Polymer-anchored Organosilyl Protecting Group in Organic Synthesis

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Polymer-anchored dimethyl- and diphenyl-chlorosilanes (**1a**) and (**1b**) have been prepared and polymer (**1b**) was found to be useful for the protection of the hydroxy functional group; its use in the synthesis of an insect sex pheromone is reported.

Since their introduction in the early seventies, the organosilyl protecting groups[1—3] have become the most widely used protecting group in organic synthesis. This is due to the relative ease by which a functional group can be silylated, their compatibility with many organic transformations, their non-interference with other protecting groups, and finally, the ease and the specificity by which the silyl group can be removed with fluoride ion. We report here the use of a polymer-anchored silyl protecting group in synthesis, in the expectation of combining the aforementioned advantages with the potential of solid-phase synthesis.[4]

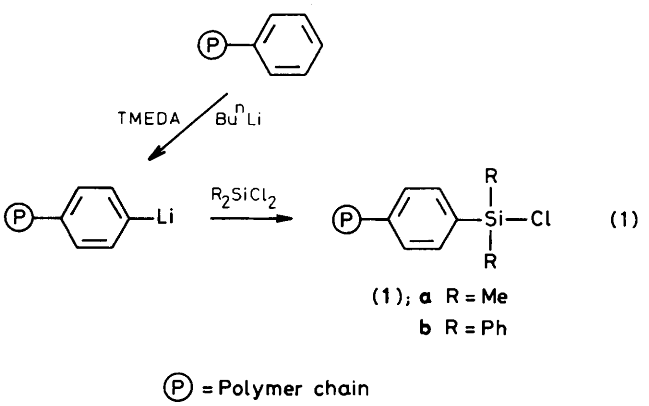
Styrene–divinylbenzene copolymer (1% cross-linking) was directly lithiated at 65 °C with the complex of n-butyl-lithium and tetramethylethylenediamine (TMEDA) (1:1) in cyclohexane.[5] Dimethyl- or diphenyl-dichlorosilane in benzene was added to the lithiated resin (equation 1). The mixture was stirred for 3 h and washed with benzene. The polymer (**1**) was dried *in vacuo* and stored for use.[6] The active silyl chloride content of the polymer (**1b**) was determined by hydrolysis followed by acid–base titration to be between 1.10—1.65 mmol/g resin. The i.r. spectrum of the polymer showed absorption bands at 1250 and 835 cm^{-1} (SiMe) for (**1a**) and at 1430 and 1108 cm^{-1} (SiAr) for (**1b**).

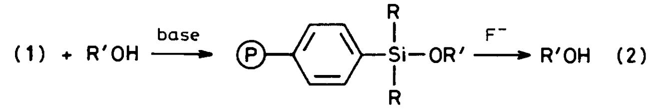
The ability of (**1**) to silylate alcohols (equation 2) has been

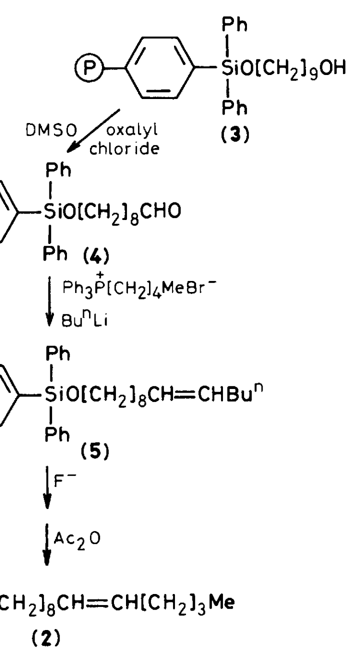
Table 1. Silylation of octan-1-ol with polymer (**1a**) or (**1b**).[a]

Entry	Polymer	Amine	Polymer-bound alcohol[b] mmol/g
1	(**1a**)	$\mathrm{Pr^i{}_2NEt}$	0.58
2	(**1b**)	$\mathrm{Pr^i{}_2NEt}$	1.19
3	(**1b**)	Pyridine	0.73
4	(**1b**)[c]	$\mathrm{Pr^i{}_2NEt}$	1.20
5	(**1b**)[d]	$\mathrm{Pr^i{}_2NEt}$	0.53

[a] Excess alcohol with polymer and amine in CH_2Cl_2 at room temperature for 48 h. [b] Determined by cleavage with $\mathrm{Bu^n{}_4NF}$. [c] Polymer (**1b**) had been stored for 33 days.[d] Polymer (**1b**) had been stored for 191 days.







Scheme 1

evaluated under a variety of conditions.† It is clear from Table 1 that (**1b**) is more effective as a silylating agent than (**1a**).‡ With the same batch of polymer (**1b**), di-isopropylethylamine is better than pyridine in promoting silylation. Storage of polymer (**1b**) in the dry form, up to a period of one month, has no deleterious effect (compare entries 2, 4, and 5). Polymer (**1b**) is thus reasonably stable in air.

Polymer (**1b**) preferentially silylates sterically less hindered alcohols. This can be demonstrated by the following experiment. To polymer (**1b**) (1 g) in pyridine (10 ml) was added a 1 : 1 mixture of octan-1-ol and octan-2-ol (total 8 mmol) which was stirred for 48 h at room temperature. After filtration and washing with diethyl ether, the polymer was treated with tetrabutylammonium fluoride (2 mmol) (TBAF) in methylene chloride (15 ml) for 5 h followed by treatment with water. The alcohol recovered (0.96 mmol) was found to be a mixture of 90% octan-1-ol and 10% octan-2-ol. Since alcohols can be silylated easily by polymer (**1b**) and the recovery is easy, the overall process may provide a way of separating and purifying mixtures of compounds of biological interest.[7] For example, to polymer (**1b**) (1 g) was added a 1 : 1 mixture (total 4 mmol) a 3β-cholestanol and testosterone in CH_2Cl (20 ml) and di-isopropylethylamine (2 ml). The slurry was stirred at 55 °C for 16 h. The polymer was filtered and washed with diethyl ether in a Soxhlet extractor and dried *in vacuo*. The dried polymer (1 g) was treated with TBAF as above. The organic residue recovered was found by t.l.c. and ^1H n.m.r. spectroscopy to be 3β-cholestanol (0.16 mmol) with no detectable amount of testosterone.

The use of polymer (**1b**) in synthesis can be illustrated by the following example. Fall army worm moth sex pheromone,[8] (**2**), was synthesized according to Scheme 1. Polymer (**1b**) was treated in pyridine with excess nonane-1,9-diol (10 equiv.) at ambient temperature for 40 h to give (**3**) (0.72 mmol alcohol/g resin). The polymer (**3**) (1 g) was oxidized with Swern reagent [dimethyl sulphoxide (DMSO) + oxalyl chloride][9] to give polymer-bound aldehyde (**4**) (i.r. 1726 cm^{-1}). Reaction of (**4**) with pentyltriphenylphosphonium bromide (2 mmol) and butyl-lithium in tetrahydrofuran (THF) yielded polymer (**5**). Treatment of polymer (**5**) with TBAF (2 mmol/g resin) in CH_2Cl_2 followed by purification with flash column chromatography (eluent: light petroleum–ethyl acetate 3 : 7) gave 0.30 mmol of nonane-1,9-diol [presumably from 'double-binding' of diol[10] on (**1b**)] and 0.36 mmol of tetradec-9-en-1-ol per g resin. The latter was acetylated to give 0.31 mmol of tetradec-9-en-1-yl acetate (**2**), which had the diastereoisomeric ratio of $E : Z = 12 : 88$. The overall yield from (**3**) to (**2**) was 43% (or 74% based on reacted diol). Of interest is the oxidation step [(**3**) to (**4**)] in which the Swern reagent was found to be superior than di-t-butyl chromate.[10] Using a similar approach, the sex pheromone of *Archips saniferamus* (Walker), tetradec-10-en-1-yl acetate, was synthesized. It is clear that polymer-anchored diphenylchlorosilane (**1b**) can be a useful protecting group in organic synthesis.

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† To (**1b**) (1.0 g) in methylene chloride (20 ml) was added octan-1-ol (1.3 g, 10 mmol) and di-isopropylethylamine (1.7 ml, 10 mmol). The mixture was stirred under a nitrogen atmosphere at ambient temperature for 24 h. The polymer was filtered and continuously washed with diethyl ether in a Soxhlet extractor for 4 h. Silylated polymer was dried at 60—70 °C under reduced pressure.

‡ A similar observation on the greater effectiveness of polymer (**1b**) over (**1a**) was found on the silylation of alkane-1, *n*-diols (*n* = 6, 8, and 10).

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