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Preparation of Designer Resins via Living Free Radical Polymerization of Functional Monomers on Solid Support

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Merrifield resin is converted to a solid-supported free radical initiator by reacting with the TEMPO-Na. Heating TEMPO-methyl resin with a variety of functionalized styrene and acrylate monomers gives larger resin beads via living free radical polymerization. We have coined the term Rasta resin to describe resin beads prepared in this fashion. The process can be described as a solvent-free suspension polymerization. It is particularly well suited for preparation of resin beads from monomers which contain electrophilic groups that would be destroyed upon suspension polymerization in water. Rasta resins have a novel macromolecular architecture wherein long straight chain polymers bearing reactive functional groups emanate from the phenyl groups of a cross-linked polystyrene core. With judicious choice of co-monomers and polymerization strategy, the solvent affinity, loading capacity, and distance of functionality from the cross-linked core may be controlled giving beads with properties that are tailored to specific uses as synthesis supports and scavenging resins.

Introduction

Solid supports have been used in a variety of ways to facilitate combinatorial synthesis. The method of solid phase synthesis, whereby a starting material is attached to a solid support and subsequently modified by one or more synthetic transformations prior to cleavage of the final product from the support in substantially pure form, is in fact responsible for the genesis of the field of combinatorial chemistry.[1] More recently, solid-supported scavengers have been employed in solution phase parallel synthesis in order to purify combinatorial libraries prepared via solution phase methods.[2] A variety of solid-supported nucleophiles and electrophiles make excellent scavengers for the sequestration of excess reactants, thereby facilitating parallel isolation of the desired library members in a process that is amenable to automation.

Methylisocyanate polystyrene is a scavenger resin which is useful for sequestration of amines.[3] The loading of isocyanate groups that is possible by converting aminomethyl polystyrene to methylisocyanate polystyrene is limited. Despite a considerable effort at process optimization, the maximal reproducible loading in our hands is about 1.5 mmol NCO groups per gram of resin. The formation of urea cross-links competes with isocyanate formation at higher loading. Increasing the isocyanate loading above 1.5 mmol/g is desirable for the purpose of scavenging since it would allow a decrease in reaction workup volume. Additionally, the three-step process of preparing methylisocyanate polystyrene from polystyrene resin uses expensive (chloromethylphthalimide) and hazardous (hydrazine and phosgene) reagents and therefore results in an expensive resin. A simpler process for producing scavenger resins bearing isocyanate groups would be more cost-effective, particularly if loading is increased. A number of alternatives to methylisocyanate polystyrene resin for scavenging amines have recently been described.[4]

Most solid-supported syntheses utilize polystyrene that is cross-linked with 1−2% divinylbenzene as the support. In the vast majority of cases, the linker functionality is attached to the phenyl rings of the pre-polymerized polystyrene-divinylbenzene beads via chemical reactions.[1b,5] Alternatively, selected functional styrenes have been employed and used in suspension polymerization to create polystyrene resins with desirable linker functionality.[6] A major requirement of this latter technique is that the functional monomers neither react with nor dissolve in water, the most frequently used suspending solvent. Regardless of the method of preparation, a nonpolar resin-swelling solvent is normally required for reagents to penetrate all of the attachment sites on low cross-linked polystyrene beads.

A second popular solid phase synthesis resin is Tentagel.[7] Tentagel resin consists of a cross-linked polystyrene core from which tentacles of poly(ethylene glycol) emanate. The hydroxy terminus of each poly(ethylene glycol) tentacle serves as the attachment point for a variety of linkers that are useful in solid phase synthesis. Unlike polystyrene resins, Tentagel swells in a wide variety of both polar and nonpolar solvents. However, the price paid for this solvent flexibility is the added mass of the ethylene glycol tentacles which decreases the loading of attachment sites. The result is that Tentagel resin is generally not considered useful for preparation of scavenger resins and is reserved for solid phase synthesis.

Soluble polymer supports provide an alternative to insoluble solid supports in combinatorial synthesis. Most widely used is poly(ethylene glycol) which may be attached to a starting material and then subjected to synthetic transformations.[8] After each reaction, the polymer-supported material is isolated by precipitation following addition to diethyl ether. Soluble dendrimers have also been employed as supports for combinatorial chemistry.[9] Synthetic inter-

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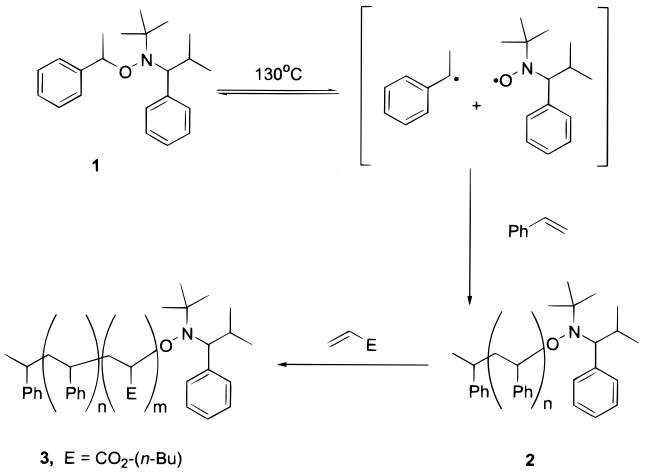
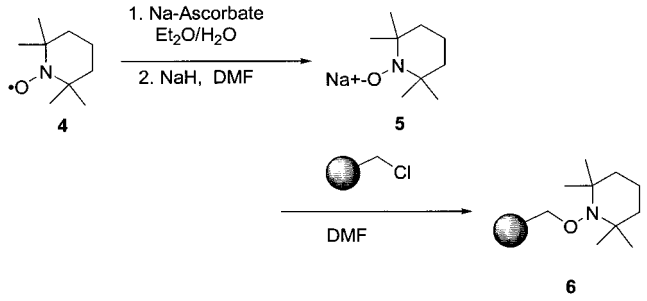
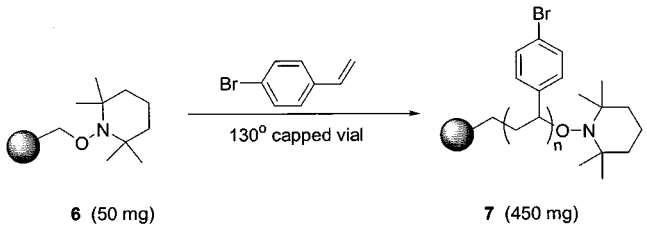
Scheme 1. Nitroxide-Mediated Living Free Radical Polymerization of Block Copolymers[12b]



Scheme 2. TEMPO-Methyl Resin Synthesis



Scheme 3. Solid-Supported Polymerization of 4-Bromostyrene



mediates and products that are attached to dendrimers are easily isolated by size exclusion chromatography or ultrafiltration. Since the large molecular size is shared by all library members, a common and parallel means of separation is easily achieved. One reported advantage of using soluble polymer or dendrimer supports is that synthetic route development is simplified since the reactions are homogeneous and predictable solution phase reaction kinetics are more apt to apply.

Initially, the search for a high loading isocyanate scavenger resin led us to consider polymerization of isocyanate bearing monomers. One report of suspension polymerization of methacryloyloxyethyl isocyanate in perfluorocarbon solvent which prepared resin beads bearing 5.2 mmol nitrogen per gram (presumably 5.2 mmol NCO per gram) looked most promising.[10] This process is complicated by the fact that methacryloyloxyethyl isocyanate appears on the Environmental Protection Agency's list of chemicals with high acute toxicity, making the monomer difficult to obtain and clearly undesirable to use on a large scale. Additionally, perfluorocarbon solvents are expensive albeit potentially easy to recycle.

The subject of living free radical polymerization has received considerable attention in the recent literature.[11] One method by which straight chain soluble polystyrenes and polyacrylates with low polydispersity may be prepared involves heating these monomers with a benzylic nitroxide initiator such as 1-phenylethyl-TEMPO[12a] and 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane.[12b] Benzylic nitroxides reversibly thermolyze above 123 °C, generating a benzyl radical and nitroxyl radical. The benzyl radical is free to react with the monomer, and polymerization ensues. Chain termination reactions such as the condensation of two benzyl radicals are inhibited by the presence of nitroxyl radicals. Upon cooling, the nitroxyl radical recombines with the benzyl radical at the polymer terminus to generate a polymer that can serve as an initiator in subsequent rounds of polymerization (Scheme 1).

A variety of strategies for solid-supported polymerization have appeared in the recent literature. Included are methods for radical polymerization of acrylamides onto acrylamide derivatized polystyrene,[13] dendrimer growth on various solid supports,[14] ring opening olefin methathesis on vinyl polystyrene,[15] and the use of nitroxide-mediated living free radical polymerization to attach polystyrene combs to silicon wafers.[16] To this growing body of literature on solid-supported polymerization we add the following results.

Results and Discussion

As shown in Scheme 2, reduction of commercially available TEMPO radical, **4**, by treatment with sodium ascorbate followed by deprotonation with NaH in DMF gives the sodium salt of TEMPO, **5**. Addition of a solution of excess of **5** in DMF to Merrifield resin affords TEMPO-methyl resin, **6**. We have noticed that complete displacement of chlorine from Merrifield resin by TEMPO-Na is difficult to achieve with some lots of resin and easy to achieve with others even when the Merrifield resin was purchased from a single manufacturer. In general, higher loading Merrifield resin is more difficult to react quantitatively with TEMPO-Na. These inconsistencies aside, resin bearing 0.8 to 1.0 mmol TEMPO-methyl groups per gram is easily achieved from Merrifield resin that was ~1.2 mmol Cl per gram. In those cases where traces of Cl remain, no deleterious effect on subsequent living polymerization reactions was observed.

Heating **6** with ~92-fold molar excess of freshly distilled 4-bromostyrene under an inert atmosphere at 130 °C leads to nearly complete solidification of the monomer in 3 h (Scheme 3). After cooling the resulting polymeric mass, addition of DCM dissolves any remaining monomer and some soluble polymer. Filtration and washing with several cycles of alternating portions of DCM and MeOH affords free flowing resin beads following drying at reduced pressure. These beads, **7**, are visibly larger than **6**, show a 9-fold increase in mass, and contain 40.4% Br and 0.13% N by elemental analysis. They remain round in shape, swell in DCM, and shrink in MeOH.

We have coined the term "Rasta resin" to describe this new type of resin bead wherein linear polymers emerge from some of the phenyl rings of the core polystyrene bead.[17] In

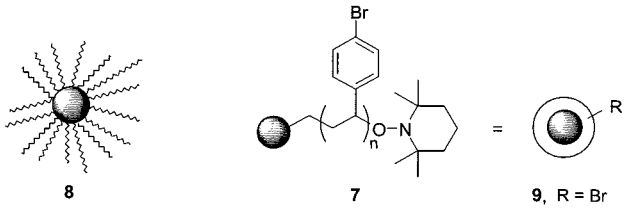


Figure 1. Rasta resin cartoon architecture and shorthand representation.

Scheme 4. Attempted Polymerization of TMI

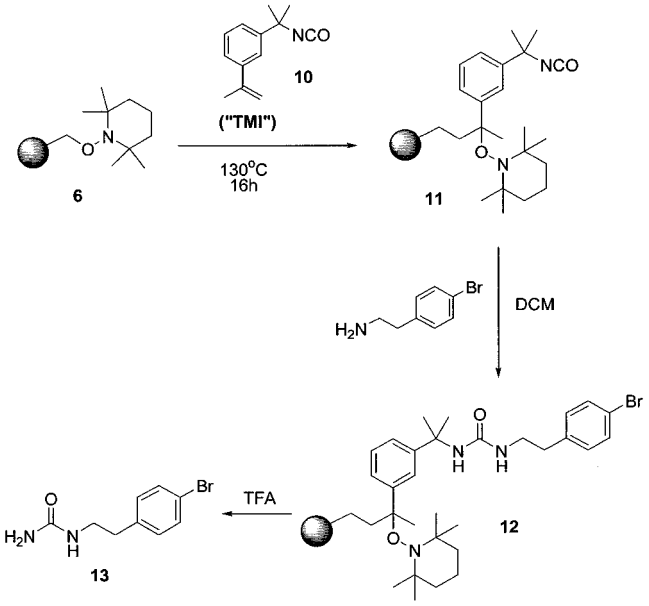
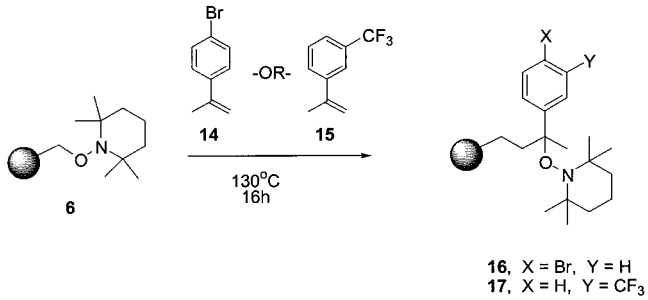


Figure 1, the architecture of a Rasta resin is represented by the cartoon structure, **8**. The original cross-linked bead is depicted by the shaded circle, and the new polymer growth is represented by the hair-like appendages. A shorthand representation of **8** is shown by **9** wherein the shaded inner circle represents the original cross-linked bead, the white outer circle represents the new linear polymer, and R is any functionality on this new polymer. It is interesting that **7** is difficult to crush with a mortar and pestel whereas **6** is readily ground to a powder. This resistance to crushing is shared by other Rasta resins described below and is likely a result of the lack of cross-linking in the new polymer growth.[15]

Encouraged by the above results, we attempted to prepare a Rasta resin from the inexpensive monomer, 3-isopropenyl-α,α-dimethylbenzyl isocyanate (TMI, **10**). When **6** is heated with TMI as above for 18 h, a polymeric mass does not result (Scheme 4). The beads remain suspended in TMI monomer. Recovery of the beads by filtration, washing with alternating cycles of DCM and hexanes, and drying affords small product beads (**11**) with a strong isocyanate stretch in the IR spectrum. Elemental analysis of **11** is consistent with the addition of a single TMI residue. Treatment of **11** with an excess of 2-(4-bromophenyl)-ethylamine in DCM affords **12**. Again, elemental analysis is consistent with a ratio of three N for each Br. Finally, treatment of **12** with 30% TFA in DCM affords the primary urea **13** as an analytically pure solid upon evaporation of solvents. No evidence of TEMPO cleavage was seen by NMR. The yield of **13** is consistent with 1 mmol NCO per gram of **11**.

Scheme 5. Resins with Tertiary Benzylic TEMPO Ethers



While the initial result with TMI polymerization was disappointing, it points out a potentially useful transformation. When **6**, which is a solid-supported initiator that contains primary benzylic TEMPO ether residues, is heated with an α-methylstyrene it is converted to a solid-supported initiator with tertiary benzylic residues. Secondary benzylic nitroxides have been shown to be superior initiators compared to primary benzylic nitroxides in homogeneous versions of living free radical polymerization.[11,12] The former have a shorter half-life at 123 °C and thereby reduce the degree of polydispersity in the polymeric product. Tertiary benzylic nitroxides have not previously been described, but based upon well established patterns of free radical stability (3° > 2° > 1°) one would expect that a tertiary benzylic TEMPO adduct would also have a short half-life above 123 °C and promote uniform polymer length. For comparative purposes, 4-bromo-α-methylstyrene (**14**) and 3-trifluoromethyl-α-methylstyrene (**15**) were prepared and heated with **6** for 24 h (Scheme 5). Halogen analyses for **16** and **17** are consistent with limited incorporation of the α-methylstyrene moiety (∼1.3 α-methylstyrene equivalents per TEMPO initiator site); however, lower than expected *N* values were obtained in both cases, indicating the possible elimination of TEMPO-H from tertiary benzylic positions on prolonged heating at 130 °C. It is noteworthy that the filtrates from these two polymerization reactions both turn red upon standing, consistent with air oxidation of TEMPO-H to TEMPO•. On the basis of elemental analysis, approximately half of the TEMPO ether residues appear to have been lost from the polymer in both cases.

Though TMI is known not to self-polymerize by a free radical mechanism, it has been shown to copolymerize with other less hindered monomers such as butyl acrylate (BA) and styrene (ST). With proper ratios of co-monomers, a polymer of alternating monomers results.[18] Thus, when **6** (∼1 mol % TEMPO) is heated with a mixture that is 61 mol % TMI and 39 mol % BA, the Rasta resin **18** is formed (Scheme 6). The IR spectrum of **18** shows both isocyanate and ester absorbances at 2259 and 1733 cm^{-1}, respectively. Figure 2 shows photographs of **6** and **18** at equal magnification. Reaction with 2-(4-bromophenyl)-ethylamine and subsequent TFA cleavage as described above for **11** provides a consistent trail of evidence supporting a loading of ∼2.5 mmol NCO per gram of **18**. Similarly, when **6** (∼1.3 mol % TEMPO) is heated with a mixture that is 64 mol % TMI and 36 mol % ST, the Rasta resin **19** is formed. The IR spectrum for **19** shows a strong isocyanate absorbance. The loading was analogously established to be ∼2.5 mmol NCO

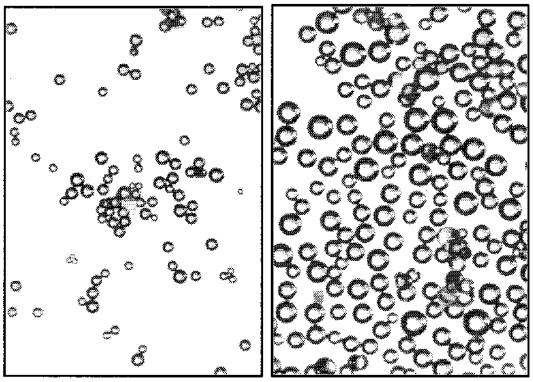
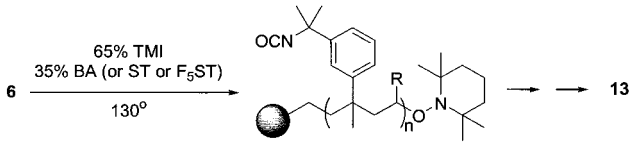


Figure 2. Resin photographs (equal magnification).

Scheme 6. High Loading Rasta-NCO Resins



18, R = CO_2Bu
19, R = Ph
20, R = pentafluorophenyl

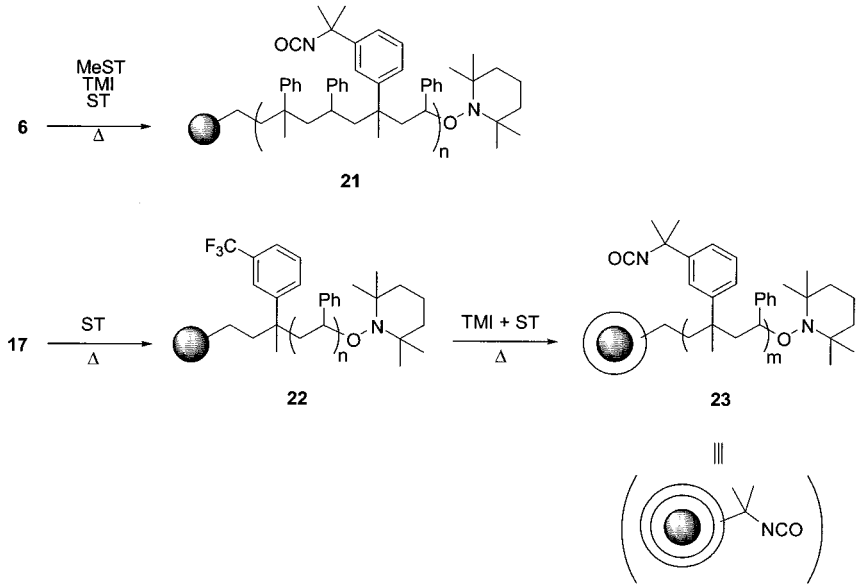
per gram of **19**. In yet another variation, heating of **6** with a 64:36 mixture of TMI and 2,3,4,5,6-pentafluorostyrene (F_5ST) affords **20** with a loading of ~2.3 mmol NCO per gram. In all three cases, **13**, which is produced from **18**, **19**, and **20**, crystallizes as an analytically pure solid upon evaporation of DCM and TFA and shows no traces of TEMPO or resin fragments by NMR.

If desired, the loading of isocyanate groups may be attenuated by diluting the polymerization mixture with α-methylstyrene (MeST). Thus heating **6** (~0.7 mol %) in a mixture of TMI (32 mol %), MeST (32 mol %), and ST (36 mol %) provides **21** with a loading established at ~1.4 mmol NCO per gram (Scheme 7). Furthermore, the isocyanate groups may be confined to the tips of the new polymer growth by stepwise growth of a triblock copolymer. Heating of **17** with ST gives **22** which is isolated and subsequently heated with TMI and ST to afford **23**. The loading for **23** was established as previously described to be ~1.0 mmol NCO per gram. A shorthand representation for **23** wherein the two rounds of living polymerization provide the outer two colorless layers of the bead is shown in parentheses below the structure.

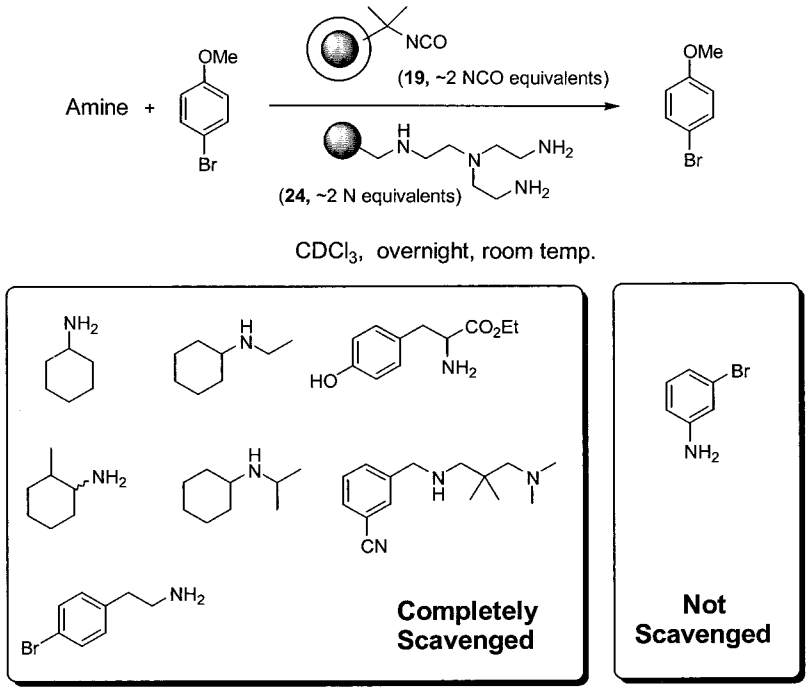
The facile preparation, cleavage, and isolation of pure **13** in high yield, while not a rigorous test of suitability for solid phase synthesis applications, at least demonstrates convenient loading and cleavage reactions on Rasta-NCO resins. Within the constraints of urea reactivity, it is reasonable to expect that it would be possible to attach an amine to the resin, perform additional synthetic transformations, and cleave the product from the resin as a primary urea adduct. Furthermore, it should be possible to fine tune the solvent affinity and linker reactivity of Rasta-NCO resins through the appropriate choice of the co-monomer(s) for TMI and location of the isocyanate groups in the new polymer growth. Detailed studies using **19**, **21**, and **23** as supports in solid phase syntheses are in progress and will be reported in due course.

The scope and limitations of **19** as a solid-supported scavenger were investigated with a variety of amines under a protocol that mimics a typical parallel purification for a solution phase library (Scheme 8). Equimolar quantities of an amine and 4-bromoanisole were dissolved in $CDCl_3$ and the solution was then shaken with a 2-fold excess each of resin **19** and polyamine resin[3b] **24** overnight. An NMR spectrum of the filtrate shows that all of the amines were completely scavenged except 3-bromoaniline which remained in virtually identical concentration with the internal standard. Only resonances attributable to 4-bromoanisole and hexanes (trapped in the resin on drying) were visible in the NMR spectra. Under the conditions of this experiment, no difference in reactivity between **19** and methylisocyanate polystyrene was detected. It is worth noting that visual inspection of the recovered bead mixture shows no evidence of reaction between **19** and **24**. In other words, the reactive functionality on the Rasta-NCO beads remains isolated from that of the polyamine beads.

Scheme 7. Controlled Loading and Spacing



Scheme 8. Scope and Limitations of **19** as a Scavenger Resin



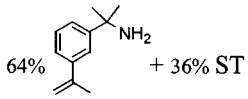
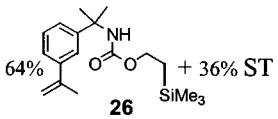
The scope and limitations of monomers and co-monomers in forming Rasta resins are described in Table 1. A variety of functional monomers were successfully polymerized on TEMPO-methyl resin either alone or when mixed with co-monomers. It is worth noting that the preservative that is added to commercial monomers can in some instances inhibit the living polymerization process. This was most dramatically observed in the case of BA which did not appreciably polymerize onto **6** unless the preservative was inactivated. Aside from distillation, there are two other convenient methods for avoiding the deleterious effects of preservatives in commercially obtained monomers: (1) filtration from highly basic resins and (2) in situ inactivation by an acylating reagent. In our hands, a convenient reagent for in situ inactivation of phenolic preservatives is *m*-tolyl isocyanate (0.5−1 mol % added directly to the polymerization mixture). In those cases where TMI is used as a monomer, the addition of another isocyanate is obviously unnecessary.

One monomer that illustrates a potential limitation is the amine **25** which is prepared by hydrolysis of TMI. In a single attempt where **6** was heated with **25** and styrene, a polymeric mass was not formed and the beads do not gain significant mass. Nitrogen content of the resulting resin is increased by about 50% relative to **6** and a small amino absorbance is seen at 3367 cm^{-1} in the IR spectrum. Better results were obtained with monomer **26** where the amine is protected as its trimethylsilylethyl carbamate which allowed in situ inactivation of the preservative in ST.

The use of acrylic anhydride (AA) as a monomer also proved troublesome in three different experiments. AA is reported to undergo cyclopolymerization to form a chain of cyclic anhydrides when heated with radical initiators such as AIBN.[19] Depending upon concentration, solvent polarity, and temperature, the chain can be either predominantly six-membered rings or five-membered rings. The effect of nitroxide initiators on AA cyclopolymerization is not described in the literature. In our hands, heating **6** with neat AA provided a hard polymeric mass in only 2 h. Visual inspection shows beads imbedded in the polymeric mass which could not be liberated with common solvents including DCM, DMF, dioxane, EtOAc, and toluene, even upon heating. Similarly, heating **6** with a mixture of TMI (64 mol %) and AA (36 mol %) produced a polymeric mass in 3 h from which the beads could not be liberated. Alternatively, heating **6** at 130 °C with a solution of AA (64 mol %) in dichlorobenzene (36 mol %) gave a gelatinous mass after 20 min. Upon cooling, the resin beads could be separated from this mass by washing with two cycles of dioxane, DMF, DCM, and hexanes; however, the isolated beads showed no increase in mass. In this last case, it would appear that incomplete polymerization of AA happened in solution to give polymer of low enough molecular weight and sufficient solubility to be washed away. There is no evidence for polymerization on the bead by a living process.

A limited study of the scope and limitations of starting resins is shown in Figure 3. Three types of resins with varying degrees of cross-linking and levels of TEMPO-methyl loading were compared, side by side, in polymerization reactions with TMI plus ST. For a high cross-linking, macroreticular resin, chloromethyl Argopore (60−140 mesh bead size) was used. This was compared to two resins with 1% (100−200 mesh) and 2% (200−400 mesh) cross-linking. The TEMPO-methyl loading was modulated by partial displacement of Cl with substoichiometric amounts of sodium methoxide, followed by displacement of the remaining Cl with excess TEMPO-Na. Nitrogen analysis was used to estimate the TEMPO-methyl loading. The following trends were observed: (1) The two low cross-linked resins grew more new polymer than the high cross-linked resin. (2) With both low cross-linked resins, the amount of new polymer growth on the bead is proportional to the TEMPO-methyl

Table 1. Monomer Scope and Limitations

Monomer(s)	Initiator (Mol %)	Inhibitor Removal	Time (hr.)	P / I *	IR (cm^{-1})	Analysis
ST	**16** (0.25)	*m*-Tolyl-NCO	24	12.6	697 1069	C 91.44; H 7.48; N 0.07; Br 0.64
ST	**17** (0.25)	*m*-Tolyl-NCO	24	12.6	1126 1328	C 91.72; H 7.75; N 0.07; F 0.71
4-BrST	**6** (1.0)	PS-base[#]	3	9	1072 1484	C 55.74; H 4.39; N 0.13; Br 40.40
F_5ST	**6** (0.8)	*m*-Tolyl-NCO	18	13.1	959 1496	C 52.56; H 2.02; N 0.19; F 44.83
3 & 4-$ClCH_2$ST	**6** (1.0)	none	15	>6[+]	1265 2924	C 73.73; H 6.22; N 0.05; Cl 19.35
3 & 4-$HOCH_2$ST	**6** (1.5)	none	18	1.8	3150 to 3550	C 81.89; H 7.34; N 0.21
BA	**6** (2.4)	*n*-Bu-NCO	5	1.8	1734 2923	C 78.37; H 8.85; N 0.81
AA	**6** (1.7)	none	2	?[++]	-	-
64% AA + 36% 1,2-dichlorobenzene	**6** (2.1%)	none	0.33	1.0	-	-
61% TMI + 39% BA	**6** (1.6)	none	24	5.6	1733 2259	C 76.04; H 8.33; N 3.81
62% TMI + 38% BA	**11** (0.7)	none	20	5.9	1731 2258	C 74.21; H 8.05; N 3.96
64% TMI + 36% ST	**6** (1.25)	none	20	5.2	699 2251	C 83.65; H 8.00; N 3.67
64% TMI + 36% ST	**11** (1.4)	none	24	4.2	697 2249	C 84.20; H 8.03; N 3.63
64% TMI + 36% F_5ST	**6** (0.9)	none	18	9.2	1499 2250	C 67.63; H 5.44; N 3.48; F 17.26
64% TMI + 36% ST	**22** (0.02)	none	18	1.35	697 2259	C 88.62; H 7.92; N 1.55; F 0.55
64% TMI + 36% AA	**6** (0.6)	none	3	?[++]	-	-
68% MeST + 32% (3 & 4-$ClCH_2$ST)	**6** (1.2)	none	18	2.3	697 1265	C 81.93; H 7.27; N 0.20; Cl 9.66
 **25**	**6** (1.2)	none	24	1.04	697 3368	C 87.17; H 8.45; N 2.58
 **26**	**6** (4.0)	*m*-Tolyl-NCO	15	1.7	697 1730	C 81.56; H 8.57; N 1.97; Si 1.85
32% TMI + 32% MeST + 36% ST	**6** (0.8)	none	18	6.5	697 2259	C 86.95; H 8.21; N 2.30

*Weight of product beads/weight of initiator beads. [#] 1,5,7-Triazabicyclo[4.4.0]dec-5-ene on polystyrene-divinylbenzene beads (Fluka). [+] Some beads could not be freed from the polymeric mass and are not included. [++] All beads stuck in an intractable polymeric mass.

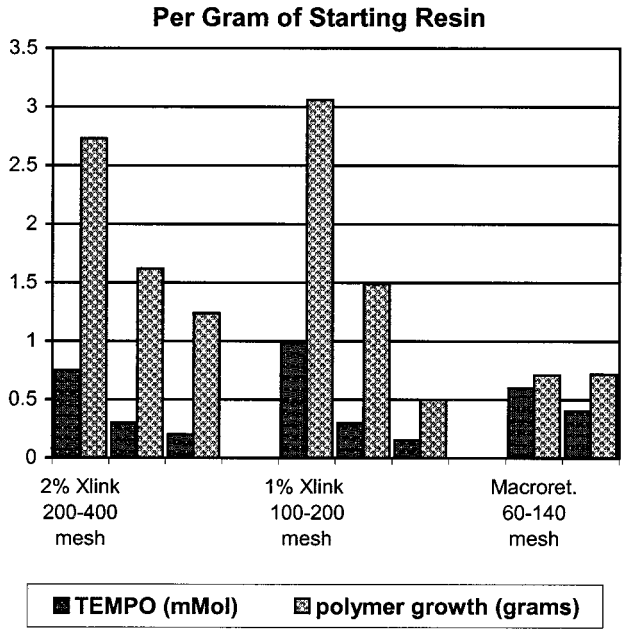


Figure 3. Scope and limitations for solid support.

loading. (3) Bead size (surface area) had no obvious effect in the range tested.

Summary

We have demonstrated the use of nitroxide-mediated living free radical polymerization in the generation of novel supports for combinatorial chemistry, called Rasta resins. This solvent-free process compliments existing methods for preparation of functionalized resins that are intended for combinatorial chemistry applications. It is particularly useful for the suspension polymerization of monomers bearing water-sensitive functionality; however, a wide variety of water-insensitive functional monomers may also be employed, leading to a broad range of functional resins. Rasta resins have a unique bead architecture wherein long linear functional polymer chains emanate from a nonfunctional, cross-linked core. This architecture allows for the preparation of designer resins with fine-tuned solvent affinity, functional group loading, functional group spacing, and solution phase reagent accessibility. The strategic use of α-methylstyrenes as co-monomers with styrenes and acrylates is integral to control of functional group spacing and loading in many Rasta resins. Stepwise block polymerization provides control of the distance of desired functionality from the cross-linked core. TEMPO-methyl resin, **6**, is a conveniently prepared and broadly applicable polymer-supported initiator from which Rasta resins or other solid phase initiators may be prepared. Particularly noteworthy from this investigation is the high loading isocyanate resin **19** which is prepared from **6** by heating with TMI and ST. This resin is a useful parallel purification tool with reactivity suited for scavenging a wide variety of primary and secondary amines.

Experimental Section

General. Merrifield resin was purchased from Novabiochem (product number 01-64-0070, 100−200 mesh, 1% cross-linking, 1.2 mmol Cl per gram of resin). TEMPO• was purchased from Aldrich Chemical Co. Except for those monomers with preparation described below, monomers were used as obtained from commercial suppliers without distillation. Polymerization reactions were carried out under N_2 atmosphere in septum capped tubes. Heating was provided by an aluminum well dry bath (Barnstead Thermolyne model DB28215) with temperature monitored by a thermometer inserted into the aluminum block. Gentle agitation was achieved at early stages of the polymerization reactions by shaking the dry bath on an orbital shaker. Unless otherwise stated, drying of resins and solids was accomplished by heating at 45−50 °C in a vacuum oven (10−12 mmHg) to constant weight (generally overnight). IR spectra were obtained by pulverizing the resin beads and fixing the powder in a KBr pellet. IR absorptions are reported in cm^{-1}. Elemental analyses were performed by Quantitative Technologies Inc.[20]

TEMPO-Methyl Resin (6). A solution of sodium ascorbate (12 g, 60 mmol) in water (150 mL) was shaken with a solution of TEMPO• in Et_2O (125 mL) until the deep burgundy color faded to pale orange. The Et_2O layer was separated and dried over $MgSO_4$ and evaporated on a rotary evaporator (bath temperature did not exceed 20 °C) to give an orange oil. This oil was dissolved in 50 mL of anhydrous DMF (50 mL) and added dropwise over 10 min to a stirred, septum-capped flask containing NaH (60% suspension in mineral oil, 1.5 g, 37.5 mmol) and DMF (50 mL) under N_2 atmosphere. After the mixture was stirred for an additional 30 min at room temperature, the septum was removed, Merrifield resin (5.0 g, 6 mmol) was quickly added, and the septum was immediately replaced. Stirring was continued for 16 h at 22 °C. The reaction flask was then cooled in an ice water bath and quenched carefully with cold water while swirling the contents of the flask. The resin was collected by filtration and washed successively with 35−40 mL portions of DMF, H_2O, MeOH, H_2O (×2), MeOH (×2), DCM then MeOH (×3), DCM (×2), and hexanes. It was then dried at 0.5 mmHg, 25 °C overnight, to afford 5.6 g of **6** as a sand-colored resin. Found: C, 87.87; H, 8.59; N, 1.39; Cl, 0.12; indicates 1.0 mmol TEMPO-methyl residues per gram.

TMI/TEMPO Resin (11). A suspension of **6** (200 mg, 0.2 mmol) in TMI (2 mL, 10.1 mmol) was heated at 130 °C for 18 h. After cooling, the reaction mixture was diluted with DCM (5 mL) and the resin beads were collected by filtration. Washing with dichloromethane then hexanes (5 cycles) followed by two hexane washes afforded **11** (247 mg, 103%) upon drying. IR: 2250 (NCO). Found: C, 86.01; H, 7.97; N, 2.27. Calcd for **11**: N, 2.33.

4-Bromo-α-methylstyrene/TEMPO Resin (16). A suspension of **6** (150 mg, 0.15 mmol) in **14** (2.0 g, 10.2 mmol) was heated at 130 °C for 24 h. After cooling, the reaction mixture was diluted with DCM (3 mL) and the resin beads were collected by filtration. Washing with dichloromethane then MeOH (5 cycles) followed by an additional MeOH wash afforded **16** (167 mg, 93%) upon drying. Found: C, 81.97; H, 7.35; N, 0.52; Br, 8.88. Calcd for **16**: N, 1.16; Br, 6.77. The filtrate was saved to recover unused **14**. Initially colorless, it develops a red color upon standing.

3-Trifluoromethyl-α-methylstyrene/TEMPO Resin (17). A suspension of **6** (150 mg, 0.15 mmol) in **15** (2.0 g, 10.7 mmol) was heated at 130 °C for 24 h. After cooling, the reaction mixture was diluted with DCM (3 mL) and the resin beads were collected by filtration. Washing with dichloromethane then MeOH (5 cycles) followed by an additional MeOH wash afforded **16** (160 mg, 90%) upon drying. Found: C, 85.15; H, 7.52; N, 0.61; F, 6.24. Calcd for **16**: N, 1.18; F, 4.81. The filtrate was saved to recover unused **15**. Initially colorless, it develops a red color upon standing.

Rasta-NCO Resin (19): A Representative Procedure for Living Free Radical Polymerization on Solid Support. A suspension of **6** (1.0 g, 1.0 mmol), TMI (10 mL, 50.6 mmol), and ST (3.3 mL, 28.8 mmol) was heated at 130 °C for 20 h. (See comments in General section above.) After cooling, the resulting polymeric mass was shaken with DCM (25 mL) for about 5 min until the resin beads float free. The resin was collected by filtration and washed with DCM then hexanes (5 cycles), followed by an additional two hexane washes before drying. Isolated was **19** (5.2 g, 47.5% based on ST). IR: 2251 (NCO). Found C, 83.65; H, 8.00; N, 3.96. Calcd for **19** based upon mass increase, assuming alternating TMI and ST residues in the new polymer growth and no TEMPO loss: N, 3.97; NCO loading, ~2.6 mmol per gram (see below).

NCO-Loading Verification for 19: A General Procedure for NCO Estimation. A suspension of **19** (50 mg, ~0.04 mmol) in DCM (0.9 mL) was treated with 4-bromophenylethylamine (0.1 mL, 0.65 mmol). The resulting mixture was shaken at 22 °C for 24 h. After the mixture was diluted with MeOH (1 mL), the resin was collected by filtration and washed with DCM then MeOH (5 cycles). Two additional washes with MeOH were performed before drying to afford the urea derivative resin (55 mg). IR shows no NCO absorption at 2250, 1646 (CO), 3350 (NH). Found: C, 69.5; H, 6.55; N, 4.61, Br, 17.44, indicating 2.5 mmol NCO per gram of **19**. This urea derivative resin was treated with DCM (0.7 mL) and TFA (0.3 mL) and shaken at 22 °C for 4 h. The red colored resin was removed by filtration and rinsed with DCM (2 × 1.5 mL). The combined filtrate and washings were evaporated. The residue was dried overnight to afford urea **13** (27 mg). MS (APCI+): 243, 245 (m+1). ^{1}H NMR ($CDCl_3$ + MeOD): δ 7.36 (d, 2H), 7.02 (d, 2H), 3.30 (t, 2H), 3.14 (br, 3H), 2.69 (t, 2H). Calcd for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52; Br, 32.87. Found: C, 44.40; H, 4.40; N, 11.12; Br, 32.57. Recovery of **13** is consistent with ≥2.2 mmol NCO per gram of **19**.

Triblock-Rasta-NCO Resin (23). A suspension of **17** (50 mg, ~22 μmol) in ST (1.0 mL, 8.7 mmol) was treated with *m*-tolylisocyanate (50 μL, 0.38 mmol) and heated at 130 °C for 15 h. After cooling, the resulting polymeric mass was shaken with DCM (6 mL) for 1 h. The resin was collected by filtration and washed with DCM then MeOH (5 cycles), followed by an MeOH wash before drying. Isolated was **22** (628 mg). Found: C, 91.72; H, 7.75, N, 0.07; F, 0.71. A suspension of **22** (100 mg, ~3.5 μmol) in TMI (1.5 mL, 7.58 mmol) and ST (0.5 mL, 4.35 mmol) was heated at 130 °C for 18 h. After cooling, the resulting syrup/bead mixture was diluted with DCM (5 mL). The resin was collected by filtration and washed with DCM then hexanes (5 cycles), followed by an additional two hexane washes before drying. Isolated was **23** (135 mg). IR: 2259 (NCO). Found: C, 88.62; H, 7.92; N, 1.55; F, 0.55.

1-Bromo-4-isopropenylbenzene (14). To a solution of methyltriphenylphosphonium bromide (26 g, 72.8 mmol) in tetrahydrofuran at 0 °C was added a solution of *n*-butyllithium in hexanes (72.8 mmol) dropwise with stirring under N_2 atmosphere. After the mixture was stirred for 2 h, 4-bromoacetophenone (5.0 g, 25.1 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred 18 h, then heated to 80 °C for 6 h under nitrogen with stirring. Half the volume of solvent was evaporated at reduced pressure, then Et_2O and water were added. The water layer was discarded, and the Et_2O layer was washed with water, 1 M aqueous hydrochloric acid, and water. It was then dried over $MgSO_4$ and concentrated. The resulting mixture was filtered through a plug of silica gel (50/50 EtOAc/hexanes), product containing fractions were concentrated, and the product was distilled by Kugelrohr to afford **14** (3.4 g, 68%). ^{1}H NMR ($CDCl_3$): δ 2.109 (s, 3H), 5.082 (s, 1H), 5.342 (s, 1H), 7.3 (d, 2H), 7.4 (d, 2H). Calcd for C_7H_9Br: C, 54.85; H, 4.60; N, 0.00; Br, 40.55. Found: C, 55.12; H, 4.68; N, 0.07; Br, 40.57.

1-Trifluoromethyl-3-isopropenylbenzene (15). The procedure for **14** was followed, substituting 4-trifluoromethylacetophenone to afford **15** (52% yield). ^{1}H NMR ($CDCl_3$): δ 2.635 (s, 3H), 5.157 (s, 1H), 5.403 (s, 1H), 7.4 (m, 1H), 7.5 (d, 1H), 7.61 (d, 1H), 7.668 (s, 1H). Calcd for $C_{10}H_9F_3$: C, 64.51; H, 4.87; N, 0.00, F, 30.61. Found: C, 62.31; H, 4.69; N, 0.11.

3-Isopropenylbenzyl-α,α-dimethyl Trimethylsilylethyl Carbamate (26). To a mixture of TMI (2.4 mL, 12.1 mmol) dissolved in 1,2-dichloroethane (40 mL) were added 2-trimethylsilylethanol (4.5 mL, 31.4 mmol) and catalytic Dabco (135 mg, 1.2 mmol). The reaction mixture was heated to 65 °C with stirring for 20 h under static N_2. DCM was added, and the product was washed (1× aqueous $NaHCO_3$, 1× 5% aqueous citric acid, and 1× water), dried over $MgSO_4$, and concentrated to afford crude **26** which was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford pure **26** (2.0 g, 52%). ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 9H), 0.941 (m, 2H), 1.666 (s, 6H), 2.142 (s, 3H), 4.061 (m, 2H), 5.068 (s, 1H), 5.334 (s, 1H), 7.295 (m, 3H), 7.480 (s, 1H). Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15; N, 4.38. Found: C, 67.41; H, 9.24; N, 4.42.

3-Isopropenylbenzyl-α,α-dimethyl Isocyanate (25). To a mixture of **26** (2.3 g, 7.2 mmol) dissolved in dimethylformamide (15 mL) was added tetrabutylammonium fluoride as a 1 M solution in tetrahydrofuran (14.4 mL, 14.4 mmol). The reaction mixture was stirred at room temperature for 48 h, concentrated at reduced pressure, and purified by chromatography on silica gel (EtOAc) to afford **25** (510 mg, 42%). MS(APCI+): 176 (m+1). ^{1}H NMR ($CDCl_3$): δ 1.487 (s, 6H), 2.149 (s, 3H), 5.065 (s, 1H), 5.343 (s, 1H), 7.28 (m, 2H), 7.404 (m, 1H), 7.594 (m, 1H). Calcd for $C_{12}H_{17}N\cdot 0.1H_2CO_3$: C, 80.08; H, 9.55; N, 7.72. Found: C, 80.24; H, 9.57; N, 7.29.

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