

# SCAVENGER

## strategies in organic synthesis

Part I of this article (*DDW*, Winter 2003/4) discussed the fundamental principles of the use of scavenging techniques in combinatorial and organic synthesis. In this article, more recent developments are introduced that illustrate the broadening appeal of scavengers in organic chemistry. Specifically, the following topics are covered: Part I: Polymeric scavengers; reactive filtration; ion exchange scavengers for product purification and sequestration enabling techniques. Part 2: Alternative resins; polyaromatic scavenger reagents; fluoruous quenching scavenger protocols and microwave assisted scavenging protocols.

The loading capacity is of considerable importance when choosing a scavenger resin for purification as higher loadings allow the use of less reagent which minimises cost. Therefore the search for higher loading alternatives that are cheap and easily handled has become increasingly important. Furthermore the majority of polymeric scavenger reagents consist of reactive functional groups linked to poly(styrene-divinylbenzene) that require suitable solvents to swell the resin to access the reactive sites. Solvents with good swelling properties include DMF, dichloromethane and THF. Now a number of alternative resins exist that can be used with a broad spectrum of solvents.

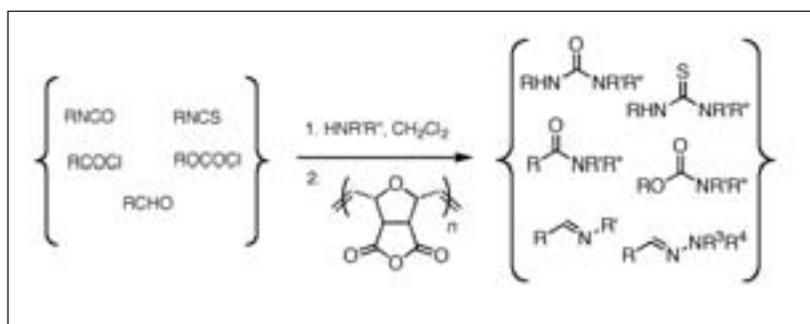
Alternatives to polystyrene-based scavengers include ROMPGEL scavengers. Arnault et al reported a ring-opening metathesis (ROM) polymer supported anhydride as a selective high-loading scavenger for amines and hydrazines<sup>1</sup>. The ROMPGEL polymer is readily synthesised from commercially available and inexpensive materials. Ureas, thioureas, amides, sulfonamides, carbamates, imines and hydrazones were obtained in high purity and yield after sequestration of the

excess amine by the ROMPGEL scavenger (Scheme 1).

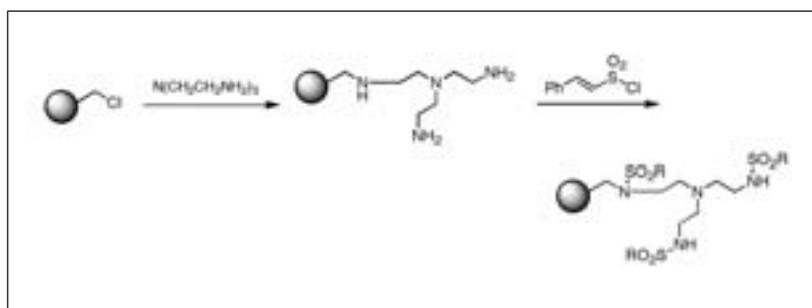
Another report uses a macroporous, highly crosslinked poly(styrene-divinylbenzene) as a base matrix for solid phase scavengers (Scheme 2). This matrix is superior to Merrifield resins when non-wetting solvents such as acetonitrile are used. A 12-membered test library of sulfonamides was generated in high purity<sup>2</sup>.

Bradley et al developed a route for the large scale preparation of magnetic, chloromethylated functionalised polystyrene-based resin beads for solid

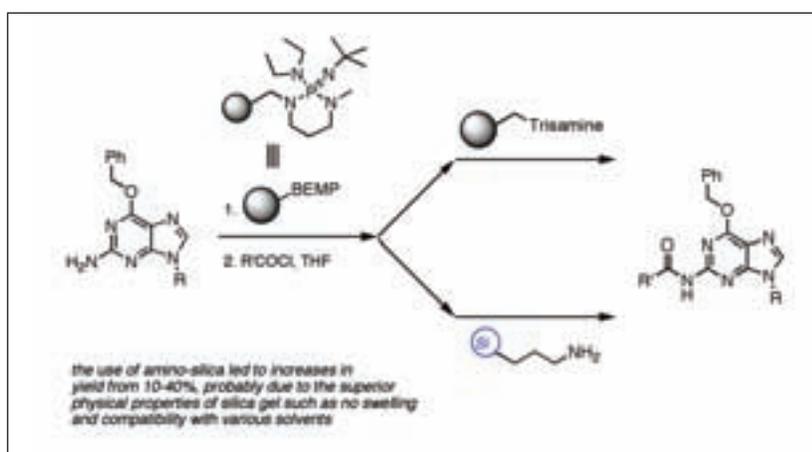
**By Professor Peter Wipf and Dr Claire M. Coleman**



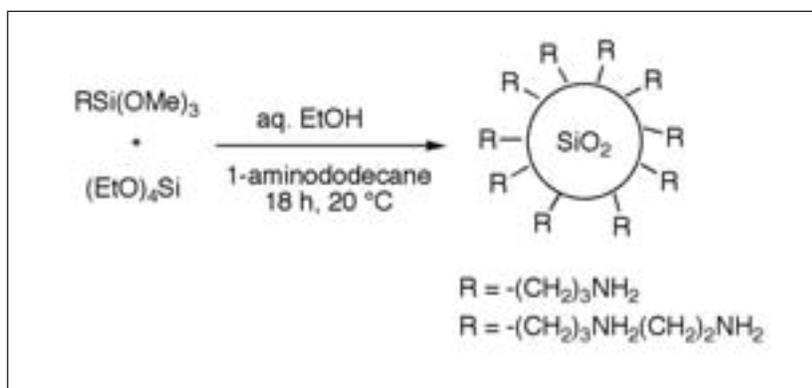
**Scheme 1:** A high loading supported anhydride for sequestering amines and hydrazines



**Scheme 2:** Synthesis of macroporous Tris-resin and subsequent quenching of a sulfonyl chloride



**Scheme 3:** The use of amino functionalised silica to sequester excess acyl chloride in the preparation of 2,9-disubstituted guanines



**Scheme 4:** Synthesis of high loading organofunctionalised silica

phase synthesis and reaction scavenging<sup>3</sup>. The beads compared favourably with the standard Merrifield in several reactions and showed the same swelling properties. The magnetic beads were used as scavengers in the preparation of sulphonamides and were removed from solution with a small array of magnets.

Most recently, functionalised silica gels have proved to be attractive alternative scavengers. Modified silica gels produced by Silicycle ([www.silicycle.com](http://www.silicycle.com)) and HP (combizorb) show a broad solvent compatibility, do not swell and are considerably less expensive than traditional polystyrene based scavengers. Amino silica gel has been used to remove excess acyl chloride in the synthesis of 2,9-disubstituted guanines (Scheme 3)<sup>4</sup>.

Macquarrie et al prepared high loading amino and diamino functionalised silica gels that were easily synthesised and used to efficiently scavenge a range of electrophiles including phenylisocyanate, benzene sulfonyl chloride and benzoyl chloride (Schemes 4,5)<sup>5</sup>.

Other silica-based scavengers included thiols, isocyanates, epoxides, triamines, imidazoles, dimethyl amines, isothiocyanates, silane, pyridine, acid chloride, sulfonyl chloride, imine, sulfonamide and diol. A caveat is that scavengers of this type do not resist aqueous base (at pH>12).

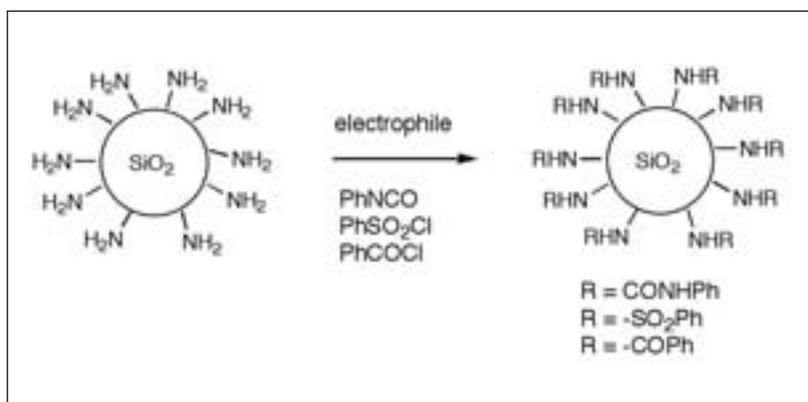
### Polyaromatic Scavenger Resins (PAHSR)

The development of a chemically relatively inert pyrene anchor with a reactive scavenger attachment allowed unreacted reagents and impurities to be removed from a reaction by adsorption of the PAHSR to charcoal and simple filtration (Scheme 6)<sup>6</sup>. However, during this research the authors became aware of a sensitivity to the pyrene reagent that caused allergic dermatitis that was enhanced by sunlight.

Atom transfer radical polymerisation (ATRP) provides a method for the controlled synthesis of polymers. One drawback however is the contamination of the polymer by ligand/metal when standard homogenous catalysis is used. Wilcox et al developed 'Precipitons' for copper catalyst removal in ATRP (Scheme 7, Figure 1)<sup>7</sup>. Precipitons are E/Z-isomerisable compounds that can be attached to a reactant. After the reaction is complete, they can be isomerised to cause precipitation of the attached product. Nitrogen ligands bearing Precipitons were prepared and used in ATRP. After polymerisation was complete, the polymer solution was exposed to UV light to precipitate the Precipiton lig-

and/CuBr complex. However, the ligand in this system cannot be reused or recycled, further work to recycle the Precipiton would provide an attractive method for the removal of metals from ATRP systems.

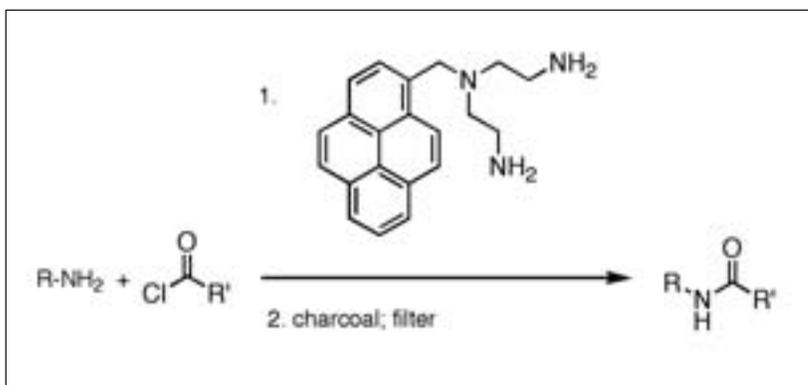
Ligands 3 and 5 were successfully used to remove CuBr. Upon completion of the polymerisation, the solution was cooled and exposed to UV radiation for two hours. The precipiton ligand precipitated and remained complexed with the Cu catalyst. The precipitated product can be isolated by decantation, filtration or sedimentation. The copper content of the polymer solution was determined by UV spectroscopy and indicated no detectable copper based on the lack of absorbance at 680nm.



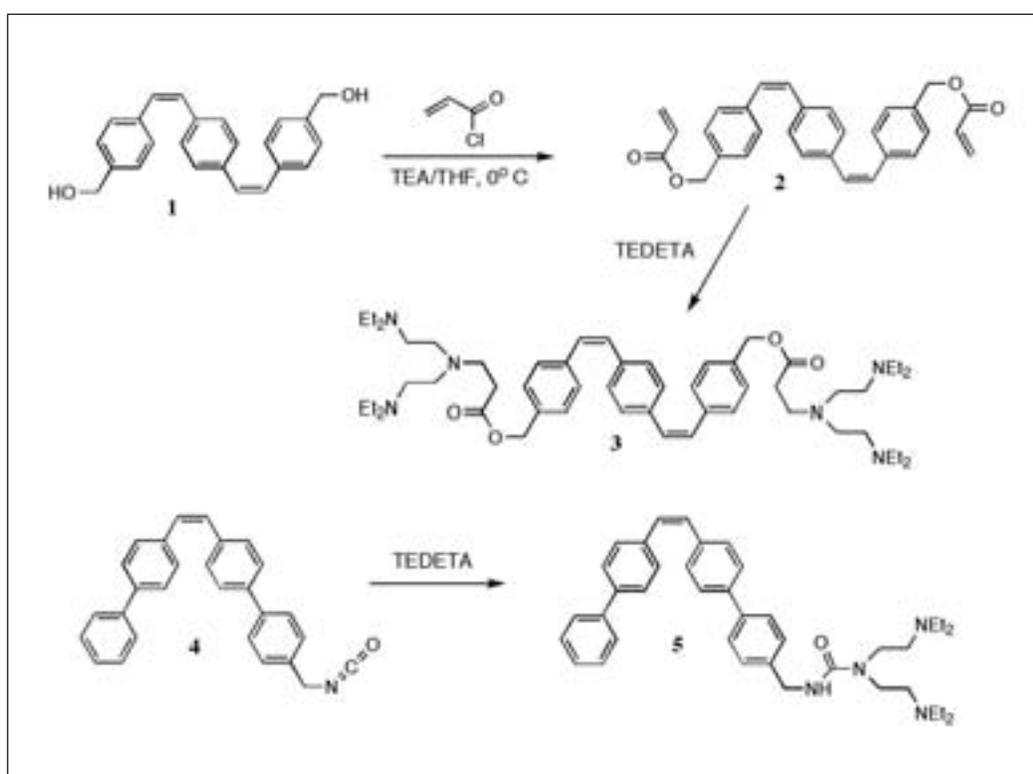
Scheme 5: Scavenging of electrophiles by organofunctional silicas

### Fluorous quenching scavenger protocols

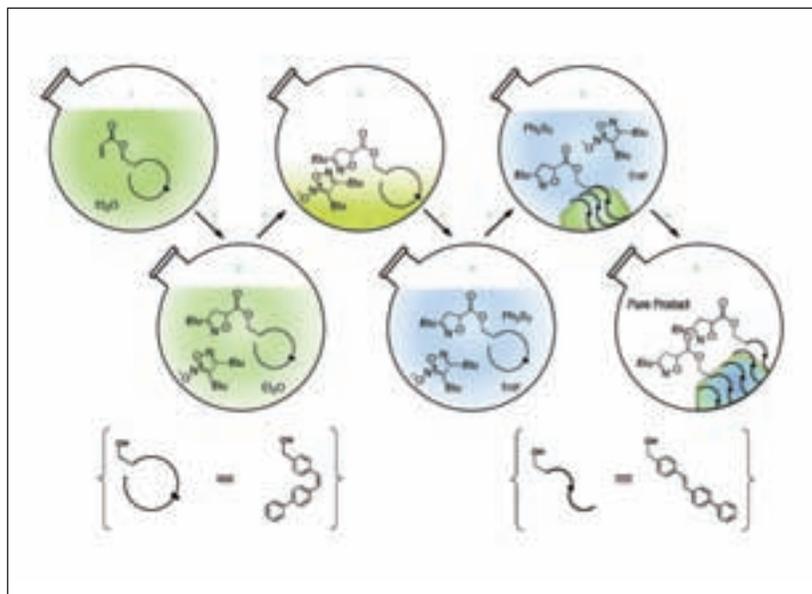
The fluorous phase can be regarded as a third phase that is immiscible with both aqueous and most organic phases. Organic compounds are typically not soluble in fluorous solvents but can be rendered soluble by the incorporation of a fluorous tag. The purification is based on a fluorous/organic liquid-liquid extraction. Curran et al reported the use of a fluorous amine scavenger in the automated solution phase parallel synthesis of a small library of ureas (Scheme 8). The



Scheme 6: A polyaromatic scavenger reagent



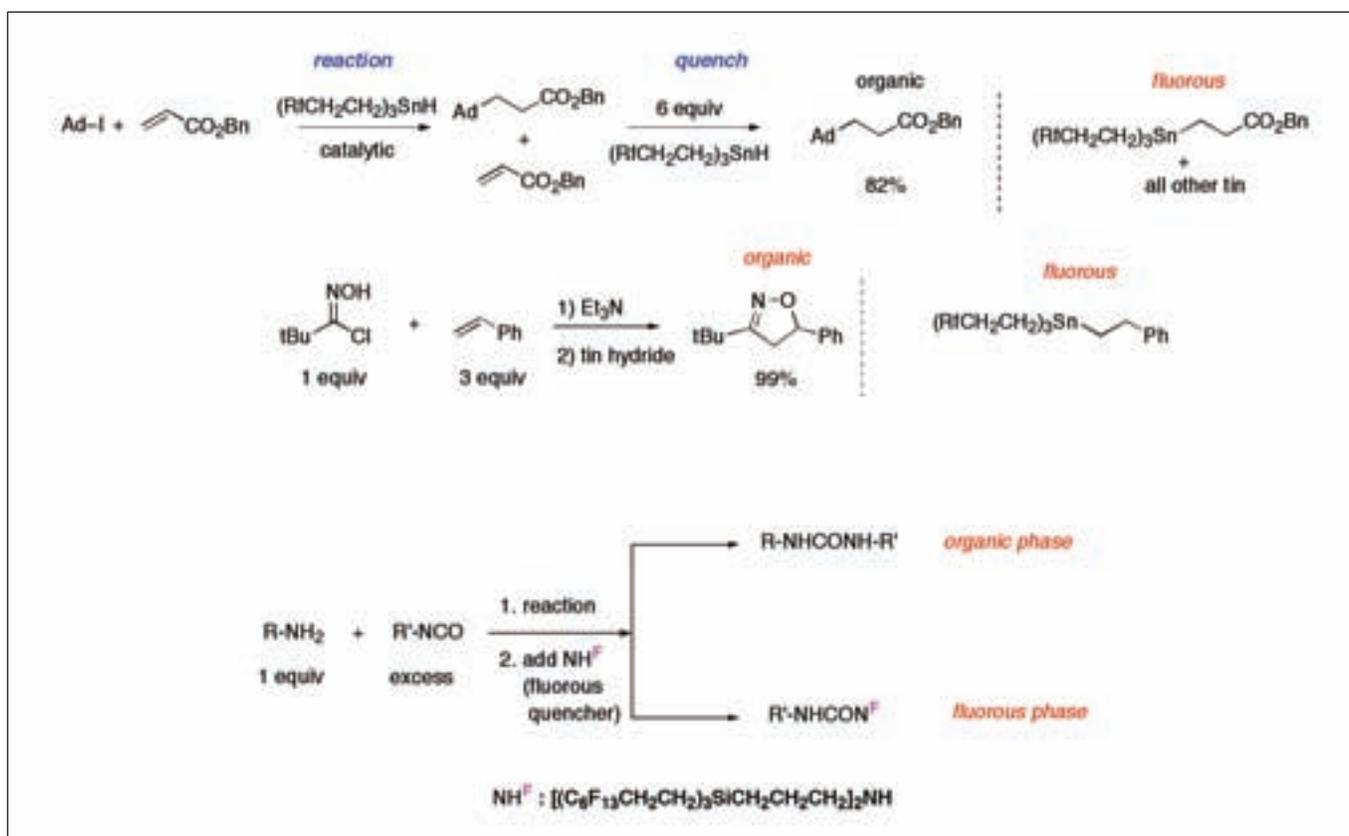
Scheme 7: Synthesis of scavenger 3 starting from diol 1 and synthesis of scavenger 5 from isocyanate 4



**Figure 1:** Precipitons for copper catalyst removal in ATRP

ureas were synthesised from organic amines and excess isocyanates<sup>8</sup>. The fluorous amine scavenger sequesters the excess isocyanate and the resulting adduct is soluble in the fluorous phase that can be removed by a fluorous-organic extraction. The urea products were obtained in high yields and purities.

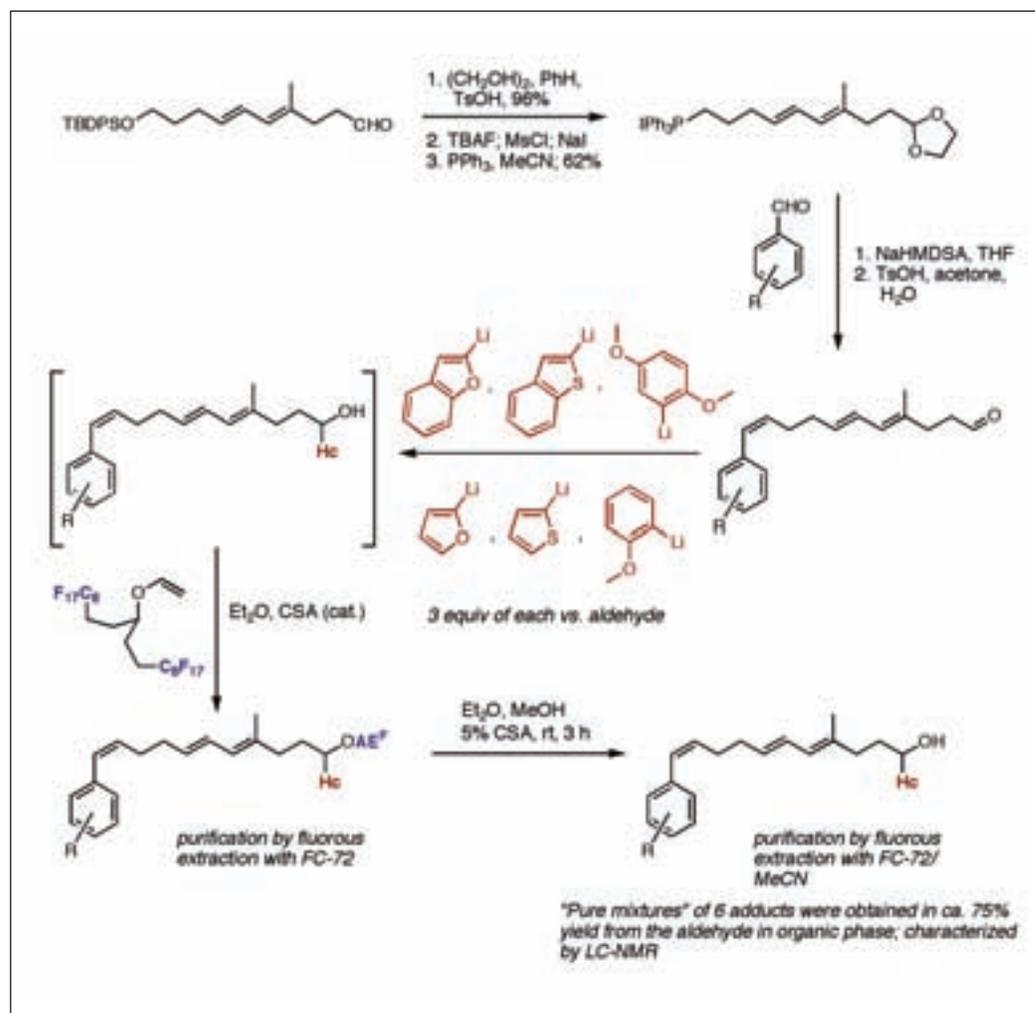
Natural products remain a significant source of promising lead structures for drug development. In recent years, an expansion of the structural diversity pool by preparation of libraries of natural products or natural product-like molecules has become a major focus of libraries of combinatorial chemistry. Wipf et al devised an efficient synthetic strategy for the preparation of 6-compound mixture combinatorial libraries that incorporated important structural elements of the marine natural product Curacin A<sup>9</sup>. Fluorous trapping was used to streamline purification of the heterogenous multicomponent reaction products after the diversification step of the library synthesis to provide structurally defined mixtures. Subsequent biological testing warranted synthesis of the individual components with identification of some of the most potent synthetic curacin A analogues to date (Scheme 9).



**Scheme 8:** Fluorous quenching scavenger protocols for the purification of solution phase parallel urea libraries

## References

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**Scheme 9:** Synthesis of combinatorial mixtures using a fluorous quench strategy

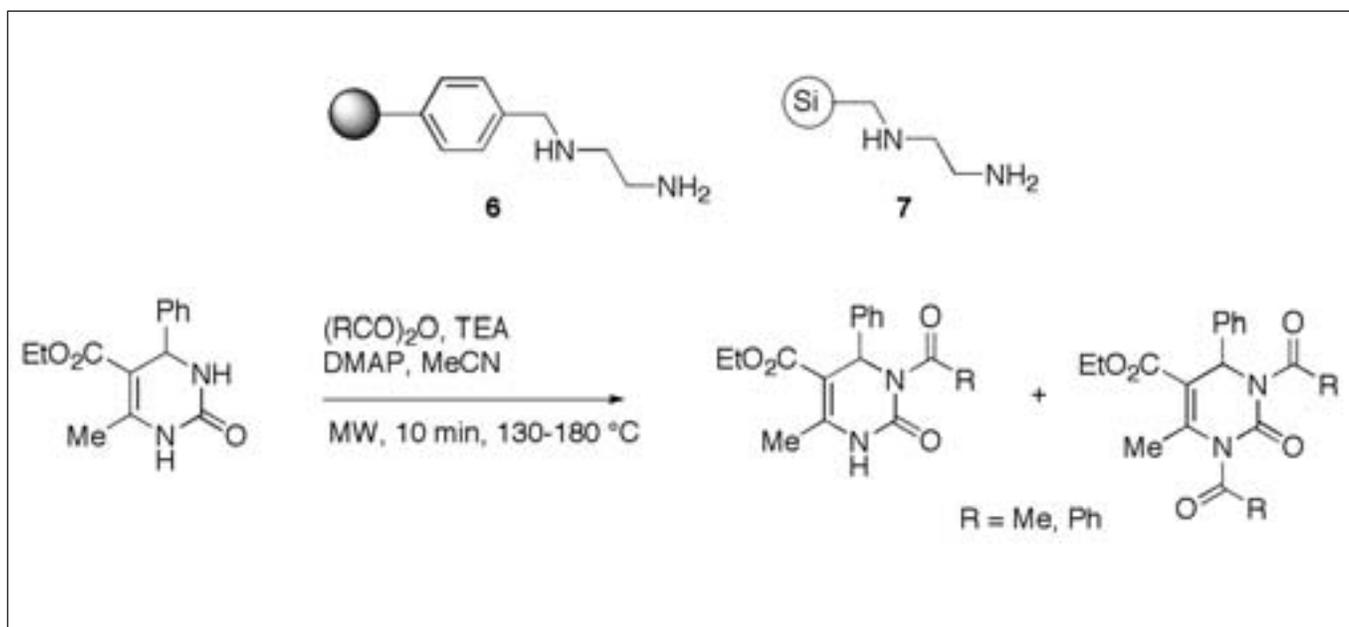
## Microwave-assisted scavenging protocols

As scavenging techniques often require long reaction times due to the heterogeneous nature of the reaction conditions any technology that can speed up the process is of considerable interest. Surprisingly, there are relatively few reports of the use of microwave technology used in conjunction with scavenging techniques. However Kappe et al recently reported the solution phase synthesis of N $\beta$ -acylated dihydropyridines utilising microwave heating in both the synthesis and purification (scavenging) steps (Scheme 10)<sup>10</sup>. After microwave promoted acylation with excess anhydride in sealed vessels at 130-180°C in 10 minutes, the authors examined the use of polymer supported amine scavenging reagents to remove any remaining excess anhydride and bisacylated byproduct. The polymer bound diamine 6 and silica based diamine 7 were found

to be similar in efficiency with the main advantage being the reduction in time required for excess anhydride quenching from 4-6 hours to 5-7 minutes.

## Conclusion

While solution phase combinatorial chemistry is far from being optimised, the key to further improvements in efficiency is not to abandon it altogether but to combine the advantages of solution phase with those of the solid phase. Both the preparation stage, the planning of the synthetic strategy and the procurement and weighing of reagents, as well as the reaction workup stage are serious bottlenecks in high throughput synthesis. Due to the importance of purification techniques both for combinatorial chemistry and natural product synthesis, the development of general scavenging strategies will undoubtedly continue to be refined. This will involve the development of



**Scheme 10:** Microwave assisted scavenging

higher loading, cheaper solid supported scavengers of alternative materials and physical forms. In conjunction with accelerated technologies including microwave protocols, the use of scavengers will ensure that purification of compounds will no longer be a major bottleneck in drug discovery projects.

### Acknowledgement

Support for our research programme in chemical methodologies and library synthesis by the NIH, in particular the NIGMS CMLD programme (P50-GM067082), is gratefully acknowledged. **DDW**

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