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Alternative base matrices for solid phase quenching reagents

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Abstract

In this paper we describe the use of macroporous, highly cross-linked poly(styrene-divinylbenzene) as a base matrix for solid phase scavengers. We demonstrate that this matrix is superior to the more traditional Merrifield resins when non-swelling solvents like acetonitrile are used. A small library of sulfonamides is generated in high purity as an example. © 2000 Elsevier Science Ltd. All rights reserved.

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Introduced in this decade, combinatorial chemistry is widely practiced in the pharmaceutical and biotechnology industry and is regarded as an important component of the drug discovery process. While traditional combinatorial chemistry is carried out on solid supports, the use of solution phase techniques for library generation is gaining momentum. Approximately 30–40% of all published libraries in 1998 utilized this technique.[1] The introduction of solid-supported scavengers facilitated this trend[2,3] and now several types are commercially available. Reactive groups (e.g. amine, aldehyde, thiol, hydrazine, isocyanate) linked to poly(styrene-divinylbenzene) beads (typically 1 or 2% crosslinked) are used to quench excess or unreacted starting materials of complementary reactivity in solution. These quenching reagents are particularly useful in combinatorial chemistry, where the purification of large numbers of compounds is difficult to achieve using traditional methods such as recrystallization or flash chromatography. However, the commercially available quenching reagents do have some drawbacks. First, they must be used in solvents with good swelling properties, such as DMF, methylene chloride, or THF. These solvents are undesirable when running thousands of reactions — DMF is difficult to remove from the final product, methylene chloride is toxic, and THF may contain peroxides. Secondly, according to most manufacturers' instructions, an excess of quenching reagent is required for a few hours to overnight to completely remove impurities. This translates into longer synthesis times when running large numbers of reactions. Kaldor et al. reported that polystyrene linked benzaldehyde could be used to quench excess primary amines in methanol with dichloromethane as a cosolvent.[4] The reaction used two equivalents of quenching resin and required an overnight reaction time to completely remove all of the excess reagents. Our goal was to find alternative base matrices for solid phase quenching reagents that would rapidly

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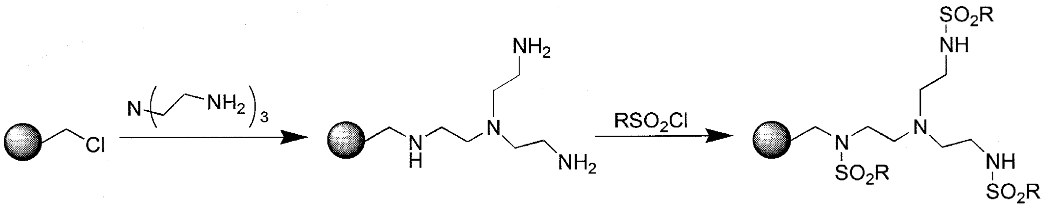
(15 minutes or less) remove impurities in solvents more suited for parallel solution phase combinatorial chemistry, such as acetonitrile.

Macroporous, highly cross-linked polystyrenes are the base matrices of choice for solid phase organic synthesis in acetonitrile because they swell equally in polar and non-polar solvents as long as the solvent wets the surface.[5] In addition, macroporous resins are widely used as chromatography matrices, where good mass transfer between the pores and the bulk solvents can overcome the slow diffusion kinetics experienced when 1–2% crosslinked gels are used.[6] Based on these facts, we investigated the use of macroporous, highly cross-linked resins as matrices for quenching reagents in non-swelling solvents.

We chose the following resins for our investigation: ArgoPore-Cl (Argonaut Technologies, 190-micron beads, pore size of 90 Å) and two highly cross-linked chloromethyl resins (Polymer Laboratories, 60-micron beads, pore size of 300 Å and 1000 Å). For comparison, we included PS-Tris (Argonaut Technologies) — this is a 1% DVB crosslinked poly(styrene-divinylbenzene) which represents a typical base matrix used for quenching reagents. The various halo-resins were reacted with an excess of tris(2-aminoethyl)amine to yield the aminated polystyrene.[7] The total quenching capacity in acetonitrile of each resin was measured by reacting overnight with an excess of *trans*-β-styrene sulfonyl chloride (Scheme 1).[8] Results are shown in Table 1 below. It is clearly seen that the scavenging activity is inversely proportional to the pore size and consequently, directly proportional to the surface area. The measured activity of PS-Tris in acetonitrile is significantly lower than that in methylene chloride (3.8 mmol/g as provided by the manufacturer). This is most likely due to the low level of swelling in acetonitrile.



Scheme 1. Synthesis of macroporous Tris-resin and subsequent quenching of a sulfonyl chloride

Table 1
Amount of *trans*-β-styrene sulfonyl chloride that could be quenched in an overnight reaction in acetonitrile

Base Matrix	Quenching activity (mmol/g)
ArgoPore 90Å	0.91
PL Macroporous 60micron 300Å	0.82
PL Macroporous 60micron 1000Å	0.57
PS-Tris	0.88

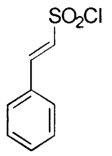
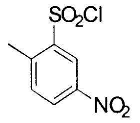
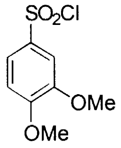
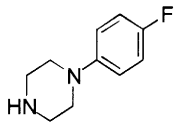
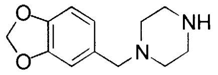
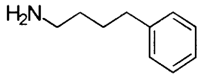
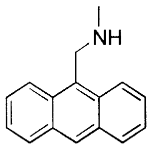
Since we wanted to limit our quench time to 15 minutes, we performed 'rapid quenching experiments' on each of the matrices. For each sample four different amounts of resin (approximately 20, 40, 60, and 80 mg) were allowed to react with 50 μmol of *trans*-β-styrene sulfonyl chloride for 15 minutes. Then the supernatants were analyzed by reversed-phase HPLC. The amount of resin was plotted against the peak area of the unquenched sulfonyl chloride. Extrapolating the curves to 0 μmol sulfonyl chloride allowed us to calculate how much resin was needed to quench 50 μmol. These values are shown in Table 2. There is a good correlation between the total activity and the 'rapid quenching' activity. The higher the total activity the less resin is needed for rapid quenching. It should be noted that the traditional Merrifield type PS-Tris was unable to quench any sulfonyl chloride in this short time presumably due to the non-swelling.

Table 2
Amount of *trans*-β-styrene sulfonyl chloride that could be quenched in a 15 minute reaction in acetonitrile

Base Matrix	**mg required to quench 50μmol**	**mmol/g/15 min**
ArgoPore	94	0.53
PL Macroporous 60micron 300A	124	0.40
PL Macroporous 60micron 1000A	163	0.31
PS-Tris	No quenching	

To demonstrate the usefulness of these resins in a parallel format, we synthesized an array of 12 sulfonamides by reacting four different amines with a two-fold excess of three sulfonyl chlorides.[9] The purity of each of the products is indicated in Table 3.[10]

Table 3
Percent purities (as judged by HPLC/ELSD) of sulfonamides derived from the corresponding amine and sulfonyl chloride

			
	100	95	100
	100	100	100
	100	96	100
	100	100	100

In conclusion, we demonstrated for the first time that highly cross-linked macroporous poly(styrene-divinylbenzene) is a very viable base matrix for generating solid phase scavenger resins. In less than three hours we could generate an array of sulfonamides in extremely high purity using only acetonitrile as a solvent. The quenching of excess sulfonyl chloride required no co-solvent and was complete within

15 minutes. Synthesis of other scavengers and solid phase reagents, as well as further investigation of the effect of particle and pore sizes is underway.

Acknowledgements

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7. To a mixture of macroporous highly cross-linked polystyrene beads (1.75 g) in *N*-methyl pyrrolidine (20 mL) was added tris(2-aminoethyl)amine (3 mL). The mixture was agitated overnight in a heater/shaker at 60°C. The beads were washed three times each with DMF, methanol, methylene chloride, ether and then dried in vacuo.
8. To a sample of Tris resin (approximately 20 mg) was added a 0.025 M solution of *trans*-β-styrene sulfonyl chloride in acetonitrile. The mixture was shaken overnight at ambient temperature, then spun down in a centrifuge. An aliquot (100 μL) was removed and added to acetonitrile (900 μL). Reverse-phase HPLC was performed and the amount of quenched sulfonyl chloride was calculated from a standard curve.
9. To a 0.025 M solution of amine (1 mL) was added a 0.050 M solution of sulfonyl chloride (1 mL) and triethyl amine (60 μL). The solution was shaken for two hours before the addition of the Tris resin derived from Argopore-Cl (1.2 equiv. based on the ‘rapid quenching’ activity). The mixture was shaken for an additional 15 minutes and then spun down in a centrifuge. An aliquot was removed and subjected to reverse-phase HPLC/ELSD to obtain the purity.
10. The purity of the reaction is in reference to only the amine and sulfonyl chloride. No attempt was made in these experiments to remove the triethylamine and triethylammonium chloride.