Pergamon

Tetrahedron Letters 39 (1998) 8695–8698

TETRAHEDRON LETTERS

A Chemically Inert Hydrophilic Resin for Solid Phase Organic Synthesis.

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Received 9 July 1998; accepted 18 August 1998

Abstract

A new mechanically stable and chemically inert resin for solid phase organic synthesis is described. The resin, POEPS-3 (**1**), is prepared by bulk and inverse suspension radical polymerisation of macromonomers consisting of polyethylene glycol 1500 partially derivatised with 3-(4-vinylphenyl)propyl groups. Synthesis of the macromonomer (**4**) is described as well as the properties of the resin which show compatibility with Lewis acids and solvents ranging from toluene to water in polarity.

Keywords: macromonomer, polymer, polymerisation.

Introduction

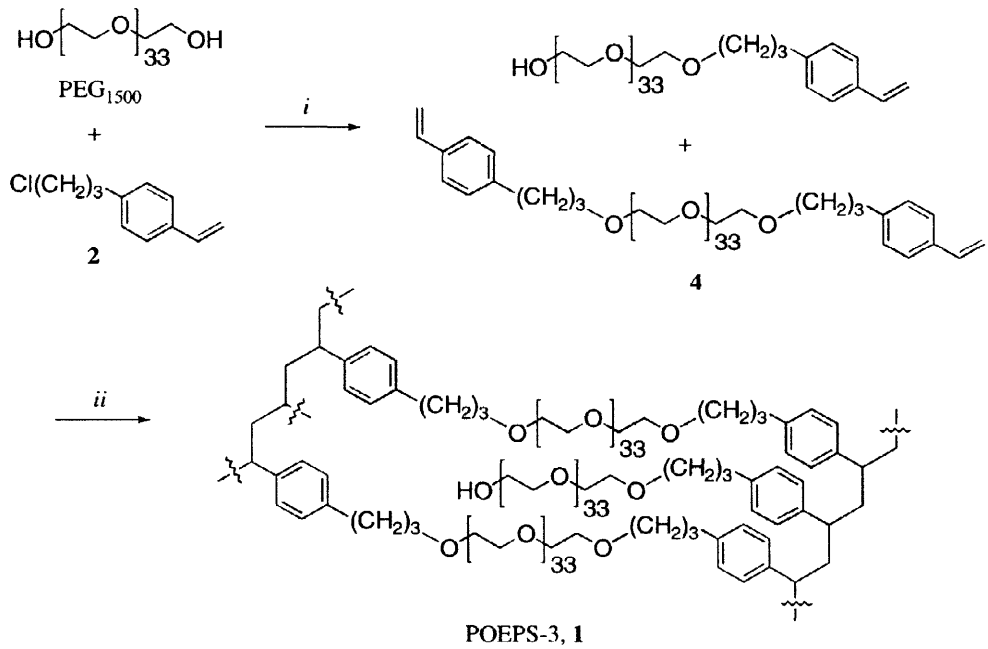
The character of the solid support has a large influence on the result of reactions [1] in solid phase organic chemistry (SPOC) [2,3]. Since Merrifield introduced the concept using a crosslinked polystyrene solid support [4], other resins designed for peptide synthesis have been developed to overcome the initial limitations of the Merrifield resin. Among these are dimethyl acrylamide based resins [5,6] and the PEG (polyethylene glycol) [7] grafted polystyrene resin, TentaGel [8], which have been used extensively for both SPOC and peptide synthesis. More recently, the PEGA resin was introduced [9,10]. This hydrophilic PEG-polydimethyl acrylamide hybrid resin is compatible with a variety of solvents and has an open structure due to long PEG molecules acting as crosslinkers. As a result, reagents, including large enzymes [11,12], have ready access to the interior of the resin. In fact, enzyme assays can be carried out with compounds attached to the support [13]. However, a resin which is designed for general SPOC must be stable towards harsh chemicals and heating, and the content of amide bonds in the PEGA resin makes it unsuitable for this purpose. POEPS (polyethylene glycol-polystyrene based) and POEPOP (polyethylene glycol-polyoxypropylene based) resins which have a polar, open structure and yet are chemically inert have also been developed [14]. However, in the POEPS resin, as well as the TentaGel, PEG is attached to the

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01737-7

polystyrene backbone by a benzylic ether bond and use of Lewis acids or hydrogenolytic conditions would therefore destroy the resin by cleaving these bonds. Considering the extensive use of benzyl ether protection of hydroxyl groups, [15] a non benzylic attachment to the PEG molecules is thus desired in the otherwise rather inert resin. Here, we present an improved resin, POEPS-3 (**1**), containing three methylenes between the PEG molecule and the polystyrene backbone.

Results and Discussion

The preparation of POEPS-3[1] (**1**) follows the outline in Scheme 1. The resin is prepared by radical polymerisation of macromonomers consisting of PEG_{1500} molecules either non, mono or disubstituted with a styrene derivative. Synthesis of the macromonomer involves the



Scheme 1. *i*: NaH (1.5 eq.), **2** (1.5 eq.), THF, 50°C, 20 h; *ii*: $(NH_4)_2S_2O_8$, TMEDA, sorbitan monolaurate, 70°C, 2.5 h.

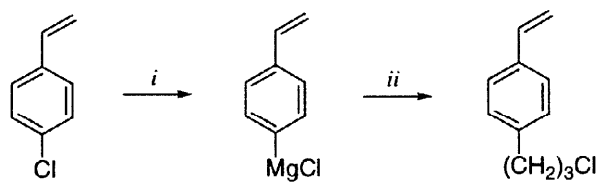
[1] **Experimental conditions:**

Macromonomer **4b'**: Anhydrous [7] PEG_{1500} (12.4 g) was dissolved in THF (25 mL) under Ar at 50°C and NaH (497 mg, 60% in oil, 1.5 eq.) was added. After 5 min. **2** (2.2 mL, 1.5 eq.) was added over a period of 15 min. Addition of NaH/**2** (1.5 eq. each) was repeated after 3 h and again NaH (1.5 eq.) was added after 6 h. The brown mixture was stirred for another 16 h, concentrated, dissolved in water (75 mL), neutralized, water (125 mL) was added and the solution washed with light petroleum (50 mL). Concentration of the water phase and subsequent coevaporation with toluene (3x35 mL) gave a brown, opaque residue which was dissolved in CH_2Cl_2 (150 mL) and dried with $MgSO_4$ (35 g). Filtration through Celite and concentration to dryness yielded 13.1 g brown solid (94%), pure according to proton NMR.

Resin **1b'** was prepared in beaded form by inverse supension polymerisation of **4b'** (12.6 g) at 70°C for 2.5 h using $(NH_4)_2S_2O_8$ (148 mg, 0.07 eq.), tetramethyl ethylenediamine (443 µL, 0.32 eq.), sorbitan monolaurate (133 mg) and the procedure described previously [10]. Yield: 65%. Resins **1a**, **1b** and **1c** were prepared by bulk polymerisation in water at r.t. for 24 h using $(NH_4)_2S_2O_8$ (0.06 eq.) and tetramethyl ethylenediamine (0.25 eq.) followed by sieving, washing and lyophilization. Yields: **1a**: 63%, **1b**: 71%, **1c**: 83%.

reaction of the partially sodiated PEG_{1500} with an alkyl halide. However, in contrast to the POEPS resin, the alkyl halide (**2**) is not commercially available, and was synthesized in a two step procedure from commercial *p*-chlorostyrene (Scheme 2) [16].

Coupling of the styrene derivative **2** to PEG_{1500} was accomplished by an iterative method. In agreement with similar reactions in previous literature [17] it was observed that the S_N2 substitution of the primary halide **2** by sodiated PEG_{1500} was accompanied by extensive elimination. Reaction of PEG_{1500} with 1.5 eq. of NaH followed by 1.5 eq. of **2** gave a product (**4a**) containing an average of only 0.63 eq. of styrene groups pr. PEG_{1500} molecule as measured by integrals in the ^{1}H-NMR spectrum [18]. Only by repeating the addition of NaH and **2** *in situ*, macromonomers with higher styrene substitution (*f*-value) could be obtained (Table 1).



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Scheme 2. *i*: Mg (1.5 eq.), $Br(CH_2)_2Br$ (0.04 eq.), I_2 (small grain), THF, Δ; *ii*: $Br(CH_2)_3Cl$ (2 eq.), $LiCuCl_4$ (0.01 eq.), THF, 0°C.

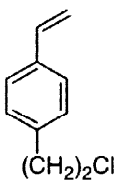

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Figure 1

Attempts to prepare a macromonomer with two methylene units from sodiated PEG_{1500} and the halide **3** (Figure 1) were unsuccessful, due to complete elimination, in accordance with previously published data [17].

Monomer	Addition of NaH/2	*f*[a]	Resin	Loading mmol/g	Swelling mL/g		
					H_2O	DMF	DCM
4a	1 time	0.63	**1a**	-[b]	9	10	12
4b	2 times	1.18	**1b**	0.22	4	4	6
4b'[c]	2 times	1.21	**1b'**	0.22	6	6	9
4c	3 times	1.62	**1c**	0.04	3	3	5

[a]Number of styrene groups pr. PEG_{1500} molecule. [b]Resin could not be filtered. [c]Beaded resin.

Table 1.

Macromonomers **4a-c** were all polymerized by radical initiation (Scheme 1) to obtain resins **1a-c** (Table 1), however only **1b/b'** had a desired set of properties: it was mechanically stable and had a satisfactory loading capacity and swelling ability in a range of solvents. The beaded resin **1b'** was prepared from macromonomer **4b'** by inverse suspension polymerisation as previously described for the PEGA-resin [10]. Although **1a** was highly swelling, it proved to be soft and difficult to filter. It was therefore not characterised further. Resins **1c** and **1b/b'** had similar mechanical properties, however, the loading of **1c** was unacceptably low. This

was expected due to the large fraction of disubstituted PEG_{1500} molecules resulting in a highly crosslinked resin. Loading capacities were obtained by esterifying the resin with Fmoc-Gly-OH by the MSNT method [19] and subsequently measuring the loading spectrophotometrically after Fmoc release by piperidine [20]. Swelling capacities of the resins were measured by the syringe method [10].

The stability of the resin **1b/b'** towards Lewis acids was compared to that of the POE-PS-resin (f=1.10). Thus both resins were treated with trimethylsilyl trifluoromethanesulfonate (2 eq.) and Ac_2O (45 eq.) in dichloromethane at room temperature. Such acetolysis conditions can be used e.g. in carbohydrate chemistry to remove benzylic protective groups [21]. Under these conditions the benzylic POEPS resin was completely dissolved after 10 min, whereas **1b/b'** was stable and did not change appearance even after 50 min.

In summary, a chemically inert, yet water swellable resin, containing only C-C, C-H and ether bonds has been prepared and characterized. This resin has a potential for synthesis and analysis of small organic molecule combinatorial libraries. The stability of the resin allows many different reaction conditions during the solid phase organic synthesis and, because of the open resin structure, enzyme assays can be performed in aqueous buffer directly on the resin bound product. Further characterisation, modifications and applications of the resin will be reported elsewhere.

Acknowledgment

This work was performed under the SPOCC program supported by The Danish National Research Foundation.

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