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Synthesis of a Triphenylphosphine Reagent on Non-Cross-Linked Polystyrene Support: Application to the Staudinger/Aza-Wittig Reaction

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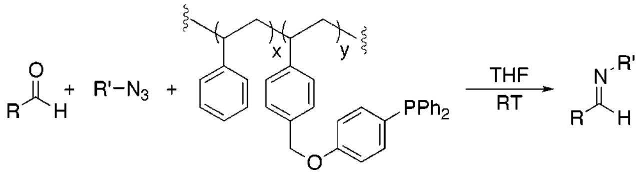
ABSTRACT



A new triphenylphosphine reagent linked to a linear polystyrene was synthesized. The reactivity of this phosphine-bound polymer is superior to that of the phosphine bound to cross-linked polystyrene. The polymer reacted very rapidly with azides to generate iminophosphoranes which could then react with aldehydes to generate imines in good yields and high purities.

Triphenylphosphine is one of the most widely used phosphorus-containing reagents in organic synthesis for many types of transformations such as the Mitsunobu,[1] the Wittig,[2] and the Staudinger[3] reaction. However, the triphenylphosphine oxide that is usually generated as a byproduct in all these reactions is very difficult to separate from the desired reaction product. Typically, flash chromatography or precipitation of the phosphine oxide by the addition of hexane has been used successfully to remove it. However, these purification techniques require that the desired product is also soluble in hexane or stable to chromatography. Our interest in the development of new synthetic methods for the stereoselective nucleophilic additions to C=N led us to study the reactivity of imines of general structure "$YCH_2N=CHR$" in which $Y = RO, R_2N$, etc. These imines, which were prepared by the Staudinger reaction,[4,5] are quite sensitive and some of them do not survive purification attempts by chromatography on silica gel. It became obvious that a method which would allow us to remove triphenylphosphine oxide would be quite useful. One possible solution is to use a triphenylphosphine polymer-bound reagent. Ford[6] has synthesized a triphenylphosphine-bound insoluble cross-linked polystyrene, but this polymer usually requires an excess of one of the reagents. A possible solution would be to use Janda's PEG-bound reagent,[7] but the loading in this case is quite low and the solubility and structural properties were not adequate for our applications.[8] In this Letter, we report the synthesis of a triphenylphosphine-bound non-cross-linked polystyrene soluble support.[9] This polymer should have a reasonably high loading and it should allow stoichiometric reactions to take place between azides and aldehydes.[10] Finally, the removal of the phosphine oxide byproduct should

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[1] Mitsunobu, O. *Synthesis* **1981**, 1−28.
[2] Maryanoff, R. *Chem. Rev.* **1989**, *89*, 863−927.
[3] (a) Staudinger, H. *Helv. Chim. Acta* **1919**, *2*, 635−646. (b) Gololobov, Y. G.; Zhmurova, I. N.; Nasukhin, L. F. *Tetrahedron* **1981**, *37*, 437−472.
[4] Scriven, E. F. V.; Thurbull, K. *Chem. Rev.* **1988**, *88*, 297−368.
[5] Johnson, A. W. In *Ylid Chemistry*; Blomquist, A. T., Ed.; Academic Press: New York and London, 1966; Vol. 7, pp 222−236.
[6] Bernard, M.; Ford, W. T. *J. Org. Chem.* **1983**, *48*, 326−332.
[7] (a) Wentworth, P., Jr.; Vandersteen, A. M.; Janda, K. D. *Chem. Commun.* **1997**, 759−760. (b) Sieber, F.; Wentworth, P., Jr.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188−5192.
[8] The maximum loading of Janda's PPh_3-bound PEG is 0.5 mmol/g.
[9] For recent examples of non-cross-linked polystyrene-supported reagents, see: (a) Enholm, E. J.; Gallagher, M. E.; Moran, K. M.; Lombardi, J. S.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 689−691. (b) Enholm, E. J.; Schulte, J. P. *Org. Lett.* **1999**, *1*, 1275−1277.
[10] Reactions involving polymer-supported reagents often require a significant excess of the reagent.

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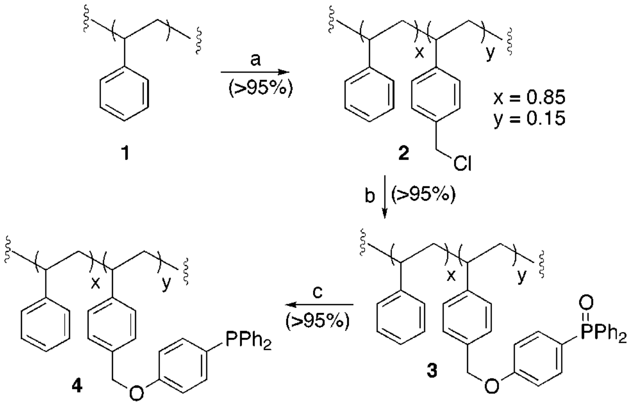
be accomplished by a simple precipitation/filtration or extraction procedure.

The polymer was synthesized in three steps from non-cross-linked polystyrene (**1**) ($M_w = 230\,000$, $M_n = 140\,000$) (Scheme 1).[11] Tin chloride-mediated chloromethylation of polystyrene[12] followed by nucleophilic displacement with the cesium phenoxide derived from *p*-hydroxyphenyldiphenylphosphine oxide[13] gave the phosphine oxide **3**. A subsequent reduction of the phosphine oxide with trichlorosilane and *N*,*N*-dimethylaniline at 100 °C led to the phosphine **4** in quantitative yield. The purity of each compound was checked by ^{1}H and ^{31}P NMR, and the final polymer contained less than 5% of the oxide and can be stored for many months on the benchtop at room temperature in a closed bottle. This polymer is highly soluble in DMF, DMSO, THF, *p*-dioxane, PhH, PhMe, CH_2Cl_2, $CHCl_3$, and CCl_4. It is insoluble in Et_2O, MeOH, EtOH, and H_2O.

Scheme 1[a]



[a] (a) MOMCl, $SnCl_4$(cat.), CCl_4; (b) *p*-hydroxyphenyldiphenylphosphine oxide, Cs_2CO_3, DMF, 60 °C; (c) $HSiCl_3$, *N*,*N*-dimethylaniline, *p*-dioxane, 100 °C.

It is important to note that the final loading of the polymer is approximately 1 mmol/g as calculated by ^{1}H NMR. Although we could easily increase the loading to 3 mmol/g, this was not suitable since the solubility and mechanical properties of the phosphine oxide polymer **3** became quite different from those of **4**.

To evaluate the reactivity of the phosphine-bound polymer **4**, the Staudinger/aza-Wittg process was monitored by ^{31}P NMR (Figure 1). A rapid and quantitative conversion to the polymer-supported iminophosphorane was observed within 30 min when 1.0 equiv of the phosphine-bound polystyrene was mixed with 1.1 equiv of the azide at room temperature in C_6D_6. The imine formation took place quantitatively within 24 h when 1.1 equiv of the aldehyde was added to the iminophosphorane. The rates of both reactions are comparable to those observed when triphenylphosphine is used as the reagent, indicating that the reactivity of the reagent-bound polymer is comparable to that of free triphenylphosphine.

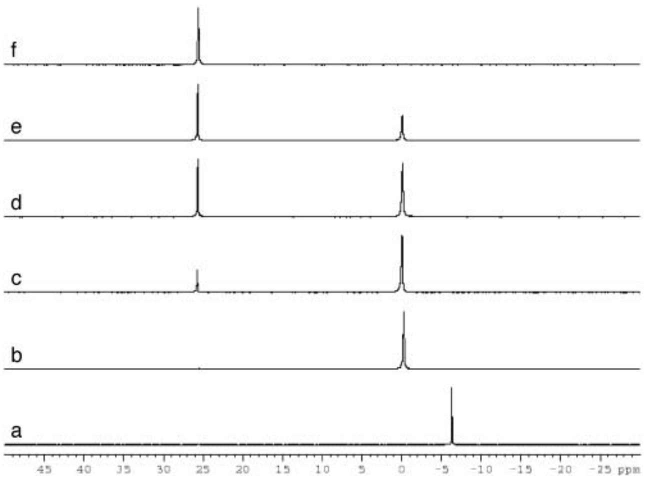


Figure 1. Monitoring of the imine formation process by ^{31}P NMR: (a) polymer **4**; (b) polymer **4** (1.0 equiv) + BnN_3 (1.1 equiv), C_6D_6, rt, 30 min; (c) polymer **4** (1.0 equiv) + BnN_3 (1.1 equiv) + PhCHO (1.1 equiv), C_6D_6, rt, after 2 h; (d) after 9 h; (e) after 18 h; (f) after 24 h.

A preparative-scale procedure involves adding a solution of the azide to a mixture of the aldehyde and of the soluble polymer in THF. Nitrogen evolution is quite rapid, and the reactions are generally completed within 24 h (Table 1).

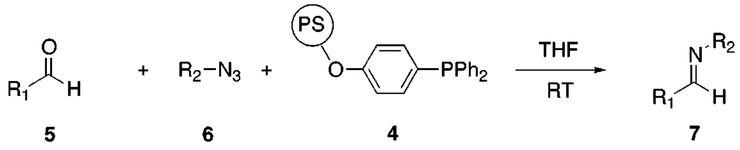
Isolation of the imine was accomplished according to two procedures. Optimal recovery generally requires concentration of the reaction mixture under reduced pressure. The

Table 1. Staudinger/Aza-Wittig Reaction with Phosphine Polymer **4**[a]

entry	R_1	R_2	yield, %[b]	entry	R_1	R_2	yield, %[b]
1	phenyl (**5a**)	benzyl (**6a**)	89 (**7a**)	9	3-pyridyl	phenethyl	100 (**7i**)
2		phenethyl (**6b**)	96 (**7b**)	10		(**6c**)	92 (**7j**)
3		(**6c**)	97 (**7c**)	11		phenyl (**6e**)	66 (**7k**)
4		*p*-anisyl (**6d**)	75 (**7d**)	12		*p*-anisyl	100 (**7l**)
5	cyclohexyl (**5b**)	benzyl	90 (**7e**)	13	cinnamyl (**5d**)	benzyl	99 (**7m**)
6		phenetyl	98 (**7f**)	14		phenethyl	96 (**7n**)
7		*p*-anisyl	76 (**7g**)	15		phenyl	75 (**7o**)
8	3-pyridyl (**5c**)	benzyl	94 (**7h**)	16		*p*-anisyl	98 (**7p**)

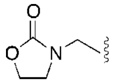
[a] The conversions were >95% in all cases. [b] Isolated yields of analytically pure imines (^{1}H and ^{13}C NMR).

Scheme 2

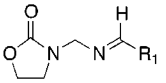


polymeric phosphine oxide crashes upon addition of MeOH. Quantitative extraction of the imine generally requires that the mixture is heated under reflux for a few hours. Alternatively, in cases where the imine is only slightly soluble in MeOH, quantitative imine recovery generally requires extraction of the solid polymeric material in a Soxhlet with MeOH. The phosphine-bound polymer can be quantitatively recovered by reducing the phosphine oxide with trichlorosilane and *N*,*N*-dimethylaniline.

The scope of the reaction is shown in Table 1. The formation of imines by the reaction of the corresponding azides and aldehydes proceeded smoothly with alkyl- and aryl-substituted aldehydes and azides. Analysis by crude NMR indicated that all the conversions were >95%. The efficiency of the isolation depended upon the nature of the substrate and on the stability of the imine in CH_3OH. For example, imines **7d**, **7g**, **7k**, and **7o** were significantly less stable than the others, and the lower isolated yields in these cases are a reflection of partial hydrolysis (Scheme 2). Finally, the imine formation of the more sensitive azide **6c** proceeded smoothly to yield **7c** and **7j** in high yields.



6c



R_1 = Ph (**7c**)
R_1 = 3-pyridyl (**7j**)

The reaction rate of the Staudinger/aza-Wittig reaction using the soluble polymer was compared to that observed with triphenylphosphine and its cross-linked version (Figure 2). The data show that the reactivity of the soluble polymer by far superior to that of the insoluble polymer. It is even superior to that observed with triphenylphosphine.[14]

In conclusion, we have obtained a variety of imines by the Staudinger/aza-Wittig reaction with a new soluble triphenylphosphine polymer with excellent yields and conversions higher than 95%. Furthermore, the loading of the polymer is about 1 mmol/g, which is superior to that found in PEG-supported triphenylphosphine. This version should be especially useful when the imine is soluble in MeOH but not in hexane. We are currently testing this polymer in other phosphine-mediated processes, and results will be reported in due course.

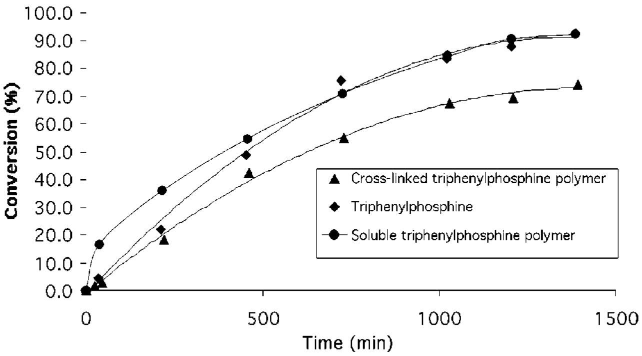


Figure 2. Relative reaction rates of the imine formation using various phosphine reagents.

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Supporting Information Available: General procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] The polystyrene prepared by copolymerization of styrene and 4-vinylbenzyl chloride gave a lower molecular weight polymer that was not as easily manipulated: Kondo, S.; Ohtsuka, T.; Ogura, K.; Tsuda, K. *J. Macromol. Sci.-Chem.* **1979**, *A13*, 767−775.

[12] Green, B.; Garson, L. R. *J. Chem. Soc. C* **1969**, 401−406.

[13] Senear, A. E.; Valient, W.; Wirth, J. *J. Org. Chem.* **1960**, *25*, 2001−2006.

[14] The faster reaction observed with the soluble triphenylphosphine polymer in comparison to triphenylphosphine may be a consequence of the more electron rich phosphine (*p*-RO substituent of the linker).