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A practical process for polymer-supported synthesis

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Abstract

Various complex structures can be attached to a polystyrene oligomer using the simple but powerful xanthate transfer technology; the material obtained is soluble in many of the common organic solvents allowing further reactions under homogeneous conditions, but can be precipitated with methanol making this technique especially suitable for conducting parallel syntheses.

Keywords: xanthates; radicals; supported reactions; oligomers.

The construction of libraries of compounds using combinatorial and parallel synthesis has witnessed dramatic development in recent years.[1] The need for fast delivery of large numbers of diverse molecules for high-throughput screening assays has triggered a huge effort in industry and academia aimed at designing and adapting reactions for solid-supported synthesis. Insoluble polymers of all kinds have thus been examined as possible supports, building on the early pioneering work of Merrifield.[1] However, working with a substrate fixed on an insoluble support has several drawbacks: (i) generally slower kinetics and variations in behaviour, which often result in a long developmental phase required to adapt a given reaction to a solid-supported substrate (only a tiny fraction of the reactions in the organic chemist's arsenal can so far be routinely used); (ii) difficulty in following reactions and characterising products still attached to the polymer (sophisticated and custom-designed techniques are often needed); (iii) the attachment of the substrate is itself a non-trivial operation (incomplete use of active sites for example); (iv) mechanical breakdown of the polymeric support upon stirring, heating, etc.; and (v) high cost of the specially modified polymers.

The use of soluble polymers, i.e. polymers which are soluble in one medium but insoluble in another and can therefore be precipitated after each operation, have not yet found widespread use, mainly because of a lack of a suitable support, which allies the desired properties of solubility, flexibility for substrate attachment, and compatibility with various reaction types.[2] So far,

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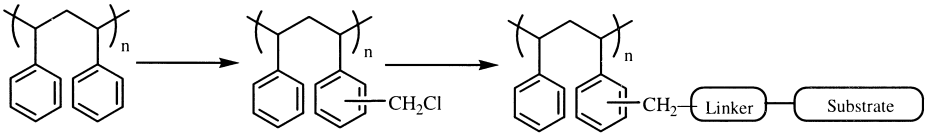
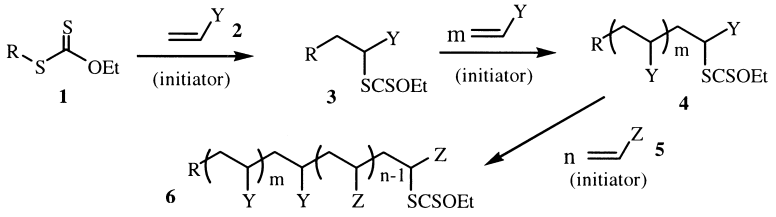
polyethylene glycol (PEG)-based systems appear to be the most promising. In this preliminary communication, we describe an alternative strategy, hinging on a new, powerful polymerisation system, and allowing the custom synthesis of supported substrates (or reagents) in a way not easily feasible hitherto. Our initial efforts have centred on polymerising styrene, but the same approach can be applied in principle to other monomers (or combinations thereof). The use of linear (as opposed to cross-linked) polystyrene has relied in the past on commercial, high molecular weight polymer (average MW 200 000), which has to be functionalised, for example by chloromethylation, as shown in Scheme 1.[2,3] Such randomly functionalised material does not always exhibit the desired solubility profile, and its properties can vary from one batch to another. Moreover, the limited number of reactions for functionalising polystyrene imposes serious constraints on the type of attachments that can be envisaged.



Scheme 1.

Over the past few years, we have examined the radical transfer of a xanthate (and other dithiocarbonate derivatives) as a convenient method for the inter- or intramolecular creation of carbon–carbon bonds.[4] The general scheme is outlined in Scheme 2. Upon heating a mixture of xanthate **1** and olefin **2** in the presence of a small amount of an initiator such as a peroxide, an adduct **3** is formed, whereby the elements of the xanthate have added across the olefinic bond. This adduct is itself a xanthate and can act as a starting point for another addition to an olefin resulting in the ultimate polymerisation of the olefin (or 'monomer') if the olefin is easily polymerisable. Moreover, the resulting polymer **4** is also a xanthate that can act as the starting point of another polymerisation process to give a bloc polymer **6**. Thus, depending on the way the starting materials and reaction conditions are selected, the radical process may be directed towards the formation of either a small monoadduct **3** or a large macromolecular structure such as **4** or **6**.[5]

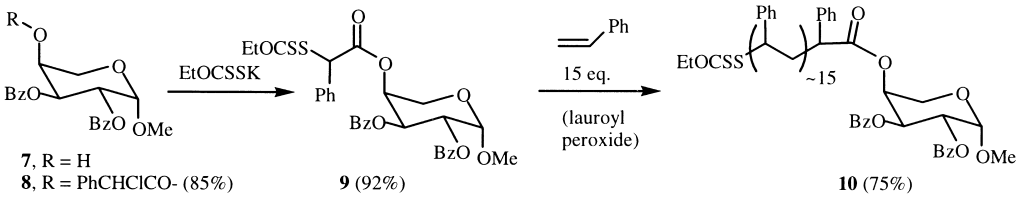


Scheme 2.

This polymerisation system exhibits the characteristics of a controlled living radical polymerisation, namely the obtention of narrow polydispersity and the possibility of constructing block copolymers. The rapid exchange of the xanthate group in comparison to addition to monomer allows the chains to grow throughout the duration of the reaction at a comparable rate, resulting in an averaging of the molecular weights. Whence the narrow polydispersity.

The area of controlled radical polymerisation is growing at a tremendous rate.[6] For the purpose of polymer-supported synthesis, one can envisage incorporating the substrate in the R portion of the xanthate and using this material to accomplish the oligomerisation of styrene (Y = Ph in Scheme 2). The number of styrene units can be varied at will in order to optimise the loading capacity and solubility profile. A ratio of substrate to styrene of 1:15 appears to be a reasonable compromise, leading (at least in the cases we have studied) to an easily handleable, powdery solid that is soluble in many of the common organic solvents but that can be precipitated by methanol. For a substrate of molecular weight of about 300, this gives a loading of approximately 0.5 mmol/g, which is quite respectable.

These considerations are illustrated by the preparation of the polymer-bound protected arabinose **7** (Scheme 3). The preparation of the corresponding xanthate **9** is trivial and involves the formation of the chlorophenylacetate ester **8** of the free hydroxy group, followed by displacement of the halide with commercially available potassium *O*-ethyl xanthate. Heating this compound with 15 equivalents styrene in refluxing toluene for 18 hours in the presence of 12 mol% of lauroyl peroxide, followed by concentration under vacuum and precipitation with methanol gave the corresponding polymeric derivative **10** in 75% yield as a white powder. This material is readily soluble in chloroform and may be further analysed by the usual spectroscopic techniques (we have used IR and NMR, but UV and certain MS techniques are applicable; in the NMR, the wide region between the aromatic and aliphatic hydrogens or carbons of the styrene units remains useful).



Scheme 3.

A similar, smooth polymerisation could be achieved starting with various substrates, using both phenylacetate or propionate derived xanthates. The polymerisation conditions are especially mild, and complex structures with various functional or protecting groups generally encountered in organic synthesis are readily tolerated (Fig. 1). Thus, carbohydrates (maltose derived polymer **11**), cyclitols (polymer **12**), nucleosides (thymine derived polymer **13**), steroids (hecogenin and bile acid derived polymers **14** and **15**) were easily prepared. Other types of substrates, belonging to other families may also, in principle, be attached in the same way: β-lactams, amino acids, and various aromatic, heteroaromatic, and heterocyclic derivatives may be easily manipulated using this new radical chemistry of xanthates.[4,7]

The linking directly through the phenylacetate or propionate group serves to illustrate the technique. These are quite hindered esters, close to the bulky polystyrene residue, but can nevertheless be saponified. For example, the bile acid fragment in derivative **15** could be detached in 75% yield by treatment with KOH in a mixture of methanol and THF. It is also possible to

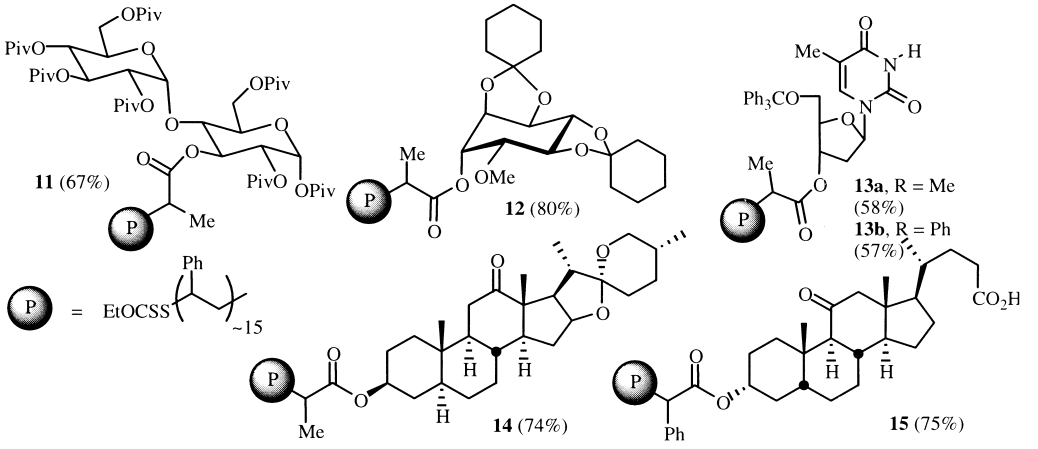
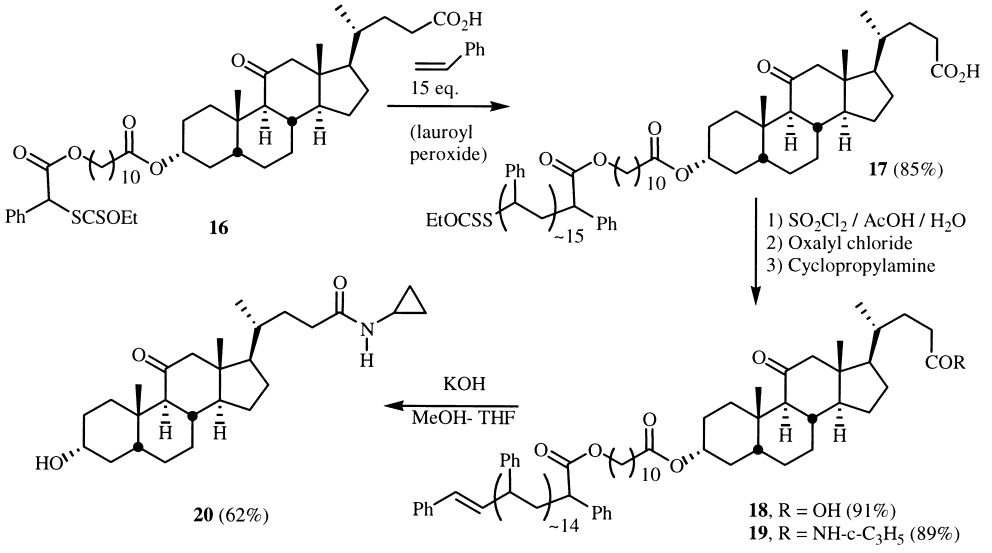


Figure 1.

intercalate a linker separating the polymer units from the actual substrate. This is illustrated by the bile acid derivative **16** (Scheme 4). This compound is easily prepared from 3α-hydroxy-11-oxo-cholanic acid by treatment with 11-(α-bromophenylacetoxy)undecanoyl chloride, followed by displacement of the bromide with potassium *O*-ethyl xanthate in acetone. The usual reaction with 15 equivalents of styrene then provides the polymer bound steroid **17** in 85% yield.



Scheme 4.

The xanthate group at the other terminus of the polymer represents an additional but different site for substrate attachment or for the placement of a label.[1] The xanthate may for instance be cleaved by base or an amine to give a thiol, which may be alkylated by the substrate (or a labelling) molecule. Alternatively, to improve compatibility with subsequent reactions one wishes to use, it may be desirable to remove the xanthate group. Thus, exposure of **17** to sulfuryl

chloride in acetic acid caused the formation of the corresponding benzylic sulfonyl chloride,[8] which underwent elimination of sulfur dioxide and HCl to give **18** in 91% yield. Elemental microanalysis showed the absence of sulfur in the product whereas olefinic hydrogens appeared in the NMR spectrum. Treatment of **18** first with oxalyl chloride in CH_2Cl_2 then with cyclopropylamine furnished *N*-cyclopropylamide **19** (89%), after precipitation with methanol. Free amide **20** was obtained in 62% yield by saponification with KOH in methanol/THF. This sequence illustrates an application of the present approach for polymer-supported synthesis.

In summary, this preliminary work shows that it is possible to attach complex molecules to a polystyrene oligomer, cheaply and in a flexible manner. One molecule of the substrate is linked to one terminus of the linear oligomeric unit. Fairly large amounts of polymer bound material can be obtained rapidly and the properties may be tailored by adjusting the ratio of substrate to styrene (or even another monomer if desired). The polystyrene subunit is reasonably inert to most reaction conditions: it may be viewed as just a bulky protecting group which modifies the solubility properties of the substrate. In the same way, a given reagent (or a ligand for a transition metal catalyst) may in principle be grafted on such an oligomeric backbone. Further studies aimed at exploring and extending the scope of this technology are in progress.

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