 h at rt, at which time the resin was filtered off, and washed sequentially with dichloromethane, diethyl ether, and hexanes. The shrunken beads 2b were dried in vacuo. Elemental analysis was used to determine the chlorine content (4.6%) and thus the loading level of 1.3 mmol Cl/g of 2b.

4.4.2. Poly(styrene-co-[2-chlorophenyl]-[4-ethenylphenyl]phenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (Janda/EI-2-Cl-Tr-OH, 3b). This was prepared by procedure C using of 1e (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]phenyl methanol-co-1,4-bis[4-vinylphenoxy]butane) (Janda/EI-4-Cl-Tr-OH, 3c). 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 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/EI-Tr-Cl, 4). To a magnetically stirred suspension of 3a (2.0 g) in anhydrous CH$_2$Cl$_2$ (20 mL) at rt and under a N$_2$ atmosphere was added tert-butyl dimethylsilyl 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/EI-Tr-NHCH$_2$Ph, 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.

Acknowledgments

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

References


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.; Ferderigos, N. G. Tetrahedron Lett. 1994, 35, 1767-1768.)


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

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


