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Polymer-supported triphenylphosphine ditriflate: a novel dehydrating reagent ☆

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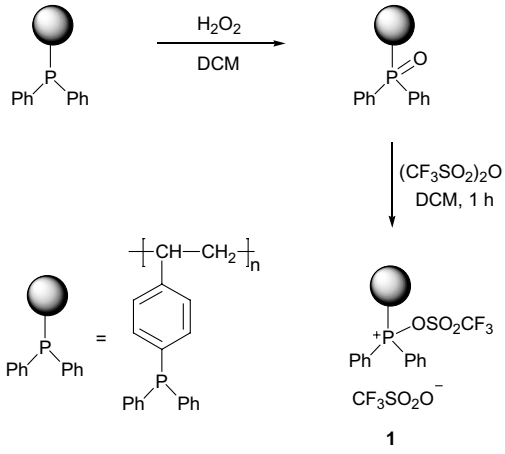
Abstract—A new type of polymeric dehydrating reagent, readily prepared by the treatment of polymer-supported triphenylphosphine oxide with triflic anhydride, was found to be effective in a variety of dehydration reactions such as ester and amide formation; the polymer-supported triphenylphosphine oxide was easily recovered and reused several times without the loss of activity.

With the advent of combinatorial chemistry and multiple parallel synthesis in drug discovery, there has been increased interest in new synthetic methods, which afford clean products without time consuming work-up and purification procedures.[1] As part of an ongoing study of the Hendrickson reagent and the Mitsunobu reaction,[2] we have found that polymer-supported triphenylphosphine ditriflate **1** is a useful new reagent for a range of dehydration reactions such as anhydride, ester, ether, amide and peptide formation.

Polymer-supported triphenylphosphine ditriflate **1** was prepared by treatment of polymer-supported triphenylphosphine oxide[3] in dichloromethane (DCM) with triflic anhydride (Scheme 1). The structure of **1** was supported by gelphase ^{31}P NMR (δ 53.3 ppm).

Polymer-supported triphenylphosphine ditriflate **1** was subsequently used in a series of dehydration reactions to demonstrate its versatility. To avoid side reactions by triflic anhydride, a small excess of the polymer-supported triphenylphosphine oxide was employed in all cases. Initially, the reaction conditions were optimised for the formation of the ester, 4-nitrobenzyl 4-nitrobenzoate. Treatment of **1** with 4-nitrobenzyl alcohol,



Scheme 1.

4-nitrobenzoic acid and diisopropylethylamine for 2 h at room temperature afforded 4-nitrobenzyl 4-nitrobenzoate in high yield (95%) (Table 1). The product was obtained cleanly following filtration and washing of the filtrate with sodium hydrogen carbonate to remove the diisopropylethylammonium triflate. In a similar fashion, 4-toluic anhydride was formed in high yield (95%), from the reaction of 2 equiv of 4-toluic acid with **1** and diisopropylethylamine in DCM. 4-Chlorobenzyl thioacetate was obtained in high yield (91%) by treatment of a mixture of **1** and 4-chlorobenzyl alcohol in DCM with thiolacetic acid and diisopropylethylamine. Amide formation via **1** was also investigated. In contrast to ester synthesis, the polymer-supported acyloxyphosphonium

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Table 1. Examples of useful synthetic transformations using polymer-supported triphenylphosphine ditriflate **1**

Entry[a,b]	Substrate	Nucleophile	Product	Yield (%) (mp °C)	Lit. mp (°C)[ref]
1	4-NO_2–C_6H_4–CH_2–OH	4-NO_2–C_6H_4–COOH	4-Nitrobenzyl 4-nitrobenzoate	95 (165–167)	168[6]
2	4-CH_3–C_6H_4–COOH	4-CH_3–C_6H_4–COOH	4-Toluic anhydride	95 (87–89)	93[7]
3	4-Cl–C_6H_4–CH_2–OH	CH_3–C(O)–SH	4-Chlorobenzyl thioacetate	91 (oil)	—[2]
4	4-NO_2–C_6H_4–COOH	C_6H_5–CH_2–NH_2	*N*-Benzyl 4-nitrobenzamide	96 (140–143)	141.5–143[8]
5[c]	Z-Gly-Phe-OH	H-Val-OMe·HCl	L,L-Z-Gly-Phe-Val-OMe	65 (95–97)	98[5]
6	4-NO_2–C_6H_4–CH_2–OH	4-MeO–C_6H_4–OH	*O*-(4-Nitrobenzyl)-4-methoxyphenol	88 (88–90)	88[9]
7	*meso*-$C_6H_5CH(OH)CH(OH)C_6H_5$	—	(*E*)-Stilbene oxide	85 (64–66)	65–67[10]
8	4-Cl–C_6H_4–CH_2–OH	NaN_3[d]	4-Chlorobenzyl azide	89 (oil)	—[2]
9	C_6H_5–C(O)–NH_2	—	Benzonitrile	88 (oil)	—
10	Cyclohexanol	4-NO_2–C_6H_4–COOH[e]	Cyclohexyl 4-nitrobenzoate	85 (49–51)	47–48[11]

[a] Reaction conditions: polymer-supported triphenylphosphine oxide (1.35 equiv), triflic anhydride (1.0 equiv), substrate (1.0 equiv), nucleophile (1.0 equiv), diisopropylethylamine (3.5 equiv), DCM (10 mL).
[b] Reaction times: entries 1, 4 (2 h, rt); entries 2, 3, 5–8, 10 (overnight, rt); entry 9 (overnight, reflux).
[c] Excess of diisopropylethylamine (5.5 equiv) used.
[d] Added as a suspension in DMF.
[e] Active ester generated using DMAP (1.0 equiv).

salt was preformed by addition of 4-nitrobenzoic acid to **1** in DCM. This order of addition ensured that the primary amine did not react competitively with **1** to form the (unreactive) polymer-supported aminophosphonium triflate. Subsequent addition of benzylamine and diisopropylethylamine formed *N*-benzyl 4-nitrobenzamide in good yield (96%) after 2 h at room temperature.[4] After recycling the recovered polymer three times, the yield of *N*-benzyl 4-nitrobenzamide dropped from 96% to 92%. The use of **1** for peptide bond formation was also explored. The extent of racemisation was examined using Arteunis' test[5] (the coupling of Z-Gly-Phe-OH and Val-OMe·HCl). Addition of Z-Gly-Phe-OH to a mixture of **1** and diisopropylethylamine in DCM, followed by stirring at room temperature for 2 h formed the activated acid. Subsequent treatment with Val-OMe·HCl (in the presence of the racemisation-suppressing agent 1-hydroxybenzotriazole, HOBT) formed the desired tripeptide Z-Gly-Phe-Val-OMe after stirring at room temperature overnight as a single epimer (L,L) (none of the D,L-epimer was observed by ^{1}H NMR) in reasonable (65%) yield. Racemisation occurred in the absence of HOBT. Ether formation using **1** was examined. Addition of 4-methoxyphenol and diisopropylethylamine to a mixture of 4-nitrobenzyl alcohol and **1** gave *O*-(4-nitrobenzyl)-4-methoxyphenol in high yield (88%). In other examples, (*E*)-stilbene oxide was synthesised in good yield (85%) from **1**, *meso*-hydrobenzoin and diisopropylethylamine. Treatment of a solution of **1** and 4-chlorobenzyl alcohol with a suspension of sodium azide in dimethylformamide (DMF) and diisopropylethylamine gave 4-chlorobenzyl azide in high yield (89%). Benzonitrile was generated in good yield (88%) by refluxing **1** with benzamide and diisopropylethylamine overnight. Finally, the esterification of a secondary alcohol with **1** was investigated. Conversion of cyclohexanol to its corresponding 4-nitrobenzoate ester was achieved in good yield with **1** but only in the presence of an activating agent such as 4-dimethylaminopyridine (DMAP) or HOBT.

In conclusion, the polymer-supported triphenylphosphine oxide was obtained by oxidation of the corresponding commercially available phosphine with hydrogen peroxide. The novel dehydrating reagent, polymer-supported triphenylphosphine ditriflate **1**, was prepared by subsequent addition of triflic anhydride. The potential of **1** as a general dehydrating reagent/activating agent was displayed by the synthesis of esters from primary and secondary alcohols, an anhydride, thioacetate, amide, tripeptide, ether, epoxide, azide and nitrile. The beauty of the polymer-supported triphenylphosphine ditriflate **1** lies in the fact that the main by-product, the phosphine oxide, remains attached to the polymer-support. All products can be obtained cleanly following filtration of the polymer beads and a sodium hydrogen carbonate wash of the filtrate to remove the diisopropylethylammonium triflate. An additional advantage of this polymeric reagent **1** is that after reaction, the polymer is again obtained as its oxide, ready for reconversion to **1**. The recovered polymer could be recycled at least three times without loss of efficiency. Thus, **1** is an effective dehydrating reagent, which avoids the use of azodicarboxylates and chromatography to remove the phosphine oxide. Further investigations to examine the scope and limitations of this reagent are currently in progress.

Supplementary material

A ^{31}P gelphase NMR spectrum of polymer-supported triphenylphosphine ditriflate **1** is available.

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3. Prepared by oxidation of commerically available polymer-supported triphenylphosphine (purchased from Aldrich with a loading of 3 mmol/g on polystyrene cross-linked with 2% divinylbenzene): Polymer-supported triphenylphosphine (2 g, 9 mmol) was placed in DCM (50 mL). Hydrogen peroxide (20 mL, 30% wt solution in water) was added and the slurry left to stir overnight. The resulting yellow beads were collected by filtration, washed with DCM (60 mL) and dried under high vacuum. ^{31}P NMR (162 MHz, $CDCl_3$, gelphase) δ 30.0 (br s).
4. Representative experimental procedure for the synthesis of *N*-benzyl 4-nitrobenzamide: Before use, the polymer-supported triphenylphosphine oxide was washed by stirring with each of the following solutions for 40 min: 1 M NaOH 60 °C, 1 M HCl 60 °C, 1 M NaOH 60 °C, 1 M HCl 60 °C, H_2O 25 °C, DMF 40 °C, 1 M HCl 60 °C, H_2O 60 °C, MeOH 25 °C, DCM–MeOH (2:3) 25 °C, DCM–MeOH (3:1) 25 °C, DCM–MeOH (9:1) 25 °C, DCM 25 °C. The resin beads were then dried at 125 °C for 48 h at 100 mmHg (house vacuum) on a Kugelrohr apparatus. Polymer-supported triphenylphosphine oxide (0.3 g, 0.9 mmol, 3 mmol/g) was stirred gently under nitrogen in dry DCM (10 mL) for 30 min. Addition of freshly distilled triflic anhydride (0.12 mL, 0.66 mmol) generated a dark brown slurry, which was left to stir for 1 h. 4-Nitrobenzoic acid (0.11 g, 0.66 mmol) was added and the solution stirred at room temperature for 2 h. Consecutive addition of benzylamine (72 μL, 0.66 mmol) and diisopropylethylamine (0.4 mL, 2.3 mmol) produced a light brown slurry, which was stirred at room temperature for 2 h. The polymer beads were collected on a filter and washed with DCM (60 mL). The yellow filtrate was washed with sodium hydrogen carbonate (5% aqueous solution, 3×50 mL) and the combined DCM layers dried (anhydrous $MgSO_4$) and concentrated in vacuo. The resulting yellow oil was dried under high vacuum to yield *N*-benzyl-4-nitrobenzamide as a light yellow solid (0.16 g, 96%). Mp 140–143 °C (lit.,[8] 141.5–143 °C).
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