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Polyaromatic Scavenger Reagents (PAHSR): A New Methodology for Rapid Purification in Solution-Phase Combinatorial Synthesis

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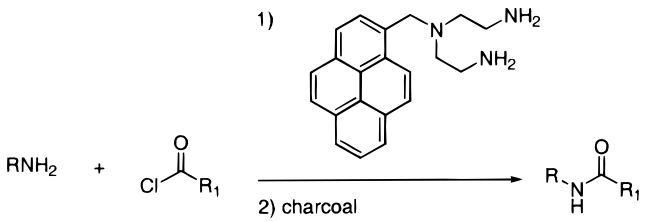
ABSTRACT



A new method of purification of solution-phase combinatorial libraries has been developed. Development of a chemically inert polyaromatic anchor with a reactive "scavenger reagent" (PAHSR) allows unreacted reagents and impurities to be removed from a reaction by absorption of the PAHSR to charcoal and simple filtration.

Combinatorial synthesis has become commonplace in industry today. Increasingly, solution-phase parallel synthesis has proven useful in the preparation of both lead generation libraries and in lead optimization in the pharmaceutical industry.[1−4] Inherent in the solution-phase synthetic strategy is the need for rapid purification of large numbers of compounds.[5] A number of methods are used routinely, including liquid-phase[6] and fluorous-phase[7] reactions, ion exchange chromatography,[8] and more recently the use of automated HPLC systems.[9−11]

One of the more utilized strategies for parallel reaction purification has been the use of polymer-supported scavenger reagents[12,13] or the PASP (polymer-assisted solution-phase) strategy.[14−17]

In fact, a number of scavenger resins are now commercially available.[18] This technique allows the removal of excess reagents and byproducts by removal of resin via filtration. This strategy has recently been extended to the use of magnetic beads, thus facilitating the removal of the resin.[19]

This technique has drawbacks, namely, difficulty in automation of resin addition and removal, longer reaction

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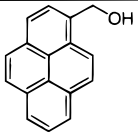
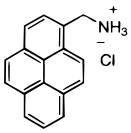
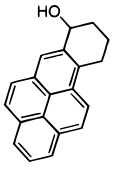
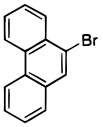
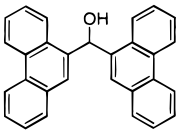
time due to solid−liquid interface, and difficulty in preparation of new or specialized reagents.

We sought to develop a reagent scavenger system that would avoid these limitations. To this end, we were intrigued by the work of Ramage's group using the polyaromatic tetrabenzo[*a*,*c*,*g*,*i*]fluorene (Tbf) group for purification of peptides.[20−22] The TBF group is absorbed onto charcoal in polar solvents and can be desorbed using a nonpolar solvent. Recently, Ramage has shown that this strategy can be used for parallel synthesis.[23] In this strategy, the substrate was attached to the Tbf group via a linker and chemistry carried out in solution. The TBF substrate was absorbed onto charcoal, allowing excess reagents to be removed by filtration. The Tbf substrate could then be desorbed and further chemistry carried out.

In contrast, we envisioned using the PAH as an anchor for a scavenging functionality. This would allow a homogeneous reaction, thus allowing simple robotic addition and rapid reaction time. After scavenging of unreacted starting materials with the PAH scavenger reagent (PAHSR), simple addition of charcoal and filtration would provide pure material. In addition, this strategy would allow simple modification of the scavenging moiety, thus allowing rapid synthesis of specialized scavenger reagents. To be cost-effective, we looked for a commercially available, inexpensive polyaromatic hydrocarbon that could be easily modified.

We tested five simple substrates for the ability to be absorbed onto charcoal (Table 1). In each case, 0.1 mmol of the core was dissolved in 2 mL of a 0.05 M solution of *p*-bromoanisole (an internal standard) in $CDCl_3$. A 1 mL aliquot was treated with 250 mg of charcoal, and the solution was stirred for 30 min. The solutions were filtered and analyzed by NMR.

Table 1. Survey of PAH Cores

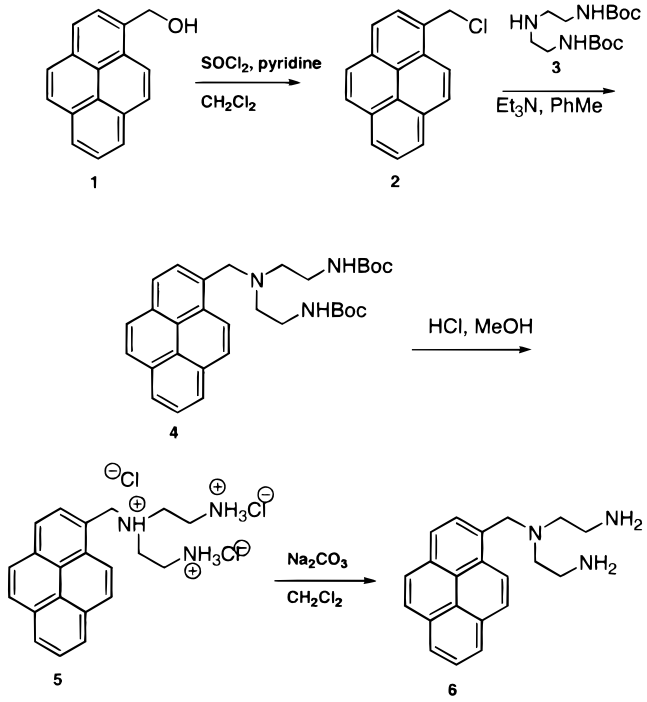
Polyaromatic Core	% remaining (30 min)	% remaining (12h)
	5	0
	0	--
	19	--
	55	--
	94	--

As shown in Table 1, pyrene appeared to be an ideal core, as both the amine hydrochloride and the alcohol were >95% absorbed onto charcoal. In the case of the alcohol, the experiment was repeated, but carried out to 12 h, at which time the solution was filtered and analyzed by NMR, showing no trace of pyrene alcohol.

On the basis of this simple experiment, we decided to use the pyrene alcohol as a starting point for investigation of this strategy.

We set out to prepare a tris-amine scavenger reagent similar to the available polymer-supported tris-amine resin.[18] Pyrene methyl alcohol **1** was converted to chloride **2** with thionyl chloride (Scheme 1). The bromide could also be prepared using phosphorus tribromide. Displacement of the benzylic chloride with bis-BOC triamine **3** [24] went smoothly to the protected PAHSR **4**.

Scheme 1. Preparation of PAHSR Reagent



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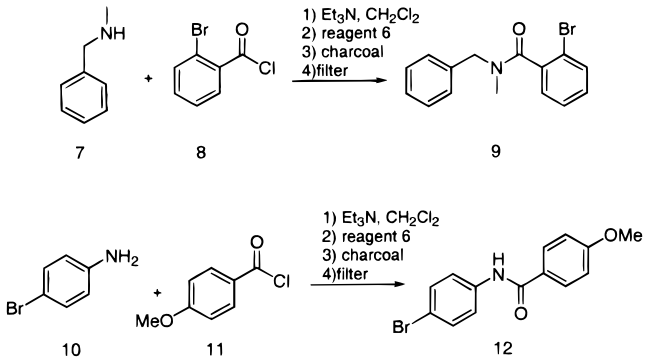
This could be deprotected in acidic methanol. We found salt **5** to be a convenient way to store and handle the PAHSR. Prior to use, the desired quantity was taken up in CH_2Cl_2 and Na_2CO_3 added. Simple filtration provided a solution of free amine **6** for use.[25]

To test the methodology, two simple acylation reactions were chosen (Scheme 2) In both, amine (0.4 mmol), Et_3N (3 mmol), and acyl chloride (0.64 mmol) were combined in CH_2Cl_2 and stirred for 5 h. At this point, a solution of the PAH scavenger reagent **6** (0.7 equiv) was added and the reaction stirred overnight. Charcoal (500 mg) was added and the reaction monitored by MS and TLC for disappearance of the bis-amide of the pyrene reagent.

Scheme 2. Reaction Purification by PAHSR Reagent



The reaction was filtered and concentrated. NMR indicated pure product in both reactions. No trace of the PAH reagent, or products from the scavenger reagent, was detected.

These experiments showed that a PAHSR could be used for parallel synthesis. During the course of this work, it was noted that the researchers became sensitized to the pyrene reagent, in particular the pyrene chloride or bromide. This caused repeated cases of allergic dermatitis that were exacerbated by sunlight. It was therefore deemed prudent to discontinue research with this reagent. Work has continued with another PAH anchor group that is devoid of these toxic effects. This research will be reported in due course.

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(25) Data for PAHSR reagent **6**: ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 1H, J = 9.1 Hz), 7.97(m, 8H), 4.2 (s, 2H), 2.67 (t, 2H, J = 5.9 Hz), 2.55 (t, 2H, 5.9 Hz); MS (CI) M(+1) 486; melting point of the HCl salt, 157 °C.