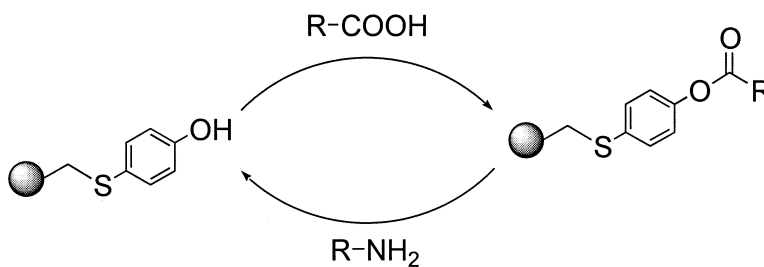Report

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Repeated Use of Solid Supports in Combinatorial Synthesis: The Case of Marshall Resin Recycling

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Combinatorial chemistry[1] plays an important role in lead discovery and optimization for both pharmaceutical and other discovery research programs. A recent survey[2] shows that solid-phase synthesis continues to hold a dominant position (80% during 1992−1995; 50% in 1996; 67% in 1997 and 1998; 80% in 1999) in combinatorial synthesis as more and more chemistries are redeveloped on this medium. However, the distinction between solid-phase and solution-phase combinatorial synthesis is blurred. Some solid-phase syntheses are better performed when one or more solution-phase reaction steps are incorporated. On the other hand, solution-phase synthesis often requires polymer-bound reagents or scavenger resins for effective reaction and product cleanup. In both solid-phase and solution-phase approaches, the application of resins or resin-bound reagents has expanded the scope of reactions that can be carried out in parallel.

Considerable effort has been dedicated to the development of solid-phase and solution-phase chemistry and monitoring of reactions. One issue that receives little attention is the fate of used resins. Resins routinely used for combinatorial synthesis can be as expensive as $150/g, and the resin cost for synthesizing a library of 5000 compounds in a 25 mg scale is about $30,000−50,000. The current practice is that once the desired material is cleaved from the solid support or scavenger resin has been used, the resin is discarded as chemical waste that results in extra expenses. However, if the active functional group of the resin can be regenerated, there is the possibility the resin could be used again (recycled). For reactions on a large scale, the potential saving from recycling is substantial. In this work, we use Marshall linker[3a] as an example to demonstrate the feasibility of resin recycling.

The Marshall linker and the closely related tetrafluorophenol linker[3b] have been widely used to synthesize compounds that can be cleaved by primary and secondary amines to afford the corresponding amides.[3,4] Marshall linker has been used in the synthesis of three or more diversity-site libraries because it allows the addition of one more diversity element at the cleavage step. While the original report on the Marshall linker involved the oxidation of the linker before cleavage, the efficient release of the resin-bound

Scheme 1

Marshall Resin based on 1% cross-linked polystyrene, 100-200 mesh
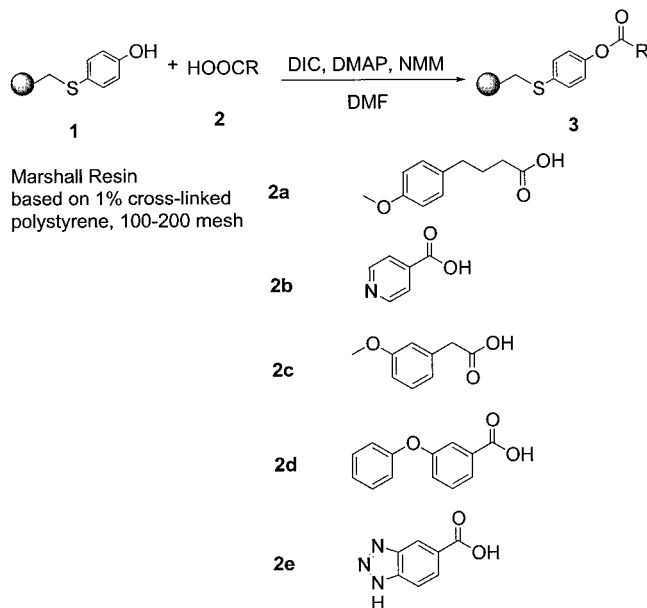
compounds using nucleophiles from the unoxidized linker has been reported.[3,4] We employ parallel solid-phase and solution-phase synthesis methods to make lead discovery libraries containing ∼5000 compounds in each library. Marshall resin has been used widely in our combinatorial syntheses.[4,5]

In this study, Marshall resin was subjected to reaction with five different activated esters made *in situ* from acids, and then the phenol ester products were cleaved with *n*-butylamine (Scheme 1). Since the hydroxyl group on the thiophenol is regenerated after cleavage, the used resin is expected to be functional again. To test the reusability of the used resins, cleaved resins from the five different reactions were pooled and split into five portions, and the five reactions depicted in the first synthesis step in Scheme 1 were repeated. After the second synthesis round, the used resins were pooled and then subjected to the third round of synthesis.

The crucial information needed to quantitatively evaluate the synthesis efficiency and determine the effectiveness of such recycling is the available thiophenol reactive sites or the loading capacity of the resin after each reaction cycle. We determine this qualitatively using solid-phase FTIR spectroscopy[6] and quantitatively by a loading quantitation method. Both analyses are outlined below.

The functionality change from a hydroxyl group to an ester linkage can be monitored by observing two distinct regions of the FTIR spectrum. The FTIR signal from the unreacted thiophenol resin should contain a broad peak from 3200 to 3500 cm^{-1} attributable to the hydrogen-bonded O−H stretch mode. The reaction product containing a phenol ester should not exhibit this broad peak and instead have a sharp band at 1750 cm^{-1} corresponding to the carbonyl stretching mode. IR spectra of resins undergoing three rounds of
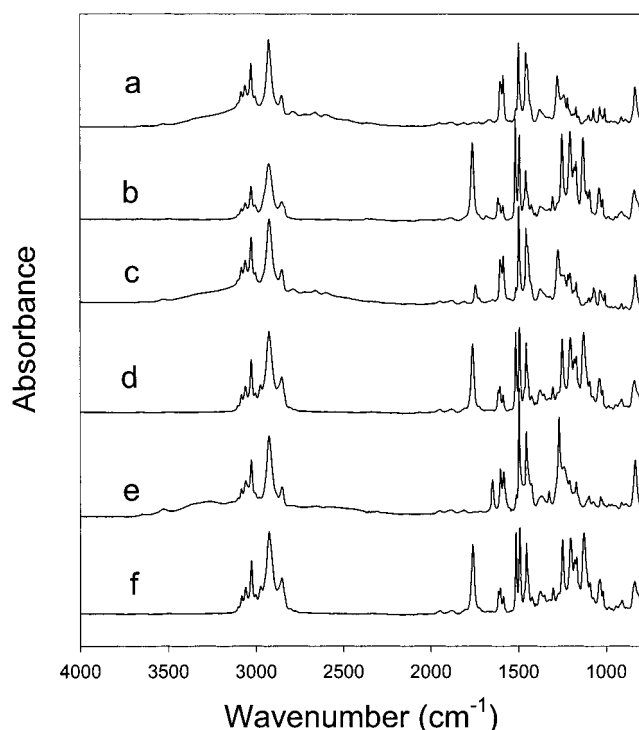
Figure 1. Single-bead FTIR spectra of resins (a) before any reaction and treatment; (b) after the reaction depicted in Scheme 1; (c) after cleavage; (d) after the second round reaction (Scheme 1); (e) after the second cleavage; (f) after the third round of reaction.

reaction-cleavage treatments are illustrated in Figure 1. Spectrum a is the spectrum of the original Marshall resin displaying the broad hydroxyl bending peak between 3200 and 3500 cm^{-1}. Spectrum b is the spectrum of the first-round synthetic product. Note that the broad hydroxyl peak is significantly diminished, and a new peak at 1755 cm^{-1} corresponding to the carbonyl group is observed. Spectrum c is the spectrum of the cleaved resin and indicates the disappearance the carbonyl peak and the return of the hydroxyl IR band. Spectra d and e are the spectra of the second-round synthetic product and the cleaved resins from the second reaction cycle, respectively. Spectrum f is from the synthetic product after the third-round synthesis.

The quantitative assessment of the reaction yield and the cleavage efficiency was accomplished by performing a "furoyl chloride test" as shown in Scheme 2. In this analysis, the resins from the first step in the sequence were treated with the large excess of highly reactive 2-furoyl chloride to convert any unreacted phenol groups to the furoyl ester. This resin sample is then treated with *n*-butylamine and the cleaved product collected and dried under high vacuum to remove residual solvents. If the initial loading was successful, the collected sample will contain **8**; if the loading was incomplete, then the sample will be a mixture of **8** and **9**. The product **9** was quantified by HPLC analysis using a calibration curve made from HPLC analyses of a series of calibration solutions of **9**. The HPLC peak areas from the sample are analyzed and quantified based on this calibration curve. To corroborate results obtained from this method, the loading is also determined by the sulfur content (%) from combustion elemental analysis of the Marshall resin. All the loading of synthetic resins were compared to these values.
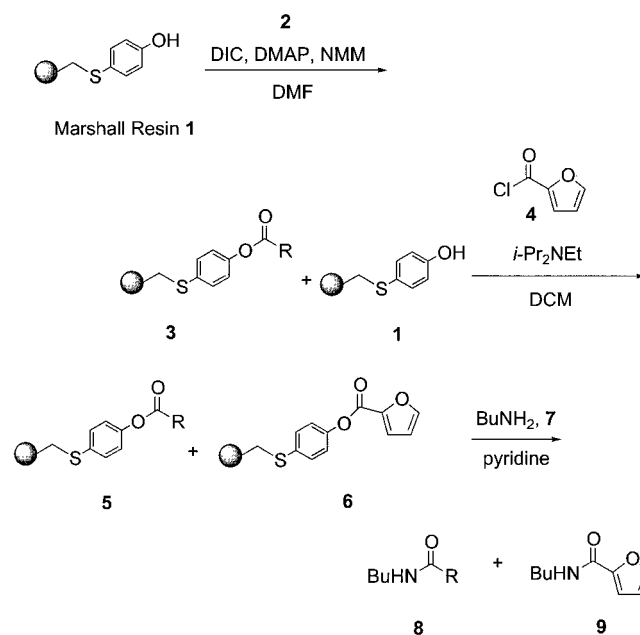
Scheme 2

Table 1. Loading Values of **1** from Three Reaction Cycles[a]

reacting acid	new resin (1.03 mmol/g)	after cycle 1 (1.13 mmol/g)	after cycle 2 (1.11 mmol/g)
2a	0.99	1.12	1.10
2b	0.97	1.06	0.96
2c	0.69	1.08	1.05
2d	0.73	1.12	1.10
2e	0.77	0.85	0.85

[a] Note: All data are from duplicate analyses.

Table 1 summarizes the results obtained from three reaction-cleavage cycles. Loading reported here was determined by a quantitative HPLC/calibration curve method outlined above. The first column (cycle 1) contains results from the reaction performed on resins directly purchased from the manufacturer, with no pretreatment except a solvent washing step. All reactions were carried out in duplicate. It is not clear why the lower yield was found for three reactions in the first cycle. It appears that the reactivity of resins improved in subsequent experiments. The significance of the results from Table 1 is the achievement of a relatively consistent resin reactivity and the loading capacity from cycle to cycle. This demonstrates the potential of Marshall resin recycling. It is interesting to note that although some resins became dark color, this had a negligible effect on the resin reactivity or the loading.

The results discussed above demonstrate the potential for resin recycling applicable for resins without being chemically altered during the synthesis. For example, oxidized Marshall resins (to sulfone and sulfoxide) cannot be recycled. Both an increased economic saving and the decreased environmental contamination will benefit those involved. Since our ultimate goal is to recycle resins that are used in a large-scale production setting, we are currently performing recycling experiments on a large scale. Furthermore, as mentioned before, as long as the active functional group of the resin can be regenerated, this recycling principle can be extended to other solid supports such as other synthesis and scavenger resins.

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