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Polymer-assisted solution-phase organic synthesis: Advances in multi-step synthetic applications

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Polymer-assisted solution-phase synthesis has emerged as a versatile approach for high throughput generation of focused chemical libraries. The strategy provides an integrated solution for chemical synthesis and purification by assimilating the advantages of product isolation and purification of solid-phase organic synthesis with the flexible choice of solution-phase chemistry. The ongoing surge in the generation of small molecule libraries by parallel synthesis has spawned keen interest in the development of novel immobilized reagents, catalysts and scavengers. This short review will focus only on the advances of this technology in multi-step organic synthesis.

Introduction

Novel strategies for high throughput synthesis of chemical libraries providing an integrated solution for synthesis, isolation and purification are central to discovery research today. Solid-phase and solution-phase organic syntheses are the two principal domains for the expedient production of chemical libraries. Solid-phase organic synthesis has been the dominating concept for the production of large libraries for lead discovery during the early years of combinatorial chemistry. As new techniques for library synthesis has evolved, attention has shifted to the generation of smaller, focused libraries containing individual, pure compounds. This shift in focus has generated a surge in parallel array synthesis of small molecule libraries. In this context, the use of immobilized reagents, catalysts and scavengers in solution-phase chemistry has emerged as a leading concept since it provides an expedited solution for synthesis and purification. This hybrid approach exploits the benefits of both solid- and solution-phase chemistries. The strategy combines the ease of product isolation and purification in solid-phase synthesis with the high-speed development and flexible choice of chemistry from the vast repertoire of solution-phase organic reactions. Some of the notable advantages of this approach are: the bound reagents may be used in excess to drive a reaction to completion, the byproducts remains support-bound, the solid-supported scavengers may be employed to remove excess reagents or byproducts, the reactions can be monitored by standard TLC and NMR methods, and the work-up involves only simple filtration and evaporation of the solvent. During the recent years, polymer-assisted solution-phase synthesis has made excellent advances in multi-step reaction sequences. This mini-review will only highlight the application of this technology in multi-step reaction syntheses.

A detailed discussion on polymer-assisted reagents and catalysts, and purification strategies for solution-phase library synthesis is excluded from the purview of this article, as these areas have been the subject of many recent review papers.

Polymer-bound reagents

In general, these reagents are employed in stoichiometric excess to drive the reaction to completion. Depending on chemistry, it may be beneficial to use them in conjunction with scavenger resins. Simple filtration removes the spent resin from the reaction solution and, thus, eliminates the need for any time-consuming chromatographic work-up. A representative example is shown in Scheme 1.

Polymer-bound catalysts

Polymer-bound catalysts offer the same advantages as the polymer-bound reagents in that the spent catalyst can be removed by simple filtration. In many cases, the catalyst system can be regenerated and

1Dedicated to Prof. U. R. Ghatak on his 70th birthday.
recycled several times without any loss of activity. The resin-bound catalyst systems with transitional metals are particularly beneficial in reducing metallic contamination in the final products (Scheme II).

**Polymer-bound scavengers**

Scavenger resins selectively sequester excess starting materials and or byproducts. These are added to the reaction mixture after the reaction is over. The resulting bound impurities are then removed by filtration followed by concentration of the solution to afford the pure product (Scheme III). Apart from the benefits of dry work-up and no chromatographic separation, another advantage of this technique is the ability to use an excess starting material to drive a reaction to completion. A number of advances on scavenger resins have been reported in the literature allowing flexibility in the reaction design. Another related technique is ‘Catch and Release’. In this method, a reaction product is selectively captured on an appropriately functionalized solid support by ionic or covalent interaction. The resin is then washed to remove soluble byproducts and the pure product is subsequently released from the solid support.

**Applications in multi-step synthesis**

The continued innovation of new strategies for polymer-assisted solution-phase chemistry and development of novel bound reagents are attracting chemists to perform high throughput, multi-step synthesis of complex molecules. The reports on multi-step reactions by sequential application of polymer-supported reagents are rare in the literature before 1995. A number of comprehensive multi-step sequences employing polymer-bound reagents and scavengers in multiple steps of the synthesis have recently been reported from multiple laboratories. The products from each of the reaction steps involving polymer-bound reagents were isolated in their pure form by simple filtration of the spent resin without any chromatographic separation. Some of these important contributions are summarized below.

Parlow and Flynn have described a five-step parallel synthesis of benzoxazinones 6 in solution-
Covalent reaction with Scavenger

\[
\begin{align*}
\text{1 equiv} & \quad \text{+} \quad \text{1.5 equiv} \\
\text{Prod} & \quad \text{1. Incubation} \quad \text{2. Filtration}
\end{align*}
\]

Ion Exchange with Scavenger

\[
\begin{align*}
\text{1 equiv} & \quad \text{+} \quad \text{1.5 equiv} \\
\text{Prod} & \quad \text{1. Incubation} \quad \text{2. Filtration}
\end{align*}
\]

Scheme III—Scavenging of carboxylic acid/acid chloride

Booth and Hodges\(^7\) have disclosed an elegant multi-step parallel synthesis of a pyrazole library using bound reagents and scavengers in all steps. As outlined in Scheme V, the synthesis involved the use of a polymer-bound morpholine as a catalyst and HCl scavenger, a bound isocyanate to sequester excess primary amines, and a bound trisamine to scavenge excess isobutyl chloroformate.

Ley and coworkers have reported\(^8\) the synthesis of a library of \(\beta\)-hydroxy amino alcohols starting from primary alcohols (Scheme VI). Clean oxidation of the primary alcohols to the corresponding aldehydes was achieved under mild conditions in high yield using a polymer-supported perruthenate catalyst and molecular oxygen. The aldehydes, thus obtained by filtration of the resin-bound catalyst, were converted in high yields and purities to alkenes by the Wittig olefination reaction using a range of polymer-bound Wittig reagents. These alkenes were next converted to the corresponding epoxides by treatment with dimethylsulfonium in high yield. Finally, aminolysis of the epoxides with various amines afforded the \(\beta\)-hydroxyamines.

A clean three-step synthesis for the generation of a 4,5-dihydro-1\(H\)-pyrazole library has been reported\(^9\) from Ley's laboratory employing polymer-bound reagents in multiple steps (Scheme VII). A range of aromatic aldehydes was prepared in high yield by clean oxidation of benzyl alcohols using a polymer-supported perruthenate and molecular oxygen. Each of these aldehydes was next converted to \(\alpha,\beta\)-
unsaturated ketones under Mukaiyama aldol reaction conditions by treatment with trimethylsilyl enol ethers and Nafion-TMS. In the final step of the synthesis, the \( \alpha,\beta \)-unsaturated ketones were treated with hydrazines to afford 4,5-dihydro-1H-pyrazoles in excellent yields. The synthesis is summarized in Scheme VII.

Xu, Mohan and Morrissey have described\(^9\) a parallel synthesis of piperidinopyrazole library employing polymer-bound bases with different basicities for regio-selective N-alkylation reactions. A polymer-bound tertiary amine base was used for selective N-alkylation of a piperidine derivative in the presence of a weakly acidic pyrazole "NH". In the second step of the synthesis, a bound superbase was employed to N-alkylate the pyrazole derivative (Scheme VIII). In both steps, excess alkyl halides were removed using a bound primary amine.

In another multi-step sequence, Ley's group described\(^1\) the preparation of secondary amines and amine derivatives starting from primary alcohols (Scheme IX). A polymer-bound per ruthenate catalyst was employed to oxidize a host of primary alcohols to the corresponding aldehydes in the presence of molecular oxygen. The product aldehydes were reductively aminated with primary amines using a polymer-bound cyanoborohydride reagent to afford a wide range of secondary amines. Further derivatization of these secondary amines to sulphonamides was
accomplished by employing polymer-bound sulphonylated amino pyridine derivatives.

In another study, Ley et al.\textsuperscript{12} described a six-step synthesis of a piperidino-thiomorpholine library employing polymer-bound reagents in each step of the sequence (Scheme X).

4-Piperidone 7 was converted to the sulphonamides 8 by treatment with a polymer-bound DMAP and the excess amine was sequestered by a resin-bound sulphonic acid. In the second step of the synthesis, the sulphonamides 8 were transformed to the \( \alpha \)-bromo keto compounds 9 by a polymer-bound pyridinium bromide perbromide reagent. The \( \alpha \)-bromo ketones 9 were reacted with \( N \)-Boc-protected 1-aminoethan-2-thiol in the presence of Amberlyst A21 base to furnish the coupled products 10. Deprotection of the Boc group in 10 with TFA followed by intramolecular reductive amination of the resulting free amine with a polymer-supported cyanoborohydride afforded the thiomorpholine derivatives 11. Finally, the thiomorpholines were converted to urea derivatives 12 by treatment with a range of isocyanates and isothiocyanates.

Ley and coworkers have reported\textsuperscript{13} the synthesis of an array of hydroxamic acid derivatives as potential matrix metalloproteinase inhibitors using a host of polymer-bound reagents and sequestering agents. The synthesis is outlined in Scheme XI.

A five-step synthesis of an array of 1,2,3,4-tetrasubstituted pyrroles has been reported\textsuperscript{14} by Ley and coworkers employing a host of polymer-bound reagents in all five steps (Scheme XII). Aromatic aldehydes 14 were obtained from the oxidation of aryl methanols 13 in the first step using a polymer-bound permanganate. The next step involved Henry reaction of these aromatic aldehydes 14 with nitroalkanes. A
polymer-bound base, IRA-420-OH was employed to effect the nitroaldol reaction to afford the aldol products 15. Dehydration of 15 with TFAA followed by treatment with triethylamine furnished the nitrostyrenes 16. The work-up included the sequential use of a polymer-bound base and a polymer-bound acid as scavenger resins. The pyrrole derivatives 17 were formed by a clean 1,3-dipolar cycloaddition of tert-butyl isocyanacetate with the nitrostyrenes 16 in the presence of a polymer-bound guanidine base. Further derivatization of the pyrroles 17 at the nitrogen atom was effected by reaction with an excess of alkyl halides in the presence of a polymer-bound phosphazene base to obtain the derivatives 18. The excess alkyl halide used in this reaction was sequestered with an aminomethyl functionalized polystyrene and the products 18 were isolated in their pure forms.

Cresswell et al. have disclosed a multi-step library synthesis of aminopiperidine derivatives 24 using a range of polymer-bound reagents and scavengers for synthesis and purification. The synthesis is outlined in Scheme XIII. The first step of the synthesis involved a hetero Diels-Alder reaction between Danishefsky’s diene 20 and the imines 19 prepared in situ from the reaction of a range of aldehydes with a range of primary amines. This reaction introduced two diversities, R and R₁ in the
Scheme XI

1. Pyridine
2. NH₂
3. NEt₂

Scheme XII

1. TFA-DCM
2. CBr₄, NH₂OBn, NEt₂, PPh₂
3. DCM, NH₂
4. Pd/C, H₂, EtOAc, MeOH

13

14

15

16

17

18
product 21. A polymer-bound trisamine was employed to remove the butenone byproduct as well as any excess aldehydes and imines. L-selectride reduction of 21 afforded the piperidones 22. The third step of the synthesis utilized a bound cyanoborohydride to perform reductive amination of 22 and added the third diversity, R2. A polymer-bound aldehyde resin was employed to scavenge any excess primary amines from the secondary amine products 23. In the final step, the fourth diversity, R3, was added to obtain the final products 24. A resin-bound morpholine base was used to couple a host of acid chlorides with 23. Any excess acid chloride was sequestered with a bound trisamine.
In our laboratories, Porco et al. has developed a catch and release protocol for the synthesis of 1,2,3-thiadiazoles (Scheme XIV). A bound sulphonic acid was used to quench the reaction of a Weinreb amide with Grignard reagents. The product ketones were captured on a bound sulphonyl hydrazide resin. Thionyl chloride mediated Hund-Mori cyclization of the bound sulphonyl hydrazones released the products 1,2,3-thiadiazoles.

Ley's group has also described an elegant total synthesis of the potential analgesic compound (±)-epibatidine in ten steps employing a highly organized sequence with polymer-bound reagents and scavengers. The synthesis is summarized in Scheme XV. The
synthesis afforded the final product in greater than 90% purity. All products from each step were isolated in their pure form by simple filtration of the polymer-support without any chromatography.

In another multi-step, comprehensive synthesis employing polymer-bound reagents, Ley and coworkers have reported the total syntheses of the alkaloids (±)-oxomaritidine and (±)-epimaritidine in five- and six steps respectively. The reactions are delineated in Scheme XVI. Another important illustration of the application of polymer-bound reagents in multi-step synthesis comes from the same group. An efficient route to 3-phenylbenzofuran derivatives has been described by a three-step reaction sequence employing polymer-bound reagents in each step (Scheme XVII).
Scheme XVII

Scheme XVIII

1. R_3S_2Cl
2. N(Pr)_2
3. N(Pr)_2
1. R_4SO_2Cl
2. N(Pr)_2
3. N(Pr)_2

1. R_3NCO (excess)
2. N(Pr)_2
3. N(Pr)_2

1. R_1N(Pr)_2
2. N(Pr)_2
3. N(Pr)_2

1. R_1N(Pr)_2
2. N(Pr)_2
3. N(Pr)_2

1. R_1N(Pr)_2
2. N(Pr)_2
3. N(Pr)_2

1. R_1N(Pr)_2
2. N(Pr)_2
3. N(Pr)_2
Very recently, we have reported a multi-step synthesis of amide, sulphonamide and urea libraries that employed a number of polymer-bound reagents and scavengers. The synthesis is outlined in Scheme XVIII. The secondary amines, prepared from a host of primary amines and carbonyl compounds, were purified by a catch and release strategy employing a bound sulphonic acid, MP-TsOH. A bound Huenig’s base was used in the coupling reactions of the amines with sulphonyl chlorides, acid chlorides and isocyanates. The excess electrophiles were scavenged by a polymer-bound trisamine.

Conclusions
Polymer-assisted solution-phase organic synthesis have emerged as an important tool for high throughput generation of compound libraries. The strategy provides an integrated, expedient solution for compound synthesis, isolation and purification. The technology is equally applicable to multi-step, complex organic synthesis and can be adapted into automated and semi-automated organic synthesis. Further advances in the development of new resin-bound reagents, catalysts and scavengers will continue to expand the repertoire of application of this strategy in parallel solution-phase synthesis.

References