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Parallel Suspension Polymerization for High-Throughput Resin Synthesis

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Abstract—A simple, straightforward approach for parallel suspension polymerization is described. This technique utilizes equipment common to most organic chemistry laboratories and should facilitate the custom synthesis of new polymers.

We have recently initiated a program aimed at developing new resins for use in solid-phase organic synthesis (SPOS).[1] While substantial research has been dedicated toward optimizing linker groups for the attachment of organic molecules to resins and to developing chemistries compatible with a particular support, relatively little effort has been made toward identifying new insoluble polymer supports with improved physical and chemical properties.[2] This is somewhat surprising since the interaction of the support with the reaction solvent can profoundly affect the course of a solid-phase reaction.[3]

Our initial results saw the preparation of a range of poly(tetrahydrofuran)-based cross-linkers (**1a**–**c** and **2a**–**c**) (Fig. 1) that were co-polymerized with styrene to produce hybrid polystyrene resins.[1] Each of the six cross-linkers was incorporated at 1, 2, 5, and 10 mol%, bringing the total number of different polymers prepared to 24. One of these resins (that derived from cross-linker **2a** at 2 mol%) has been successfully utilized as a support in the parallel synthesis of phthalide,[4] tertiary amine,[5] and oxazole[6] libraries, as well as for catalysts for asymmetric epoxidation,[7] kinetic resolution of racemic epoxides,[8] and asymmetric Strecker reactions.[9]

In this earlier work, each resin was prepared individually using a conventional polymerization reactor. In an effort to not only identify novel polymers, but also to streamline the process by which these materials are produced, we sought a method that would allow entry to libraries of solid-phase resins. Combinatorial techniques are now firmly rooted in industrial settings and have more recently been applied to materials discovery. In particular, the generation of libraries of pigments, dyes, conducting polymers, and catalysts has been reported.[10] Additionally, our group has previously described a parallel methodology for the synthesis of soluble block co-polymers[11] and Fréchet and co-workers very recently disclosed a high-throughput approach to functionalized star polymers.[12] Further, libraries of degradable polymers for tissue engineering applications[13] and for use as transfection vectors in gene

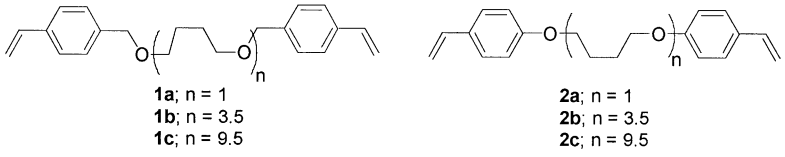

Figure 1.

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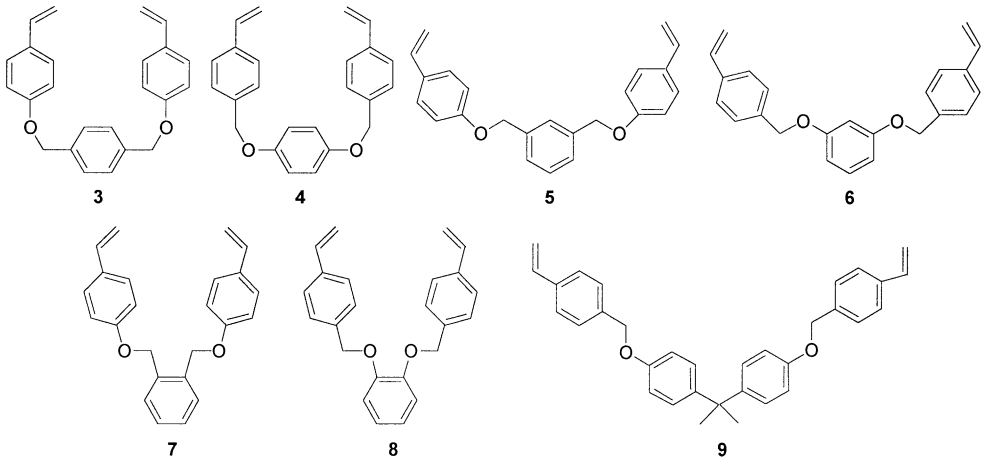

Figure 2.

therapy[14] have been synthesized. Finally, a specialized, non-commercially available apparatus for multiparallel polymerization was very recently detailed.[15] This has prompted us to report our technique for parallel suspension polymerization that is simple to use and readily available from common laboratory equipment.

Results and Discussion

For this study, we have chosen to examine three polymerization variables that greatly affect the properties of the resulting polymers: cross-linker structure, % cross-linking, and porogen. The porogen acts as an organic co-solvent and, based on its structure, can affect the size of the micropores in the resulting gel-type resin. Consequently, swelling properties of a polymer are intrinsically linked to the nature of the porogen in addition to the two other variables under examination.

The seven cross-linkers **3**–**9** shown in Figure 2 have been prepared in one step from commercially available materials.[16] They are related to the original cross-linkers **1** and **2** in that two *para*-substituted styrene units are linked by a bis-oxygen containing tether. However, this tether now contains a disubstituted aromatic ring (**3**–**8**) in which the two substituents (each styryl unit) can be disposed in either a *para* (**3**–**4**), *meta* (**5**–**6**), or *ortho* (**7**–**8**) manner. Cross-linker **9** was prepared from bisphenol A and contains two aromatic units between the capping styryl moieties. It was expected that the differing connectivities of the cross-linkers would be reflected in the properties of the polymer products. The remaining two variables will also be examined systematically. Cross-link percentages of 1, 2, 5, 10, and 20 as well as a number of porogens including chlorobenzene, veratrole, toluene, trifluoromethyl benzene, and 1,3-bis(trifluoromethyl)benzene were probed.

For the purpose of determining a reliable experimental set-up and suitable reaction conditions, a polystyrene-based polymer was prepared utilizing cross-linker **6** at 2 mol% with chlorobenzene as the porogen. This reaction was effectively carried out on a 500 mg scale in 15-mL screw-cap test tubes with vigorous magnetic stirring by a small 'flea' stir bar. This ensured proper formation of tiny organic droplets (each of which becomes a resin bead) that are suspended in the aqueous phase. The potential for parallel reactions was illustrated by simultaneously running eight identical test tube polymerizations as per the reaction in Figure 3 (cross-linker = 2 mol% **6**, porogen = chlorobenzene). Each reaction tube, supported by a heat-resistant divider grid immersed in an oil bath, stood upright in the bath that was resting on top of a magnetic stirrer/hotplate. In each case, good quality polymer was produced in modest to high yield (60–80% of 40–200 mesh). The reaction was next performed on a larger scale (10 g) in a conventional polymerization apparatus to give polymer with nearly identical swelling characteristics[17] as that produced in the parallel set-up, thus demonstrating that the integrity of the resin is not compromised when prepared under the parallel conditions.

With this success, we were in a position to evaluate the three critical polymerization variables using the parallel format. Every combination of seven cross-linkers at 5 cross-link percent with five porogens—a total of 175 reactions—was studied. Through this series of experiments, which took about 2.5 weeks to complete, a number of trends emerged. The *para* cross-linkers **3**–**4** were soluble in the porogens examined only upon heating and tended to precipitate upon addition to the polymerization mixture. As a result, no polymer was formed. Cross-linkers **5**–**9** did not have solubility problems, with the exception of 20 mol% incorporation, and reliably produced resin beads. In general, the *meta*-disposed cross-linkers **5**–**6** as well as cross-linker **9** produced resin with superior swelling characteristics compared to the *ortho* cross-linkers **7**–**8**. Predictably, in

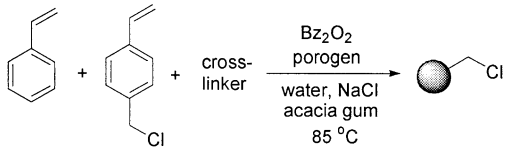

Figure 3.

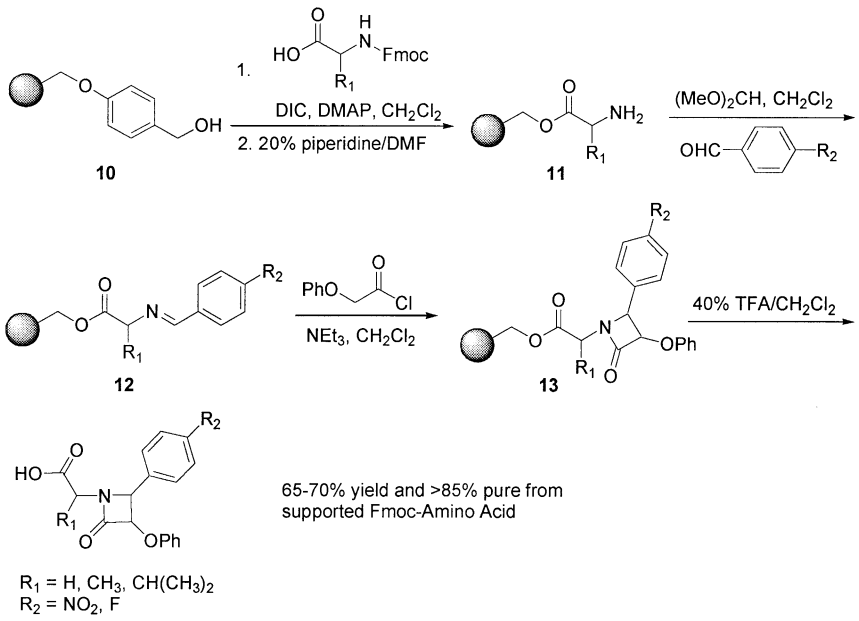

Figure 4.

every case, increased cross-linker incorporation resulted in decreased resin swelling. In terms of the porogen, no apparent differences in resins prepared from chlorobenzene, veratrole, or toluene were noted; use of the two remaining porogens provided inferior results in terms of polymer yield (related to cross-linker solubility) or polymer swelling.

The resin derived from cross-linker **9** at 2 mol% with chlorobenzene as porogen was prepared on a large scale in a traditional polymer reactor and used in a short synthetic sequence (Fig. 4). A small library of six β-lactams was prepared from three different amino acids and two benzaldehydes using methodology developed by Gallop and co-workers.[18] Thus, to the benzyl chloride resin taken from the parallel library was attached the Wang linker[19] to give resin **10**. Fmoc-protected glycine, alanine, and valine were then coupled followed by Fmoc removal. Each supported amino acid was condensed with either 4-nitro- or 4-fluorobenzaldehyde and the resulting imine was reacted with phenoxyacetyl chloride and triethylamine to give the supported β-lactam **13**. This reaction was readily monitored by the presence of an IR stretch in the range of 1760–1775 cm^{-1} corresponding to the amide carbonyl group. Cleavage from the resin with 40% TFA in CH_2Cl_2 gave the expected products as mixtures of diastereomers in 65–75% and ~85% purity as judged by ^1H NMR spectroscopy.

In conclusion, the parallel suspension polymerization method described herein will make custom bead synthesis an efficient and realistic process. This is important since commercially-available supports do not always provide the ideal properties for a given application. Through this technique, polymer properties can be tuned in a systematic manner by slight adjustments to the monomer and cross-linker structure and/or ratios. While it is clear that the parallel procedure described here is somewhat rudimentary when compared to the many robotic-driven systems available for parallel organic molecule synthesis, we feel that it is simple enough to be exploited by any researcher. The equipment required is standard in any synthetic laboratory, requires little or no training for familiarity, and is novel in its simplicity. This methodology is currently being exploited in our laboratories for the synthesis of diverse libraries of aqueous-compatible polyacrylamide resins for potential use in biomedical applications.

Acknowledgements

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