ORGANIC LETTERS

2000
Vol. 2, No. 2
195−198

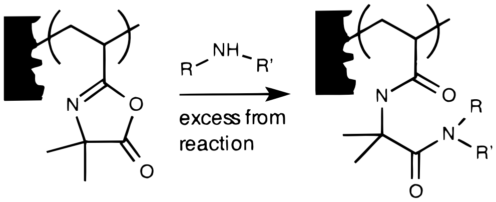
"Reactive Filtration": Use of Functionalized Porous Polymer Monoliths as Scavengers in Solution-Phase Synthesis

Jennifer A. Tripp, Jason A. Stein, Frantisek Svec, and Jean M. J. Fréchet*

Department of Chemistry, University of California, Berkeley, California 94720-1460
frechet@cchem.berkeley.edu

Received November 29, 1999

ABSTRACT



Solid functionalized porous monolithic disks with reactive polymer chains grafted to their inner pore surface have been developed for scavenging excess reagents from reaction mixtures. A poly(chloromethylstyrene-*co*-divinylbenzene) monolith was cut into disks and activated by graft polymerizing 4-vinyl-2,2-dimethylazlactone to its pore surface. In contrast to the direct copolymerization of reactive monomers, grafting increases the accessibility of the reactive groups. Application of the reactive disks is demonstrated in the scavenging of excess amines from reaction mixtures in different solvents.

Combinatorial chemistry, which has revolutionized the drug discovery process during the past decade, frequently utilizes the solid-phase synthesis methodology pioneered by Merrifield.[1] This technique has gained in popularity as a result of the ability to use a large excess of reagents to drive reactions to completion and the ease of separation of polymer-bound products from the reaction mixture. However, a number of reactions cannot be adapted to current polymer-supported chemistries and are therefore carried out in solution. This process may be tedious if libraries of compounds are involved and if purification after each step of the synthesis is required to remove excess reagents and byproducts from the mixture. This has led to the development of solid-phase auxiliaries that are added to the reaction mixture, where they interact with the undesired components and eliminate them from the liquid system by their conversion to an easily removable solid.[2] The concept of complementary molecular reactivity and molecular recognition[3] is demonstrated in various scavenger resins,[4] reactive extraction or "quenching" reagents,[5] and specific ion exchangers.[6] These resins are primarily based on slightly cross-linked functionalized

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10.1021/ol9912837 CCC: $19.00

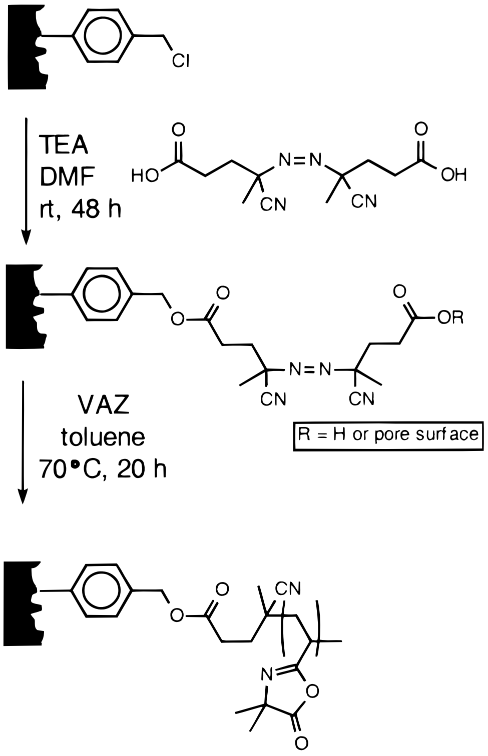
polystyrene beads, although the use of macroporous beads has also been reported.[2e]

In the early 1990s, we introduced macroporous polymers in an entirely new monolithic format.[7] The original monoliths have proven to be very useful as separation media for chromatography and as supports in catalysis.[8] The potential utility of the first generation monoliths as reagents has been limited by their small internal surface area and consequently by their low capacity. However, the use of monolithic materials in the "flow-through" fashion is intrinsically amenable to the automated processes required for the preparation and screening of large combinatorial libraries. Because an increase in internal surface area is often accompanied by a reduction in permeability, we chose another approach consisting of grafting reactive chains on the surface of the very large permeable pores of the monoliths. In contrast to typical reagents with functionalities located in close proximity to the matrix surface, the grafted polymer chains stretch out into the pore volume. Grafting increases the number of functionalities emanating from each surface site, and the location of the chains within the pore improves the accessibility.

One possible implementation of our technique starts with the preparation of macroporous poly(chloromethylstyrene-*co*-divinylbenzene) monoliths by direct polymerization of the mixture of monomers, initiator, and porogen.[9] The mixture is placed within shrinkable polyethylene (PE) tubing that acts as a mold inside a sealed glass tube. After the polymerization process is completed, the glass tube is broken, and the monolith, tightly embraced by the polyethylene tubing, is sliced into disks of required thickness. In contrast to the recently published method of slicing the monolith using a razor blade,[10] our approach affords disks encircled with a PE ring that endows the polymer with remarkable mechanical stability, greatly facilitating its manipulation. In addition, the ring also allows the use of the disk in a cartridge. Obviously, monoliths can also be prepared in other types of "molds" such as the wells of a microtiter plate or microcolumns.

Following polymerization, the chloromethyl groups localized at the pore surface within the disks react with 4,4′-azobis(4-cyanovaleric acid) (ACVA), a functional free radical initiator. Finally, the pores of these disks are filled with a solution of a monomer with the required functionality and heated to achieve polymerization initiated by radicals anchored at the pore surface.[11] Several monomers such as 4-vinyl-2,2-dimethylazlactone (VAZ), 2-aminoethyl methacrylate, 2,3-epoxypropyl methacrylate, and chloromethylstyrene were successfully used in this polymerization. Scheme 1 shows an example of the procedure with immobilized initiator and VAZ.

Scheme 1. Preparation of Monolith Grafted with 4-Vinyl-2,2-dimethylazlactone (VAZ)



The total amount of grafted polymer and thus the capacity of the monolithic scavenger is controlled by the concentration of functional monomer in the solution. For example, a capacity of 0.18 mmol/g was achieved using 20% VAZ in toluene, whereas the use of a 40% solution leads to 1.5 mmol/g. The latter value is too high as it impairs the permeability of the disk. Addition of 2% divinylbenzene (DVB), a cross-linking monomer, during the graft polymerization of a 20% solution of monomer allows an increase in the capacity to 0.85−1.0 mmol/g without affecting the "flow through" properties of the monolith. The DVB allows most of the monomer present in the pores during the polymerization to

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(9) **Preparation of Macroporous Poly(chloromethylstyrene-*co*-divinylbenzene) Monolith.** A mold consisting of a glass tube sealed at one end and containing shrinkable PE tube is filled with a solution of 0.12 g of azobisisobutyronitrile in chloromethylstyrene (4.8 g), divinylbenzene (tech grade, 7.2 g), toluene (5.25 g), and 1-dodecanol (12.75 g), and the open end of the mold is sealed using a proper size rubber septum secured with wire and electrical tape. The polymerization is achieved by heating the mold to 70 °C for 20 h. The glass tube is carefully broken, and the monoliths are sliced using a table saw and cleaned by THF extraction in a Soxhlet apparatus. The mean pore diameter of this monolith as determined by mercury porosimetry is 1.2 μm.

(10) Hird, N.; Hughes, I.; Hunter, D.; Morrison, M. G. J. T.; Sherrington, D. C.; Stevenson, L. *Tetrahedron* **1999**, *55*, 9575−9584.

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be incorporated into the grafted polymer, because any chain growing in solution has a chance to become attached through the cross-linker. All capacities were calculated from elemental analysis data. For example, a monolith grafted using a 20% solution of VAZ and 2% DVB contained 2.11% nitrogen. Subtracting the 0.70% nitrogen that originates from the nitrile moiety of the initiator, the calculated capacity of azlactone groups is ca. 1.0 mmol/g.

Using the monolithic disks with grafted reactive chains, we developed a scavenging technique that we term “reactive filtration”. This technique reduces the purification of the solution-phase mixtures to a simple single-step filtration-like process and is particularly useful for the rapid workup of reaction mixtures containing both desired product and excess reagent. As the solution passes through the disk “filter”, one or more components of the solution react with the functional groups within the disk. The extent of reaction depends both on the reaction rate of the compound that has to be removed from the system with the grafted functionalities and on the time the solution is allowed to reside within the disk. This, in turn, depends on the flow rate of the solution through the monolith.

Figure 1 shows the effect of residence time of solutions of benzylamine in tetrahydrofuran, methanol, and 2-propanol in a disk with a capacity of about 1 mmol/g grafted using a solution of 20% VAZ and 2% DVB in toluene. In these experiments, the benzylamine solution in various solvents was pumped through a monolithic disk placed in a cartridge that contained a 3-fold molar excess of azlactone functionalities with respect to the amine. The amount of residual amine was determined using gas chromatography. Figure 1 shows that, as a result of the high reaction rate of the amine with azlactone moieties, about 50% of the amine is consumed within the first minute of reaction regardless of the solvent used. In THF 100% of the amine is scavenged in about 30 min, whereas the reactions run in alcohol solutions reach a maximum conversion of about 55%. It should be noted that while benzylamine is the only reactive species in a THF solution, the alcohol solvents used in other reactions also react with the azlactone functionalities. Although the reaction of alcohols with the azlactone functionality is slower than reaction with amines, the alcohol depletes the scavenging capacity of the resin. IR monitoring of the process reveals a complete depletion of the azlactone functionalities after 8 min. Whereas the azlactone carbonyl peak at 1820 cm^{-1} disappears after reaction of the monolith with amines, the ester peak at 1740 cm^{-1} remains unchanged, suggesting that, as expected, there is no reaction between the amine and the ester linkage connecting the grafted polymer to the monolith. To scavenge all of the amine in alcohol solution, larger amounts of azlactone functionalities would be required. This can be achieved by using multiple disks in series or by cutting thicker disks.

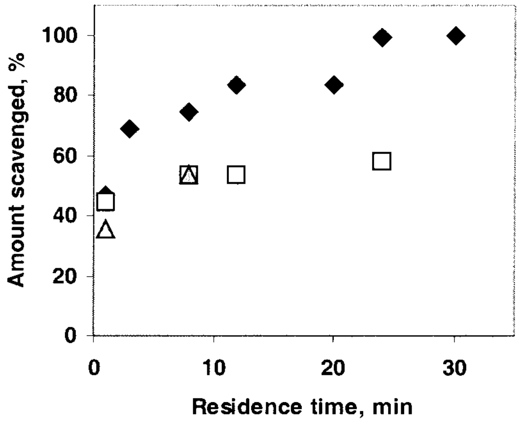

Figure 1. Kinetics of scavenging benzylamine in different solvents. Solution: 0.1 mmol benzylamine, 1.5 mL solvent; ◆, THF; □, methanol; △, 2-propanol. Porous disk: 5 mm × 13 mm diameter, grafted with 20% VAZ and 2% DVB.

To confirm the superior reactivity of the grafted polymer over a monolith containing reactive groups on its pore surface only, a monolith with similar porous properties and content of azlactone functionalities was prepared directly by copolymerization of VAZ with ethylene dimethacrylate and used in similar scavenging experiments.[12] This copolymerized monolith scavenged 37% of the benzylamine in THF within the 8 min residence time, significantly less than the 75% observed for the grafted material.

To examine the utility of grafted monolithic disks in combinatorial chemistry, a model reaction was carried out involving reaction of an excess of different amines with *tert*-butylisocyanate (Scheme 2). The reaction product was pumped through the disk grafted with VAZ to remove the excess amine. Table 1 shows the results of this scavenging reaction. Clearly, highly basic diethylamine is scavenged

Scheme 2. Model Reaction To Test Monolithic Scavenger Disk

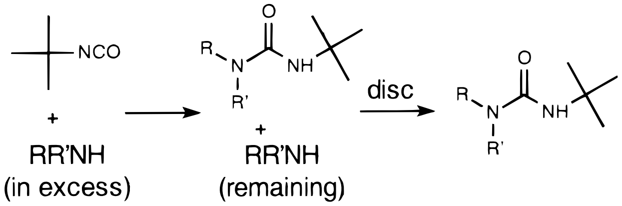

Table 1. Scavenging Efficiencies of Amines in Model Reactions[a]

amine	solvent	amount scavenged, %
benzylamine	THF	74.7
phenethylamine	THF	76.9
butylamine	DCM	78.0
diethylamine	DCM	90.1
3,5-dimethylaniline	THF	47.6

[a] Reaction mixture: 0.2 mmol *tert*-butylisocyanate, 0.3 mmol amine, 1.5 mL tetrahydrofuran (THF) or dichloromethane (DCM). Porous disk: 5 mm ×13 mm diameter, grafted with 20% VAZ and 2% DVB. Flow rate: 3 mL/h. Residence time: 8 min.

most efficiently, and 3,5-dimethylaniline, a poor nucleophile, reacts less efficiently. The residence time for these experiments was kept at 8 min to better observe the differences between reactions with different amines.

These preliminary experiments clearly confirm the applicability of versatile disc-shaped reactive objects as aids in organic synthesis. The new materials can be prepared using reactive functionalities ill-suited for the preparation of classical beads by suspension polymerization in water. They also appear to be more convenient and easier to handle than beads, for which reactions frequently involve slow diffusion processes.

Acknowledgment. The authors thank the National Institute of General Medical Sciences, National Institute of Health (GM-48364) for funding.

OL9912837

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(12) **Preparation of Macroporous Poly(4-vinyl-2,2-dimethylazlactone-*co*-ethylene dimethacrylate) Monolith.** The poly(4-vinyl-2,2-dimethylazlactone-*co*-ethylene dimethacrylate) monolith is prepared in the same mold as described above. A solution of 0.24 g of azobisisobutyronitrile in 4-vinyl-2,2-dimethylazlactone (0.33 g), acrylamide (0.24 g), styrene (0.63 g), ethylene dimethacrylate (1.2 g), and 1-tetradecanol (3.6 g) is polymerized at 65 °C for 20 h. The workup and the preparation of the discs is identical with the other procedure.