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Review

Solid-supported reagents for multi-step organic synthesis: preparation and application☆

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Abstract

Since the early days of combinatorial chemistry solid-phase organic synthesis has been the method of choice for the production of large libraries. Solution-phase synthesis is again gaining importance especially for the synthesis of parallel arrays of smaller, focussed libraries containing single compounds with high degrees of purity. In the field of solution-phase library generation, the use of solid-supported reagents, catalysts and scavengers is emerging as a leading strategy, combining the advantages of both solid-phase organic synthesis (e.g. allowing the employment of an excess of reagent without the need for additional purification steps) and solution-phase chemistry (e.g. the ease of monitoring the progress of the reactions by applying LC-MS, TLC or standard NMR techniques). An account of some of the most recent advances in this area of research will be presented. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Polymer-supported reagents; Review; Scavengers; Solution-phase

1. Introduction

The rapid development of high throughput strategies for the preparation of arrays of low molecular weight organic molecules is a topic of great importance in modern drug discovery programmes. Various methods have been developed in combinatorial chemistry so far which include solid-phase synthesis, solution-phase synthesis, fluorous-phase synthesis and other combinations of the above. Perhaps as a consequence of the original extension of combinatorial chemistry from peptide and oligonucleotide synthesis, the use of solid-phase techniques have been considered for a long time the method of choice for the production of chemical libraries. Among the various advantages that solid-phase synthesis offers are the ability to use excess quantities of reagents to drive reactions to completion and the ease of product isolation by simple filtration and washing of the resins.

Although combinatorial chemistry has its roots in solid-phase synthesis, over the last few years the use of solution-phase methods has received a considerable amount of attention particularly in the area of lead optimisation for the parallel synthesis of small libraries containing single compounds requiring a high degree of purity. Compared to solid-phase, solution-phase synthesis offers many inherent benefits: in principle, the whole repertoire of organic reactions can be employed; reactions can be monitored in real time using conventional techniques (TLC, NMR, LC-MS); no additional steps are required to attach and cleave substrates from the solid support.

In the field of solution-phase library generation, the use of polymer-supported reagents is emerging as a leading strategy that combines the advantages of product isolation and purification of solid-phase chemistry with the benefits of traditional solution-phase reactions [1]. The concept of immobilising reagents on a support material is not new; catalytic hydrogenation and numerous other heterogeneous reactions that occur at the interface of a solid can be classified as examples of supported-reagent systems. It is conceivable that

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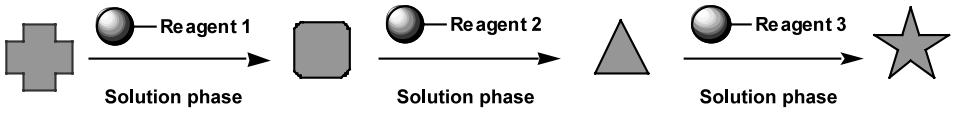


Scheme 1. Multi-step synthesis using polymer-supported reagents.

with the appropriate choice of support a diverse array of reagents could be tethered. Indeed, not only have supported variants of many commonly used reagents been prepared, but also a growing number of scavenging agents capable of sequestering unwanted by-products and excess reactants from solution have also been described [1–6]. In general these reagents are employed in stoichiometric excess to force the reaction to completion. Removal of the spent reagent is achieved by simple filtration thus affording the clean products with no further need for conventional work-up and purification (Scheme 1).

2. Development of supported reagents

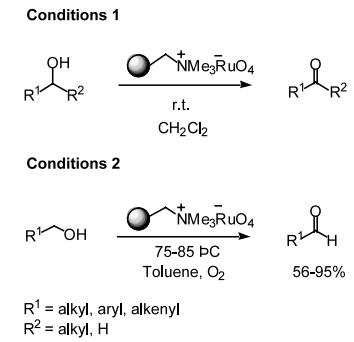
The utility of solid-supported reagents has been proven by application in a large number of diverse and interesting chemical manipulations [1]. The practical advantages and novel synthetic properties of these reagents has created extensive demand for additional chemical entities to supplement the existing chemistry. In order to exemplify the development of these reagents we will describe a number of examples from our laboratories including the versatile polymer-supported perruthenate (PSP) oxidant (PSP), a thionating reagent and a number of hypervalent iodine reagents.

The mild oxidation catalyst tetra-*n*-propylammonium perruthenate (TPAP) has become one of the principal reagents for the conversion of primary and secondary alcohols to their corresponding aldehydes and ketones [7,8]. This reagent posed an ideal candidate for immobilisation onto solid support to enable facile work-up and purification of reactions and provide an opportunity for recycling of the spent reagent. The PSP was easily generated by an ion exchange reaction of a commercially available Amberlyst resin, functionalised as the quaternary ammonium chloride, using an aqueous solution of potassium perruthenate [9–11]. This novel reagent was shown to be effective for the stoichiometric oxidation of alcohols to their corresponding carbonyl compounds at room temperature and in high yields (Scheme 2, conditions 1) [12,13]. A further important development of this process enabled the reaction to proceed catalytically, using atmospheric air or molecular oxygen as the co-oxidant, in toluene at ~ 80 °C (Scheme 2, conditions 2) [14–16].

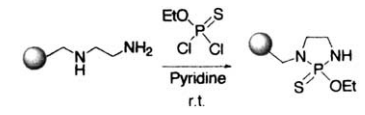
A polymer-supported thionating reagent has also been developed by our group [17,18]. This low odour solid is easily handled and can be dispensed on the open bench. The preparation of the reagent is via a simple one step reaction between a commercially available diamine resin and ethyldichlorothiophosphate in pyridine at ambient temperature (Scheme 3).

The reactions involving this reagent were carried out using both conventional heating conditions and with microwave irradiation. When heated in an oil bath the reactions occurred in excess of 30 h but heating with microwave irradiation dramatically reduces the reaction times to 15 min (Scheme 4). In this way both secondary and tertiary amides were quantitatively converted to the corresponding thioamides in excellent purity. Interestingly, primary amides were shown to undergo spontaneous dehydration to form the analogous nitriles. Investigations are currently underway to extend the application of this reagent to other carbonyl functionalities and the synthesis of heterocyclic systems.

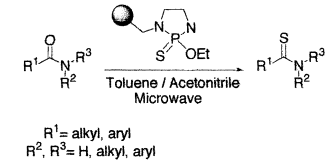
Hypervalent iodine reagents, such as bis(acetoxy)- and bis(trifluroacetoxy)-iodobenze, are a class of extremely versatile oxidising agents. We have prepared



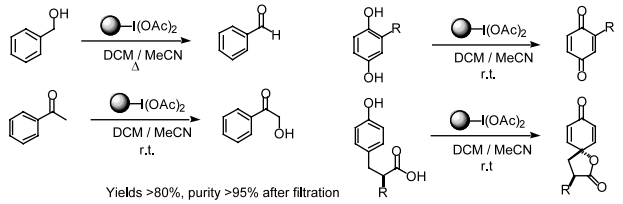
Scheme 2. Oxidation of alcohols using the PSP reagent.



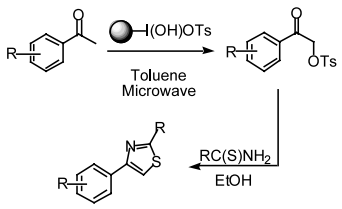
Scheme 3. Preparation of a polymer-supported thionating reagent.



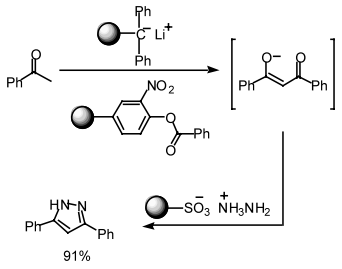
Scheme 4. Conversion of amides to thioamides.



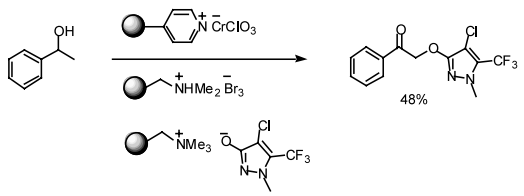
Scheme 5. Polymer-supported hypervalent iodine reagents.



Scheme 6. Polymer-supported hypervalent iodine reagents in library synthesis.



Scheme 7. One-pot, multi-step synthesis using a combination of polymer-supported reagents.



Scheme 8. One-pot, multi-step synthesis of a pyrazole derivative employing three different polymeric reagents simultaneously.

the polymer-supported versions of these reagents and demonstrated their successful application to a number of synthetic transformations (Scheme 5, see also the synthesis of epimaritadine below) [19]. The polymer-supported bis(acetoxy)iodobenzene reagent promotes the oxidation of benzylic alcohols to the corresponding aldehydes. This reagent also effects the conversion of substituted 1,4-dihydro aromatics to the quinone system and the α-hydroxylation of various acetophenones all of which proceed smoothly in high yields and purity. Furthermore, the oxidative spirocyclisation of protected tyrosine derivatives has been carried out to yield pure spirodienones. These compounds are useful starting points for further combinatorial decoration, and represent the core structure of some interesting natural products processing antibiotic properties. As an additional feature we have shown that it is possible to regenerate and recycle the spent resin from these reactions with only minor loss of activity making the use of these reagents even more advantageous.

Another hypervalent iodine reagent that we have developed is a polymer bound version of Koser's reagent. This has been used to prepare α-tosyloxyketones from substituted acetophenones, using microwave irradiation. These products were then further elaborated in the synthesis of a small library of 1,3-thiazoles (Scheme 6).

The clean and efficient chemistry that has been displayed by these new reagents shows them to have clear advantages over the proceeding solution phase alternatives. With an expanding assortment of these reagents it becomes increasingly viable to construct advanced synthetic routes based on multi-step, -reagent conversions to generate both combinatorial libraries and more complex architectures [20–28].

Another important feature of using functionalised resins is a concept known as the 'wolf and lamb' reaction [29,30]: due to site isolation, resins with mutually incompatible functionality do not interact with each other and may be used together to achieve one-pot transformations that would not be possible employing their soluble phase counterparts. This was demonstrated by the Cohen group in 1977 (Scheme 7) [29,30]. The initial part of this process involves the use of a polymer-bound tritylithium base to remove an acidic proton from acetophenone. The anion generated then undergoes a *C*-acylation reaction with a benzoyl-transfer polymer and is then passed without isolation into a suspension of Amberlyst A-15 resin (hydrazine form), affording 3,5-diphenylpyrazole in 91% yield when filtered from the spent polymer reagent.

A number of groups have reported on similar synthetic transformations including Cainelli [11], Frechet [31,32], Bessodes [33,34], Regen [35] and in a more recent demonstration Parlow [36] described a procedure for a three-step synthesis of a pyrazole derivative using three different polymer-supported reagents simultaneously. In addition, it was noted that when the reagents were employed sequentially, the product was obtained in much lower yield, underlying in this case a further advantage of a one-pot multi-step strategy (Scheme 8).

3. Polymer-supported purification

In addition to the use of polymer-supported reagents, a complementary approach has been developed that enables poorer yielding chemical transformations to be utilised followed by the use of polymeric scavenger agents to effect purification. Scavengers are

functionalised resins, designed to react selectively with the impurities present in the reaction mixture so that upon immobilisation they can be easily removed by filtration leaving clean products in solution. Two different classes of scavengers are commonly employed a selection of which are shown in Fig. 1: those that are ionic (acidic and basic resins, normally refereed to as ion exchange resins) and those that are covalent (electrophilic and nucleophilic reagents).

Most standard scavenging protocols are based on the concept of complementary reactivity. In the simplest cases electrophilic and nucleophilic species are sequestered via a reciprocally fuctionalised polymer, likewise acids and bases can be removed via neutralisation with a polymeric acid or base. This method, commonly

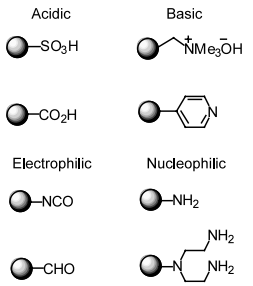
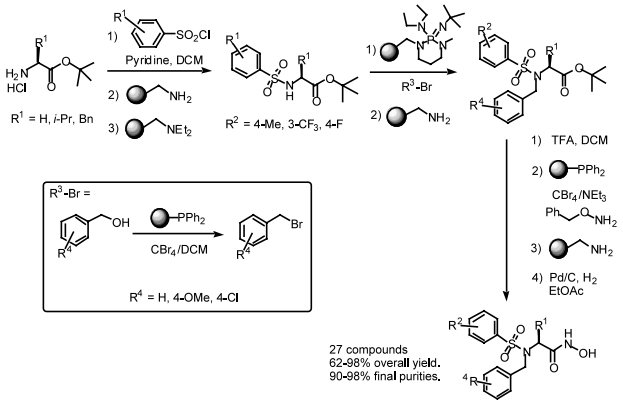
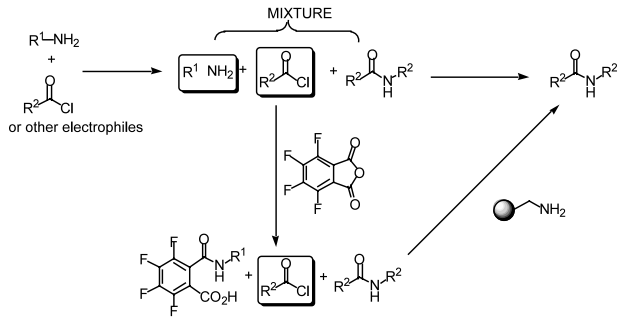


Fig. 1. Some examples of polymeric scavenger reagents.



Scheme 9. Preparation of an array of hydroxamic acid derivatives.



Scheme 10. Use of tetrafluorophthalic anhydride as scavenging enabling reagent of poorly reactive nucleophiles.

known as polymer-assisted purification [37,38], has been considerably expanded upon during the last few years with many ingenious techniques now being available. A description of the most widely used purification protocols is discussed below.

3.1. Reactant sequestration

In these systems the reaction is driven to completion using an excess of reactant, thus generating a reaction mixture containing the desired product together with some starting material. A resin is then added to selectively bind the excess reactant and allow purification of the product by simple filtration and evaporation. This concept was used in our laboratory to great advantage in the combinatorial synthesis of a library of hydroxamic acids (Scheme 9) [24]. This generic 10 step sequence involving seven polymer-supported reagents (four of which are scavengers) gave a library of 27 derivatives in high overall yield and in good to excellent purities *without the need for standard chromatographic purification*.

3.2. Scavenging-enabling reagents

When reactions are performed using poorly reactive starting materials (e.g. anilines or alcohols), product mixtures will contain reactants difficult to remove with polymeric scavengers. The addition of a highly reactive, bifunctional reagent to the product mixture quantitatively transforms the poorly reactive molecule into an activated intermediate easily trapped by a scavenger. Both electrophilic and nucleophilic reagents have thus been employed. An example of this strategy is shown in the following scheme. Treatment of an excess of amine with the highly electrophilic tetrafluorophthalic anhydride, leads to an addition product, which can then be removed with a polymer-supported amine [39]. This approach also enables any excess electrophiles, in this case unreacted acid chloride (or hydrolysed material) and tetrafluorophthalic anhydride to be removed in parallel generating a clean solution of the product (Scheme 10).

3.3. 'Tagged' reagents

Closely related to the concept of scavenging-enabling is the use of soluble, 'tagged' reagents to mediate chemical transformations. These reagents bear a functional group that does not affect their reactivity, is preserved in the reagent by-products and reacts with a complementary functionalised polymeric scavenger at the end of the reaction. Only a limited number of soluble tagged reagents have so far been reported [40–42]. An interesting example was reported by Parlow who applied a tertiary amine tagged carbodimide (**1**) to

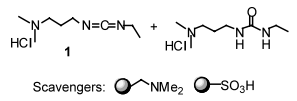


Fig. 2. Pfitzner–Moffat oxidation using a soluble, 'tagged' carbodiimide reagent.

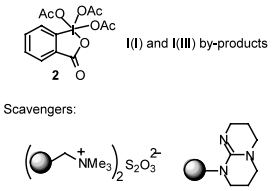
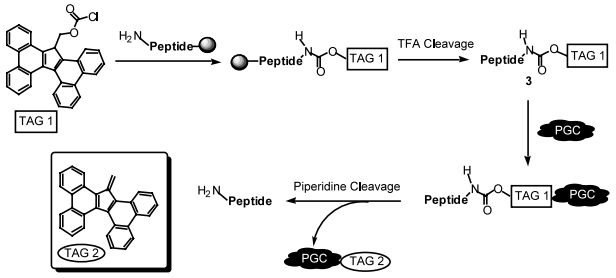
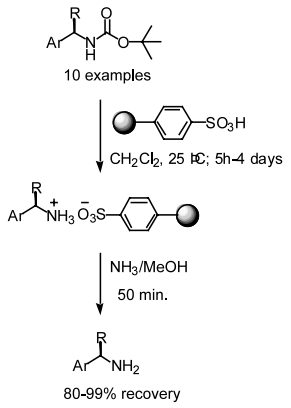


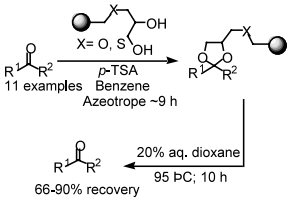
Fig. 3. Purification of Dess–Martin oxidation reaction mixtures.



Scheme 11. Affinity binding purification of polypeptides.



Scheme 12. 'Catch and release' purification involving an ionic process.



Scheme 13. 'Catch and release'purification involving a covalent process.

the Pfitzner–Moffat oxidation of alcohols. The 'tagged' urea and remaining excess carbodimide were subsequently removed by employing two ion-exchange resins: a polymeric tertiary amine was used to neutralise the hydrochloric acid salts of the amine tag followed by a sulfonic acid resin to scavenge the newly generated free base (Fig. 2) [41].

Following a similar strategy, an elegant purification was devised for hypervalent iodine oxidation reactions. In fact, Dess–Martin periodinane (**2**) contains an inherent masked carboxylic acid tag that is revealed at the end of the reaction. Therefore, purification can easily be achieved by treatment of the reaction mixture with a mixed-resin bed containing a thiosulfate resin to destroy excess periodinane and a strong polymeric base to scavenger the carboxylic acid by-products (Fig. 3) [41,42].

3.4. Molecular adsorption

In an interesting variation on this theme Ramage [43] has employed a hydrophobic absorption technique for the purification of synthetic polypeptides (Scheme 11). Attachment of the 'tag' onto the N-terminus of a resin bound peptide followed by cleavage from the resin gives the solution species (**3**) along with a number of possible impurities. Treatment with porous graphitised carbon (PGC), which absorbs large aromatic structures with high affinity, allows the washing of the now immobilised material and hence, removal of the impurities. Subsequent base catalysed removal of the 'tag' followed by elution provides a facile recovery process for the peptide.

3.5. Catch and release purification

This technique involves the selective binding of the desired reaction product onto a solid phase to form a stable intermediate that is thoroughly washed to remove soluble impurities. The intermediate is then subjected to a second transformation that 'releases' the pure product back into solution. Both covalent and ionic resins have been thus employed (Schemes 12 and 13) [44,45].

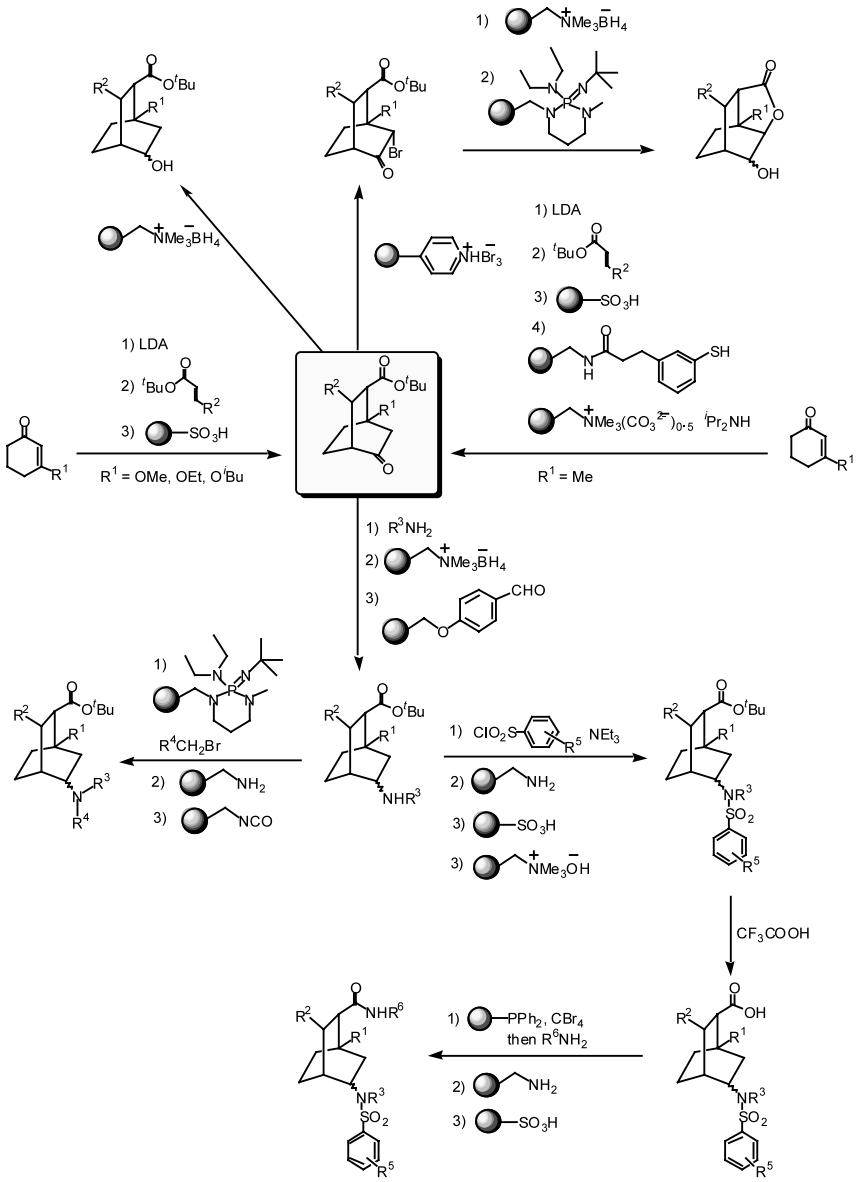
The application of a comprehensive selection of polymer-supported reagents combined with advanced scavenging protocols removes the tedious and time-consuming requirements of conventional chromatographic purification. It then becomes easy to envisage carrying out many more elaborate synthetic programmes directed to the generation of both small molecule libraries and more complex architectures including targeted natural product synthesis. In order to demonstrate these concepts and reagents in practice we will describe in brief a number of preparations that have originated from our own laboratories.

4. Application of polymer-supported reagents to library generation

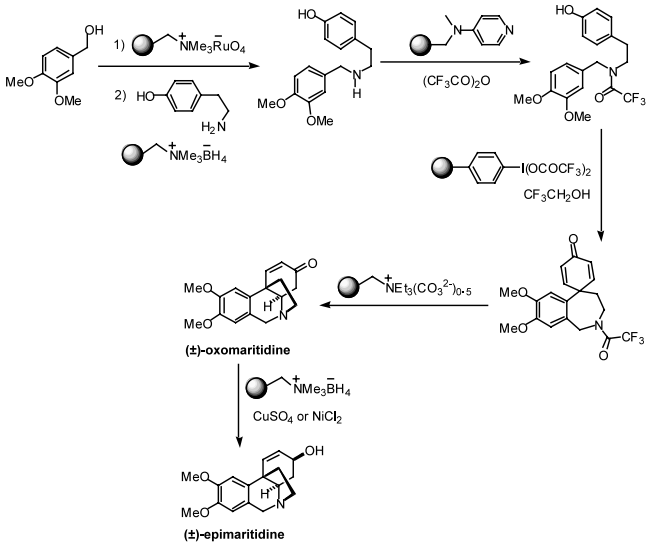
Using a combination of the above reagents and techniques we have constructed a bicyclo[2.2.2]octane library using a tandem Michael addition of enolates of 2-cyclohexenones with various substituted acrylates [46–51]. In this way it was possible to prepare a rigid scaffold, from readily available substrates, which could be further elaborated by transformation of the functional groups to give a large array of compounds (Scheme 14). This synthesis required only minimal optimisation and was a considerable improvement over a previous route which had been developed with the substrate supported on a Wang resin [46,47].

5. Application to the synthesis of natural products

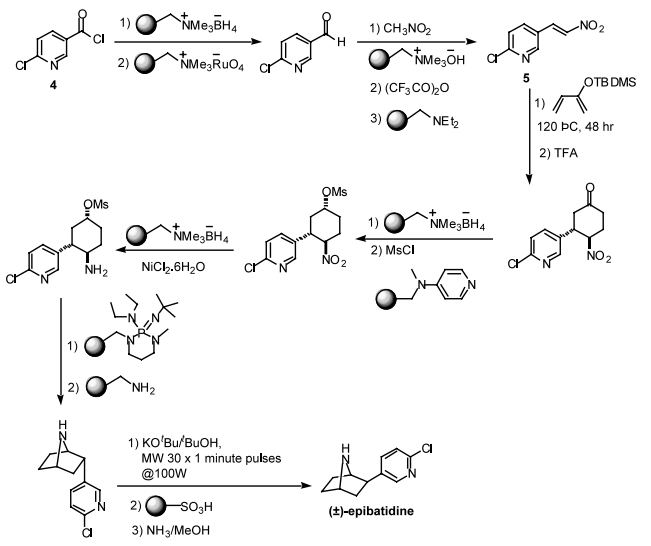
The absence of conventional work-up and purification requirements combined with the ease of optimisation, suggested that the use of solid-supported reagents would be beneficial in the assembly of more complex structures such as natural products. We therefore, investigated the synthesis of the natural alkaloid (±)-epimaritidine (Scheme 15) [52]. This molecule was obtained through a linear six step reaction sequence involving only simple filtration of the spent reagents in an overall yield of 50%. This short synthetic route allows direct access to (±)-epimaritidine (or its precursor (±)-oxomaritidine) in multigramme quantities, which can be further decorated, in a combinatorial



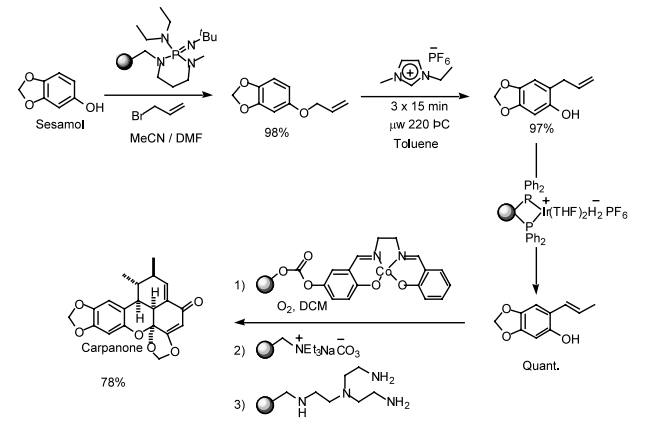
Scheme 14. Rapid library generation using polymer-supported reagents.



Scheme 15. Synthesis of (±)-epimaritidine and (±)-oxomaritidine.



Scheme 16. Synthesis of the potent analgesic (±)-epibatidine.



Scheme 17. Synthesis of (±)-carpanone.

fashion to provide large numbers of analogous compounds for biological evaluation.

The power of these multi-step processes, using supported reagents, was again demonstrated in the extended synthesis of the potent analgesic (±)-epibatidine (Scheme 16) [53]. This compound was obtained in an overall yield of 32% and in >90% purity. The combination of polymer-supported reagents and scavengers in this linear 10 step sequence highlights the tremendous opportunities for complex molecule synthesis. Furthermore, in this synthesis the polymer-supported reagents were contained in sealed pouches to aid separation of the phases. The reaction sequence starting from the acid chloride (**4**) through to the intermediate nitroalkene (**5**) could thus be performed in a one-pot procedure. The reaction progress as effected by the pouched reagent could be easily monitored by TLC. When the reaction was judged to have reached completion the pouch was removed, with washing, and the next set of pouched reagents was added, thus eliminating the need for individual filtrations between steps. Clearly these processes lend themselves to automated synthesis techniques.

The natural product (±)-carpanone and related molecules, possess an attractive complex architecture that can be generated from simple starting materials and, moreover, we have demonstrated that these in turn can be efficiently obtained using a combination of supported-reagents and scavengers in a multi-step process (Scheme 17) [54]. The key advantages of these methods are the ability to run reactions at reasonable scale yet be able to obtain pure products by the simple task of filtration and solvent removal.

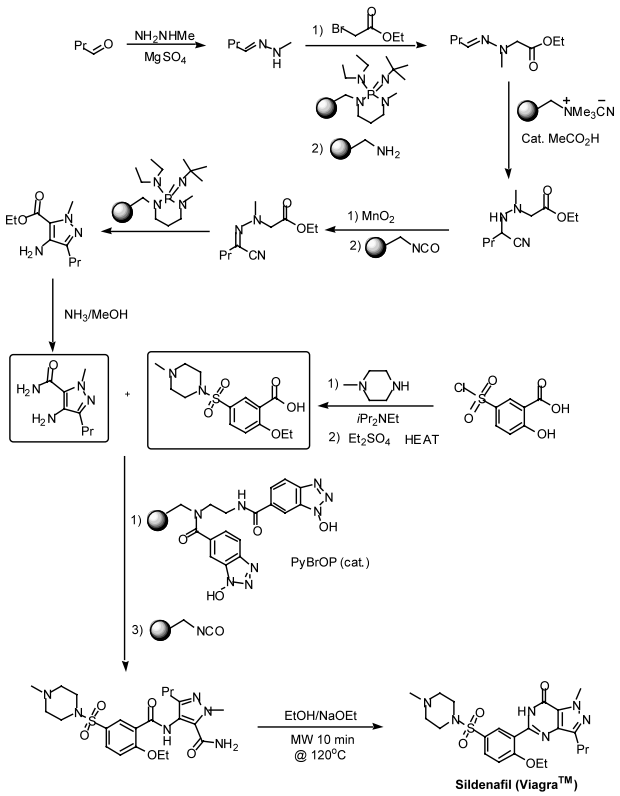
6. Supported reagents for the development of drug targets

The Pfizer drug Sildenafil (Viagra™) has attracted world-wide attention as a treatment for male erectile dysfunction [55–60]. Our showcase synthesis of this commercially important pharmaceutical molecule (Scheme 18) demonstrated the principles of using supported reagents in both a sequential and convergent fashion [61]. These concepts could be easily extended to encompass the synthesis of many other chemical substances in target directed synthesis or in a multi-parallel fashion. As demand drives down the unit cost of these reagents the potential for their integration into existing chemical processes or establishing new dedicated routes based on industrial plant scale synthesis will also become increasingly economically viable. Consequently, the many advantages in safety and speed of purification that these reagents offer will undoubtedly pass from the laboratory bench into the manufacturing work place.

7. The future

To date, we have only scratched the surface of what might be possible with a fully integrated approach to the use of solid-supported reagents in multi-step organic synthesis. In order to progress this field we need to develop additional reagent systems to supplement the chemists synthetic tool-kit. This will involve the development of many more catalytic and recyclable species, which will become of increasing importance if solid-supported reagents are to be used in larger scale chemical processes. Greatly improved loadings of the supported reagents and more efficient scavenging and quenching agents are also needed in order to allow a wider range of chemistry to be carried out in a more efficient fashion. This will invariably mean that new polymers and support materials will have to be developed. Particularly new materials that remove the problem of static electricity, and enable the delivery of a more precise quantity of reagent. Other improvements in the physical form of the reagents that would make them easier to handle and endowing them with increased mechanical stability are also highly desirable.

We believe it is possible to use these reagents in many more elaborate one-pot multi-reagent combinations, even with the aim of discovering new chemical reactions. This exciting concept opens up phenomenal opportunities for organic synthesis in the future especially so when immobilised enzymes are similarly incorporated into the multi-step sequences.



Scheme 18. Preparation of Sildenafil using solid-supported reagents.

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References

[1] S.V. Ley, I.R. Baxendale, R.N. Bream, P.S. Jackson, A.G. Leach, D.A. Longbottom, M. Nesi, J.S. Scott, R.I. Storer, S.J. Taylor, Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation, J. Chem. Soc., Perkin Trans. 1 (2000) 3815–4195.

[2] L.A. Thompson, Recent applications of polymer-supported reagents and scavengers in combinatorial, parallel, or multistep synthesis, Curr. Opin. Chem. 4 (2000) 324–337.

[3] S. Kobayashi, Immobilized catalysts in combinatorial chemistry, Curr. Opin. Chem. 4 (2000) 338–345.

[4] A. Kirschning, H. Monenschein, R. Wittenberg, Functionalized polymers: emerging versatile tools for solution-phase chemistry and automated parallel synthesis, Angew. Chem., Int. Ed. Engl. 40 (2001) 650–679.

[5] R.J. Booth, J.C. Hodges, Polymer-supported quenching reagents for parallel purification, J. Am. Chem. Soc. 19 (1997) 4882–4886.

[6] S.W. Kaldor, M.G. Siegel, B.A. Dressman, P.J. Hahn, Use of solid supported nucleophiles and electrophiles for the purification of nonpeptide small-molecule libraries, Tetrahedron Lett. 37 (1996) 7193–7196.

[7] S.V. Ley, J. Norman, W.P. Griffith, S.P. Marsden, Tetrapropylammonium perruthenate, Pr_4N^+ RuO_4^-, TPAP. A catalytic oxidant for organic synthesis (RuO_4), Synthesis 7 (1994) 639–666.

[8] W.P. Griffith, S.V. Ley, G.P. Whitcomb, A.D. White, Preparation and use of tetra-*n*-butylammonium per-ruthenate (TBAP reagent) and tetra-*n*-propylammonium per-ruthenate (TPAP reagent) as new catalytic oxidants for alcohols, J. Chem. Soc., Chem. Commun. (1987) 1625.

[9] J.J. Parlow, The use of anion-exchange resins for the synthesis of combinatorial libraries containing aryl and heteroaryl ethers, Tetrahedron Lett. 37 (1996) 5257–5260.

[10] B.P. Bandgar, P.K. Ghorpade, N.S. Shrotri, S.V. Patil, Polymer-supported reactions in organic synthesis. 2. Synthesis of some sulfides, Indian J. Chem. 34B (1995) 153–155.

[11] G. Cainelli, M. Contento, F. Manescalchi, R. Regnoti, Polymer-supported phosphonates: olefins fron aldehydes, ketones and dioxolans by means of polymer-supported phosphonates, J. Chem. Soc., Perkin Trans. 1 (1980) 2516.

[12] B. Hinzen, S.V. Ley, Polymer-supported perruthenate (PSP). A new oxidant for clean organic-synthesis, J. Chem. Soc., Perkin Trans. 1 (1997) 1907–1908.

[13] B. Hinzen, S.V. Ley, Synthesis of isoxazolidines using polymer-supported perruthenate (PSP), J. Chem. Soc., Perkin Trans. 1 (1998) 1–2.

[14] B. Hinzen, R. Lenz, S.V. Ley, Polymer-supported perruthenate (PSP). Clean oxidation of primary alcohols to carbonyl-compounds using oxygen as cooxidant, Synthesis 7 (1998) 977–979.
[15] F. Haunert, M.H. Bolli, B. Hinzen, S.V. Ley, Clean 3-step synthesis of 4,5-dihydro-1*H*-pyrazoles starting from alcohols using polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1998) 2235–2237.
[16] S.V. Ley, M.H. Bolli, B. Hinzen, A.-G. Gervois, B.J. Hall, Use of polymer-supported reagents for clean multistep organic-synthesis: preparation of amines and amine derivatives from alcohols for use in compound library generation, J. Chem. Soc., Perkin Trans. 1 (1998) 2239–2241.
[17] S.V. Ley, A.G. Leach, R.I. Storer, A polymer-supported thionating reagent, J. Chem. Soc., Perkin Trans. 1 (2001) 358–361.
[18] B.S. Pedersen, O.S-. Lawesson, Studies on organophosphorus compounds. XIX. About $PSCl_x(NMe_2)_{3-x}$ compounds as thiation reagents, Bull. Soc. Chim. Belg. 86 (1977) 693–697.
[19] S.V. Ley, A.W. Thomas, H. Finch, Polymer-supported hypervalent iodine reagents in 'clean' organic synthesis with potential application in combinatorial chemistry, J. Chem. Soc., Perkin Trans. 1 (1999) 669–671.
[20] S.V. Ley, L. Lumeras, M. Nesi, I.R. Baxendale, Synthesis of trifluoromethyl ketones using polymer-supported reagents, Comb. Chem. High Throughput Screen (2001) 0000.
[21] I.R. Baxendale, G. Brusotti, M. Matsuoka, S.V. Ley, Synthesis of nornicotine, nicotine and other functionalised derivatives using solid-supported reagents and scavengers, J. Chem. Soc., Perkin Trans. 1 (2001) 143–154.
[22] M. Caldarelli, I.R. Baxendale, S.V. Ley, Clean and efficient synthesis of azo dyes using polymer-supported reagents, J. Green Chem. 2 (2000) 43–45.
[23] M. Caldarelli, J. Habermann, S.V. Ley, Clean five-step synthesis of an array of 1,2,3,4-tetra-substituted pyrroles using polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1999) 107–110.
[24] M. Caldarelli, J. Habermann, S.V. Ley, Synthesis of an array of potential matrix metalloproteinase inhibitors using a sequence of polymer-supported reagents, Biorg. Med. Chem. Lett. 9 (1999) 2049–2052.
[25] J. Habermann, S.V. Ley, R. Smits, Three-step synthesis of an array of substituted benzofurans using polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1999) 2421–2423.
[26] J. Habermann, S.V. Ley, J.J. Scicinski, J.S. Scott, R. Smits, A.W. Thomas, Clean synthesis of alpha-bromo ketones and their utilisation in the synthesis of 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes, 2-amino-4-aryl-1,3-thiazoles and piperidino-2-amino-1,3-thiazoles using polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1999) 2425–2427.
[27] M.H. Bolli, S.V. Ley, Development of a polymer-bound Wittig reaction and use in multistep organic-synthesis for the overall conversion of alcohols to beta-hydroxyamines, J. Chem. Soc., Perkin Trans. 1 (1998) 2243–2245.
[28] J. Habermann, S.V. Ley, J.S. Scott, Clean 6-step synthesis of a piperidino-thiomorpholine library using polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1998) 3127–3130.
[29] B.J. Cohen, M.A. Kraus, A. Patchornix, Organic synthesis involving multipolymer reactions. Polymeric trityllithium, J. Am. Chem. Soc. 99 (1977) 4165–4167.
[30] B.J. Cohen, M.A. Kraus, A. Patchornix, 'Wolf and Lamb' reactions equilibrium and kinetic effects in multipolymer systems, J. Am. Chem. Soc. 103 (1981) 7620–7629.
[31] J.M.J. Frechet, P. Darling, M. Farrall, Poly(vinylpyridinium dichromate): an inexpensive recyclable polymeric reagent, J. Org. Chem. 46 (1981) 1728–1730.
[32] D.E. Bregbreiter, R. Chandran, Concurrent catalytic/stoichiometric oxidation using oligomerically ligated catalysts and polymer-bound reagents, J. Am. Chem. Soc. 107 (1985) 4792–4793.
[33] M. Bessodes, K. Antonakis, One pot solid phase cleavage of alpha-diols to primary alcohols. An attractive route to trihydroxy nucleosides, antiviral precursors, Tetrahedron Lett. 26 (1985) 1305–1306.
[34] N. Hebert, A. Beck, R.B. Lennox, G. Just, A new reagent for the removal of the 4-methoxybenzyl ether: application to the synthesis of unusual macrocyclic and bolaform phosphatidylcholines, J. Org. Chem. 57 (1992) 1777–1783.
[35] S.L. Regen, M. Kodomari, Polymer-supported chain homologation, J. Chem. Soc., Chem. Commun. 19 (1987) 1428–1429.
[36] J.J. Parlow, Simultaneous multistep synthesis using polymeric reagents, Tetrahedron Lett. 36 (1995) 1395–1396.
[37] J. Eames, M. Watkinson, Polymeric scavenger reagents in organic synthesis, Eur. J. Org. Chem. 7 (2001) 1213–1224.
[38] J.J. Parlow, R.V. Devraj, M.S. South, Solution-phase chemical library synthesis using polymer-assisted purification techniques, Curr. Opin. Chem. 3 (1999) 320–336.
[39] J.J. Parlow, W. Naing, M.S. South, D.L. Flynn, In-situ chemical tagging: tetrafluorophthalic anhydride as a sequestration enabling reagent (SER) in the purification of solution-phase combinatorial libraries, Tetrahedron Lett. 38 (1997) 7959–7962.
[40] D.L. Flynn, J.Z. Crich, R.V. Devraj, S.L. Hokerman, J.J. Parlow, M.S. South, S.S. Woodard, Chemical library purification strategies based on principles of complementary molecular reactivity and molecular recognition, J. Am. Chem. Soc. 119 (1997) 4874–4881.
[41] J.J. Parlow, B.L. Case, M.S. South, High-throughput purification of solution-phase periodinane mediated oxidation reactions utilizing a novel thiosulfate resin, Tetrahedron 55 (1999) 6785–6796.
[42] J.J. Parlow, D.L. Flynn, Solution-phase parallel synthesis of a benzoxazinone library using complementary molecular reactivity and molecular recognition (CMR/R) purification technology, Tetrahedron 54 (1998) 4013–4031.
[43] A.R. Brown, S.L. Irving, R. Ramage, G. Raphy, 17-Tetrabenzo[*a*,*c*,*g*,*i*]fluorenyl)methylchloroformate (TbfmocCl): a reagent for the rapid and efficient purification of synthetic peptides and proteins, Tetrahedron 51 (1995) 11815–11830.
[44] Y.-S. Liu, C. Zhao, D.E. Bergbreiter, D. Romo, Simultaneous deprotection and purification of Boc-amines based on ionic resin capture, J. Org. Chem. 63 (1998) 3471–3473.
[45] P. Hodge, J. Waterhouse, Preparation of a polymer-supported diol and its use in isolating aldehydes and ketones from mixtures and as a protecting group for aldehydes and ketones, J. Chem. Soc., Perkin Trans. 1 (1983) 2319–2323.
[46] S.V. Ley, A. Massi, Parallel solution-phase synthesis of functionalized bicyclo[2.2.2]octanes: generation of a library using orchestrated multi-step sequences of polymer-supported reagents and sequesterants, J. Chem. Soc., Perkin Trans. 1 (2000) 3645–3654.
[47] S.V. Ley, D.M. Mynett, W.-J. Koot, Solid-phase synthesis of bicyclo[2.2.2]octane derivatives via tandem Michael addition-reactions and subsequent reductive amination, Synlett 10 (1995) 1017–1018.
[48] J.H. Bateson, C.F. Smith, J.B. Wilkinson, Stereochemistry of substituted 1-alkoxybicyclo[2.2.2]octenes; Diels–Alder synthesis versus tandem–Michael strategy, J. Chem. Soc., Perkin Trans. 1 (1991) 651–653.
[49] D. Spitzner, P. Wagner, A. Simon, K. Peters, Diastereoselective synthesis of bicyclo[2.2.2]octanes by double Michael addition, Tetrahedron Lett. 30 (1989) 547–550.
[50] B.K. White, W. Reusch, The synthesis of bicyclo[2.2.2]octan-2-ones by sequential Michael reactions, Tetrahedron 34 (1978) 2439–2443.
[51] R. Lee, Reactions of dienolates with Michael acceptors. Synthesis of bicyclo[2.2.2]octan-2-ones, Tetrahedron Lett. 35 (1973) 3333–3336.

[52] S.V. Ley, O. Schucht, A.W. Thomas, P.J. Murray, Synthesis of the alkaloids (+/−)-oxomaritidine and (+/−)-epimaritidine using an orchestrated multi-step sequence of polymer supported reagents, J. Chem. Soc., Perkin Trans. 1 (1999) 1251–1252.
[53] J. Habermann, S.V. Ley, J.S. Scott, Synthesis of the potent analgesic compound (+/−)-epibatidine using an orchestrated multi-step sequence of polymer-supported reagents, J. Chem. Soc., Perkin Trans. 1 (1999) 1253–1255.
[54] I.R. Baxendale, A.-L. Lee, S.V. Ley, A concise synthesis of the natural product carpanone using solid-supported reagents and scavengers, Synlett 9 (2001) 1482–1484.
[55] D.J. Dale, P.J. Dunn, C. Golightly, M.L. Huges, A.K. Pearce, P.M. Searle, G. Ward, A.S. Wood, The chemical development of the commercial route to Sildenafil: a case history, Org. Process Res. Dev. 4 (2000) 17–22.
[56] N.K. Terrett, A.S. Bell, D. Brown, P. Ellis, Sildenafil (Viagra), a potent and selective inhibitor of type-5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction, Bioorg. Med. Chem. Lett. 6 (1996) 1819–1824.
[57] A.S. Bell, D. Brown, European Patent, 1992, 0 463 756 A1.
[58] C.G. Stief, S. Ückert, A.J. Becker, W. Harringer, M.C. Truss, W.-G. Forssmann, U. Jonas, Effects of Sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue, Urology 55 (2000) 146–150.
[59] D. Schulthesis, N. Schlote, C.G. Steif, U. Jonas, Erectile dysfunction and anejaculation, Eur. Urol. 37 (2000) A1.
[60] R.G. Manecke, J.P. Mulhall, Medical treatment of erectile dysfunction, Ann. Med. 31 (1999) 388–398.
[61] I.R. Baxendale, S.V. Ley, Polymer-supported reagents for multi-step organic synthesis: application to the synthesis of Sildenafil, Biorg. Med. Chem. Lett. 10 (2000) 1983–1986.