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Stealth Star Polymers: A New High-Loading Scaffold for Liquid-Phase Organic Synthesis

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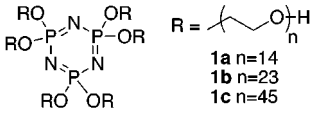
ABSTRACT



Polyethylene glycol (PEG) has proven to be a versatile soluble–polymer support for organic synthesis, though the use of PEG has been limited by its relatively low loading (0.5 mmol/g or less). We have developed a new high-loading (1 mmol/g) soluble-star polymer based on a cyclotriphosphazene core with PEG arms that exhibit superior precipitation properties compared with those of linear PEG. Additionally, the heterocyclic core does not add interfering signals to the ^{1}H or ^{13}C NMR.

Soluble-polymer supported organic synthesis continues to be a rapidly growing field.[1] While PEG has proven to be a versatile platform for liquid-phase organic synthesis, only recently has work been done toward developing soluble PEG analogues.[2] We report herein a new PEG star[3] for use as a versatile PEG alternative. Prepared in an arm-first manner from monoprotected PEG diol and phosphonitrilic chloride trimer, this star combines remarkable chemical stability, low cost, and high loading while retaining the properties of PEG.

Cyclotriphosphazenes containing polyoxyethylene substituents are easily prepared[4] and have been investigated primarily as phase-transfer catalysts,[5] as photocross-linkable polymers,[6] and for liquid crystalline behavior.[7] The known polyether derivatives are either oils or amorphous solids, and none have contained polyoxyethylene chains longer than heptaethylene glycol[4b] nor have these star polymers been investigated for use as soluble-polymer supports for organic synthesis.

To prepare our new PEG star, we required a supply of suitably monoprotected PEG. Although monosubstituted PEG of MW > 1000 can be prepared from PEG diol, the purification is problematic. Tedious, labor intensive purifications or the use of hazardous reagents (e.g., tolylene-2,4-diisocyanate)[8] preclude this approach for the preparation of anything more than small quantities of monoprotected PEG. However, the anionic polymerization of ethylene oxide using a suitably monoprotected glycol initiator provides rapid access to pure monoprotected PEG.

Monobenzyl PEG has been reported in the literature by anionic polymerization of ethylene oxide starting from 2-(*tert*-butyldimethylsiloxy)ethanol, followed by quenching

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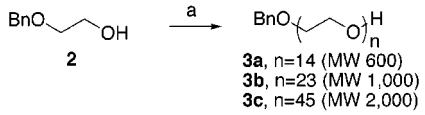
the living polymerization with benzyl chloride and removal of the silyl group.[9] Since 2-benzyloxyethanol is commercially available, using this alcohol would provide the monobenzyl PEG directly. Initial attempts to produce monobenzyl PEG from 2-benzyloxyethanol using potassium naphthenylide as the base resulted in contamination by significant quantities of diol formed from slow radical anion induced deprotection of the monobenzylated PEG. We found that potassium hydride is ideal for generation of the initiator and this anion reacted smoothly in THF with ethylene oxide to give nearly quantitative amounts (95−99%) of pure monobenzyl PEG **3a**−**c** (Scheme 1).[10] The polymerizations were quenched with

Scheme 1[a]

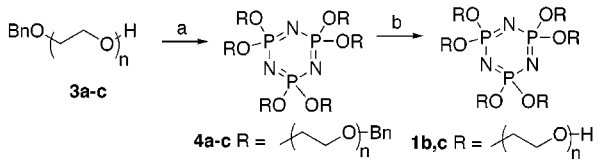


[a] (a) (i) KH, THF; (ii) ethylene oxide; (iii) H^+ resin (95−99%).

Amberlite IR-120(+) strongly acidic ion-exchange resin and filtered from the resin directly into cold diethyl ether to precipitate the product. These polymerizations were routinely performed on a 15−20 g scale with polydispersities (M_w/M_n) of 1.04.[11] Although residual potassium ions were still coordinated to the monobenzylated PEG, we found that this did not affect later reactions. However, desalting was easily accomplished by treatment with a mixed-bed anion-exchange resin.

Preparation of the PEG star was readily accomplished by treating the anion of monobenzyl PEG **3a**−**c** (using KH in THF) with commercially available $P_3N_3Cl_6$ (Scheme 2).

Scheme 2[a]



[a] (a) (i) KH, THF; (ii) $P_3N_3Cl_6$; (iii) methylisocyanate resin; (iv) Amberlite IR-120(+) (90−99%); (b) H_2, 10% Pd/C, 4:1 EtOAc:CH_2Cl_2 (95−98%).

Unreacted monobenzyl PEG was removed from the star by reaction of the mixture with a polystyrene-bound isocyanate to scavenge any remaining alkoxide. Removal of the isocyanate resin, followed by quenching with Amberlite IR-120-(+) resin and filtration directly into cold diethyl ether, provided the product in high yields (93−99%). ^{13}C NMR showed no free hydroxyl groups ($CDCl_3$, δ = 61.5), indicating complete removal of any excess monobenzyl PEG. Hydrogenolysis of the terminal benzyl protecting groups afforded the hydroxyl-terminated PEG stars **1b** (95%) and **1c** (98%). Throughout this sequence, the integrity of the tricyclophosphazene core was easily monitored by ^{31}P NMR, giving a clean singlet at δ = 18.5.

Three different molecular weight (MW) PEG stars were synthesized. Monobenzyl PEGs of MW 600, 1000, and 2000 (**3a**−**c**) were appended to the cyclotriphosphazene core to produce stars of MW 3.5K, 6K, and 12K (**4a**−**c**). The 3K star **1a** was an oil and could be purified by chromatography (10% MeOH/$CHCl_3$), while the two higher MW stars **1b** and **1c** were free-flowing powders. Although **1b** and **4b** had solubilities identical to that of PEG_{1000} and **1c** and **4c** had solubilities identical to that of PEG_{2000} (see Supporting Information), we found that PEG star **1b** was far easier to manipulate than linear PEG_{1000}. PEG_{1000} is a waxy, sticky material that does not give high recoveries upon precipitation. In contrast, the precipitates obtained from the stars **1b** and **1c** were powders (Table 1) and precipitated nearly quantitatively from diethyl ether. This superior precipitation property is envisioned to be useful in applications where lower loading monomethoxy PEG (MPEG) or PEG diol is unsuitable.

Table 1. Physical Form of PEG Stars

	DP_n[a]	MW	form
PEG diol	13	500	oil
star **1a**	14	3500	oil
PEG diol	23	100	wax
star **1b**	23	6000	dry powder
PEG diol	45	2000	dry powder
star **1c**	45	12000	dry powder

[a] DP_n (degree of polymerization) for the PEG stars refers to the number of monomer units per arm.

In addition to the improved precipitation properties, these new star polymers have other advantages. Previous PEG-based stars have used carbon cores which could interfere with NMR characterization of substrates attached to the star termini, e.g., 3,5-dihydroxymethylphenol branching units used by Cozzi which display aromatic and benzylic peaks.[2a] This new star gave ^1H and ^{13}C spectra nearly identical to those of linear PEG, allowing unobstructed proton and carbon NMR characterization of bound substrates. We therefore refer to this as a "stealth star". The heterocyclic core also readily lends itself to ^{32}P or ^{14}N radiolabeling, and the arm-first manner of construction allows differentiation of PEG termini for attachment of labels or use in a combinatorial format. The cyclotriphosphazene core was chosen due to its high reactivity as the hexachloride (for complete substitution), low cost, and the remarkable stability exhibited by the phosphorus−oxygen bond after substitution.

We recently reported the preparation of triphenylphos-

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phine−PEG derivatives **5**[12] and **6**[13] (Figure 1) and demonstrated the use of this reagent for aqueous Wittig reactions and ozonide reductions.[12] As an extension of this research,

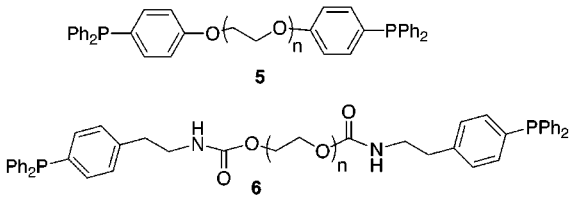
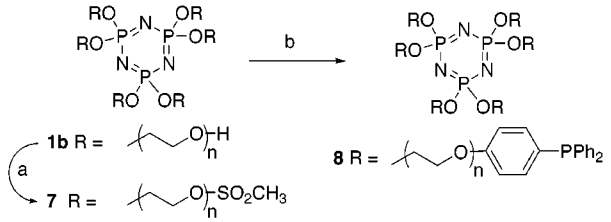


Figure 1. Previous triarylphosphine−PEG reagents.

we prepared the high-loading PEG star−triphenylphosphine conjugate **8** (Scheme 3) and report its use for the Mitsunobu etherification of phenol.

Scheme 3



[a] (a) MsCl, Et_3N, CH_2Cl_2; 92%; (b) $HOC_6H_4PPh_2$, Cs_2CO_3, DMF, 91%.

The PEG star−triphenylphosphine conjugate **8** was prepared by conversion of **1b** to the hexamesylate **7**, followed by displacement of the mesylates with diphenyl (4-hydroxyphenyl)phosphine (Scheme 3). The phosphine end groups were clearly visible in the ^{31}P NMR ($CDCl_3$, $\delta = -6.75$) with no contamination by phosphine oxide ($\delta = 29.56$).

To demonstrate the utility of reagent **8**, several examples of Mitsunobu etherification were carried out (Table 2). Yields

Table 2. Alkyl Aryl Ethers Prepared with **8** or **6**

	star **8**		**6**	
alcohol	yield (%)	*t*/h	yield (%)	*t*/h
butan-1-ol	93	3	85	3
2-propanol	89	5	88	5
allyl alcohol	85	2	87	2
benzyl alcohol	68	18	75	10

[a] Phenol (1.0 equiv), alcohol (1.0 equiv), DEAD (1.1 equiv), **8** or **6** (1.2 equiv), CH_2Cl_2 (0.1 M).

and reaction times were comparable with those reported by our group for the PEG-supported triphenylphosphine reagent **6**.[13] Upon completion of the reactions, the phosphine oxide reagent was isolated by precipitation from diethyl ether in good yield (>85%).

Regeneration of phosphine **8** by reduction with freshly prepared alane[14] (AlH_3, THF, 1 h) proceeded cleanly.[15] ^{31}P NMR showed complete reduction from P(V) to P(III) with no degradation of the cyclotriphosphazene core, and isolated yields of the recovered reagent (73%) were comparable to that previously reported for **5** (75%).

Given the ease of synthesis, high loading, stability, and improved precipitation properties of **8**, we envision that the range of existing soluble-polymer supported methodology can be expanded through the use of our new stealth stars.

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Supporting Information Available: Full experimental details available. This information is available free of charge via the Internet at http://pubs.acs.org.

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