Pergamon

Tetrahedron Letters 41 (2000) 8417–8420

TETRAHEDRON
LETTERS

Improved synthesis of (4-ethenylphenyl)diphenyl methanol and its application in the preparation of trityl functionalized polystyrene resin containing tetrahydrofuran derived cross-linker

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Received 31 August 2000; accepted 11 September 2000

Abstract

An improved and straightforward synthesis of (4-ethenylphenyl)diphenyl methanol is described. This monomer was used in the preparation of trityl functionalized polystyrene containing a flexible tetrahydrofuran cross-linker, giving rise to a suitable support for solid-phase organic synthesis. © 2000 Elsevier Science Ltd. All rights reserved.

Polymer-immobilized trityl alcohol and chloride moieties are useful protecting groups for solid-phase organic synthesis (SPOS). Furthermore, they allow the attachment of a variety of bifunctional building blocks such as amino acids, amino alcohols, and diamines via the carboxyl, hydroxyl, or amino groups, respectively. In the field of the base-stable anchor groups for linking substrates to solid support, trityl functionalized resins such as the chlorotrityl-PS/DVB resin[1–3] are widely used as platforms for the immobilization of nucleophiles.

We recently reported the synthesis of a new class of resins (termed *J*anda*J*els[4]) for SPOS containing a flexible tetrahydrofuran derived cross-linker **1** (Fig. 1) that offered several advantages over the other commercially available polystyrene resins.[5] These resins were prepared with a variety of common functionalities such as chloromethyl,[5] hydroxymethyl,[6,7] aminomethyl,[8] and the Wang-type linker.[9] Due to the interesting features of the trityl linker and its usefulness in SPOS, we decided to copolymerize (4-ethenylphenyl)diphenyl methanol **2** with styrene and with 2 mol% of our flexible tetrahydrofuran derived cross-linker **1** (Fig. 1).[5]

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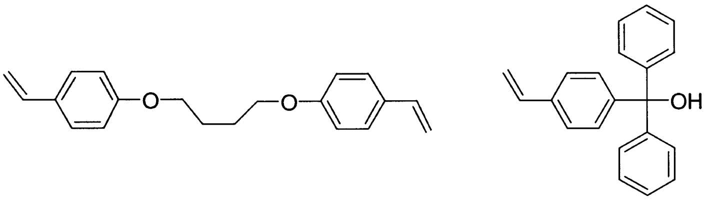
PII: S0040-4039(00)01529-X

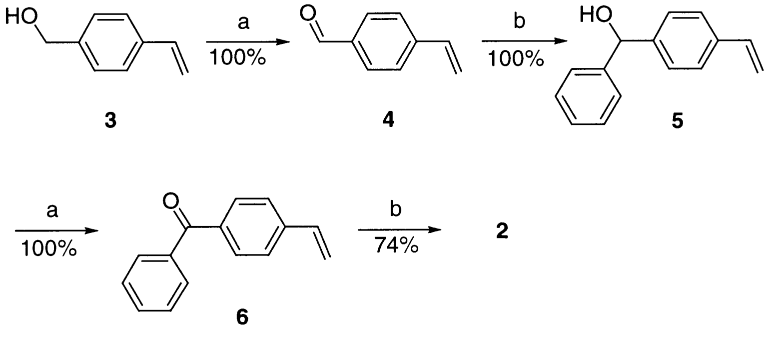


1 **2**

Figure 1.

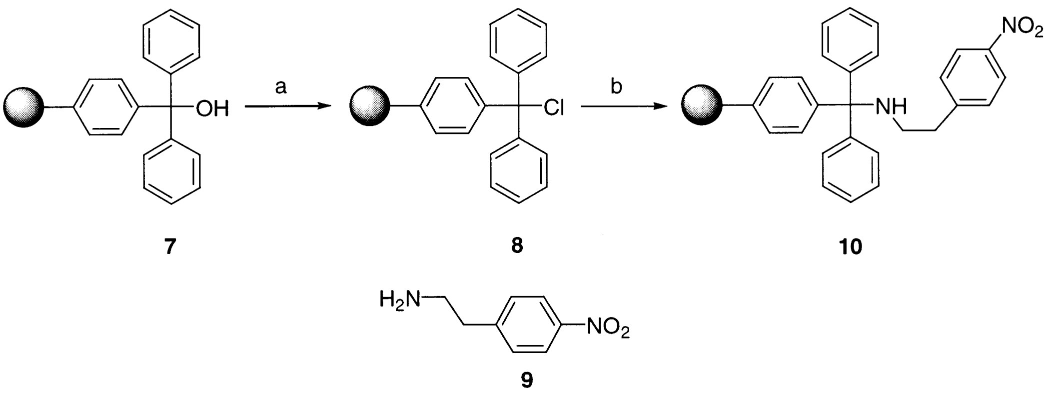
The preparation of trityl monomer **2** was first performed by adding 4-bromostyrene to *tert*-butyllithium followed by the slow addition of benzophenone, as described by Rimmer et al.[10] In the literature, an isolated yield of 55% was reported; however, in our hands it was not possible to obtain pure **2** either by crystallization or chromatography with a chemical yield better than 41%. Furthermore, the chromatographic purification of monomer **2** from unreacted benzophenone was troublesome and tedious (especially for scale-up) and always afforded mixed fractions besides the desired compound **2**.

An alternative route to the functional monomer **2** was therefore investigated (Scheme 1). The previously reported 4-vinyl-benzyl alcohol **3**[11] was quantitatively oxidized to the corresponding aldehyde **4** using Swern's methodology.[12,13] Grignard reaction with phenyl magnesium bromide gave alcohol **5**,[14] which underwent Swern oxidation to provide ketone **6** in 100% yield for the two steps. Finally, monomer **2** was obtained in 74% yield by another Grignard reaction with phenyl magnesium bromide. Although our synthetic route to **2** is longer than that reported by Rimmer,[10] it is more convenient in terms of chemical yield and ease of purification. In fact, the first three steps of the synthesis did not require any purification and the only chromatography was performed at the last step, giving rise to pure monomer **2** as white needles (mp, 55°C).



Scheme 1. (a) DMSO-$(COCl)_2$, −60°C, Et_3N, 20 min then rt. (b) PhMgBr, Et_2O, rt, 10 min

Trityl alcohol-functionalized resin **7** was obtained in 89% yield by suspension copolymerization[5] of styrene, trityl monomer **2**, and 2 mol% of cross-linker **1**. Conversion to the trityl chloride **8** was accomplished by refluxing resin **7** with acetyl chloride in benzene (Scheme 2).[2] Chloride content determination indicated that the bead loading was quite low (0.3 mmol/g) in comparison to the theoretically calculated value (~1 mmol/g, based on the amount of monomer **2** used in the polymerization reaction).



Scheme 2. (a) CH_3COCl, benzene, reflux, 48 h. (b) **9**, THF, rt, 48 h

As the trityl chloride functionality is prone to hydrolysis, chlorine content determination might not give a reliable result. Therefore, resin **8** was converted into **10** by reaction with 4-nitrophenethylamine **9** in THF at room temperature for 48 h (Scheme 2). Resin **10** contained a more stable amine moiety and nitrogen content analysis indicated that the bead loading was 0.68 mmol/g, which corresponds to a loading capacity of 0.75 mmol/g for resin **8**. The swelling properties of resin **7** were measured in solvents typically used for organic synthesis and were compared with those measured for commercially available trityl alcohol-functionalized Merrifield-type resin that is cross-linked with divinylbenzene (Table 1).

Table 1
Volumes of swollen resins

	Volume of swollen resin (mL/g)[a]				
Resin	Dioxane	THF	DMF	Benzene	DCM
Merrifield-1%[b]	5.8	6.0	5.6	5.4	6.6
*J*anda*J*el-Trt-OH-2% (**7**)	10.6	11.0	8.0	10.2	9.6

[a] Volumes were measured in syringes equipped with a sintered frit after equilibrating for 1 h.[15]

[b] Resin with a loading capacity of 1.1 mmol/g was purchased from Advanced Chemtech and was used as received.

From Table 1, it is clear that our resin **7** has outstanding swelling properties in comparison to the commercially available Merrifield trityl functionalized resin. It is noteworthy that our 2% cross-linked resin swells nearly twice as much as the 1% DVB cross-linked analogue. As the degree to which a given resin absorbs a particular solvent and swells is considered to be indicative of site accessibility and consequently resin functionalization,[15] resin **7** might constitute a suitable support for reactions which require basic or neutral conditions. As such, we are currently utilizing **7** in the SPOS of other organic reactions of interest to our laboratory.

In summary, we have provided a new high-yielding entry to the functional monomer **2** which allows for its large scale preparation in pure form. Monomer **2** was used in the preparation of a polystyrene resin containing a flexible tetrahydrofuran cross-linker and showed excellent swelling properties compared to the commercially available Merrifield-type resin. This combination of support and linker should find application in solid-phase organic synthesis and investigations along these lines will be reported in due course.

Acknowledgements

This work was supported by funding from The Skaggs Institute for Chemical Biology and the National Institutes of Health (GM-56154). K.D.J. is an Arthur C. Cope Scholar and R.M. is a Fulbright Fellow.

References

1. Barlos, K.; Gatos, D.; Kapolos, S.; Papaphotiu, G.; Schaefer, Y.; Wenqing, Y. *Tetrahedron Lett.* **1989**, *30*, 3947–3950.
2. Frechet, J. M. J.; Haque, K. E. *Tetrahedron Lett.* **1975**, *35*, 3055–3056.
3. Cramer, F.; Koester, H. *Angew. Chem.* **1968**, *78*, 180–181; Cramer, F.; Koester, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *5*, 473–474.
4. *J*anda*J*el is a registered trademark of Aldrich Chemical Co.
5. Toy, P. H.; Janda, K. D. *Tetrahdron Lett.* **1999**, *40*, 6329–6332.
6. Toy, P. H.; Reger, T. S.; Janda, K. D. *Org. Lett.* **2000**, *2*, 2205–2207.
7. Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929–6934.
8. Garibay, P.; Toy, P. H.; Hoeg-Jensen, T.; Janda, K. D. *Synlett* **1999**, 1438–1440.
9. Toy, P. H.; Reger, T. S.; Garibay, P.; Garno, J. C.; Malikayil, J. A.; Liu, G.-Y.; Janda, K. D. *J. Chom. Chem.*, submitted for publication.
10. Nzeru, A.; Ebdon, J. R.; Rimmer, S. *J. Org. Chem.* **1997**, *62*, 8928–8929.
11. Bamford, C. H.; Lindsay, H. *Polymer* **1973**, *14*, 330–332.
12. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
13. Marx, M.; Tidwell, T. T. *J. Org. Chem.* **1984**, *49*, 788–793.
14. Analytical data for compound **5** has not been previously reported: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (d, $^3J_Z = 10.9$ Hz, 1H), 5.70 (d, $^3J_E = 17.6$ Hz, 1H), 5.84 (s, 1H), 6.7 (dd, $^3J_Z = 10.9$ Hz, $^3J_E = 17.6$ Hz, 1H), and 7.35 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.9, 113.9, 126.3, 126.5, 126.7, 127.5, 128.4, 136.4, 136.8, 143.3, and 143.6; HRMS (MALDI-FTMS) calcd for $C_{15}H_{14}O$ $[MH^+-H_2O]^+$ 193.1012, found 193.1010.
15. Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951–8954.