Poly(ethylene glycol) (PEG) as a reagent support: the preparation and utility of a PEG–triarylphosphine conjugate in liquid-phase organic synthesis (LPOS)

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The preparation and application in the Staudinger and Mitsunobu reactions of a liquid-phase, poly(ethylene glycol)-arylphosphine conjugate 1 is described.

The development of both soluble and insoluble functionalized polymers is currently of tremendous interest in the fields of combinatorial chemistry, peptide synthesis and nucleic acid synthesis.[1] The conversion of reactions in solution to either soluble or insoluble polymer-supported chemical methodologies, with the benefits of ease of product isolation, minimization of side-reactions and the ability to use an excess of reagents to drive a reaction to completion, is an on-going challenge.

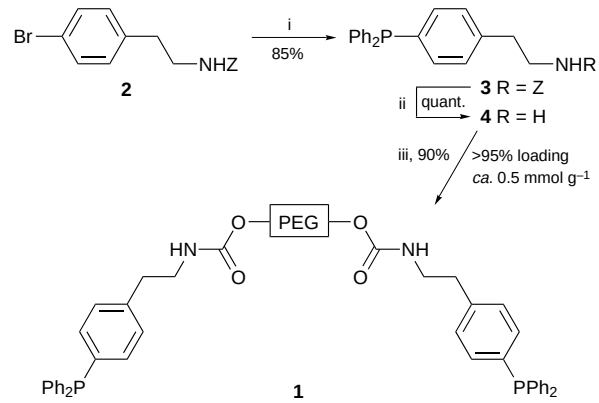
Because of problems associated with the use of insoluble polymeric reagents and substrates under heterogeneous conditions, such as lowered reactivities, extended reaction times, diffusion-limited reactivity and reagent leaching,[2] soluble-matrices such as poly(ethylene glycol) (PEG),[3] fluorous supports,[4] linear polystyrenes[5] and polyethylene[6] are receiving increasing attention for combinatorial synthesis[7] and as supports for heterogeneous catalysts.[8] Previous work from our group has demonstrated the preparation and utility of PEG derivatives for liquid-phase combinatorial synthesis (LPCS),[7] peptidomimetic synthesis[9] and as ligand supports for the Sharpless dihydroxylation reaction.[10]

We now report an extension of liquid-phase synthesis into the field of reagent supports.[11] In our latest effort, we have conjugated PPh_3 to PEG_{3400} and studied its utility in the Staudinger and Mitsunobu reactions. There are a number of reports highlighting the utility of PPh_3 bound to solid polymeric supports, such as polystyrene and copolymers of styrene and divinylbenzene, in the Wittig reaction[12] and for azide reduction.[13] An important component of this work is a comparison between the liquid- and solid-phase reagent approaches.

For any successful polymer-supported strategy optimal loading is essential, therefore two important considerations biased our choice of a suitable matrix. First, the PEG polymer was chosen to have two free hydroxy groups per polymer strand. Second, we chose the PEG polymer with the lowest molecular weight possible which did not suffer from changes in its physical properties after attachment of the triphenylphosphine moiety. PEG_{3400} was found to satisfy both of these requirements. Two synthetic strategies were developed for the preparation of the PEG-triarylphosphine conjugates. In the first, PEG_{3400} was reacted with an excess of *p*-bromophenyl isocyanate in dichloromethane, to generate a carbamate linked *p*-bromophenyl PEG derivative in greater than 95% yield. The loading was almost quantitative as judged by the ^1H NMR resonance of the PEG methylene protons α to the carbamate linkage. The diphenylphosphine group was incorporated by a modification of the method of Relles and Schluentz.[14] A stirred suspension of the carbamate PEG derivative in THF was reacted with lithium diphenylphosphide under reflux for 16 h. ^1H NMR Spectral analysis showed that this reaction was accompanied by significant decomposition of the PEG support, determined by the appearance of multiple methylene signals outside the methylene envelope (δ_H 3.2–3.8) of the PEG polymer, reducing the yield of reagent to < 70%. No attempt was made to further characterize the PEG decomposition products, rather in a second approach, the substituted triarylphosphine derivative was synthesized separately from the polymer and incorporated in the final step (Scheme 1). Benzyloxycarbonyl (Z) protected *p*-bromophenethylamine **2** was reacted with potassium diphenylphosphide in degassed THF under reflux for 8 h. After silica gel chromatography, the triarylphosphine derivative **3** was obtained in 85% yield. Following a quantitative deprotection of the Z group of **3** by catalytic hydrogenation (Pd–C), amine **4** reacted smoothly with the bis-*p*-nitrophenyl carbonate of PEG_{3400} (Shearwater Polymers Inc.) in degassed CH_2Cl_2 at room temp. for 2 h. Repeated precipitation of the reaction mixture from diethyl ether gave the PEG–phosphine reagent **1** in 90% yield, with no accompanying decomposition of the polymer. The oxidation state and purity of the phosphine reagent were confirmed by ^{31}P NMR spectroscopy (δ_P $CDCl_3$ −5.8) with no detectable arylphosphine oxide (δ_P $CDCl_3$ 28.4) being formed during the conjugation reaction. Polymer loading, measured by both ^1H NMR spectroscopy and by following the formation of *p*-nitrophenol during the course of reaction, was excellent (> 95%, 0.5 mmol of phosphine per gram of polymer).

One of the many chemoselective procedures available for the reduction of azides is the Staudinger reaction.[15] A recent report has shown that PPh_3 linked to polystyrene beads can perform the Staudinger reaction for a number of azides.[13] However, no precedence exists for a soluble polymer supported approach for this reaction. By using the soluble support **1** a range of alkyl and aryl azides were smoothly converted into their respective amines at room temperature. The reaction times were all faster than with an insoluble PPh_3 reagent and in one case no reduction was observed with the polystyrene-supported phosphine highlighting the improved utility of this liquid-phase methodology (Table 1).

The Mitsunobu[16] reaction is a commonly used procedure, with wide-ranging application throughout organic chemistry. It



Scheme 1 *Reagents and conditions*: i, $KPPh_2$ (6.0 equiv.), THF, reflux, 24 h; ii, 10% Pd–C, H_2 (30 psi), CH_2Cl_2, room temp. 2 h; iii, PEG_{3400}–PNP_2, 2 h CH_2Cl_2, room temp.

can be complicated by side-product formation with the result that isolation of the products is usually accompanied by chromatography. In an attempt to address such problems for combinatorial library synthesis, an insoluble polymer-supported approach to Mitsunobu ether formation has been reported.[17] However, in this example, the alcohol substrate was linked to the support and the reagent, PPh_3, was in solution, so the reaction was still heterogeneous in nature.

By utilising our liquid-phase approach, reaction of PEG–phosphine **1** with phenol and each of the alcohols outlined in Table 2, in the presence of diethylazodicarboxylate (DEAD), gave etherification under ambient conditions. Precipitation of the oxidized PEG–phosphine conjugate **1** from diethyl ether allowed isolation of the product, aryl alkyl ethers, in analytically pure form, without the need for silica gel chromatography. As found for the preceding Staudinger reduction, reaction times were shorter with the soluble reagent than for the heterogeneous reaction. In addition benzyl alcohol gave no ether product when treated with the solid phase reagent.

In summary, we have shown that a soluble PEG–phosphine reagent can be readily prepared and utilised in the liquid-phase Staudinger and Mitsunobu reactions. Product isolation is routine and the reactions are high yielding. The use of this novel liquid-phase reagent in LPOS offers considerable advantages over solution-based methodologies because the side-product is removed by simple filtration after precipitation of the spent reagent, so no chromatography is necessary. Furthermore, an excess of the reagent can be used without subsequent problems during purification. By comparison with the heterogeneous reaction, product yields are equivalent but reaction times are shorter and the reagent proved much more versatile, reacting with all the substrates tested. This work has highlighted a novel soluble polymer-supported reagent approach to LPOS and offers a new addition to polymer-bound phosphorane chemistries. Perhaps one of the most exciting features of this reagent is its generality, with potential application to many other phosphine-based methodologies such as the Wittig olefination and bromination of alcohols. More generally, for most reactions that are accompanied by unwanted side-products, this procedure may offer a routine solution to the problems encountered during product purifications. Finally this soluble polymer-supported reagent methodology should be compatible with high-throughput organic synthesis and automation technology.

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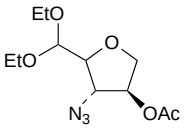
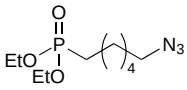
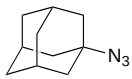
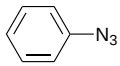
Table 1 Comparative Staudinger reactions using **1** and polystyrene–PPh_3 with azides

	1		Polystyrene–PPh_3	
Azide	Yield (%)	*t*/h[a,b]	Yield (%)	*t*/h[b,c]
	95	2	–	No reaction
	98	1.5	82	8
	91	4.5	95	11
	90	3	94	3.5

[a] In a typical reaction the azide (1 mmol) and PEG_{3400}–PPh_3 conjugate (1.1 mmol) were dissolved in CH_2Cl_2 (5 ml), water was then added (1.1 equiv.) and the reaction mixture was stirred at room temp. On completion, the reaction mixture was concentrated to half its volume and poured onto cold diethyl ether. The spent PEG reagent was filtered under aspirator pressure using a frit and the mother liquor was evaporated to dryness to give the amines in analytically pure form. [b] The reaction was considered complete when no starting azide was detected by TLC. [c] In a typical reaction the conditions were the same as above with the exception that **1** was replaced by a polystyrene–PPh_3 resin (1.1 mmol) (Aldrich Chem. Co.). The work-up involved filtration of the resin followed by evaporation of the filtrate.

Table 2 Alkyl aryl ethers prepared[a] with either **1** or polystyrene–PPh_3

	1		Polystyrene–PPh_3	
Alcohol	Yield (%)	*t*/h[b]	Yield (%)	*t*/h[c]
Butan-1-ol	85	3	87	8
Isopropanol	88	5	94	7
Allyl alcohol	87	2	82	5
Benzyl alcohol	75	10	—	No reaction

[a] In a typical reaction, phenol (1 mmol) was added to **1** or polystyrene–PPh_3 (1.5 mmol) in CH_2Cl_2 (3 ml) and stirred for 20 min. Then the listed alcohol (1 mmol) and DEAD (1.1 mmol) were added and the reaction stirred at room temp. [b] On completion, the reaction mixture was concentrated to half volume and the urea side-product filtered. The reaction mixture was then poured onto diethyl ether. The used PEG reagent was filtered and the mother liquor concentrated to give the pure ether products. [c] The workup procedure involved filtration of the resin and concentration to allow removal of the hydrazine side-product. The pure ether products were isolated by evaporation of the CH_2Cl_2.

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