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Solid-Supported Reagent Strategies for Rapid Purification of Combinatorial Synthesis Products

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Introduction

The drug discovery process has undergone some dramatic changes in the last two decades. Among these was the development of high-throughput screening (HTS) methods which permit enormous numbers of compounds to be evaluated in biochemical assays against macromolecules of therapeutic relevance. A similar high-throughput transformation of the field of medicinal chemistry began with the pioneering work in efficient synthesis strategies by Geysen,[1] Houghten,[2] Furka,[3] and Lam[4] which introduced the discipline of combinatorial chemistry. In its early days combinatorial chemistry was a means by which large collections of peptides were efficiently prepared via solid-phase synthesis. Such collections of peptides, commonly known as combinatorial libraries, were frequently synthesized as mixtures which were then tested in aggregate in vitro. Active mixtures were subsequently deconvoluted to determine the active component(s). The success of solid-phase approaches to peptide libraries led numerous research groups to investigate the solid-phase organic synthesis (SPOS) of low molecular weight, drug-like molecules via combinatorial paradigms. Today there is an explosion of interest in SPOS methods as combinatorial synthesis strategies.[5,6] Increasingly, these methods allow the preparation of lead prospecting libraries in the form of individual compounds, rather than mixtures. HTS thus immediately identifies active leads which may be further optimized in subsequent rounds of combinatorial synthesis.

While SPOS and combinatorial synthesis methods provide the principal source of lead prospecting libraries to HTS in many emerging biotech companies, established pharmaceutical companies often also rely on historical collections of drug-like molecules for prospecting. Invariably these historical collections were mostly prepared via traditional, solution-phase synthesis. An active molecule found by screening of such a historical collection poses a tactical dilemma to optimization by SPOS. The time necessary to deduce a suitably robust SPOS method for a given lead is frequently too lengthy to meet the needs of research programs which require only 100−1000 molecules to optimize a screening lead into a drug candidate. This dilemma has stimulated investigations into alternative solution-phase approaches to combinatorial synthesis. Since the typical lead from a historical collection was originally prepared by a solution-phase method, adapting that synthesis to automation is usually less time-consuming than developing an SPOS route, provided that one can simplify purification steps. Moreover, regardless of whether they are completed for the purposes of lead prospecting or lead optimization, short syntheses are simply more practical in solution than on a solid phase when an efficient purification strategy exists since no resin attachment and cleavage reactions are required.

This Account provides an overview of some new strategies for the use of solid-supported reagents in the rapid purification of combinatorial synthesis products obtained via solution-phase syntheses. To maintain a reasonable scope, we will focus upon methodologies that involve some form of covalent modification of the offending impurity, before and/or concurrent with the purification step. Occasionally such covalent purification methodologies are inextricably combined with other purification techniques such as liquid−liquid extraction, liquid−solid extraction (also known as solid-phase extraction or SPE), or ion exchange chromatography, but publications which exclusively highlight these noncovalent purification techniques in the practice of combinatorial chemistry will not be detailed herein.

General Concepts

The first report of the use of solid-supported reagents to facilitate purification was published by Kaldor and coworkers[7] and was soon followed by disclosures of similar methodologies by others.[8,9] The general concept involves adding one or more solid-supported reagents which selectively bind to impurities on the basis of principles of chemical reactivity. Either covalent bond forming reactions or ionic interactions or a mixture thereof serves as an acceptable means for attaching the impurities to the solid phase. A subsequent filtration completes the sepa-

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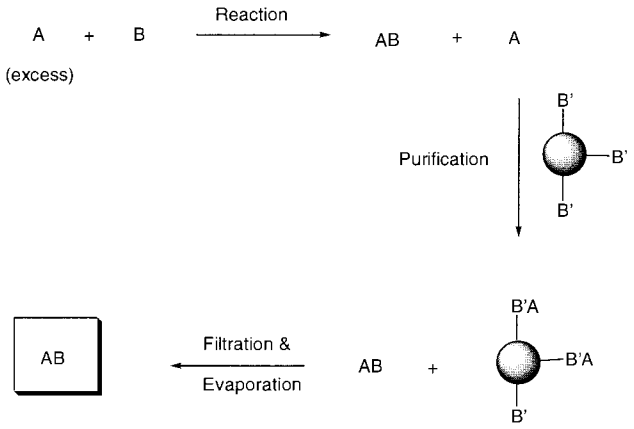
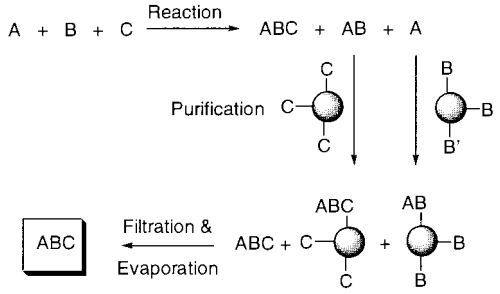
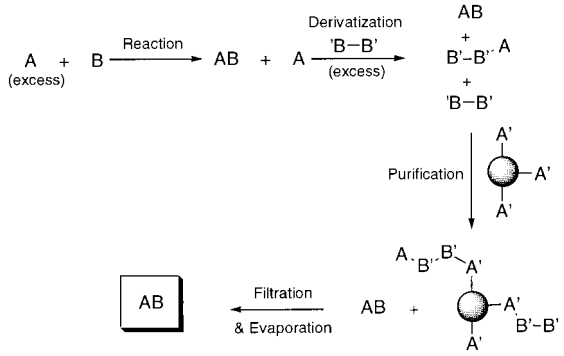
Scheme 1



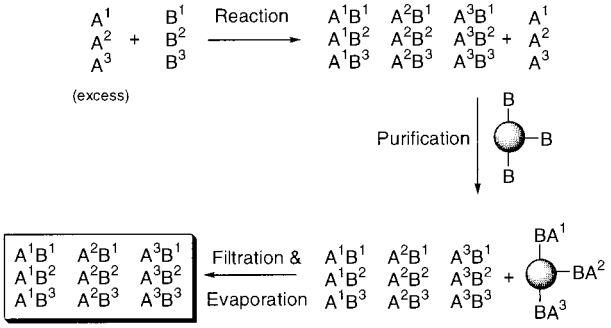
Scheme 2



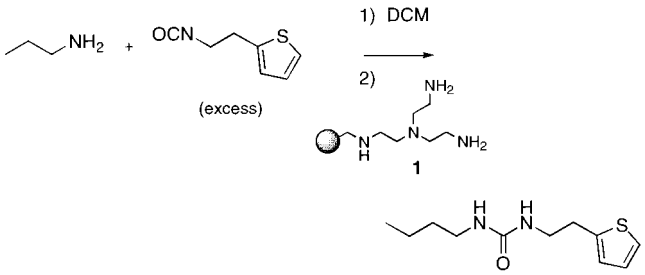
Scheme 3



Scheme 4



Scheme 5

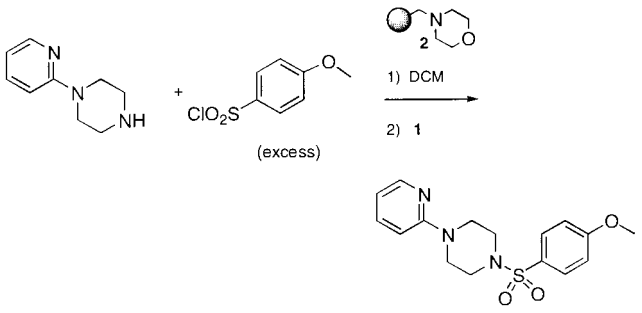


ration, leaving a solution of the desired product(s) of enhanced purity. Several names for these solid-supported purification methodologies have been coined in the literature, including solid-phase scavenging,[7] polymer-supported quench (PSQ),[8] and complimentary molecular reactivity and molecular recognition (CMR/R).[9] The attractiveness of these techniques lies in the convenience in which they may be employed, thereby significantly reducing time and effort expended upon purification. Additionally, their simplicity greatly facilitates parallel application and automation thereof which make solution-phase approaches to combinatorial synthesis feasible. The ability to do purification in parallel is of critical importance to solution-phase combinatorial synthesis since the split and pool strategy of solid-phase synthesis does not apply in a solution-phase synthesis environment. Parallel arrays of synthetic reactions are required if discrete products are desired. Likewise, a purification that is simple enough to automate in a parallel fashion dramatically increases the time saved as opposed to automation of serial processes such as HPLC.

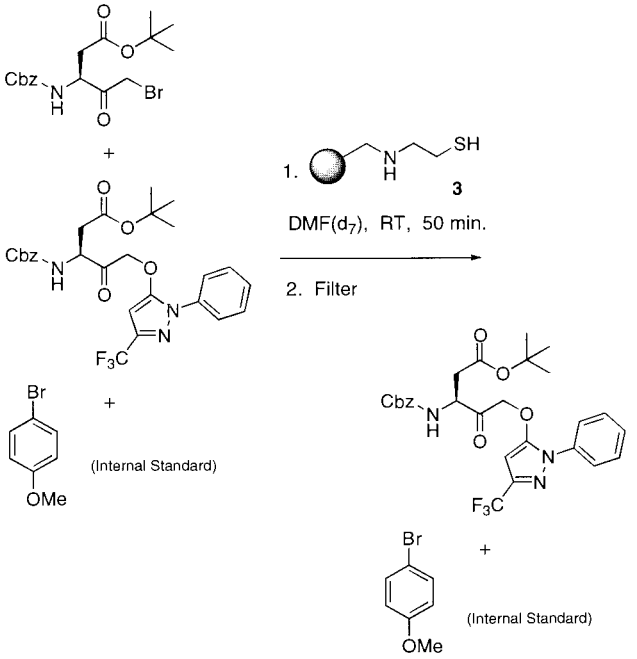
The details of a prototypical covalent solid-supported purification process are shown in Scheme 1. In a reaction between **A** and **B**, a slight excess of reagent **A** is used to drive the reaction to completion. At the conclusion of this hypothetical reaction, a mixture of the product **AB** and excess reagent **A** exists. An excess of an insoluble polymer which bears reactive functionality that is similar to the limiting reagent **B** is added to consume the remainder of starting reagent **A**. Product isolation is achieved by filtration and solvent evaporation. This rationally designed purification strategy takes advantage of the fact that the products are usually less reactive and chemically distinct from the excess starting materials. The degree of purity achieved depends on a knowledge of the relative chemical differences between desired products and impurities.

In an ideal situation, the impurity in each of many parallel reactions is limited to a single chemical class of unreacted starting material, in which case development of a strategy for removal with a single complementary solid-supported reagent is straightforward. Crude reaction products which contain multiple unreacted starting materials and/or undesired byproducts propose a greater but not insurmountable challenge in developing a suitable purification strategy. So long as the identity and reactivity of each impurity is known and a sufficiently selective solid-supported reagent is available, multiple solid-supported reagents may be added, allowed to interact with impurities, and subsequently filtered concurrently (Scheme 2). In some cases where a complimentary solid-supported reagent is not available, the reactivity of the offending impurity can be manipulated via derivatization in a second solution-phase reaction before attachment to a solid support (Scheme 3).

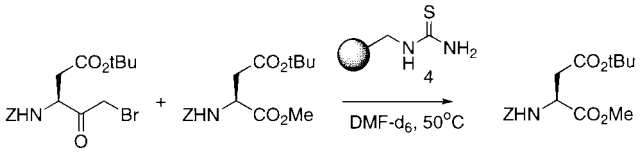
Scheme 6



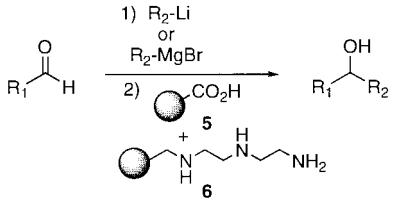
Scheme 7



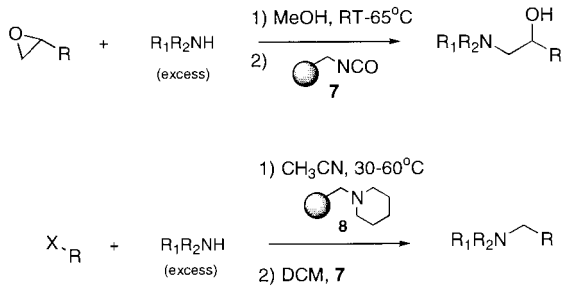
Scheme 8



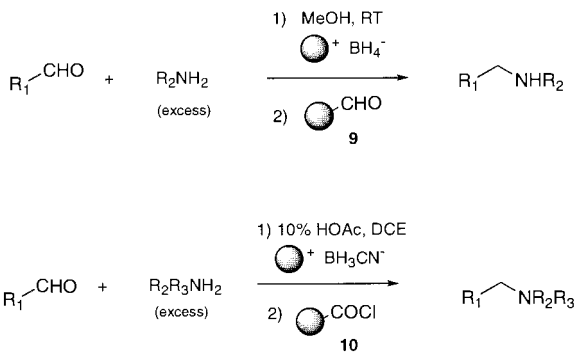
Scheme 9



Scheme 10



Scheme 11

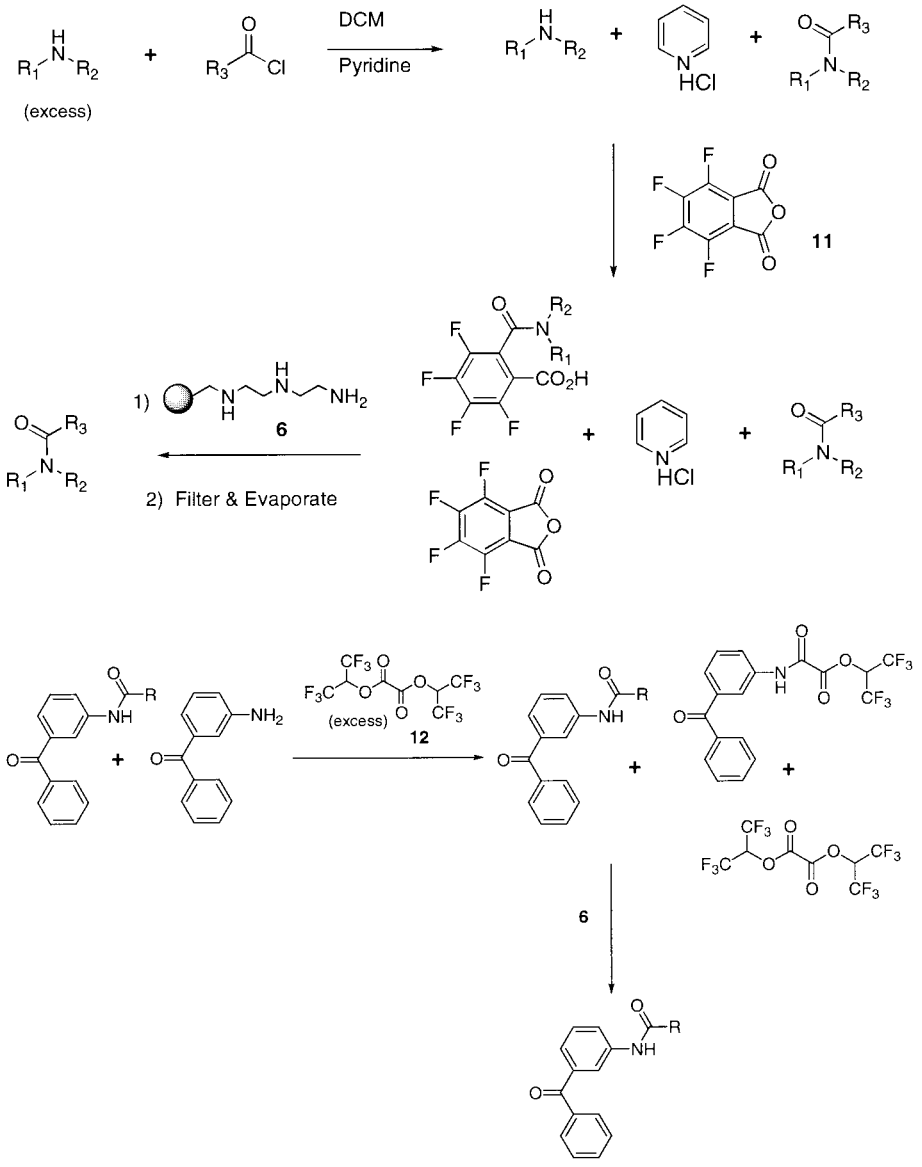


The chemical rather than physical nature of the rapid purification techniques described above permits their use in generation of both discreet compound libraries and mixture libraries by solution-phase syntheses. In the former case, it is noteworthy that a single set of conditions can be used to purify all members of a diverse set of discrete compounds that were produced in parallel reactions. This alleviates the need for customized conditions associated with conventional purification methodologies which depend on the physical characteristics of each compound in a product mixture. In the case of intentional product mixtures (Scheme 4), it is noteworthy that traditional purification methods such as distillation, crystallization, and chromatography typically do not easily afford a means for efficiently removing a set of physically diverse impurities from a larger and even more diverse mixture of products.[10] Furthermore, in the practice of combinatorial chemistry, it is frequently desired that a maximally diverse set of products be prepared, a factor that exacerbates the difficulty associated with using physical properties as the basis for separations.

The importance of reagent, staring material, and solvent purity used in conjunction with solid-supported reagent purification should not be underestimated. Reagents that have partially decomposed over time may unduly complicate the purification problem at hand. Solvents that contain nonvolatile impurities likewise contribute to difficulty in achieving facile purification. For example, in the case of the reaction of an amine with an isocyanate, the presence of a symmetrical urea contaminant resulting from degradation of the isocyanate by exposure to atmospheric moisture will prove difficult if not impossible to separate from the desired unsymmetrical urea on the basis of chemical reactivity. In all cases the use of fresh, pure reagents greatly simplifies the use of solid-supported reagents in purification strategies.

In contrast to solid-phase synthesis where resins of limited loading offer the tactical advantage of site isolation, resins which have a high loading of functional groups per gram are preferred in purification applications. A high loading both facilitates the use of excess solid-supported reagent in a small volume and minimizes costs due to the amount of resin and solvent needed per reaction. Since multiple resin reagents may be required for purifications

Scheme 12



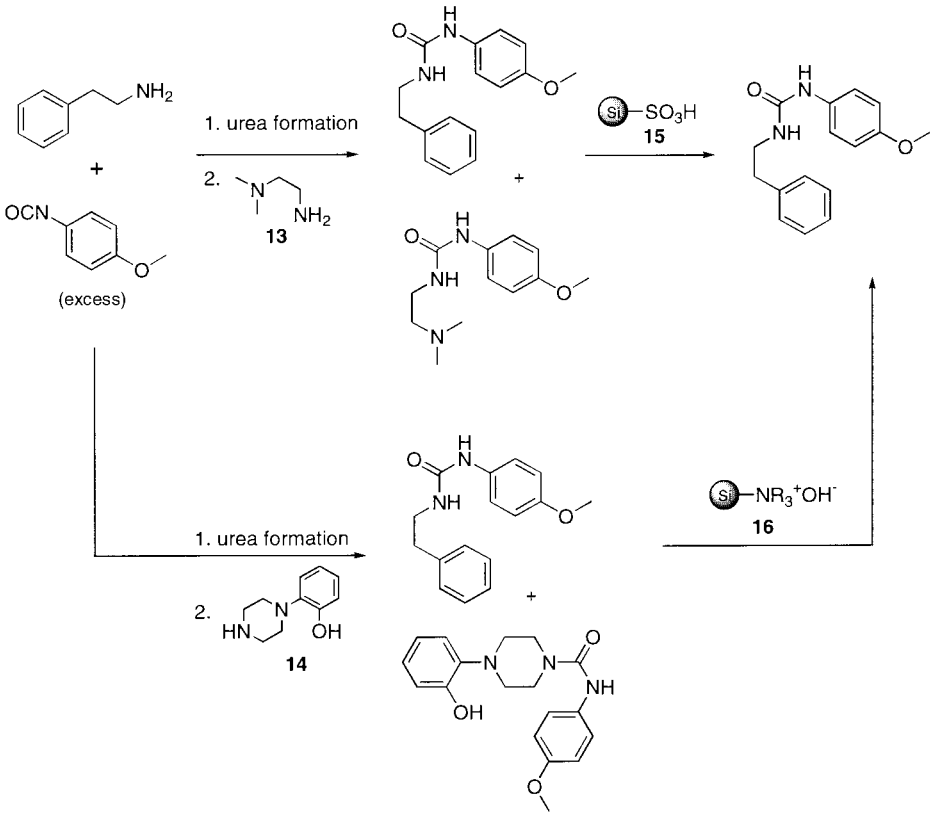
during the course of a synthesis, it is desirable that their cost be low relative to that of the single solid support used in SPOS.

Removal of Electrophiles by Covalent Attachment to Nucleophilic Resins

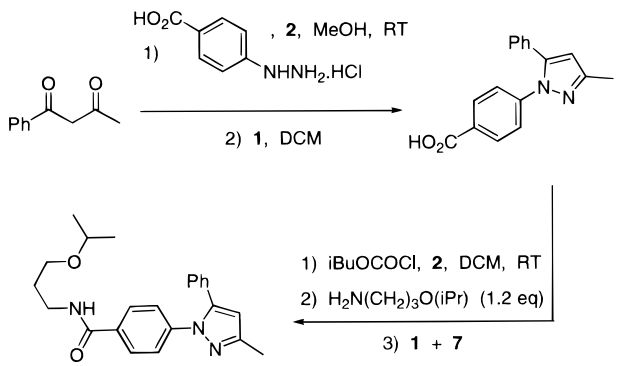
The solution-phase syntheses of amides, sulfonamides, ureas, and thioureas from amines typically involve very efficient and clean reactions. The relative ease with which these important pharmacophores can be prepared, coupled with the commercial availability of large numbers of subunits in their synthesis, makes them logical initial targets for parallel solution-phase synthesis and purification. If the sole synthetic purpose is to react a diverse set of amines with a diverse set of acylating and sulfonylating reagents, carrying out such a transformation on solid supports unduly complicates the task, regardless of which group of synthons is attached to the solid support. For example, it is unlikely that all of the amines would bear a common attachment functionality; hence, multiple resin linkers, including some of the traceless variety, would need to be employed. Optimizing a parallel solid-phase synthesis to accommodate several resin linkers would be a formidable task.

Consider the formation of ureas[8] (Scheme 5). The reaction of *n*-butylamine with the isocyanate in slight excess followed by the addition of polyamine resin **1** gives, after filtration and concentration, products of good yield and excellent purity. The fact that only a slight excess of isocyanate is required is actually of minor impact in this individual example since the isocyanate is relatively inexpensive. If one were to contemplate a parallel synthesis of ureas that employ expensive custom isocyanates, however, there would be a much bigger cost benefit to the fractional molar excess that is required to ensure completion of the solution-phase reaction as opposed to the multiple molar equivalents that are often employed to ensure completion of solid-phase reactions.

Scheme 13



Scheme 14



Acid chlorides, sulfonyl chlorides, and isothiocyanates have also been successfully removed from solution using high-loading polyamine resins such as **1** and **6**.[8,9] Commercially available (aminomethyl)polystyrene **16** may be used as a lower loading alternative.[7] Acylation and sulfonylation reactions are conveniently carried out when a polymer-bound base such as morpholinomethyl resin **2** is used (Scheme 6).[8] Other polymer-supported bases such as piperidinomethyl resin **8**,[7] poly(vinylpyridine),[9] or Amberlyst A-21[9] have been reported in acylation reactions. Thus, a single filtration step can be used to remove the reagent base, the HCl byproduct, the excess acylating or sulfonylating reagent, and the purification resin.

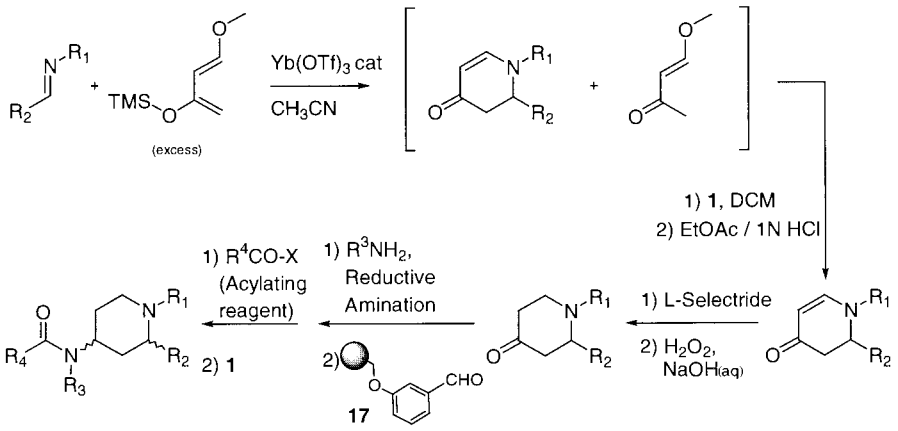
An obvious extension to this work is the removal of alkylating reagents from solution. Reactions performed in solution can be followed by traditional techniques. An internal standard enables the quantitative assessment of the selectivity of cystamine resin **3** in removing the bromoketone as opposed to the desired heterocyclic ketone in the following NMR model study (Scheme 7). The ^{1}H NMR spectrum of the product solution showed, within the limits of detection, the quantitative removal of only α-bromoketone.[11] Subsequent work revealed that the use of a polymer-bound thiourea resin **4** (Scheme 8) is superior to the use of cystamine resin **3** in instances where an ester is being separated from an α-bromoketone.

Aldehydes have been separated from alcohols via imine formation with primary amine resin **6** (Scheme 9).[9] In this reaction the carboxylic acid resin **5** was also used to quench any excess Grignard reagent, reprotonate the metal alkoxide, and scavenge the metal ions as salts of the resin.

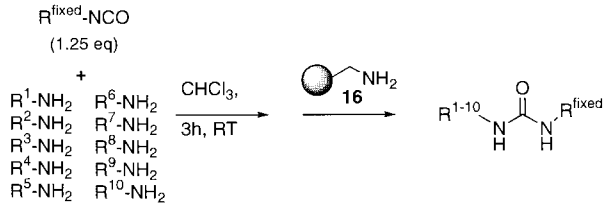
Removal of Nucleophiles by Covalent Attachment to Electrophilic Resins

A number of resins have been developed for the removal of amines from solution. The choice of resin used for purification depends on the type of reaction being performed. Polymer-bound isocyanate **7**[12] is one excellent choice for removing excess amine since no byproducts are released from the resin during the quenching reaction. It has been successfully used to remove excess primary and secondary amines from amides and sulfonamides[7,8] and to separate secondary amines from tertiary amines and tertiary amino alcohols[7] (Scheme 10). One limitation to the utility of the isocyanate resin is sluggish reaction with anilines.

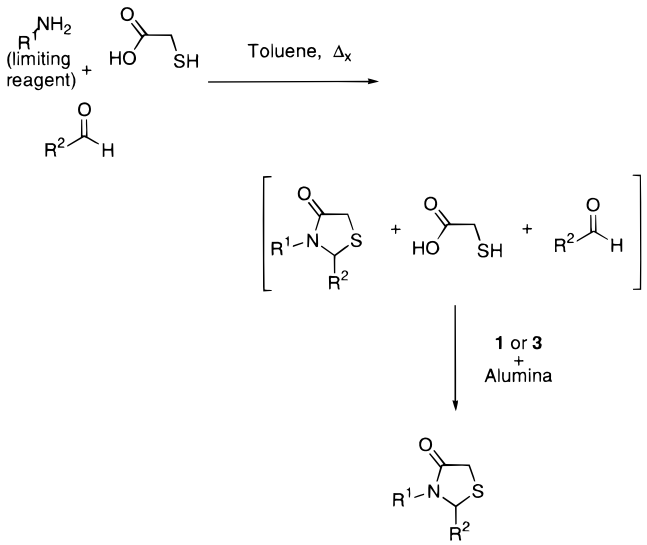
Scheme 15



Scheme 16



Scheme 17



In reductive amination reactions the resin purification method chosen depends on the products being formed (Scheme 11).[7] For the synthesis of secondary amines from primary amines a protocol involving the preformation of the imine and subsequent reduction with polymer-supported borohydride resin has been reported. In this case a polymer-bound aldehyde **9** resin was used to separate excess primary amine from the desired secondary amine product. Apparently the rate of imine formation between the aldehyde resin and primary amines is substantially greater than that of corresponding iminium ion formation. In contrast, the purification of tertiary amine products from the reductive amination reaction of aldehydes and secondary amines was effected using the polymer-bound benzoyl chloride **10**.[13,7]

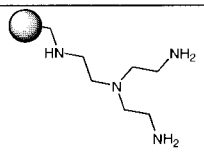
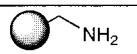
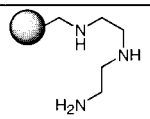
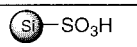
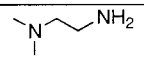
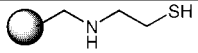
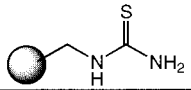
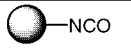
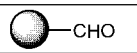
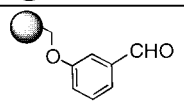
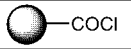
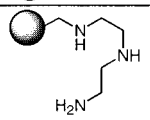
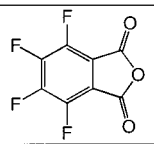
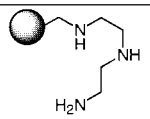
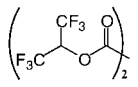
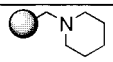
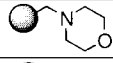
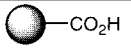
Use of Sequestration-Enabling Reagents To Facilitate the Covalent and Ionic Attachment of Impurities to Insoluble Supports

The sequestration-enabling reagent (SER) technique extends and complements the direct purification strategies which have been described thus far (Scheme 12). For example, the crude product of a reaction which employs excess amine can be treated with excess tetrafluorophthalic anhydride **11** in order to derivatize the amine as a carboxylic acid.[14] To effect purification of the desired product, the polymer-supported amine **6** is subsequently added. This last reagent plays three purification roles, removing the HCl formed during the first reaction, thus allowing the pyridine to be removed by evaporation, removing the hemi-tetrafluoropthalic acid via ionic interaction, and removing the excess of SER reagent **11** by covalent reaction. It forms a salt with both the hemi-acid and the HCl and forms a urea with the isocyanate. In addition to the amide shown, ureas, carbamates, and sulfonamides are prepared in high purity using **11** and **6** to effect the purification. A variation of this technique uses hexafluoroisopropyl oxalate **12** as an SER.[15] In this case the excess amine forms a hemi-amide. The remaining active ester functionality is subsequently covalently sequestered along with excess **12** by treatment with **6**. Both of these SER methodologies are superior to the use of isocyanate resin in the removal of anilines.

In addition to the electrophilic SER reagents described above, nucleophilic SER reagents have been described.[16] In the examples shown in Scheme 13, an amine SER, **13** or **14**, is used to quench the excess isocyanate. When **13** is the SER, the resulting basic components are removed with a cation exchange column **15**, affording products of high purity. Alternatively when **14** is the SER, the resulting phenolic components are removed with an anionic exchange column **16**.

By choosing the SER approach, one can extend the utility of a particular purification resin as is exemplified above where a polyamine resin is used to remove an amine from solution. It is often more cost-effective to perform the secondary SER reaction in order to take advantage of a readily available and inexpensive purifica-

Table 1.

Entry	Resin	SER	Reagent Type Quenched	Source/ Original Reference
1			Isocyanate Isothiocyanate Acid chloride Sulfonyl chloride Aldehyde Vinylogous ester	8, 17, 19 Commercially available
2			Isocyanate Acid chloride Sulfonyl chloride	7, 18 Commercially available
3			aldehydes Isocyanate Acid chloride Sulfonyl chloride alkyl chloroformates	9
4			Isocyanates	16 Commercially available
5			Alklating agents	11, 19 Commercially available
6			α-Halo ketones	11
7			1° & 2° Amines	7, 8, 17 Commercially available
8			1° Amines	7, 17, 25
9			1° Amines	17
10			1° & 2° Amines	18
11			1° & 2° Amines Anilines	14 SER Commercially available
12			1° & 2° Amines Anilines	15
13			HCl	7 Commercially available
14			HCl	8, 17 Commercially available
15			$MgBr^+$	9 Commercially available

tion resin than to take the time to develop a custom solid-phase reagent for the same purpose.

Examples of Multistep Heterocyclic Syntheses Employing Solid-Supported Reagents in Purification at Each Step

Purification strategies which use solid-supported reagents have been judiciously applied to a number of multistep sytheses. Heterocyclic ring formation has been a prominent theme. In such multistep syntheses, the availability of conventional analytical methods such as TLC, HPLC, ^{1}H NMR, and MS greatly facilitates the evaluation of process research that is targeted toward developing a protocol which will succeed with diverse sets of building blocks. When robust solution-phase conditions for a heterocycle are already known in the literature, it is frequently simpler to identify a solid-supported strategy for removing easily anticipated impurities than to re-invent the synthesis on a solid support.

In Scheme 14[8] the pyrazole formed in the first step utilizes morpholine resin **2** as a base during the reaction and polyamine resin **1** for removal of excess diketone. In the second step the free carboxylic acid is activated by mixed anhydride formation, again using **2** as a base. In

the third step this mixed anhydride is reacted with an amine to give the final amide product. The purifications for the second and third synthetic steps are combined, using a mixture of polyamine resin **1** and isocyanate resin **7**. This pyrazole/amide synthesis which involves three synthetic steps and two solid-supported reagent purifications affords products of high purity.

The recently reported aminopiperidine synthesis is another example which illustrates the usefulness of solid-supported reagent purification in multistep syntheses (Scheme 15).[17] In the first synthetic step, the polyamine resin **1** has two roles: to remove remaining aldehyde starting material and to trap the vinylogous ester byproduct. An aqueous extraction is also required to remove the Lewis acid catalyst. In the second step, L-selectride reduces the double bond and purification is achieved by aqueous extraction. The third step uses an aldehyde resin **17** to separate excess primary amine starting material from the secondary amine product in a reductive amination process that is highly analogous to that described in Scheme 11. In the final acylation step the polyamine resin **1** is used to quench the excess acylating reagent. This four-step sequence affords products of excellent purity via a strategic combination of liquid−liquid extraction and solid-supported reagent purifications.

Purification of Multicomponent Reactions

There are two situations where multiple building blocks are added in a single synthetic step: those where one is intentionally making a mixture of analogous products and those where more than two components combine to form a single product. In the former situation (Scheme 16), a mixture of amines is added to a single isocyanate to give, after purification, a product mixture of ureas.[18] A similar mixed amide synthesis which uses a mixture of **1** and **7** in the purification step has also been described.[8] In the latter situation (Scheme 17),[19] the syntheses of 4-thiazolidinones have been achieved by employing either polyamine resin **1** or cystamine resin **3** plus basic alumina to remove starting aldehyde, starting thioglycolic acid, and some additonal polar impurities from the desired product. Multiple chemical mechanisms by which these resins achieve this purification are conceivable.

For a summary of solid-supported reagents and their uses in rapid purification, see Table 1.

Conclusion

Solid-supported purification techniques matched with solution-phase syntheses do not obviate SPOS methods for combinatorial library generation. They do however offer a complimentary alternative. One key factor which often favors the solution-phase environment in choosing between the two approaches is the availability of conventional analytical methods such as TLC, HPLC, ^{1}H NMR, and MS during the course of both reaction and purification process development. Conventional analytical methods are often less applicable to the analysis of solid-supported products or require longer data acquisition times, thereby complicating the development of solid-phase synthesis routes. Solid-phase reagent purification of crude product solutions is desirable in the following situations:

(1) Resin loading and cleavage reactions necessary to a solid-phase route unduly complicate an otherwise short and simple solution-phase synthesis.

(2) Common polymeric supports are chemically incompatible with a particular reagent that is required by the synthesis.

(3) None of the available building blocks of a desired synthesis bear a convenient site for anchoring to a solid support.

(4) Cost considerations favor the use of precious reagents in minimal excess (e.g., 1.1−1.2 molar equivalents) to drive a solution-phase reaction to completion as opposed to the larger excess (e.g., 2−10 molar equivalents) that is typically required on a solid phase.

(5) The knowledge of solution-phase conditions for a synthetic route are well established, and a strategy for solid-supported purification is more easily developed than completely transforming the synthesis to a solid-phase route.

(6) An excess of a nonvolatile reagent is used to cleave an SPOS product from its support.[20,21]

Furthermore, polymer-supported purification techniques do not obviate the use of other phase separation techniques such as liquid−liquid extraction[16b,22,23] and ion exchange SPE.[16a,24] Frequently they may be conveniently used in conjunction with such straightforward separation techniques to afford reaction products of very high purity with minimal expenditure of time and effort. The range of synthetic transformations to which solid-supported reagent purification has been applied is growing rapidly, and the full scope of its utility is not yet known.

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